Behaviour and Management of European Ungulates

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Chapter 10

Novel Management Methods: Immunocontraception and Other Fertility Control Tools

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Impacts of overabundant ungulate populations on human activities and conservation include crop and forestry losses, collisions with vehicles, disease transmission, nuisance behaviour, damage to infrastructures, predation on livestock and native species, and reduction of biodiversity in plant and animal communities (e.g. Curtis *et al.*, 2002; Massei *et al.*, 2011; Reimoser and Putman, 2011; Ferroglio *et al.*, 2011; Langbein *et al.*, 2011).

Current trends in human population growth and landscape development indicate that human–ungulate conflicts in Europe, as well as in the United States, are likely to increase in parallel with increased expansion in numbers and range of many of these species (Rutberg and Naugle, 2008; Brainerd and Kaltenborn, 2010; Gionfriddo *et al.*, 2011a). Many of these conflicts have been traditionally managed by lethal methods. However, current trends in distribution and numbers of wild boar, feral pigs and deer in Europe and in the United States (e.g. Saez-Royuela and Telleria, 1986; Waithman *et al.*, 1999; Ward, 2005; Apollonio *et al.*, 2010) suggest that recreational hunting is not sufficient to control ungulate densities. In addition, ethical considerations regarding humane treatment of animals are increasingly shaping public attitudes about what are considered acceptable methods of mitigating human–wildlife conflicts, and lethal control is often opposed (Beringer *et al.*, 2002; Wilson, 2003; Barfield *et al.*, 2006; McShea, 2012).

Public antipathy towards lethal methods increasingly constrains the options available for ungulate management, particularly in urban and suburban areas and in protected areas where culling is often opposed on ethical, legal or safety grounds (Kirkpatrick *et al.*, 2011; Boulanger *et al.*, 2012; Rutberg *et al.*, 2013). Consequently, interest in non-lethal methods, such as translocation or fertility control, has increased (Fagerstone *et al.*, 2010).

Reviews of translocations of problem wildlife as a mechanism for reducing human–ungulate conflicts concluded that this method may cause significant stress, increase mortality and traffic accidents, is relatively expensive and has the potential to spread diseases and pathogens (Daszak *et al.*, 2000; Corn and Nettles, 2001; Conover, 2002; Beringer *et al.*, 2002; Massei *et al.*, 2010a). Examples of translocations of pathogens and hosts include the spread of bovine brucellosis and bovine tuberculosis following the translocation of bison (*Bison bison*) in Canada (Nishi *et al.*, 2006), the potential spread and dissemination of diseases such as the Aujeszky's disease virus following the translocation of wild boar between hunting estates in Spain (Ruiz-Fons *et al.*, 2008) and warble and nostril flies spread to conspecifics by caribou (*Rangifer tarandus*) after translocation of animals from Norway to Greenland (in Kock *et al.*, 2010).

Fertility control is often advocated as a safe, humane alternative to culling for managing overabundant wildlife (Fagerstone *et al.*, 2010; McLaughlin and Aitken, 2011; Kirkpatrick *et al.*, 2011). Early attempts to use fertility control to manage ungulates failed for reasons that included toxicity of the drugs used, transfer of these drugs to the food chain, manufacturing costs and the fact that repeated applications of contraceptives were required to induce long-term infertility (Gray and Cameron, 2010; Kirkpatrick *et al.*, 2011). In the last two decades, a reawakened interest in alternatives to surgical sterilisation for companion animals and livestock has led to the development of novel fertility control agents (Herbert and Trigg, 2005; Naz *et al.*, 2005; Massei *et al.*, 2010b). In parallel, several fertility control agents have emerged for wildlife applications.

In this chapter we provide a comprehensive, critical overview of fertility control to mitigate human–ungulate conflicts. In particular, we discuss the availability and use of fertility control agents in ungulates, we review delivery methods for these agents, we provide a synthesis of the conclusions of empirical and theoretical studies of fertility control applied to populations and we offer suggestions to guide decisions regarding the suitability of fertility control to mitigate human–ungulate conflicts.

10.1 Fertility inhibitors for ungulates

10.1.1 Fertility control and reproduction

Chemical fertility control can be achieved through contraception or sterilisation. Contraception prevents the birth of offspring but maintains fertility, whilst sterilisation renders animals infertile (Kutzler and Wood, 2006). In mammals, the series of events that leads to ovulation and spermatogenesis begins in the brain, where gonadotropin-releasing hormone (GnRH) is produced in the hypothalamus. GnRH is transported through small blood vessels to the anterior pituitary gland, where it binds to GnRH receptors to stimulate the release of the pituitary gonadotropins, LH (luteinizing hormone) and FSH (follicle-stimulating hormone) (Figure 10.1).

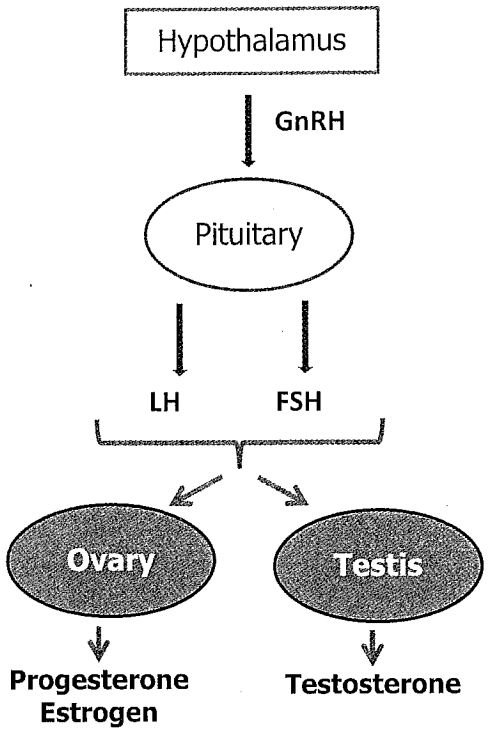

Figure 10.1 Schematic illustration of the fertility axis in male and female mammals.

These gonadotropins in turn stimulate the synthesis and secretion of sex hormones such as oestrogen, progesterone, and testosterone which are responsible for ovulation, spermatogenesis and sexual behaviour. The reproductive cycle and the production of eggs and sperm can be disrupted by administration of substances that interfere with the hypothalamic–pituitary–gonadal axis by blocking the synthesis, release or actions of hormones produced by the hypothalamus, the pituitary gland, or the testes and ovary. In females, a further target for contraception is the zona pellucida (ZP), a protein coat that surrounds the ovulated egg and allows species-specific sperm recognition and fertilization. In males, sterilisation can also be achieved by chemicals that cause testicular sclerosis and permanent sterility (Crawford *et al.*, 2011). The following section presents a brief overview of fertility control agents commercially available or widely tested on ungulates. Taking into account field applications, the review includes only those drugs that induce infertility for at least 6–12 months following administration of a single dose.

The majority of the fertility inhibitors reported in the literature target females, although some are effective for both genders and a few have been specifically developed for males. In many ungulate species the mating system is promiscuous, thus requiring extremely high levels of male sterility for fertility control to have any effect at the population level. For instance, in feral horses (*Equus caballus*) breeding still occurred even when 100% of the dominant harem stallions were sterilized (Turner and Kirkpatrick, 1991; Garrott and Siniff, 1992). In addition, some contraceptives may affect secondary sexual characteristics such as antler development (see later sections) and their use is not recommended for male deer.

A fertility control agent suitable for field applications should ideally have the following characteristics (Turner and Kirkpatrick, 1991; Fagerstone *et al.*, 2002; Massei and Miller, 2013):

1. Nil or acceptable side effects on the target animal's physiology, behaviour and welfare, including no interference with pre-existing pregnancy or lactation
2. Effective for at least one reproductive season when delivered through a single, injectable dose or implant, or when administered in one or multiple oral doses
3. Render all or the majority of treated animals infertile
4. Inhibit female reproduction but ideally prevent reproduction in both sexes
5. Relatively inexpensive to produce and deliver
6. No effect on any food chain
7. Species specificity
8. Stability under a wide range of field conditions.

Although none of the fertility control agents currently available meet all the above features, several exhibit many of these characteristics.

10.1.2 Hormonal contraceptives

Synthetic progestins such as norgestomet, melengestrol acetate (MGA), megestrol acetate (MA) and levonorgestrel have been widely used in zoo animals, livestock and wildlife. By binding to progesterone receptors, synthetic progestins disrupt ovulation and egg implantation in females and impair spermatogenesis in males (Asa and Porton, 2005). For instance, norgestomet, administered to white-tailed and black-tailed deer, caused infertility in 92–100% of the females for at least one year (Jacobsen *et al.*, 1995; DeNicola *et al.*, 1997). These drugs may cause abortion, although this effect depends on progestin type, species, dose and time of administration during pregnancy (Waddell *et al.*, 2001; Asa and Porton, 2005). MGA did not affect pregnancy in several ungulate species, but delayed or prevented parturition in treated white-tailed deer (Plotka and Seal, 1989; Asa and Porton, 2005). Progestin implants, with an estimated duration of efficacy of ≥2 years, have been widely used for suppression or synchronisation of oestrus in cattle and they have been employed as contraceptives in zoos for about 20 years. MA implants induced infertility in female mountain goats for at least 5 years, with reproduction recorded in 10% treated goats against 68% untreated controls (Hoffman and Wright, 1990).

