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Research Idea

North American red fox rabies immunity gene drive for safer (sub)urban rewilding

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Abstract

Animal-transmitted diseases such as rabies represent a barrier to successful rewilding and threaten continued human-wildlife co-existence. In North America, population growth and human settlement expansion lead to encounters with wild mammals which have the potential to transmit rabies to domestic dogs and humans. The recent development of gene drives mediated by CRISPR-Cas9 allows for ecosystem engineering at unprecedented scales given the potential to spread new traits through wild populations with biased inheritance exceeding the pattern of classical Mendelian dominant genes. This study of a possible red fox rabies immunity gene drive project contributes a novel proposal to the existing academic conversation about suitable applications of gene drive technology in wild animal populations, such as projects to fight malaria and Lyme disease. Noting the unique characteristics of rabies, such as the dire mortality rate in humans once symptoms arise, as well as the tendency for rabid wild animals to lose their fear of humans, it appears to be a suitable target for eventual eradication via gene drive to spread immunity through wild mammal reservoir populations. Introducing heritable rabies immunity into North American red fox populations through gene drive represents a strategy to both battle rabies and adjust the ecology of (sub)urban environments. Given this review of the project's possible implementation and expected outcomes, providing inherited rabies immunity to wild red fox populations in North America via gene drive appears both feasible and sensible. Similar projects may be used to eradicate

comparable infectious diseases from other wild animal populations, with likely benefits to human patients, wildlife and ecosystems.

Keywords

policy development, gene drive, CRISPR, wildlife management, rewilding, human dimensions, species interactions, urban ecology, evolutionary biology, zoonotic disease, rabies, mammals, red foxes, co-evolution, predator-prey interactions, veterinary medicine, biomedical engineering

Context

Rewilding explores new ways in which flourishing wildlife populations can co-exist with human civilisation, yet the risk of zoonotic disease transmission represents a barrier to successful rewilding projects. Gene drive has the potential to eradicate perilous zoonotic diseases, such as rabies or Lyme disease, in their wild animal reservoir populations. Targeting rabies in North American red foxes may be a suitable pilot project of this nature.

Aims

This paper explores the use of gene drive to combat zoonotic disease by evaluating detailed methods and possible downstream benefits of providing heritable rabies immunity to wild red fox populations in North America.

Introduction

Rewilding represents the attempt to discover new ways in which human civilisation and wildlife can amicably co-exist. As human population growth in North America combines with preferences for low-density housing to expand the geographic area covered by cities and suburbs, wildlife biologists can seek ways in which wild mammals can thrive amid human settlement in order to prevent habitat loss as landscapes change. In her work *Rambunctious Garden: Saving Nature in a Post-Wild World*, Emma Marris cautions against limiting the definition of nature to 'pristine wilderness' to avoid an outcome where 'urban, suburban and rural citizens believe there is no nature where they live; that is it far away and not their concern. They can lose the ability to have spiritual and aesthetic experiences in more humble natural settings.' She urges readers to encompass 'human-dominated lands' within the societal view of nature, 'making the most of every scrap of land' (Marris 2011). In *Feral: Rewilding the Land, the Sea and Human Life*, George Monbiot contends 'If rewilding took place, it would happen in order to meet human needs, not the needs of the ecosystem. […]. If rewilding happens, it will be because we value a biologically rich environment more than we value an impoverished system' (Monbiot 2014). Ambitious rewilding strategies, such as the North American Wildlands Network and the Wildlands Project that emphasise continent-wide megafauna corridor connectivity between wilderness strongholds, as described in *Rewilding North America: A Vision for Conservation in the 21st Century*, could be enhanced with complementary strategic approaches that allow mesocarnivores safer access to suburbs and cities as reclaimed habitats (Foreman 2004).

Urban and suburban parks, landscaped neighbourhoods and gardens that provide sustenance for small herbivores, such as rodents and rabbits, represent possible artificial ecosystems that could support mesocarnivore predators in the absence of severe human-wildlife conflict in the rabies-free United Kingdom (Hemmington 1997). There exists strong aversion to allowing potential rabies carriers, such as North American red foxes, in the vicinity of human habitation (AAAnimal Control Trappers 2020). If wildlife veterinarians and biological engineers intervene in the battle of natural selection between the rabies virus and the immune systems of wild North American mammals, then wildlife currently feared as rabies vectors may be able to safely colonise or rewild US cities despite ongoing human expansion or even avoid extirpation as suburban sprawl expands.

A modified, non-natural world with less suffering is already the generally preferred outcome in human society, as demonstrated by the presence of healthcare systems and the general rejection of Social Darwinism in humans. The emerging ideology of compassionate conservation may soon extend significant consideration to the well-being of non-human animals, i.e. ‘all harms to wild animals should be minimised wherever and to the extent possible’ in wildlife biology research projects (Compassionate Conservation Guiding Principles 2020). If the pervasive, mainstream ideology of 'speciesism' is rejected on ethical grounds through philosophy, one may conclude that preventative medical care for rabies ought not to be withheld from any species (Singer 2015). According to the United States Department of Agriculture, the national expenditure on rabies prevention and control exceeds $600 milion per year, with the net benefit of saving approximately 60,000 Americans' lives through post-exposure prophylaxis (PEP) treatment (United States Department of Agriculture Wildlife Services 2023). This equates to roughly $10,000 per human life saved, yet wild mammal reservoir species presently endure the disease without a comparable investment targeted towards rabies prevention in wildlife through biomedical engineering. An unprecedented intervention, such as the use of gene drives to achieve rabies eradication in North America or globally over decades, could be worth even an immense upfront expense, given that it would terminate a $6 billion per decade (in the US) problem for good, once the relevant wild mammal reservoir species had all acquired heritable rabies immunity. In particular, the annual global economic losses per year due to rabies are estimated in the billions once one accounts for how nearly all rabies-caused human mortality, to the extent of tens of thousands of deaths annually, occurs outside the US (American Veterinary Medical Association 2020, Hueffer and Murphy 2018). Evolutionary engineer Kevin Esvelt of the MIT Media Lab explains the emerging animal ethics dilemma that gene drive poses to researchers, who are on the edge of being able to stop naturally occurring suffering caused by medical ailments in wildlife:

If failing to save a drowning child when we could have done so makes us responsible for that child's death, then acquiring the ability to mitigate animal suffering renders us morally responsible if we choose not to. […]. Three weeks ago I rescued a limping stray cat. Had she not received care and antibiotics, she would likely have lost the ability to hunt and slowly starved due to her badly infected wound. How is that stray cat different from an ocelot cub stricken with a screwworm infection, which is unimaginably more painful? We didn't deliberately create either, but we can do something about the stray cat, but cannot aid the ocelot. Of course, that will not be true for much longer: we eradicated the screwworm from North America with sterile insect technique, and with gene drive could do the same for South America. Should we? […] since we are now developing the power to intervene, it becomes a moral issue where previously it was not (Esvelt 2020c).