Implants containing different concentrations of steriods such as ethinyloestradiol (EE), and progesterone (P) have been successful in preventing pregnancy in feral mares. Suppression of ovulation appeared to be inversely related to the concentration of EE used in the implant. The percentage of animals ovulating after 2 years was 12–20% for groups that had received a combination of P and EE or the highest dose of EE respectively, against 100% for control mares; pregnancy rate for the same groups was 0% for both P+EE and EE and 100% for control females. All animals that were pregnant at the time of contraceptive treatment delivered normal foals. The results demonstrated effective contraception of feral mares for up to 36 months without compromising pregnancy (Plotka *et al.*, 1992).

Another group of hormones widely used as contraceptives are the gonadotropin-releasing hormone (GnRH) agonists: these are synthetic peptides that mimic GnRH and stimulate the production and release of FSH and LH. Chronic administration of these drugs (e.g. >4 weeks) results in a downregulation of the pituitary gland and suppression of the secretion of FSH and LH. However, immediately following administration, a 'flare up' effect often occurs that can stimulate oestrus in females and cause temporary enhancement of testosterone and semen production in males (Patton *et al.*, 2007). As agonists have a higher affinity for and do not quickly dissociate from the GnRH receptors, the 'flare up' is followed by prolonged oestrus inhibition and infertility (Gobello, 2007) as long as the drug is present. The effectiveness of GnRH agonists depends on type of agonist, release system, dose rate and duration of treatment (Gobello, 2007; Patton *et al.*, 2007). The side-effects are equivalent to gonad removal but are reversible; however, GnRH agonists may cause abortion and thus their application to free-living ungulates is limited to those species that have a well-defined, relatively short breeding season (Asa and Porton, 2005).

Sustained-release subcutaneous implants containing GnRH agonists have been tested successfully in several livestock and wildlife species. For instance, implants of the GnRH agonist deslorelin (Suprelorin©) have been used to inhibit reproduction for 1–2 years in cattle and in several other wildlife species (e.g. D'Occhio *et al.*, 2002; Herbert and Trigg, 2005; Eymann *et al.*, 2007). Another GnRH agonist, leuprolide, administered in biodegradable implants was found effective at preventing pregnancy for one breeding season in 100% of female elk (wapiti) and mule deer with no effects on behaviour, body condition, haematology and blood chemistry (Baker *et al.*, 2002, 2004; Conner *et al.*, 2007). Regardless of proven efficacy, the use of hormonal contraceptives on free-ranging ungulates is still controversial because of potential welfare effects on pregnancy, environmental impact and possible transfer to consumers through the food chain (Kirkpatrick *et al.*, 1996; De Nicola *et al.*, 2000).

10.1.3 Immunocontraceptive vaccines

Most studies of fertility control applications in free-ranging ungulates have focussed on immunocontraceptive vaccines. These vaccines stimulate the immune system to produce antibodies to proteins or hormones essential for reproduction (Miller and Killian, 2002), thus rendering animals contracepted or infertile. To achieve long-term infertility, adjuvants are used, which are chemicals, large molecules or entire cells of killed pathogens, that enhance the immune response to a vaccine (Fraker *et al.*, 2002). Using liposome-based formulations has also been shown to increase the immune response of some immunocontraceptive vaccines (Fraker and Brown, 2011). The effectiveness, duration and side effects of immunocontraceptive vaccines can vary with species, sex, age, individual differences in immunocompetence, as well as the active component of the vaccine, its formulation, delivery system and the dose and type of adjuvant (Miller *et al.*, 2008a, 2009; Holland *et al.*, 2009; Kirkpatrick *et al.*, 2011). The most studied immunocontraceptives in ungulates are zona pellucida- and GnRH-based vaccines (Table 10.1).

Table 10.1 Effectiveness of single-dose immunocontraceptive vaccines to cause infertility in ungulate species in captivity and field trials. The effectiveness is expressed as proportion of infertile females in the control (C) and treatment (T) groups in the years following administration of the vaccine.

Species	*Type of study*	*Vaccine type, adjuvant type and vaccine dose*	*% infertile females*	*References*
White-tailed deer	Captive	GonaCon and AdjuVac various formulations	T GonaCon-KLH = 100% 60% 50% 50% 25% T GonaCon-Blue = 100% 100% 80% 80% 80%	Miller *et al.* (2008a)
White-tailed deer	Field	GonaCon-KLH and AdjuVac	T = 67% 43% C = 8% 17%	Gionfriddo *et al.* (2011a)
White-tailed deer	Field	GonaCon-KLH and AdjuVac	T = 88% 47% C = 15% 0%	Gionfriddo *et al.* (2009)
White-tailed deer	Field	PZP (SpayVac) and AdjuVac	T = 100% 100% C = 22%	Locke *et al.* (2007)
White-tailed deer	Field	PZP and AdjuVac	T = 100% C = 22%	Hernandez *et al.* (2006)
White-tailed deer	Captive	PZP and SpayVac, with AdjuVac or Alum	SpayVac-AdjuVac: 100% 100% 100% 80% 80% IVT-PZP-AdjuVac: 100% 80% 80% 80% 80% SpayVac-Alum: 80% NWRC-PZP-AdjuVac: 80% 0% (200 µg) NWRC-PZP-AdjuVac: 100% 20% 20% 20% 0% (500 µg); C = 0%	Miller *et al.* (2009)

Wapiti	Captive	GonaCon-B and AdjuVac	T = 90% 75% 50% 25% C = 0% 0% 0% 14%	Powers *et al.* (2011)
Wapiti	Captive	GonaCon-KLH and AdjuVac	GonaCon-KLH (1000 µg) = 92% 90% 100% GonaCon-KLH (2000 µg) = 90% 100% 100% C = 27% 25% 0%	Killian *et al.* (2009)
American Bison	Captive	GonaCon-KLH and AdjuVac	T = 100% C = 0%	Miller *et al.* (2004)
Wild boar	Captive	GonaCon-KLH and AdjuVac	T = 92% infertile for at least 4-6 years C = 0%	Massei *et al.* (2008) Massei *et al.* (2012)
Fallow deer	Field	PZP (SpayVac) and FCA	T = 100% 100% 100% C = 4% 3% 4%	Fraker *et al.* (2002)
Feral horse	Captive	GonaCon-KLH and AdjuVac	T = 93% 64% 57% 43% C = 25% 25% 12% 0%	Killian *et al.* (2008)
Feral horse	Field	GonaCon-B and AdjuVac	T = 61% 58% 69% C = 40% 31% 14%	Gray *et al.* (2010)
Feral horse	Captive	PZP (SpayVac) and AdjuVac	T = 100% 83% 83% 83% C = 25% 25% 12% 0%	Killian *et al.* (2008)
Feral horse	Field	PZP with FCA and QS-21	T = 95% 85% 68% 54% C = 47% 42% 49% 48%	Turner *et al.* (2007)
Feral horse	Field	PZP and AdjuVac	T= 63% 50% 56% C= 40% 31% 14%	Gray *et al.* (2010) Gray *et al.* (2011)

The zona pellucida (ZP) that surrounds an ovulated egg is composed of four types of proteins, named ZP1, ZP2, ZP3 and ZP4, each with different functions in mediating structure and species-specific sperm recognition and binding. Differences in these proteins among mammals are partly responsible for the variable results obtained when using a particular ZP vaccine on different species (Kitchener *et al.*, 2009; Gupta and Bansal, 2010). For instance, porcine ZP (PZP) immunocontraceptive vaccines, derived from ZP isolated from pig ovaries, inhibit fertilisation in many wildlife species including ungulates (Table 10.1) but not rodents, cats and wild pigs (Fagerstone *et al.*, 2002; Kirkpatrick *et al.*, 2009, 2011). Likewise, differences in the results of studies using ZP-based vaccines may reflect different formulations of native, purified or recombinant ZP vaccines and different methods of extraction of PZP from pig ovaries (Miller *et al.*, 2009; Kirkpatrick *et al.*, 2011; Bechert *et al.*, 2013).

Early immunocontraceptive vaccines had to be delivered as a primer injection followed by a booster, which made field applications impractical (Putman, 1997). Initial vaccine formulations also used Freund's complete adjuvant (FCA). Some constituents of this adjuvant, namely mycobacteria (*Mycobacterium tuberculosis*) and mineral oil, were found responsible for granulomas (thickened tissue filled with fluid) at injection sites, for false-positive results in TB skin tests in deer treated with these vaccines and for potential carcinogenicity to consumers of treated animals (Kirkpatrick *et al.*, 2011). Significant progress has been made through the development of a novel adjuvant (AdjuVac™, National Wildlife Research Center, United States), containing inactivated *Mycobacterium avium* and based on a modified version of the Johne's disease vaccine.