Assisted colonisation, ecological replacement, biocontrol, gene drives and veterinary medicine as applied to wildlife populations represent emerging, sometimes conflicting approaches that reshape the suite of available choices by which civilisation can interface with the natural world. This research proposal explores the hypothetical use of gene drive technology in North American red foxes to provide heritable, population-wide rabies immunity, such that wild red foxes would no longer serve as a reservoir of the rabies virus and would present no risk of rabies transmission to other species. With examples of human-red fox co-existence in situations where there is no risk of rabies transmission, the rabies-free islands of the United Kingdom and Japan are examined as test cases of what rewilding outcomes could be possible in a post-rabies North America (GOV UK 2020, Takahashi-Omoe et al. 2008). A successful gene drive pilot project to eliminate rabies susceptibility in North American red foxes could lead to similar strategies for eradication of rabies in other wild mammal reservoirs (skunks, raccoons, bats, rodents, arctic foxes, coyotes and wolves) in North America to eventually achieve a rabies-free continent (Howard Hughes Medical Institute 2024, Hueffer and Murphy 2018, Woodroffe et al. 2004). Red foxes and arctic foxes co-exist across substantial boreal regions of Alaska and Canada, so addressing only red fox rabies cases could be insufficient (Kim et al. 2014). Nevertheless, the territories of arctic foxes are adjusting in response to climate change, with an expected result of red foxes becoming the primary rabies reservoir in these regions (Kim et al. 2014). If North American pilot projects succeed, the use of gene drives to immunise other rabies reservoir species on other continents towards the goal of global rabies eradication could reduce human-wildlife conflict worldwide and enable the safer rewilding of suburban and urban spaces by wild mammals who would then pose zero risk of rabies transmission. This strategy could eventually be applied towards other zoonotic diseases to seek a world with no zoonotic disease transmission, where rewilding projects would then represent safer propositions from an anthropocentric viewpoint. The lethality of rabies in humans once symptoms arise and the key symptom in which afflicted wildlife lose their fear of humans suggest this disease should be tackled first on ethical and societal grounds as a key impediment to mammalian rewilding (American Veterinary Medical Association 2020).

Methods

This theoretical study explores existing literature while also contributing original ideas to advance this field of study. For such a transformative biotechnology as gene drive, academic research necessarily precedes field tests of the intervention. A review of existing strategies to counter rabies revealed various shortcomings of extant methods used to fight this virus. Given recent developments in gene drive research proposals, further study of the situation of red fox rabies carriers in North America suggested that it could be beneficial to use gene drive to provide North American red foxes with heritable immunity to rabies as a pilot project towards eventual continent-wide or global rabies eradication via immunising other wildlife reservoirs similarly. Downstream ecological consequences of the intervention were also assessed by researching red fox diet and interactions with other species in complex food web relationships. Here, we consider the possibility of a gene drive for heritable rabies immunity in North American red foxes and propose that it may be highly beneficial.

Status Quo: Rabies, a Costly Zoonotic Disease and Barrier to Mammalian Rewilding

Rabies represents a dire threat to the health and safety of wild animals and humans wherever these populations co-exist. The neurotropic rabies virus (family Rhabdoviridae, genus *Lyssavirus*) is notorious for the near 100% fatality rate in humans once symptoms occur, such that prevention of transmission is strongly preferred, as post-exposure prophylactic treatment may be inaccessible or fail to save a patient (Hueffer and Murphy 2018). This enveloped virus has a bullet-shaped capsid of approximately 180 nm length and 75 nm diameter studded with glycoproteins on its exterior while the negative sense ssRNA genome is approximately 12,000 nucleotides (Creative Diagnostics 2024, Howard Hughes Medical Institute 2024). The complex information landscape represented by the rabies virus, its carriers, viral transmission pathways and existing rabies prevention efforts suggests new approaches may be useful to address this formidable obstacle to safe mammalian rewilding.

The rabies virus presents a key barrier to the rewilding of urban and suburban communities with wild mammals (birds, fish, reptiles and amphibians do not carry rabies; all mammals are susceptible) in that rabies symptoms include aggression, staggering and behavioural changes, for example, ‘Rabid wild animals may lose their natural fear of humans, and display unusual behavior [...] an animal that is usually only seen at night may be seen wandering in the daytime’ (American Veterinary Medical Association 2020). At the same time, expansion of human habitation in sprawling cities and suburbs into habitats formerly occupied by wild mammals presents a problem for wildlife as these animals modify their behaviour via natural selection favouring adaptations to human presence. AAAnimal Control explains the situation in which human communities have placed wild mammals:

Seeing nocturnal animals during the day has been known for years to be a surefire way of telling whether or not an animal is rabid and, therefore, infected with rabies. In this day and age, however, it is not unusual to see a great number of nocturnal animals out and about during the daylight hours. In some ways, it's a kind of evolution. They have learned to stay awake at the best times to find food. Humans mean food [...] you will find nuisance wildlife and scavengers. These animals are doing whatever they need to do in order to survive (AAAnimal Control Trappers 2020).

Unless rabies eradication is achieved, any rewilding of urban and suburban areas with wild mammals can only be expected to increase human-wildlife conflict and humans' fears of encountering rabid wild mammals.

In continental Europe, efforts to vaccinate domestic dogs against rabies, while allowing red foxes to persist as a confirmed rabies reservoir, suggest that human rabies cases are ultimately the result of wild canids transmitting the virus to domestic dogs who then infect humans, given that people with presumed rabies exposure had seldom been directly exposed to foxes (Woodroffe et al. 2004). Depending on the region, wild canids may be self-sustaining rabies reservoirs or, in other cases, persistent cross-species infections are required between domestic dogs and wild canids for the virus to persist (Woodroffe et al. 2004). In North America, skunks, raccoons, bats, rodents, arctic foxes, red foxes, coyotes and wolves are the main hosts of terrestrial rabies (Howard Hughes Medical Institute 2024, Hueffer and Murphy 2018). Given the social and physiological flexibility of red foxes, coyotes and jackals with respect to immigration, litter sizes and survival rates, efforts to eliminate rabies by indiscriminate host killing have not eradicated infection and are judged ineffective at protecting humans and domestic animals from rabies (Woodroffe et al. 2004). The high death tolls of rabies control projects that used trapping, shooting, gassing and poisoning, combined with their failure to eradicate rabies suggests that these strategies have no place within the emerging paradigm of compassionate conservation (Compassionate Conservation Guiding Principles 2020, Woodroffe et al. 2004). The loss to genetic diversity when large populations of wild mammals are killed off may represent an additional cost of such programmes which nevertheless failed to achieve rabies eradication in North America.