Injectable ZP-based immunocontraceptives have been employed extensively to reduce fertility in zoo ungulates, in free-living deer, feral horses and elephants (Table 10.1). In particular, the combination of AdjuVac and PZP-vaccine made ungulates infertile for several years after a single dose (Table 10.1). In some species, such as white-tailed deer, some ZP vaccines may cause pathologies such as inflammation of the ovary (Curtis *et al.*, 2007) but in others, such as wild horses, no ovarian damage was observed after 3 years of treatment (Patton *et al.*, 2007). Following injection of ZP-based immunocontraceptives, injection site reactions such as granulomas are common, whilst the occurrence of draining abscesses is around 1% in various species (Gray *et al.*, 2010; Kirkpatrick *et al.*, 2009). As ZP-based immunocontraceptives inhibit fertilisation but not ovulation, animals treated with these vaccines tend to have multiple infertile oestrus cycles which may lead to extended breeding seasons, increased movements and potential late births (Miller *et al.*, 2000; Curtis *et al.*, 2007; Nuñez *et al.*, 2009, 2010; reviewed in Kirkpatrick *et al.*, 2009, 2011). Multiple infertile oestrus cycles following treatment with PZP vaccine were observed in white-tailed deer, wapiti and horses (Heilmann *et al.*, 1998; Killian and Miller, 2001; Curtis *et al.*, 2002; Ransom *et al.*, 2013). Other studies suggested that treatment with ZP vaccines did not affect behaviour and body condition of mares (Ransom *et al.*, 2010; Kirkpatrick *et al.*, 2011), white-tailed deer (Hernandez *et al.*, 2006) and wapiti (Heilmann *et al.*, 1998). However, an

extension of the breeding season in deer treated with PZP vaccine resulted in increased energy expenditure by males (Curtis *et al.*, 2002). PZP vaccines were found safe to administer to pregnant or lactating females (Kirkpatrick and Turner, 2002; Patton *et al.*, 2007) and had no long-term effect on health of white tailed deer (Miller *et al.*, 2001). In 2012, an injectable PZP-based vaccine, ZonaStat-H, was registered by the US Humane Society and approved by the US Environment Protection Agency (EPA) as a contraceptive for population control of wild and feral horses and feral donkeys.

Vaccines based on gonadotropin-releasing hormone (GnRH) generate antibodies towards GnRH, thus preventing the hormonal cascade that leads to ovulation and sperm production. Several multi-dose GnRH-based immunocontraceptive vaccines, developed for use in livestock are unsuitable for wildlife due to the difficulty of recapturing individuals to administer booster doses and to their relatively short-term (a few months) effectiveness (reviewed in Naz *et al.*, 2005; McLaughlin and Aitken, 2010). Single-dose injectable GnRH-based vaccines, specifically formulated for wildlife applications, offer better prospects for managing ungulates. Among these vaccines, the most studied is Gonacon™, currently registered in the United States by the EPA as an immunocontraceptive for white-tailed deer, feral horses and feral donkeys. Gonacon™ consists of a synthetic GnRH coupled to a mollusc protein (Miller *et al.*, 2008b).

Formulated as an injectable, single-dose immunocontraceptive, Gonacon™ caused infertility for several years in males and females of several ungulates (e.g. Miller *et al.*, 2000; Killian *et al.*, 2008; Massei *et al.*, 2008; Gray *et al.*, 2010; Massei *et al.*, 2012) (Table 10.1). As Gonacon™ interferes with steroid production, treated females do not exhibit oestrus behaviour. Male deer treated with GonaCon™ also showed a complete lack of sexual activity and reduced testicle size, but they also exhibited abnormal antler development (Miller *et al.*, 2000, 2009; Fagerstone *et al.*, 2008). The lack of sexual activity, in species where this behaviour might increase human–wildlife conflicts such as deer collisions with vehicles during the rut, could be advantageous, although the effect on antler development suggests GonaCon™ should not be used on male deer. Similar to ZP-based contraceptives, antibodies to GnRH decrease with time and fertility may be restored in the years after treatment unless animals are administered booster vaccinations (Miller *et al.*, 2008b; Massei *et al.*, 2012).

The main side effect of Gonacon™ is the formation of a granuloma or a sterile abscess at the injection site; the severity and incidence of injection site reactions vary with species. In white-tailed deer, injection-site granulomas and sterile abscesses occurred in the deep hind-limb musculature of >85% of treated animals, although no evidence of limping or impaired mobility was observed in these deer during a 2-year study (Gionfriddo *et al.*, 2011b). These reactions are typical responses to injection of adjuvanted vaccines formulated as water-in-oil emulsions (Miller *et al.*, 2009). On the other hand, GonaCon™ had no adverse effects on major organs, body condition, fat deposits or blood chemistry in wild boar, white-tailed deer and wapiti (Massei *et al.*, 2008, 2012; Gionfriddo *et al.*, 2009, 2011b).

When given to pregnant bison and elk, GonaCon™ did not affect pregnancy (Miller *et al.*, 2004; Powers *et al.*, 2011). Other studies found that GonaCon™ did not induce infertility and did not prevent sexual development when administered to 3–4-month-old white-tailed deer (Miller *et al.*, 2008a; Gionfriddo *et al.*, 2011a). Like ZP-based vaccines, GnRH vaccines are broken down if ingested, thus they do not pose risks to predators or human consumers.

10.2 Delivery methods

Although a fertility control agent should be ideally species specific, this is rarely the case and specificity must be achieved through the delivery method. At present, fertility control agents that induce at least 1 year of infertility are administered by direct injection following capture, by implant or are delivered remotely through biobullets and syringe-darts (see below). Subcutaneous implants that release contraceptive agents into the body 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; Coulson *et al.*, 2008; Lohr *et al.*, 2009). However, steroid implants have the potential for transferring active ingredients to predators and scavengers.

Biobullets are biodegradable projectiles used for remote administration of veterinary products (DeNicola *et al.*, 2000). Syringe-darts, routinely employed to anaesthetise wild animals, have also been used to administer contraceptives to large ungulates at ranges of ≤40 m (Rudolph *et al.*, 2000; Aune *et al.*, 2002; Delsink *et al.*, 2006). The advantages of remote administration of contraceptives to ungulates are that delivery can be targeted to specific individuals (unlike oral delivery), and that this method minimises the welfare and economic costs of trapping (Kreeger, 1997). Potential disadvantages of these delivery systems include the inability to identify successfully vaccinated animals, cost, dose regulation and incomplete intra-muscular injection (De Nicola *et al.*, 1997; Kreeger, 1997; Aune *et al.*, 2002). The inability to identify previously vaccinated animals is important because these animals can receive multiple doses: whilst this is not expected to have welfare costs, it certainly reduces the efficiency of any fertility control programme. Another approach to a single-dose, multiple-year immunocontraceptive is to mimic the effects of booster injections by incorporating the vaccine into controlled-released polymers formulated as injectable pellets. This approach was successfully tested with wild horses by using simultaneous intramuscular injection of 1-, 3- and 12-month pellets to provide *in vivo* delivery of booster doses of the PZP vaccine (Turner *et al.*, 2007; Rutberg *et al.*, 2013).

Injectable forms of fertility control vaccines have been shown to effectively block fertility in a number of species. However, to be of further practical use in wildlife management, more efficient means of delivery are required. There is great interest in the development of mucosal (e.g. oral or intranasal) vaccines in human pharmaceuticals (reviewed in Woodrow *et. al.*, 2012) and this will aid in efforts towards wildlife applications where some research has already

been conducted (Cui *et al.*, 2010). Once developed, oral fertility control agents are likely to be less expensive to administer than injectable forms, in part, because capture and handling of animals will not be necessary for the delivery of these contraceptives. However, unlike injectable vaccines, oral fertility control agents will likely require repeated applications to cause infertility (Cross *et al.*, 2011). As oral forms of fertility control might also affect non-target animals, species specificity could be achieved through targeted delivery methods. One example is the BOS (Boar-Operated System) developed as a specific delivery system for wild boar and feral pigs (Massei *et al.*, 2010c; Long *et al.*, 2010; Campbell *et al.*, 2011) (Figure 10.2).

Immunocontraceptive vaccines delivered through genetically modified, self-sustaining infectious vectors have been developed in Australia. Criticism of this approach involved concerns regarding irreversibility, the difficulty of controlling the vectors once released, possible mutations of the vectors that could affect non-target species and possible development of resistance (Barlow, 2000; Williams,

Figure 10.2 Free-living wild boar feeding on maize-based baits from a Boar-Operated System (BOS). The metal cone slides along the pole and fully encloses the base onto which the baits are placed. Several studies found that free-living wild boar and wild pigs fed regularly from the BOS and that the device successfully prevented bait uptake by non-target species. The BOS can be used to deliver vaccines, contraceptives or other pharmaceuticals employed to manage overabundant populations of wild suids.

2002). In New Zealand genetically modified transmissible organisms, such as species-specific nematode parasites, have been explored to deliver contraceptives, although no data are available for ungulates (McDowell *et al.*, 2006; Cowan *et al.*, 2008; Cross *et al.*, 2011).

10.3 Fertility control and population responses

Most recent field studies on fertility control have used immunocontraceptives, whilst modelling studies have focussed on generic contraceptives of different levels and duration of induced infertility (Table 10.2). Comparing the relative merits of fertility and lethal control to manage overabundant populations, recent research suggests that large, long-lived species are easier to manage with fertility control than smaller, shorter-lived ones because a lower proportion of the population must be targeted each year (Hone, 1999), particularly if lifelong contraceptives are employed (Hobbs *et al.*, 2000).

Modelling the impact of fertility control versus culling for a geographically closed population of white-tailed deer, Merrill *et al.* (2003) concluded that, for instance, to achieve a 60% reduction over 4 years, culling should remove 40% of available fertile females each year. To maintain this level of reduction, only 13% of the available females should be sterilised every year. Based on this model, the authors suggest that an effective management strategy to control overabundant urban deer populations would require two steps. The first step will reduce the population to a given level: to achieve this, culling would be more efficient than sterilisation. The second step will maintain the population at a set level and sterilisation will become more efficient as the number of sterilised females increases (Hobbs *et al.*, 2000). However, in long-lived species and in populations characterised by slow turnover, the benefits of using fertility control to decrease population size will only accrue in the long term (Twigg *et al.*, 2000; Kirkpatrick and Turner, 2008; Cowan and Massei, 2008).

The effects of fertility control on population dynamics also depend on species-specific social and reproductive behaviours, on the type of contraceptive used and on its mode of action, as well as on whether a population is isolated or open. There is general consensus that fertility control is most effective for managing relatively small (50–200 animals) isolated populations of ungulates (Rudolph *et al.*, 2000; Kirkpatrick and Turner, 2008). Avoiding disruption of behaviour is crucial, as fertility-control-induced changes in immigration and emigration might prevent fertility control achieving the required reduction in population growth (e.g. Davis and Pech, 2002; Merril *et al.*, 2006).

On the other hand, using fertility control methods that inhibit normal sexual behaviour can potentially reduce disease transmission by decreasing contact rates between individuals (Caley and Ramsey, 2001; Ramsey, 2007). For instance, a reduction of reproductive behaviour would result in decreased transmission of venereal diseases such as pseudorabies and brucellosis (Miller *et al.*, 2004; Killian *et al.*, 2006). In this context, methods that prevent ovulation are

likely to be more successful at decreasing disease transmission than those that only block fertilisation. When only fertilisation is blocked, females of many ungulate species will continue to ovulate, thus attracting males (Putman, 1997; Miller *et al.*, 2000; Curtis *et al.*, 2007; Nuñez *et al.*, 2009, 2010). This may have significant effects on prolonging the duration of the rut, enhancing and extending the period of male–male competition (and thus increasing risk of injury or male exhaustion).

The factors affecting emigration and immigration in ungulate populations managed through fertility control have received little attention. For instance, a reduction in population density due to fertility control might increase immigration rate, thus negating the benefits of using non-lethal population management. On the other hand, fertility control might also encourage emigration, particularly of males looking for mating opportunities outside their normal home range. As female white-tailed deer in urban and suburban areas have relatively small home range size and high site fidelity (Grund *et al.*, 2002), it is possible to hypothesise that fertility control will not affect the movements of these animals. Other studies found that ZP-based immunocontraceptives did not affect spatial behaviour in white-tailed deer and feral horses (Hernandez *et al.*, 2006; Ransom *et al.*, 2010).

Density-dependent regulation of population should also be taken into account: Merrill *et al.* (2003) suggested that if density-dependence was occurring, it would increase the effectiveness of sterilisation as the reproductive removal (but not the physical removal) of part of the population would intensify density-dependent feedback. Clearly, this is an area where more field studies are warranted to assess the effects of fertility control on emigration, immigration, recruitment and mortality in ungulate populations with different life-history traits.

Fertility control has been associated with increased survival and improved health condition, probably due to the reduced expenditure of energy normally required for reproduction. For example, sterilisation-induced increases in survival and total food consumption in feral Soay rams caused an increase in both animal density and impact on the plant community (Jewell, 1986). Similarly, as immunocontraceptives can significantly extend lifespan and improve body condition (Turner and Kirkpatrick, 2002; Kirkpatrick and Turner, 2007; Gionfriddo *et al.*, 2011b), the impact of increased survival on population dynamics must be taken into account when using fertility control to manage ungulate populations.

Fertility control in ungulates has been used to decrease population size or growth, reduce vertical or horizontal transmission of diseases or reduce impacts of local populations on human activities (Table 10.2). The relative merits of fertility control and culling have been much debated, with advocates of the two methods often holding opposite, irreconcilable positions (Kirkpatrick, 2007; Curtis *et al.*, 2008; Fagerstone *et al.*, 2010). Modelling studies concluded that in several instances the outcome of the two methods in reducing population size or disease transmission depends on the definition of 'efficiency'. If efficiency is defined in terms of the time taken to achieve the desired effect, then culling is

Table 10.2 Examples of empirical and theoretical applications of fertility control (FC) at population level in wildlife and in feral ungulate populations.

Aim	*Species*	*Trial*	*Method*	*Results and conclusions*	*Reference*
Evaluate impact of FC on population size	White-tailed deer	Field	PZP vaccine	FC feasible to maintain small (<200) suburban deer populations at 30–70% of carrying capacity	Rudolph *et al.* (2000)
	White-tailed deer	Field	PZP vaccine	FC induced a 7.9% population decline in a suburban deer population	Rutberg *et al.* (2004)
	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)
	Wild horse	Field	PZP vaccine	The effort required to achieve zero population growth decreased, as 95, 83, 84, 59 and 52% of all adult mares were treated in the first 5 years. FC increased longevity and improved body condition	Turner and Kirkpatrick (2002)
	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)
	Wild horse	Model	PZP vaccine	FC can be used to reduce population size to the target number in 5–8 years	Ballou *et al.* (2008)
	African Elephant	Field	PZP vaccine	FC prevented population growth	Delsink (2006)

	African Elephant	Model	Immuno-contraception	'Rotational' FC can be used to increase calving interval, slow population growth rate and alter age structure	Druce *et al.* (2011)
	Wildlife	Model	Generic contraception	FC was more effective than culling in reducing population size for medium and large-size animals	Zhang (2000)
	White-tailed deer	Model	Generic contraceptive	FC was more efficient than culling in reducing population size provided >50% females are maintained infertile	Hobbs *et al.* (2000)
	Wapiti	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 to removal, FC resulted in smaller, less fluctuating population size	Gross (2000)
Evaluate factors affecting time to reduce a population through FC	White-tailed deer	Model	Permanent sterilisazion	FC could reduce a population by 30–60% in 4–10 years if 25–50% of fertile females were 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 sterilisazion	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)

always the most efficient solution (Bradford and Hobbs, 2008). Conversely, if efficiency is defined as the proportion of the population to be targeted, fertility control can be regarded as potentially more efficient than culling (Hobbs *et al.*, 2000; Merrill *et al.*, 2003). By defining efficiency as the proportion of the population that must be treated, the time and costs required are deliberately ignored (Merrill *et al.*, 2003). In this scenario, modelling suggests that fertility control agents that render animals infertile for many years are likely to be more efficient than culling, provided that the fertility status of the treated animals is known, for instance, through ear-tags that identify animals previously treated with contraceptives.

Other advantages of fertility control over culling include:

1. Compared to fertility control, culling is more likely to cause social perturbation, increased contact rates and hence increased likelihood of disease transmission (e.g. Ramsey *et al.*, 2006; Carter *et al.*, 2007)
2. Animals in improved body condition, following treatment with contraceptives, might be less susceptible to disease and also mount a better immune response to disease vaccines
3. Infertile animals remain in the population, thus maintaining density-dependent feedback to recruitment and survival (Zhang, 2000)
4. A growing recognition that fertility control in conjunction with disease vaccination can be as effective as culling to manage disease transmission (Smith and Cheeseman, 2002).

   As animals vaccinated against a disease reproduce, new susceptible individuals enter the population and dilute the level of herd immunity provided by disease vaccination; combining disease vaccination and fertility control, to prevent the recruitment of new susceptibles can thus reduce the effort required to eliminate the disease (Smith and Wilkinson, 2003; Carroll *et al.*, 2010).

In some instances, fertility control might be required to reduce or halt population growth rather than to decrease population size. Exploring options to manage a small, isolated population of African elephants, Druce *et al.* (2011) suggested that using reversible immunocontraceptives on an individual rotational basis would increase inter-calving intervals, stabilise population structure and lower population growth to a predetermined rate.

Some authors have 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; Magiafoglu *et al.*, 2003; Cooper and Larsen, 2006; Holland *et al.*, 2009). These authors argue that when females only are treated with immunocontraceptives, resistance might evolve if the response to the vaccine is specific for this gender and could be inherited through the maternal line. No studies have so far demonstrated such effects although unresponsiveness to immunocontraceptive vaccines was found to have a genetic component in brushtail possums (Holland *et al.*, 2009).

10.4 Can fertility control mitigate human–ungulate conflicts?

Human–ungulate conflicts often demand immediate solutions. Stakeholders have a significant impact on management options but often hold opposite opinions. For instance, animal welfare groups tend to advocate fertility control to manage these conflicts (Curtis *et al.*, 2008), whilst many hunting groups oppose the use of fertility control because of concerns that this method will replace sport hunting (Kirkpatrick, 2007; Fagerstone *et al.*, 2010).

The studies carried out so far indicate that if fertility control is the sole method employed to manage overabundant populations, a substantial initial effort is required (Rudolph *et al.*, 2000; Walter *et al.*, 2002; Merrill *et al.*, 2003, 2006). In addition, changes in survival and immigration can reduce population-level efficacy of fertility control (Ransom *et al.*, 2013). However, as the proportion of infertile females increases, this effort will decline and remain constant once the desired density has been achieved. Successful examples are the marked reduction in suburban white-tailed deer obtained over a 10-year timescale (Rutberg and Naugle, 2004, 2008), the zero-population growth of an isolated population of elephants achieved within 2 years (Delsink *et al.*, 2006) and of an island population of wild horses obtained within 2 years (Kirkpatrick and Turner, 2008). For closed populations, Merril *et al.* (2006) suggested that, at least in white-tailed deer, contraception of 30–45% of the animals would decrease population size after 2–3 years and that a population reduction of 60% would be achieved in 10 years.