In high biodiversity areas, distribution of bait laden with live rabies vaccine intended for consumption by wildlife presents unexpected risks, as a set dosage that protects one species, jackals, may induce rabies in another, such as baboons (Woodroffe et al. 2004). For instance, a research study documented a case of vaccine-induced rabies in a red fox in Poland (Smreczak et al. 2022). An alternative thermostable recombinant rabies vaccine featuring the surface glycoprotein gene within a *Vaccinia* virus carrier rather than the live virus may be safer to distribute in bait (Woodroffe et al. 2004). Nevertheless, if wildlife with abundant food options avoid eating the bait, inadequate population-wide immunity may result. Oral vaccination does not provide heritable rabies immunity and, with new susceptible mammals born every spring, this strategy is not a self-sustaining or long-term solution. In developing countries, where economic factors preclude vaccination of wild dogs, rabies causes approximately 59,000 human deaths and losses of $8 billion each year (American Veterinary Medical Association 2020, Hueffer and Murphy 2018). In the US, about 60,000 Americans receive postexposure prophylaxis (PEP) each year, at an overall average cost reaching ten thousand dollars per person (United States Department of Agriculture Wildlife Services 2023). In the event that the red fox rabies immunity gene drive proposals were successfully replicated in other rabies reservoirs to yield a North American continent (and later on, a biosphere) free of rabies, the near-total termination of annual public health expenditure on rabies diagnostics, prevention and control (in excess of $600 million) multiplied out by perpetuity represents an economic boon in the event that rabies eradication is achieved (United States Department of Agriculture Wildlife Services 2023). In the words Benjamin Franklin once addressed towards the cause of fire prevention, 'An ounce of prevention is worth a pound of cure' (Franklin 1736).

Rewilding of (Sub)Urban America with Rabies-Immune Red Foxes via Gene Drive

While a gene drive in North American red foxes to confer heritable rabies immunity is a radical idea, the Latin root word *radix*, a root, is the etymological origin of the word 'radical' applied as a modern pejorative (Porter 1913). As stated in Thoreau and Cramer (2008), 'There are a thousand striking at the branches of evil to one who is striking at the root.' In a world where tens of thousands of North American canids died in a single rabies control campaign that failed to achieve rabies eradication, one must ask whether modifying wild mammals' genomes via gene drive constitutes less of an ethical affront to wildlife and nature than failed 20th century strategies did (Woodroffe et al. 2004). Gene drive is a biotechnology that allows for the modification of a freely-breeding wild animal population with a new heritable trait even with an abundance of wild-type animals and a small initial release of modified animals, due to biased inheritance favouring the introduced genetic construct (Douglas 2020, Esvelt 2014, Esvelt et al. 2014). Potential applications for gene drive technology are wide-ranging, including modification of mosquitoes to fight malaria, while suitable uses for gene drives are the topic of much scientific discussion in recent years (Bier 2022, Buchthal et al. 2019, Ledford and Callaway 2015, Noble et al. 2019). Methods for fine-tuning gene drives through a variety of instantiations such as daisy drives, homing modification drives, homing suppression drives, underdominance drives, toxin-antidote drives, killer-rescue drives and split drives represent another area of active scientific enquiry (Bier 2022, Esvelt 2020a, Noble et al. 2019, Wang et al. 2022). These versions and their remarkable control systems may prove useful in limiting the application of a future gene drive to a particular subpopulation or geographic region.

Red foxes immunised against rabies via gene drive would not necessarily be any less red fox by nature. A genomic region encoding antibodies to the rabies virus could conceivably be isolated from a red fox with acquired immunity such that there would be no transfer of DNA across species aside from the introduction of the CRISPR-based gene drive system. Beyond such a bespoke approach, proof-of-concept research exists on the expression of functional human antibodies within transgenic research animals such as mice, rats, rabbits, chickens and cows (Chen and Murawsky 2018). The success of such work across vast evolutionary distances suggests that a more limited strategy, such as expressing a dog anti-rabies antibody gene in a transgenic red fox, would be even more readily feasible. This suggestion may prove useful since domestic dogs are a well-studied species in terms of medical laboratory research including rabies projects, with abundant protocols and accumulated knowledge (Liu et al. 2014). It appears reasonable that another non-human animal species, such as dogs, could provide genes for functional anti-rabies antibodies in transgenic red foxes, as the use of human anti-rabies antibody genes in a gene drive in wild red foxes could prove controversial even if this approach would be the closest approximation to existing transgenic animal research at this time (Chen and Murawsky 2018). Regardless of what species provides the original antibody genes, one should note that merely expressing antibodies may not be sufficient to provide full immunity depending on myriad organism-level processes and interactions, likely necessitating laboratory verification of functional immunity (Donaldson et al. 2017, Liu et al. 2014).

The gene drive against zoonotic disease concept is explained by researcher Kevin Esvelt with respect to a similar proposal to modify white-footed mice on Nantucket with antibodies to confer resistance to Lyme disease in order to reduce transmission to humans via ticks, using mouse DNA from Lyme-resistant mice: 'Our idea is since most ticks are infected by white-footed mice, if we could immunize the mice, then you would break the cycle of transmission. Ticks would no longer be infected. People wouldn't get disease' (Esvelt 2017). As for objections to the proposed protocol of identifying the most protective antibody-encoding genes that some mice evolved when exposed to the pathogen and then inserting about 10,000 base pairs into the mouse genome for future generations, he asserts that this is a 'pretty tiny change' compared to other Lyme disease tick control strategies and that 'there is natural gene flow between all wild populations' (Esvelt 2017). A pilot feasibility trial on an uninhabited island could use mice without gene drive carrying the introduced antibody genes subjected to ordinary Mendelian inheritance (Esvelt 2017).

An engineered gene drive involving CRISPR-Cas9 components would qualify as an artificial instance of the widespread natural phenomenon known as horizontal gene transfer, in which genetic material is moved across lineages rather than solely from parents to offspring (Emlen and Zimmer 2020). CRISPR-Cas9 refers to the molecular sequence-targeting machinery that performs engineered genetic changes at desired locations within a cell's genome (Doudna and Sternberg 2017, Kozubek 2016). Esvelt's proposal to use gene drive to modify white-footed mice to ultimately prevent ticks from transmitting Lyme disease to humans has been historically defended on grounds of allowing humans to achieve a closer connection to nature, in a world where children grow up free to explore New England summers outdoors with no fear of contracting Lyme disease (Specter 2017). Thus, the concept of using gene drive to modify wild animals to reduce the risk of zoonotic disease transmission to humans, in order that humans can better experience the wild, now has an ideological precedent (Buchthal et al. 2019, Esvelt 2020b). Modifying red foxes for rabies immunity so that they can rewild suburban and urban areas without posing a rabies transmission risk to humans or domestic dogs is ideologically aligned with Esvelt’s proposal to use biotechnology to bring humans and nature closer together by reducing or eliminating the risk of zoonotic disease.