Depending on how urgent the resolution of the conflict is, fertility control can be used alone or once the population size has been reduced through other methods (Barlow, 1997; Hobbs *et al.*, 2000). When fertility control is chosen to mitigate human–ungulate conflicts, a number of issues should be considered before field applications are implemented. These issues cover humaneness, efficacy, feasibility, cost, timeframe and sustainability as well as alternative methods for population control. As humaneness is one of the primary public concerns regarding any type of wildlife management, defining this term is crucial to obtaining and maintaining public support in relation to specific, well-defined objectives. For instance, humaneness can be defined as (i) the level of stress experienced by treated animals, (ii) the severity and type of side effects, (iii) the proportion of animals likely to experience negative side effects following treatment with a contraceptive, (iv) the proportion of animals that will suffer from capture, handling and anaesthesia associated with administering the contraceptives, or (v) a combination of all these definitions.

When lethal control is illegal, unacceptable or unfeasible, fertility control might be the only option available for managing overabundant populations of ungulates. In these instances, key issues to be discussed at the planning stage include assessing the overall proportion of the population that must be rendered infertile to mitigate the conflict, estimating the relative effort and time required to achieve the target population size and evaluating the feasibility of field application of contraceptives

(Hobbs *et al.*, 2000; Bradford and Hobbs, 2008). This feasibility in turn is likely to depend on factors such as animal density, approachability of individual animals, access to private and public land, and efficacy of the contraceptive treatment (Rudolph *et al.*, 2000; Walter *et al.*, 2002; Rutberg and Naugle, 2008; Boulanger *et al.*, 2012). In the early planning stages, modelling the impact of fertility control on population dynamics can assist determining whether the application of this method will meet specific management goals (e.g. Jacob *et al.*, 2008).

The economic cost of reducing ungulate population growth through fertility control agents that require capture and handling of the animals is expected to be high. For instance, Rutberg (2005) estimated that the cost of rendering infertile a medium-to-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 was US$98–110 per animal, inclusive of darts, vaccine, helicopter and veterinary assistance. Walter *et al.* (2002) reported that the cost of trapping and injecting 30 white-tailed deer with immunocontraceptives for 2 years (with a spring capture and vaccination followed by two boosters in autumn of year 1 and year 2) was US$1128/deer. Labour accounted for 64% of the total cost and equipment, supplies, lodging and travel accounted for the remaining 36% of the total cost. However, after the initial year, the cost per deer dropped to US$270 (Walter *et al.*, 2002). Boulanger *et al.* (2012) found that the cost of capture, handling and administering contraceptives to white-tailed deer in various studies was about US$1,000 but that 75% of this cost was due to drugs, including anaesthetics, and a veterinarian's time. It is conceivable that costs would drop significantly if immunocontraceptives were delivered by trained staff (i.e. by wildlife managers instead of veterinarians) and ungulate capture was organised with the assistance of volunteers donating their time and skills to the project. Hobbs *et al.* (2000) suggested that fertility control of deer will only be cost-effective, compared to culling, where professionals are employed to cull deer instead of recreational hunters.

Identifying who should bear the costs of population management might raise awareness of the economics of available options amongst stakeholders and add a different perspective to ungulate management. This awareness would be further enhanced if the full costs, including negative environmental and welfare consequences, associated with each option are included.

In addition to the practical challenges of using fertility control on ungulate populations, regulatory and legal requirements for field applications of contraceptives must be met. For products that have not been registered in a country, trials can often be carried out under experimental permits and on a case-by-case basis (Humphrys and Lapidge, 2008).

In summary, this review highlighted that safe, effective contraceptives are now available allowing field applications aimed at reducing population growth in ungulates. Although many challenges still exist, we believe the next decade will witness a large number of field studies carried out to manage ungulate populations through fertility control. We recommend that, for each context, the use of fertility control,

alone or in conjunction with other methods, is evaluated and compared with alternative options for population control. Only then can the costs and benefits of different methods be fully established and the optimum options selected to mitigate the conflicts between human interests and ungulate populations.

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References

Apollonio, M., Andersen, R. and Putman, R.J. (eds), (2010) *European Ungulates and their Management in the 21st Century.* Cambridge, UK: Cambridge University Press.

Asa, C.S. and Porton, I.J. (eds), (2005) *Wildlife Contraception: Issues, Methods and Applications.* Baltimore, MD: Johns Hopkins University Press.

Aune, K., Terry, J., Kreeger, T.J., Thomas, J. and Roffe, T.J. (2002) Overview of delivery systems for the administration of vaccines to elk and bison of the Greater Yellowstone Area. In T.J. Kreeger (ed.), *Proceedings of Brucellosis in Elk and Bison in the Greater Yellowstone Area.* Cheyenne, WY: Wyoming Game and Fish Department, pp. 66–79.

Baker, D.L., Wild, M.A., Conner, M.M., Ravivarapu, H.B., Dunn, R.L. and Nett, T.M. (2002) Effects of GnRH agonist (leuprolide) on reproduction and behaviour in female wapiti (*Cervus elaphus nelsoni*). *Reproduction* **60**, 155–167.

Baker, D.L, Wild, M.A., Conner, M.M., Ravivarapu, H.B., Dunn, R.L, and Nett, T.M. (2004) Gonadotropin-releasing hormone agonist: a new approach to reversible contraception in female deer. *Journal of Wildlife Diseases* **40**, 713–724.

Ballou, J.D., Traylor-Holzer, K., Turner, A., Malo, A.F., Powell, D., Maldonado, J. and Eggert, L. (2008) Simulation model for contraceptive management of the Assateague Island feral horse population using individual-based data. *Wildlife Research* **35**, 502–512.

Barfield, J.P., Nieschlag, E. and Cooper, T.G. (2006) Fertility control in wildlife: humans as a model. *Contraception* **73**, 6–22.

Barlow, N.D. (1997) Modelling immunocontraception in disseminating systems. *Reproduction Fertility and Development* **9**, 51–60.

Barlow, N.D. (2000) The ecological challenge in immunocontraception: editor's introduction. *Journal of Applied Ecology* **37**, 897–902.

Bechert, U., Bartell, J., Kutzler, M., Menino, A., Bildfell, R., Anderson, M. and Fraker, M. (2013) Effects of two porcine zona pellucida immunocontraceptive vaccines on ovarian activity in horses. *Journal of Wildlife Management* **77**, 1386–1400.

Beringer, J., Hansen, L. P., Demand, J.A. and Sartwell, J. (2002) Efficacy of translocation to control urban deer in Missouri: costs, efficiency, and outcome. *Wildlife Society Bulletin* **30**, 767–774.

Boulanger, J.R., Curtis, P.D., Cooch, E.G. and DeNicola, A.J. (2012) Sterilization as an alternative deer control technique: a review. *Human–Wildlife Interactions* **6**, 273–282.

Bradford, J.B. and Hobbs, N.T. (2008) Regulating overabundant ungulate populations: An example for elk in Rocky Mountain National Park, Colorado. *Journal of Environmental Management* **86**, 520–528.

Brainerd, S.M. and Kaltenborn, B.P. (2010) The Scandinavian model. A different path to wildlife management. *The Wildlife Professional* **4**, 52–56.

Caley, P. and Ramsey, D. (2001) Estimating disease transmission in wildlife, with emphasis on leptospirosis and bovine tuberculosis in possums, and effects of fertility control. *Journal of Applied Ecology* **38**, 1362–1370.

Campbell, T.A., Long, D.B. and Massei G. (2011) Efficacy of the Boar-Operated-System to deliver baits to feral swine. *Preventive Veterinary Medicine* **98**, 243–249.

Carroll, M.J., Singer, A., Smith, G.C., Cowan, D.P. and Massei, G. (2010) The use of immunocontraception to improve rabies eradication in urban dog populations. *Wildlife Research* **37**, 676–687.

Carter, S.P., Delahay, R.J., Smith, G.C., Macdonald, D.W., Riordan, P., Etherington, T., Pimley, E. and Cheeseman, C.L. (2007) Culling-induced social perturbation in Eurasian badgers *Meles meles* and the management of TB in cattle: an analysis of a critical problem in applied ecology. *Proceedings of the Royal Society B* **274**, 2769–2777.

Conner, M.M., Baker, D.L., Wild, M.A., Powers, J.G., Hussain, M.D., Dun, R.L. and Nett, T.M. (2007) Fertility control in free-ranging elk using gonadotropin releasing hormone agonist leuprolide: effects on reproduction, behavior, and body condition. *Journal of Wildlife Management* **71**, 2346–2356.

Conover, M.R. (2002) *Resolving Human–Wildlife Conflicts: The science of wildlife damage management.* Boca Raton, FL: Lewis.

Cooper, D.W. and Larsen, E. (2006) Immunocontraception of mammalian wildlife: ecological and immunogenetic issues. *Reproduction* **132**, 821–828.

Corn, J.L. and Nettles, V.F. (2001) Health protocol for translocation of free-ranging elk. *Journal of Wildlife Diseases* **37**, 413–426.

Coulson, G., Nave, C.D., Shaw, J. and Renfree, M.B. (2008) Long-term efficacy of levonorgestrel implants for fertility control of eastern grey kangaroos (*Macropus giganteus*). *Wildlife Research* **35**, 520–524.

Cowan, D.P. and Massei, G. (2008) Wildlife contraception, individuals and populations: How much fertility control is enough? In R.M. Timm and M.B. Madon (eds), *Proceedings of the 23rd Vertebrate Pest Conference.* Davis, CA: University of California, pp. 220–228.

Cowan, P.E., Grant, W.N. and Ralston, M. (2008) Assessing the suitability of the parasitic nematode *Parastrongyloides trichosuri* as a vector for transmissible fertility control of brushtail possums in New Zealand: ecological and regulatory considerations. *Wildlife Research* **35**, 573–577.

Crawford, J.L., McLeod, B.J. and Eckery, D.C. (2011) The hypothalamic–pituitary–ovarian axis and manipulations of the oestrous cycle in the brushtail possum. *General and Comparative Endocrinology* **170**, 424–448.

Cross, M.L., Zheng, T., Duckworth, J.A. and Cowan, P.E. (2011) Could recombinant technology facilitate the realisation of a fertility-control vaccine for possums? *New Zealand Journal of Zoology* **38**, 91–111.

Cui, X., Duckworth, J.A., Lubitz, P., Molinia, F.C., Haller, C., Lubitz, W. and Cowan, P.E. (2010) Humoral immune responses in brushtail possums (*Trichosurus vulpecula*) induced by bacterial ghosts expressing possum zona pellucida 3 protein. *Vaccine* **28**, 4268–4274.

Curtis, P.D., Pooler, R.L., Richmond, M.E., Miller, L.A., Mattfeld, G.F. and Quimby, F.W. (2002) Comparative effects of GnRH and porcine zona pellucida (PZP) immunocontraceptive vaccines for controlling reproduction in white-tailed deer (*Odocoileus virginianus*). *Reproduction* **60**, 131–141.

Curtis, P.D., Richmond, M.E., Miller, L.A. and Quimby, F.W. (2007) Pathophysiology of white-tailed deer vaccinated with porcine zona pellucida immunocontraceptive. *Vaccine* **25**, 4623–4630.

Curtis, P.D., Richmond, M.E., Miller, L.A. and Quimby, F.W. (2008) Physiological effects of gonadotropin-releasing hormone immunocontraception on white-tailed deer. *Human–Wildlife Conflicts* **2**, 68–79.

Daszak, P., Cunningham, A.A. and Hyatt, A.D. (2000) Emerging infectious diseases of wildlife – Threats to biodiversity and human health. *Science* **287**, 443–449.

Davis, S.A. and Pech, R.P. (2002) Dependence of population response to fertility control on the survival of sterile animals and their role in regulation. *Reproduction* **60**, 89–103.

Delsink, A.K., van Altena, J.J., Grobler, D., Bertschinger, H., Kirkpatrick, J. and Slotow, R. (2006) Regulation of a small, discrete African elephant population through immunocontraception in the Makalali Conservancy Limpopo, South Africa. *South African Journal of Science* **102**, 403–405.

Delsink, A.K., van Altena, J.J., Grobler, D., Bertschinger, H., Kirkpatrick, J. and Slotow, R. (2007) Implementing immunocontraception in free-ranging African elephants at Makalali Conservancy. *Journal of the South African Veterinary Association* **78**, 25–30.

DeNicola, A.J., Kesler, D.J. and Swihart, R.K. (1997) Dose determination and efficacy of remotely delivered norgestomet implants on contraception of white-tailed deer. *Zoo Biology* **16**, 31–37.

DeNicola, A.J., VerCauteren, K.C., Curtis, P.D. and Hygnstrom, S.E. (2000) *Managing White-tailed Deer in Suburban Environments: A Technical Guide.* Ithaca, NY: Cornell Cooperative Extension.

D'Occhio, M.J., Fordyce, G., Whyte, T.R., Jubb, T.F., Fitzpatrick, L.A., Cooper, N.J., Aspden, W.J., Bolam, M.J. and Trigg, T.E. (2002) Use of GnRH agonist implants for long-term suppression of fertility in extensively managed heifers and cows. *Animal Reproduction Science* **74**, 151–62.

Druce, H.C., Mackey, R.L. and Slowtow, R. (2011) How immunocontraception can contribute to elephant management in small, enclosed reserves: Munyawana population. *PLoS ONE* **6**, 1–10.

Eymann, J., Herbert, C.A., Thomson, B.P., Trigg, T.E., Cooper, D.W. and Eckery, D.C. (2007) Effects of deslorelin implants on reproduction in the common brushtail possum (*Trichosurus vulpecula*). *Reproduction, Fertility and Development* **19**, 899–909.

Fagerstone, K.A., Coffey, M.A., Curtis, P.D., Dolbeer, R.A., Killian, G.J., Miller, L.A. and Wilmot, L.M. (2002) Wildlife fertility control. *Wildlife Society Technical Review* **02–2**, 1–29.

Fagerstone, K.A., Miller, L.A., Eisemann, J.D., O'Hare, J.R. and Gionfriddo, J.P. (2008) Registration of wildlife contraceptives in the United States of America, with OvoControl and GonaCon immunocontraceptive vaccines as examples. *Wildlife Research* **35**, 586–592.

Fagerstone, K.A., Miller, L.A., Killian, G.J. and Yoder, C.A. (2010) Review of issues concerning the use of reproductive inhibitors, with particular emphasis on resolving human–wildlife conflicts in North America. *Integrative Zoology* **1**, 15–30.

Ferroglio, E., Gortazar, C. and Vicente, J. (2011) Wild ungulate diseases and the risk for livestock and public health. In R.J. Putman, M. Apollonio and R. Andersen (eds), *Ungulate Management in Europe: Problems and Practices.* Cambridge, UK: Cambridge University Press, pp. 192–214.

Fraker, M.A. and Brown, R.G. (2011) Efficacy of SpayVac® is excellent: a comment on Gray *et al.* (2010). *Wildlife Research* **38**, 537–538.

Fraker, M.A., Brown, R.G., Gaunt, G.E., Kerr, J.A. and Pohajdak, B. (2002) Long-lasting, single-dose immunocontraception of feral fallow deer in British Columbia. *Journal of Wildlife Management* **66**, 1141–1147.

Garrott, R.A. and Siniff, D.B. (1992) Limitations of male-oriented contraception for controlling feral horse populations. *Journal of Wildlife Management* **56**, 456–464.

Gionfriddo, J.P., Eisemann, J.D., Sullivan, K.J., Healey, R.S. and Miller, L.A. (2009) Field test of a single-injection gonadotrophin-releasing hormone immunocontraceptive vaccine in female white-tailed deer. *Wildlife Research* **36**, 177–184.

Gionfriddo, J.P., DeNicola, A.J., Miller, L.A. and Fagerstone, K.A. (2011a) Efficacy of GnRH immunocontraception of wild white-tailed deer in New Jersey. *Wildlife Society Bulletin* **35**, 142–148.

Gionfriddo, J.P., DeNicola, A.J., Miller, L.A. and Fagerstone, K.A. (2011b) Health effects of GnRH immunocontraception of wild white-tailed deer in New Jersey. *Wildlife Society Bulletin* **35**, 149–160.

Gobello, C. (2007) New GnRH analogs in canine reproduction. *Animal Reproduction Science* **100**, 1–13.

Gray, M.E. and Cameron, E.Z. (2010) Does contraceptive treatment in wildlife result in side effects? A review of quantitative and anecdotal evidence. *Reproduction* **139**, 45–55.

Gray, M.E., Thain, D.S., Cameron, E.Z. and Miller, L.A. (2010) Multi-year fertility reduction in free-roaming feral horses with single-injection immunocontraceptive formulations. *Wildlife Research* **37**, 475–481.

Gray, M.E., Thain, D.S., Cameron, E.Z. and Miller, L.A. (2011) Corrigendum. Multi-year fertility reduction in free-roaming feral horses with single-injection immunocontraceptive formulations. *Wildlife Research* **38**, 260.

Gross, J. (2000) A dynamic simulation model for evaluating effects of removal and contraception on genetic variation and demography of Pryor Mountain wild horses. *Biological Conservation* **96**, 319–330.

Grund, M.D., McAnich, J.B. and Wiggers, E.P. (2002) Seasonal movements and habitat use of female white-tailed deer associated with an urban park. *Journal of Wildlife Management* **66**, 123–130.

Gupta, S.K. and Bansal, P. (2010) Vaccines for immunological control of fertility. *Reproductive Medicine and Biology* **9**, 61–71.

Heilmann, T.J., Garrott, R.E., Caldwell, L.L. and Tiller, B.L. (1998) Behavioral responses of free-ranging elk treated with an immunocontraceptive vaccine. *Journal of Wildlife Management* **62**, 243–250.

Herbert, C.A. and Trigg, T.E. (2005) Applications of GnRH in the control and management of fertility in female animals. *Animal Reproduction Science* **88**, 141–153.

Hernandez, S., Locke, S.L., Cook, M.W., Harveson, L.A., Davis, D.S., Lopez, R.R., Silvy, N. J. and Fraker, M.A. (2006) Effects of SpayVac® on urban female white-tailed deer movements. *Wildlife Society Bulletin* **34**, 1430–1434.