In terms of research methodology, the red fox rabies immunity gene drive proposal may work as follows: first, it is already routine practice that North American red fox ambassador animals approved by the USDA are administered the rabies vaccine tested and approved in domestic dogs (Whatcott 2018). Identifying and isolating an antibody-encoding DNA segment from the genome of an immunised mammal would indicate what discrete, transferrable genomic region encoded immunity, though one could also work with an already identified gene from another mammalian species (such as dog or human) encoding a rabies antibody (Chen and Murawsky 2018, Esvelt 2017, Esvelt 2021, Liu et al. 2014). While most research on expressing an antibody in a transgenic animal comes from expressing human antibody genes in transgenic animals, the 'dogs first' strategy discussed at greater length under the 'social, ethical, economic and cultural issues' section also represents a possible source of a suitable anti-rabies antibody gene. Non-viral transfection, viral transduction, lipofection and electroporation represent a subset of the many strategies by which new DNA encoding CRISPR-Cas9 gene drive components can be introduced into the genome of a cell (Doudna and Sternberg 2017, Kozubek 2016). Captive breeding, gene banking, assisted reproduction, artificial insemination, *in vitro* fertilisation, embryo transfer, animal translocation and re-introductions of animals released into the wild are established research techniques in a wide variety of canid species (Boitani et al. 2004). Alternative strategies involving modification or transplantation of spermatogonial stem cells (SSCs) that give rise to spermatozoa may also allow the introduction of novel genetic material into the germline of captive-bred mammals in a manner that may be preferable on animal ethics grounds, as mammals producing their own genetically modified gametes do not necessarily require invasive IVF or AI procedures (Brinster and Avarbock 1994, Silva et al. 2013). In the case of gene drive research thus far conducted in fruit flies and mosquitoes in the laboratory, animal ethics concerns for the subjective experiences or the material animal suffering, if any, of the modified insects have not precluded such projects from taking place (Ledford and Callaway 2015). However, the intelligence and complex behaviour of red foxes suggest that much greater attention should be paid to the animal ethics implications of precisely how novel genetic material would be introduced into the red fox germline (Henry 1986, Macdonald et al. 1987). This research may involve ethical issues similar to those faced in the Siberian fox domestication project’s animal husbandry and captive breeding to introduce a gene drive into the first generation as a one-time intervention, where attention to the well-being of foxes would influence the organisational and financial choices made by researchers (Dugatkin and Trut 2017).

Captive-raised young red foxes have been released into wild populations via ‘soft release’ strategies in which they have the option of relying on humans for food or gradually adapting to hunting and foraging on their own (Chambers 1990, Macdonald et al. 1987). Licensed wildlife rehabilitators are trained in how to handle and raise orphaned or injured wildlife in preparation for an eventual return to the wild; similar protocols could be followed for the release of the gene drive carriers of heritable rabies immunity or even an initial limited geographical trial featuring carriers of inserted, genome-encoded antibodies subject to ordinary Mendelian inheritance (Fig. 1, Esvelt 2017, The Canid Project 2020). Follow-up research via non-invasive field genetic monitoring has a precedent in a case of low population sizes where any harvest was unfeasible for fox conservation reasons: hair, urine, scat and carrion tissue provided DNA evidence of a genetically distinct small population of wild foxes (Curtis 2020, Quinn et al. 2019). Furthermore, non-invasive genetic sampling alongside spatial capture-recapture modelling (SCR) has been used for comprehensive quantitative analysis of red fox density, suggesting that field monitoring of a modified red fox population could be quite thorough (Lindsø et al. 2022). Given the possible use of PCR on non-invasive samples to detect whether a gene drive sequence is being expressed, it may not be fully necessary to assess whether gene drive and anti-rabies cargo are being expressed via live-trapping, blood sampling and re-releasing future generations of red foxes. This more intensive optional strategy could be applied to assess the presence of rabies antibodies in the descendants carrying the introduced antibody gene (with or without a gene drive to boost its rate of spread through a population, per the second and first figures, respectively) to observe the expected increase in the prevalence of rabies immunity, as compared to wild-type genotypes/phenotypes, via similar methods as used in the 'genotype-by-sequencing immunogenetic assay [...] screening for variation in red fox with and without endemic rabies exposure' research project (Figs 1, 2, Donaldson et al. 2017). The differences in inheritance patterns when introducing heritable rabies immunity with and without gene drive can be important to distinguish, especially given the limitations of classical Mendelian dominant inheritance after repeated crosses with wild-type carriers of two susceptible alleles (Figs 1, 2). If a homing drive is used, conversion from Dw to DD (D: drive allele, w: wild-type allele) may take place in the germline, so it would be critical for heterozygous somatic cells to provide functional rabies immunity even if the uniformly drive-carrying gametes would appear to have been produced by an effective homozygote (Fig. 2, Champer et al. 2018). In all three figures of this paper, the purple shape represents the bullet-shaped rabies virus capsid as a projectile to be deflected (symbolically) through immunity to the rabies virus. As a gene drive presents the opportunity for unlimited spread within a species, modified variants known as daisy-chain, daisyfield, daisy quorum and daisy restoration gene drives allow the inheritance of a genetic construct to be boosted above native Mendelian inheritance mechanisms for a limited number of generations or in a limited geographic area (Esvelt 2020a, Noble et al. 2019). These are not the only variants of gene drive that may prove useful in a self-limiting gene drive release subject to engineered control, as many more options and categories exist (Bier 2022, Wang et al. 2022).