Hobbs, N.T., Bowden, D.C. and Baker, D.L. (2000) Effects of fertility control on populations of ungulates: General, stage-structured models. *Journal of Wildlife Management* **64**, 473–491.

Hoffman, R.A. and Wright, R.G. (1990) Fertility control in a non-native population of mountain goats. *Northwest Science* **64**, 1–6.

Holland, O.J., Cowan, P.E., Gleeson, D.M., Duckworth, J.A. and Chamley, L.W. (2009) MHC haplotypes and response to immunocontraceptive vaccines in the brushtail possum. *Journal of Reproductive Immunology* **82**, 57–65.

Hone, J. (1999) On rate of increase (r): patterns of variation in Australian mammals and the implications for wildlife management. *Journal of Applied Ecology* **36**, 709–718.

Humphrys, S., and Lapidge, S.J. (2008) Delivering and registering species-tailored oral antifertility products: a review. *Wildlife Research* **35**, 578–585.

Jacob, J., Singleton, G.R. and Hinds, L.A. (2008) Fertility control of rodent pests. *Wildlife Research* **35**, 487–493.

Jacobsen, N.K., Jessup, D.A. and Kesler, D.J. (1995) Contraception in captive black-tailed deer by remotely delivered norgestomet ballistic implants. *Wildlife Society Bulletin* **23**, 718–722.

Jewell, P. (1986) Survival in a feral population of primitive sheep in St Kilda, Outer Hebrides, Scotland. *National Geographic Research* **2**, 402–406.

Killian, G.J. and Miller, L.A. (2001) Behavioral observations and physiological implications for white-tailed deer treated with two different immunocontraceptives. In M. C. Brittingham, J. Kays, and R. McPeake (eds), *Proceedings of the 9th Wildlife Damage Management Conference,* Pennsylvania State University, PA, pp. 283–291.

Killian, G., Miller, L.A., Rhyan, J. and Doten, H. (2006) Immunocontraception of Florida feral swine with single-dose GnRH vaccine. *American Journal of Reproductive Immunocology* **55**, 378–384.

Killian, G., Thain, D., Diehl, N.K., Rhyan, J. and Miller, L.A. (2008) Four-year contraception rates of mares treated with single-injection porcine zona pellucida and GnRH vaccines and intrauterine devices. *Wildlife Research* **35**, 531–539.

Killian, G., Kreeger, T.J., Rhyan, J., Fagerstone, K., and Miller, L.A. (2009) Observations on the use of Gonacon™ in captive female elk (*Cervus elaphus*). *Journal of Wildlife Diseases* **45**, 184–188.

Kirkpatrick, J.F. (2007) Measuring the effects of wildlife contraception: the argument for comparing apples with oranges. *Reproduction, Fertility and Development* **19**, 548–552.

Kirkpatrick, J.F. and Turner, A. (2002) Reversibility of action and safety during pregnancy of immunization against porcine zona pellucida in wild mares (*Equus caballus*). *Reproduction* **60**, 197–202.

Kirkpatrick, J.F. and Turner, A. (2007) Immunocontraception and increased longevity in equids. *Zoo Biology* **26**, 237–244.

Kirkpatrick, J.F. and Turner, A. (2008) Achieving population goals in long-lived wildlife with contraception. *Wildlife Research* **35**, 513–519.

Kirkpatrick, J.F., Turner, J.W. and Liu, I.K.M. (1996) Contraception of wild and feral equids. In T.J. Kreeger (ed.), *Contraception in Wildlife Management.* Washington DC: US Government Printing Office, pp. 161–169.

Kirkpatrick, J.F., Rowan, A., Lamberski, N., Wallace, R., Frank, K. and Lyda, R. (2009) The practical side of immunocontraception: zona proteins and wildlife. *Journal of Reproductive Immunology* **83**, 151–157.

Kirkpatrick, J.F., Lyda, R.O., and Frank, K.M. (2011) Contraceptive vaccines for wildlife: a review. *American Journal of Reproductive Immunology* **66**, 40–50.

Kitchener, A.L., Kay, D.J.,Walters, B., Menkhorst, P., McCartney, C.A., Buist, J.A., Mate, K.E. and Rodger, J.C. (2009) The immune response and fertility of koalas (*Phascolarctos cinereus*) immunised with porcine zonae pellucidae or recombinant brushtail possum ZP3 protein. *Journal of Reproductive Immunology* **82**, 40–47.

Kock, R.A., Woodford, M.H. Rossiter, P.B. (2010) Disease risks associated with the translocation of wildlife. *Revue scientifique et technique* **29**, 329–362.

Kreeger, T.J. (1997) Overview of delivery systems for the administration of contraceptives to wildlife. In T.J. Kreeger (ed.), *Contraception in Wildlife Management.* Washington DC: US Government Printing Office, pp. 29–48.

Kutzler, M. and Wood, A. (2006) Non-surgical methods of contraception and sterilization. *Theriogenology* **66**, 514–525.

Langbein, J., Putman, R.J. and Pokorny, B. (2011) Road traffic accidents involving ungulates and available measures for mitigation. In R.J. Putman, M. Apollonio and R. Andersen (eds), *Ungulate Management in Europe: Problems and Practices.* Cambridge, UK: Cambridge University Press, pp. 215–259..

Locke, S.L., Cook, M.W., Harveson, L.A., Davis, D.S., Lopez, R.R., Silvy, N.J. and Fraker, M.A. (2007) Effectiveness of SpayVac® on reducing white-tailed deer fertility. *Journal of Wildlife Diseases* **43**, 726–730.

Lohr, C.A., Mills, H., Robertson, H. and Bencini, R. (2009) Deslorelin implants control fertility in urban brushtail possums (*Trichosurus vulpecula*) without negatively influencing their body-condition index. *Wildlife Research* **36**, 324–332.

Long, D.B., Campbell, T.A. and Massei, G. (2010) Evaluation of feral swine-specific feeder systems. *Rangelands* **32**, 8–13.

Magiafoglou, A., Schiffer, M., Hoffmann, A.A. and McKechnie, S.W. (2003) Immunocontraception for population control: will resistance evolve? *Immunology and Cell Biology* **81**, 152–159.

Massei, G. (2013) Fertility control in dogs. In N. Macpherson, F.X. Meslin and A.I.Wandeler (eds), *Dogs, Zoonoses and Public Health.* Wallingford, UK: CABI International, pp. 259–270.

Massei, G. and Miller, L.A. (2013) Non-surgical fertility control for managing free-roaming dog populations: a review of products and criteria for field applications. *Theriogenology* **80**, 829–838.

Massei, G., Cowan, D.P., Coats, J., Gladwell, F., Lane J.E. and Miller, L.A. (2008) Effect of the GnRH vaccine GonaCon™ on the fertility, physiology and behaviour of wild boar. *Wildlife Research* **35**, 1–8.

Massei, G., Quy, R., Gurney, J. and Cowan, D.P. (2010a) Can translocations be used to manage human–wildlife conflicts? *Wildlife Research* **37**, 428–439.

Massei, G., Miller, L.A. and Killian, G.J. (2010b) Immunocontraception to control rabies in dog populations. *Human–Wildlife Interactions* **4**, 155–157.

Massei, G., Coats, J., Quy, R., Storer, K. and Cowan, D.P. (2010c) The BOS (Boar-Operated-System): a novel method to deliver baits to wild boar. *Journal of Wildlife Management* **74**, 333–336.

Massei, G., Roy, S. and Bunting, R. (2011) Too many hogs? A review of methods to mitigate impact by wild boar and feral pigs. *Human–Wildlife Interactions* **5**, 79–99.

Massei, G., Cowan, D. P., Coats, J., Bellamy, F., Quy, R., Brash, M. and Miller, L.A. (2012) Long-term effects of immunocontraception on wild boar fertility, physiology and behaviour. *Wildlife Research* **39**, 378–385

McDowell, A., McLeod, B.J., Rades, T. and Tucker, I.G. (2006) Application of pharmaceutical drug delivery for biological control of the common brushtail possum in New Zealand: a review. *Wildlife Research* **33**, 679–689.

McLaughlin, E.A. and Aitken, R.J. (2011) Is there a role for immunocontraception? *Molecular and Cellular Endocrinology* **335**, 78–88.

McShea, W.J. (2012) Ecology and management of white-tailed deer in a changing world. *Annals of the New York Academy of Sciences* **1249**, 45–56.

Merrill, J.A., Cooch, E.G. and Curtis, P.D. (2003) Time to reduction: factors influencing management efficacy in sterilizing overabundant white-tailed deer. *Journal of Wildlife Management* **67**, 267–279.

Merrill, J.A., Cooch, E.G. and Curtis, P.D. (2006) Managing an over-abundant deer population by sterilization: effects of immigration, stochasticity and the capture process. *Journal of Wildlife Management* **70**, 268–277.

Miller, L.A. and Fagerstone, K.A. (2000) Induced infertility as a wildlife management tool. In T.P. Salmon and A.C. Crabb (eds), *Proceedings of the 19th Vertebrate Pest Conference.* Davis, CA: University of California, pp. 160–168.

Miller, L.A. and Killian, G.J. (2002) In search of the active PZP epitope in white-tailed deer immunocontraception. *Vaccine* **20**, 2735–2742.

Miller, L.A., Johns, B.E. and Killian, G.J. (2000) Immunocontraception of white-tailed deer with GnRH vaccine. *American Journal of Reproductive Immunology* **44**, 266–274.

Miller, L.A., Crane, K., Gaddis, S. and Killian, G.J. (2001) Porcine zona pellucida immunocontraception: long-term health effects on white-tailed deer. *Journal of Wildlife Management* **65**, 941–945.

Miller, L.A., Rhyan, J.C. and Drew, M. (2004) Contraception of bison by GnRH vaccine: a possible means of decreasing transmission of brucellosis in bison. *Journal of Wildlife Diseases* **40**, 725–730.

Miller, L.A., Gionfriddo, J.P., Fagerstone, K.A., Rhyan, J.C. and Killian, G.J. (2008a) The Single-Shot GnRH Immunocontraceptive Vaccine (GonaCon™) in White-Tailed Deer: Comparison of Several GnRH Preparations. *American Journal of Reproductive Immunology* **60**, 214–223.

Miller, L.A., Gionfriddo, J.P., Rhyan, J.C., Fagerstone, K.A., Wagner, D.C. and Killian, G.J. (2008b) GnRH immunocontraception of male and female white-tailed deer fawns. *Human–Wildlife Interactions* **2**, 93–101.

Miller, L.A., Fagerstone, K.A., Wagner, D.C. and Killina, G.J. (2009) Factors contributing to the success of a single-shot, multiyear PZP immunocontraceptive vaccine for white-tailed deer. *Human–Wildlife Conflicts* **3**, 103–115.

Nave, C.D., Coulson, G., Short, R.V., Poiani, A., Shaw, G. and Renfree, M.B. (2002) Long-term fertility control in the kangaroo and the wallaby using levonorgestrel implants. *Reproduction* **60**, 71–80.

Naz, R.K., Gupta, S.K., Gupta, J.C., Vyas, H.K. and Talwar, A.G. (2005) Recent advances in contraceptive vaccine development: a mini-review. *Human Reproduction* **20**, 3271–3283.

Nishi, J.S., Shury, T. and Elkin, B.T. (2006) Wildlife reservoirs for bovine tuberculosis (*Mycobacterium bovis*) in Canada: strategies for management and research. *Veterinary Microbiology* **112**, 325–338.

Nuñez, C.M.V., Adelman, J.S., Mason, C. and Rubenstein, D.I. (2009) Immunocontraception decreases group fidelity in a feral horse population during the non-breeding season. *Applied Animal Behaviour Science* **117**, 74–83.

Nuñez, C.M.V., Adelman, J.S. and Rubenstein, D.I. (2010) Immunocontraception in wild horses (*Equus caballus*) extends reproductive cycling beyond the normal breeding season. *PLoS ONE* **5**, e13635.

Patton, M.L., Jochle, W. and Penfold, L.M. (2007) Review of contraception in ungulate species. *Zoo Biology* **26**, 311–326.

Plotka, E.D. and Seal, U.S. (1989) Fertility control in female white-tailed deer. *Journal of Wildlife Diseases* **25**, 643–646.

Plotka, E.D., Vevea, D.N., Eagle, T.C., Tester, J.R. and Siniff, D.B. (1992) Hormonal contraception of feral mares with Silastic rods. *Journal of Wildlife Diseases* **28**, 255–262.

Powers, J.G, Baker, D.L.T.L., Conner, M.M.A.H. and Nett, T.M. (2011) Effects of gonadotropin-releasing hormone immunization on reproductive function and behavior in captive female Rocky Mountain elk (*Cervus elaphus nelsoni*). *Biology of Reproduction* **85**, 1152–1160.

Putman, R.J. (1997) *Chemical and Immunological Methods in the Control of Reproduction in Deer and Other Wildlife: potential for population control and welfare implications.* RSPCA Technical Bulletin, Royal Society for the Prevention of Cruelty to Animals, Horsham, UK.

Ramsey, D. (2007) Effects of fertility control on behavior and disease transmission in brushtail possums. *Journal of Wildlife Management* **71**, 109–116.

Ramsey, D., Coleman, J., Coleman, M. and Horton, P. (2006) The effect of fertility control on the transmission of bovine tuberculosis in wild brushtail possums. *New Zealand Veterinary Journal* **54**, 218–223.

Ransom, J.I., Cade, B.S., and Hobbs, N.T. (2010) Influences of immunocontraception on time budgets, social behavior, and body condition in feral horses. *Applied Animal Behaviour Science* **124**, 51–60.

Ransom, J.I., Hobbs, N.T. and Bruemmer, J. (2013) Contraception can lead to trophic asynchrony between birth pulse and resources. *PLoS ONE* **8**, 1–9.

Reimoser, F. and Putman, R.J. (2011) Impact of large ungulates on agriculture, forestry and conservation habitats in Europe. In R.J. Putman, M. Apollonio and R. Andersen (eds), *Ungulate Management in Europe: Problems and Practices.* Cambridge, UK: Cambridge University Press, pp. 144–191.

Rudolph, B.A., Porter, W.F. and Underwood, H.B. (2000) Evaluating immunocontraception for managing suburban white-tailed deer in Irondequoit, New York. *Journal of Wildlife Management* **64**, 463–473.

Ruiz-Fons, F., Rodríguez, O., Mateu, E., Vidal, D. and Gortázar, C. (2008) Antibody response of wild boar (*Sus scrofa*) piglets vaccinated against Aujeszky's disease virus. *Veterinary Record* **162**, 484–485.

Rutberg, A.T. (2005) Deer contraception: what we know and what we don't. In A.T. Rutberg (ed.), *Humane Wildlife Solutions: The Role of Immunocontraception.* Washington DC: Humane Society Press, pp. 23–42.

Rutberg, A.T. and Naugle, R.E. (2008) Population effects of immunocontraception in white-tailed deer (*Odocoileus virginianus*). *Wildlife Research* **35**, 494–501.

Rutberg, A.T., Naugle, R.E., Thiele, L.A., and Liu, I.K.M. (2004) Effects of immunocontraception on a suburban population of white-tailed deer *Odocoileus virginianus. Biological Conservation* **116**, 243–250.

Rutberg, A.T., Naugle, R.E., Turner, J.W., Fraker, M.A. and Flanagan, D.R. (2013) Field testing of single-administration porcine zona pellucida contraceptive vaccines in white-tailed deer (*Odocoileus virginianus*). *Wildlife Research* **40**, 281–288.

Saez-Royuela, C. and Telleria, J.L. (1986) The increased population of the Wild boar (*Sus scrofa* L.) in Europe. *Mammal Review* **16**, 97–101.

Smith, G.C. and Cheeseman, C.L. (2002) A mathematical model for control of diseases in wildlife populations: culling, vaccine and fertility control. *Ecological Modelling* **150**, 45–53.

Smith, G.C. and Wilkinson, D. (2003) Modeling control of rabies outbreaks in red fox populations to evaluate culling, vaccination, and vaccination combined with fertility control. *Journal of Wildlife Diseases* **39**, 278–286.

Turner, J.W. and Kirkpatrick, J.F. (1991) In My Experience: new developments in feral horse contraception and their potential application to wildlife. *Wildlife Society Bulletin* **19**, 350–359.

Turner, J.W. and Kirkpatrick, J.F. (2002) Effects of immunocontraception on population, longevity and body condition in wild mares *Equus caballus. Reproduction Supplement* **60**, 187–195.

Turner, J.W., Liu, I.K.M., Flanagan, D.R.J.W., Rutberg, A.T. and Kirkpatrick, J.F. (2007) Immunocontraception in wild horses: one inoculation provides two years of infertility. *Journal of Wildlife Management* **71**, 662–667.

Twigg, L.E., Lowe, T.J., Martin, G.R., Wheeler, A.G., Gray, G.S., Griffin, S.L., O'Reilly, C.M., Robinson, D.J. and Hubach, P.H. (2000) Effects of surgically imposed sterility on free-ranging rabbit populations. *Journal of Applied Ecology* **37**, 16–39.

Waddell, R.B., Osborn, D.A., Warren, R.J., Griffin, J.C. and Kesler, D.J. (2001) Prostaglandin- mediated fertility control in captive white-tailed deer. *Wildlife Society Bulletin* **29**, 1067–1074.

Waithman, J.D., Sweitzer, R.A., Van Vuren, D., Drew, J.D., Brinkhaus, A.J., Gardner, I.A. and Boyce, W.M. (1999) Range expansion, population sizes, and management of wild pigs in California. *Journal of Wildlife Management* **63**, 298–308.

Walter, W.D., Perkins, P.J., Rutberg, A.T. and Kilpatrick, H.J. (2002) Evaluation of immuno contraception in a free-ranging suburban white-tailed deer herd. *Wildlife Society Bulletin* **30**, 186–192.

Ward, A.I. (2005) Expanding ranges of wild and feral deer in Great Britain. *Mammal Review* **35**, 165–173.

Williams, C.K. (2002) Risk assessment for release of genetically modified organisms: a virus to reduce the fertility of introduced wild mice, *Mus domesticus*. *Reproduction Supplement* **60**, 81–88.

Wilson, C. J. (2003) *Current and Future Deer Management Options*. Report on behalf of Defra European Wildlife Division.

Woodrow, K.A., Bennett, K.M. and Lo, D.D. (2012) Mucosal vaccine design and delivery. *Annual Review of Biomedical Engineering* **14,** 17–46.

Zhang, Z. (2000) Mathematical models of wildlife management by contraception. *Ecological Modelling* **132,** 105–113.