Beyond the aforementioned considerations, it is also important to address the question of whether this project could be achieved prior to substantial further discoveries and upgrades concerning gene drive technology. Numerous technical barriers exist that would have to be decisively surmounted for this project to make its way out of literature and into the real world. For instance, random mutations may occur that end up disabling the resulting single guide RNA necessary to target the Cas9 machinery to the suitable spot when making a second copy of the desired rabies antibody gene and CRISPR-Cas9 system. The system might induce genetic editing at originally untargeted locations due to an sgRNA mutation that led to reaching a new sequence instead. Engaging in double-strand DNA breaks and calling DNA repair machinery to the right spot in the genome may incur a fitness cost for an animal that might not even encounter the rabies virus in its particular lifetime. Across enough instances of this situation, a new mutant allele that sufficed to disable the gene drive system might find its way to the forefront of the genetics of a population. Strategies, such as guide RNA multiplexing, a haplolethal homing drive and so forth, may help reduce the formation and effects of resistance alleles, though these existing approaches may not suffice to clear all hurdles that could arise in complex mammals, such as red foxes (Champer et al. 2018, Champer et al. 2020, Champer et al. 2020). While success has been observed in gene drive laboratory experiments involving fruit flies and *Anopheles* mosquitoes, other problems, such as the potential for resistance alleles to arise as well as fitness costs, preclude the expected success of gene drives in wild populations of more complex species, such as mice and beyond, given the current state of the art, as has been explored in existing literature (Bier 2022, Lowe 2023, Wang et al. 2022). Noting that gene drives may be expected to improve across the decades to come and that the current annual rabies expenditure in the US exceeds $600 million, it nevertheless seems plausible that a once-and-for-all strategy to eradicate rabies through providing wild mammal reservoirs with heritable immunity will become the most economical strategy once the practical technical barriers to a successful pilot project in red foxes have been surpassed (United States Department of Agriculture Wildlife Services 2023).

Regarding the timeline for this project from an initial release of gene drive carriers to the widespread permeation of heritable rabies immunity throughout wild red fox populations, it is important to recall that gene drives work more quickly in species with shorter generation times. Though the exact months involved vary by latitude and climate, red foxes mate in late winter and give birth, 52-53 days later in early spring, to litters that average four or five kits (Hemmington 1997, Henry 1986, Macdonald et al. 1987). While some vixens stay in their parents' territories and assist in raising additional litters in later years as helper adults, dog foxes (male foxes) tend to disperse further and more often to establish new territories while reaching adulthood in their first autumn and winter (Hemmington 1997, Henry 1986, Macdonald et al. 1987, Walton et al. 2018). In a Scandinavian study of long-range red fox dispersal via GPS collars, six out of thirty foxes which dispersed to new territories travelled across straight-line distances exceeding 60 km (37 miles), a metric which may provide information for modelling of the time necessary for a North American red fox gene drive to spread across populations (Walton et al. 2018). With sufficient engineered control of suitably self-limiting gene drive technology, multiple starting locations could be used rather than waiting for a single lineage to span the continent (Bier 2022, Esvelt 2020a, Noble et al. 2019, Wang et al. 2022). Given the coast-to-coast range of red fox populations across virtually all of Alaska, all of Canada and nearly all the lower 48 States excluding parts of the southwest, it seems reasonable to estimate that a red fox gene drive may take a few decades to achieve widespread heritable rabies immunity in North America, given the preponderance and distribution of wild-type individuals to begin with (Lindsø et al. 2022, Hemmington 1997, Henry 1986, Walton et al. 2018). While high precision data on the total population of red foxes in North America may not be available, existing estimates range from 1.3 million to 10 million (Wildlife Informer 2024, World Population Review 2024). The exact number may vary significantly across months given that most newly-born red fox kits may not survive to adulthood within each year (Hemmington 1997, Henry 1986, Macdonald et al. 1987). If a gene drive in red foxes and other wild mammal reservoirs is the only viable way to end rabies for good in North America and ultimately worldwide, given the non-heritable effects of oral rabies vaccination in wildlife and the potential avoidance of bait when other food sources suffice, then even a lengthy waiting period should not deter researchers from pursuing the vast economic, animal welfare and human healthcare benefits of permanent rabies elimination (Hueffer and Murphy 2018, United States Department of Agriculture Wildlife Services 2023, Woodroffe et al. 2004).

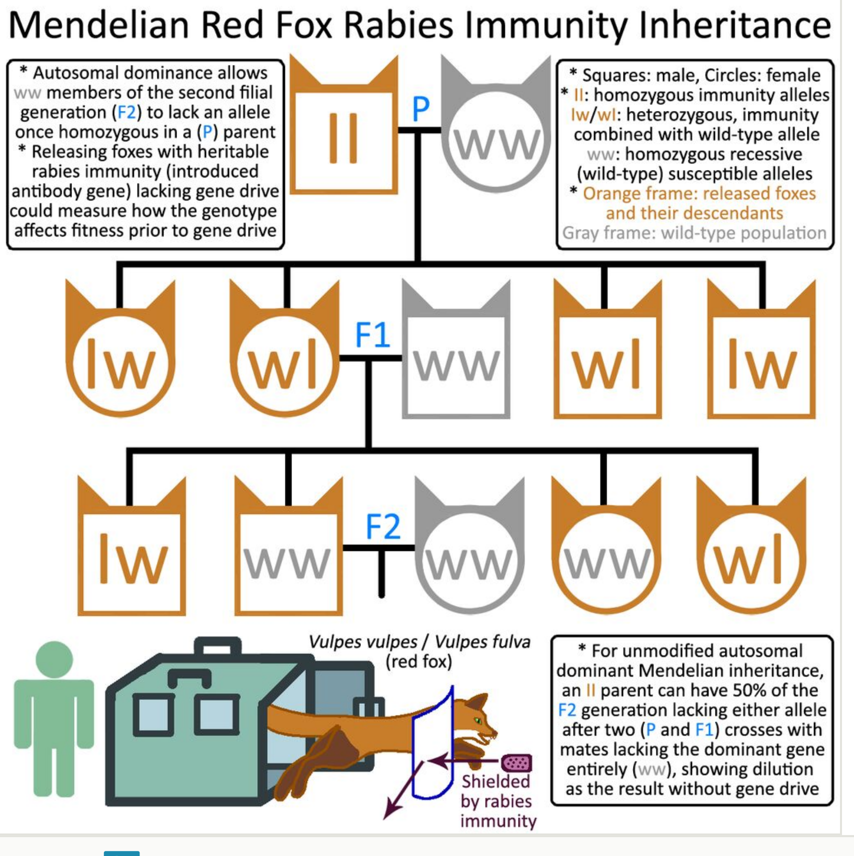

Figure 1. doi

Red Fox Rabies Immunity Inheritance featuring Mendelian Dominance in the absence of Gene Drive. This figure shows patterns of heritable immunity without the use of gene drive to accelerate spread through a wild population. Labels refer to P: parental, F1: first filial and F2: second filial generations. I: immunity allele, w: wild-type allele.

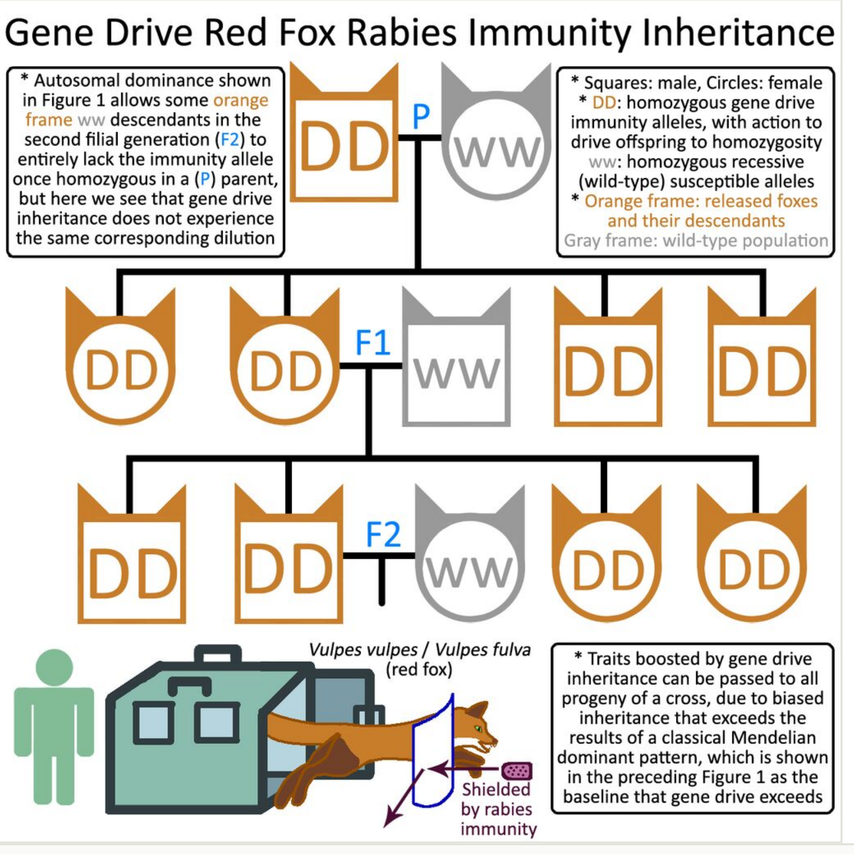

Figure 2. doi

Red Fox Rabies Immunity Inheritance featuring Gene Drive to go beyond the Mendelian Dominance baseline pattern. This figure shows patterns of heritable immunity with the use of gene drive to accelerate spread through a wild population. Labels refer to P: parental, F1: first filial and F2: second filial generations. D: gene drive allele, w: wild-type allele. n.b.: germline cells may be homozygous DD giving rise to only D-carrying gametes in drive-carrying individuals with Dw (not shown) somatic cells.

Social, Ethical, Economic and Cultural Issues of Red Fox Rabies Immunity Gene Drive

Before making persistent genetic changes in populations of wild mammals that act as reservoirs for the rabies virus, it may be judicious with respect to public opinion and research feasibility to act first in a domestic animal species whose genetic material could be manipulated as an advance trial for this proposed intervention. In particular, since most human deaths caused by rabies globally occur due to contact with dogs, a project to develop a gene drive for heritable rabies immunity in domestic dogs would have immense export value while also potentially providing a source of well-characterised antibodies for use in transgenic red foxes for the North American first trial project in the wild, based on existing prior research into similar endeavours (Chen and Murawsky 2018, Hueffer and Murphy 2018, Liu et al. 2014, Woodroffe et al. 2004). Ongoing rabies surveillance projects could monitor domestic dogs and red foxes tested for rabies to detect the presence and putative success of a gene drive in either population in addition to performing PCR on non-invasive samples of hair, urine, scat and carrion to track the spread of the genetic material of interest (Curtis 2020, Lindsø et al. 2022, Ma et al. 2023, Quinn et al. 2019). Given the existence of unplanned breeding amongst domestic dogs who are strays or whose humans opted out of surgically-induced sterility for their pets, a gene drive for rabies immunity in North American domestic dogs could begin with recognised dog breeders as sources of the intervention with the eventual downstream goal of population-wide heritable rabies immunity, at which point, dogs lacking a more traditional injected vaccine would no longer represent a rabies threat to humans (American Veterinary Medical Association 2020, Chen and Murawsky 2018, Liu et al. 2014, Ma et al. 2023).

While rabies exacts its deadliest human toll via transmission from wild dogs in India, cultural and economic barriers suggest that this is not the ideal place for western scientists to trial a radical new technology for the first time (Hueffer and Murphy 2018, Rahman 2020, Woodroffe et al. 2004). While Esvelt (2017) stresses the importance of interacting in person with an affluent, educated New England offshore community per Specter (2017) to explain the mechanisms of the gene drive proposal to seek informed community assent, this approach may not be viable to apply a gene drive against rabies in wild dogs amid a superstitious culture that does not accept prevailing western scientific knowledge concerning rabies treatment and symptoms. In India, a bite from a rabid dog may cause the patient to believe that puppies begin to develop in one's abdomen, a situation where the witch doctor's counsel that 'if you take my medicine and then go to hospital for treatment, my medicine will not work and the situation will worsen' may represent the culturally prevalent worldview of rejecting belief in western medicine's post-exposure rabies prophylaxis regimen (Rahman 2020). The approximate $750 cost of vaccinating a human against rabies may be affordable in some situations for North Americans and others in the developed world, while remaining prohibitively expensive for those living in the developing world, suggesting that first testing a gene drive against rabies in wild dogs in India could be perceived as an imperialistic means of exporting environmental externalities and risks to poorer parts of the world that already have fewer options on the table to combat zoonotic diseases (Shlim 2015). Even in continental Europe, human susceptibility to rabies from dog bites may only persist because wild canids are a persistent rabies reservoir, suggesting that the *status quo* of vaccinating primarily companion animal dogs is woefully insufficient to reach rabies eradication (Woodroffe et al. 2004).

In the rabies-free United Kingdom per GOV UK (2020), red fox advocate Martin Hemmington argues that urban foxes have become behaviourally accustomed to friendly humans who welcome their presence and offer them food:

Both town and country foxes will have what is described as a ‘flight distance’: a distance that the wild fox will put between itself and you, in the knowledge that if you were to become hostile it would have enough space to get away. In the countryside, the flight distance may be a couple of fields, whilst in an urban setting only ten feet or so, for the urban fox seems more able to live in a closer proximity with man; perhaps […] urban foxes are persecuted to a lesser degree than rural ones (Hemmington 1997).

As the absence of rabies allows United Kingdom red foxes to colonise backyard gardens and city parks in daylight without inducing humans’ fear of a rabid wild mammal, research indicates food deliberately supplied by householders was 60% of the red fox diet by volume in Bristol and weekly human-sourced scraps ranged from 4.7–8.9 kg in Oxford red fox territories (Baker and Harris 2004). In situations where rodents may be culturally regarded as pests and disease vectors, red foxes’ colonisation of UK cities as a mesocarnivore predator may be preferable to other cities that generally lack red foxes in terms of the ecological network of interactions amongst all urban fauna. The cultural, sentimental and aesthetic aspects of rewilding, where wild mammals are seen to thrive in heavily human-modified suburbs and cities, may also present a benefit to human residents in line with the late E. O. Wilson's biophilia concept (Wilson 1992). Unanticipated ecological interactions may include the dilemma that, if rabies acts as a compensatory mortality check on North American red fox populations, alternative outcomes such as death by automobile or mange would rise to replace rabies deaths. Alternatively, if rabies acts as an additive cause of mortality in North American red fox populations, prey species subjected to an increase in red fox populations may come under pressure; this seems a comparatively negligible risk given that red foxes are generalist mesocarnivores who can adapt to a wide range of diets and prey species as part of their opportunistic omnivorous diet (Henry 1986). The proposed intervention may cause short-term pressure on rodent or rabbit populations where fox predation is a major balancing factor, but natural Lotka-Volterra fluctuations may be sufficiently large that removing rabies from the equation would be negligible in comparison to natural year-over-year variation in population sizes.

Rewilding projects may be assessed in terms of what baseline they seek to restore. Two developed countries where red foxes pose no risk of rabies transmission to humans, the UK and Japan, already provide glimpses of what scenes a rabies-free, post-rewilding North America could allow (GOV UK 2020, Takahashi-Omoe et al. 2008). The Miyagi Zao Fox Village in Japan represents an artificial enclosed ecological community of approximately one hundred red foxes where human visitors provide food to foxes, directly handle foxes and even walk freely amongst the foxes without physical intervening barriers. This modern red fox population’s behavioural way of life may represent a surviving relic of previously more widespread East Asian (Sino-Japanese) cultural and religious zoolatry practices dating to long before Japan’s rabies eradication, practices which included, but were not limited to: families feeding wild foxes, construction of fox altars and shrines, believing that hunting foxes wantonly could result in vengeance by fox spirits, interpreting a fleeing fox as an omen, maintaining official buildings as places where foxes could burrow homes, publicly declaring exact fox hunting season boundaries such that 'the foxes would have time to hide themselves and leave the old, the sick and those who had committed capital crimes [*sic*; this implies foxes were considered moral actors with rule of law] among them to be hunted,' with references to 'the actual presence of biological [*sic*; as opposed to spirit or supposedly human-transformed] foxes' amid shrines erected to provide sacrifices for foxes, as 'no one dares to offend them,' such that 'officials could benefit by befriending the resident foxes' in a culture where wild mammals and their observed behaviour influenced the course of human affairs across centuries in China (Kang 2006). In the modern cultural context, the zero rabies transmission risk from handling and walking amongst red foxes allows common, non-research-biologist visitors to the Miyagi Zao Fox Village in Japan to learn more about the species' biology from the educational animal facility, while directly observing red fox genetic variation (such as the wide range of coat colors including dark silver and platinum morphs), morphology, social behaviour, vocalisations etc. with minimal risk of harm to humans (CONTA 2020, Village 2020).

The rewilding of suburban and urban North America with rabies-immune red foxes may have downstream ecological effects that promote environmental sustainability and support the persistence of biodiversity in native fauna. Feral cats and unaccompanied roaming outdoor domestic cats predate native bird species in vast numbers; the late deep ecologist Pentti Linkola, honoured with the epithet 'the last man of the deep wild', lamented that 'man's relationship with nature has never been more deranged, reckless and hypocritical than it is with the cat: when it comes to defending the cat, many environmentalists turn cunning and deceitful', as favouritism for cats may cause humans to underestimate the threat that roaming outdoor cats pose to native avian species and to oppose any conservation efforts that directly combat the threats posed by cats (Chapman 2020, Linkola 2011). In the Greater London metropolitan area, where urban red foxes are a common sight in parks, yards and on buildings, approximately 500 domestic cat casualties caused passionate, emotive and fierce speculation that a (human) serial killer of cats was at work (Murphy-Bates and White 2020). Studies by the Head of Veterinary Forensic Pathology at the Royal Veterinary College, Henny Martineau, found fox DNA in all prey bodies examined and concluded that predation and scavenging were responsible, leading to an ultimate Metropolitan Police announcement that 'every one of the cases of cat mutilation will be recorded as 'no crime'' given that no law prohibits urban red foxes from hunting cats (Murphy-Bates and White 2020). As UK urbanites passionately morally object to any human who dares to kill a cat, for example 'that evil individual will get what is coming to them' in Murphy-Bates and White (2020), yet often feed beloved urban red foxes, assisting fox survival and successful reproduction, even venerating a specific real world urban red fox in the illustrated children's literature of Soanes (2020), Soanes and Mayhew (2020), rewilding via the resurgence of a capable vulpine mesocarnivore that exerts control over outdoor cat populations in urban and suburban areas, while not posing a zoonotic disease threat to urbanites could indirectly save native avian fauna from taboo, unsustainable levels of predation by cats, while also influencing more humans to keep cats indoors (Linkola 2011, Loss and Marra 2017). Ample scientific evidence demonstrates that outdoor cat populations negatively influence a variety of vertebrate wildlife populations through the combined effects of fear, predation and disease (Loss and Marra 2017). Releasing red foxes from rabies-caused mortality may enable them to exert stronger pressure on outdoor cat populations, both through direct predation and indirect competition for territories, rodent prey and human-sourced food scraps. The resulting effects could include relieving native avian fauna from feline predation, as part of an adjustment to the complex food web of sub(urban) habitat niches (Fig. 3).

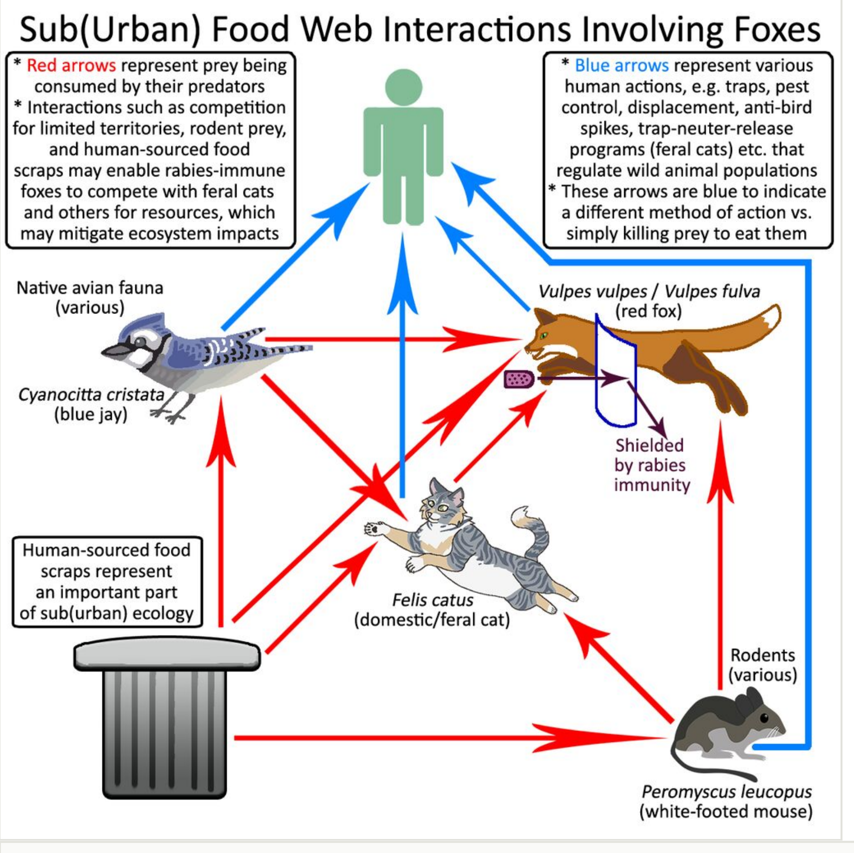

Figure 3. doi

Sub(urban) food web interactions involving foxes

In the New Yorker's profile of Esvelt's proposal for the white-footed mouse gene drive to prevent Lyme disease zoonotic transmission to humans, the article laments that 'in communities throughout the Northeast, the fear of ticks has changed the nature of summer itself — few parents these days would permit a child to run barefoot through the grass or wander blithely into the woods' as there is 'currently no approved Lyme vaccine for humans' such that pre-emptive transmission prevention is strongly preferred over post-infection treatment strategies (Specter 2017). The desire to bring up children to experience outdoor nature in New England summers with no fear of Lyme disease may yet enable the white-footed mouse gene drive to proceed. One may also observe that a

North American parent is highly unlikely to permit a youth to feed, much less personally encounter, a North American red fox at Hemmington's cited ten foot (3 m) flight distance for UK urban foxes. However, in the absence of any rabies transmission risk, meeting and feeding red foxes is an easily accessible and relatively safe behaviour for residents of rabies-free Japan and the United Kingdom.

The continued existence of numerous North American private sanctuaries with tame ambassador animals (Howler's Inn, Bearizona, Adirondack Wildlife Refuge, Wild Hearts Exotic Animals, Wild Wonders, Animal Wonders etc.) supported by patrons and/or visitors suggests that people place substantial economic value on encountering wildlife in-person and will travel distances to do so, in the event that their cities and suburbs are largely devoid of the opportunity to sight wild mammal mesocarnivores, such as foxes and coyotes. As for the cliché correlation of tree-lined streets and higher property values, it may also be the case that cities and suburbs with a wider variety of fauna (not just wild canid mesocarnivore, but avian as well, in the event that the hypothesised fox-cat-bird ecological cascading predator control interaction proposed in this paper works in practice) would experience higher home prices. Local residents could enjoy the sight of their outdoor dog frolicking with a wild fox without reason for fear if fox-originated rabies transmission were impossible (UnitedLab6476 2024). Such areas may yet become more desirable places to live in line with E. O. Wilson's observations on biophilia being evinced by worldwide preferences in specific landscape patterns where humans wish to live if they can afford the privilege (Wilson 1992).

Long term maintenance of this rewilding strategy could include local trial releases on islands, daisy gene drive variants and otherwise self-limiting refined gene drive systems in subregions for locally informed control and post-intervention compensatory feedback, as well as non-invasive DNA monitoring via collection of hair, urine, scat and carrion samples (Bier 2022, Curtis 2020, Donaldson et al. 2017, Esvelt 2020a, Lindsø et al. 2022, Noble et al. 2019, Quinn et al. 2019, Wang et al. 2022). Reliable indications of success in red foxes could light the way towards intervening with comparable rabies immunity gene drives in other wild mammal reservoirs to target rabies extirpation across expanding geographic realms.

While this rewilding via gene drive proposal does not seem inherently natural, the eradication of smallpox (and ongoing interventions against polio and COVID-19) represent precedents of humans opposing natural processes out of moral and ethical preferences to live in a less natural world with less suffering. It is seldom if ever argued sincerely that the eradication of smallpox or polio or tuberculosis should be considered ethically undesirable because the 'species count' of global biodiversity would decline by one or two or three in exchange for the elimination of mass suffering of sentient life. Per the 'devil's advocate' thought experiment in which one attempts to imagine, predict and anticipate criticisms of what one would otherwise consider a moral and ethical good, opponents may argue that the rabies virus is part of the natural world, contributes to viral biodiversity and exerts pressure via natural selection to strengthen the red fox immune system (Donaldson et al. 2017, Hueffer and Murphy 2018, Woodroffe et al. 2004).

Does this rewilding proposal seem natural? No, but that question is immaterial to whether or not it ought to be done, unless one indulges in the naturalistic fallacy with respect to ethical decision-making for animal populations, in which case veterinary medicine as a field of wildlife biology would not have any rationale to exist. Via the *status quo* of 'speciesism', North American wild red foxes are simply left behind and forgotten, save for the occasional vaccine-laden bait providing merely non-heritable immunity, when it comes to the distribution of economic resources and scientific research projects for rabies prevention and the alleviation of virus-caused suffering in mammals (Singer 2015, Woodroffe et al. 2004). One may counter-argue that the rabies virus is simply part of a diverse natural world whose unaltered persistence takes precedence over human interests and that the rabies virus contributes to global biodiversity. However, the 'naturalistic fallacy' (loosely applied to mean 'what is natural must be good', i.e. if death by untreated rabies is natural, then death by untreated rabies must be good) does not carry water in serious academic bioethics discussions. If not for deep ethical and moral preferences for acting, even at great economic cost, to biologically and socially engineer a highly non-natural world with less disease and diminished sentient mammalian suffering, the ongoing practices of human and veterinary medicine would not be able to justify their continued existence and resource consumption. The ethical, moral impulse that one ought to intervene and combat natural processes (decay, disease, pandemics and death) for the subjective well-being of sentient life is the foundational bulwark against the competing 'devil's advocate' ideology of Social Darwinism in a hypothetical alternative world where medical care for humans would be prohibited in the interest of allowing raw natural selection to strengthen the human gene pool and particularly the human immune system through the survival and reproduction of the fittest. A better world is possible for humans and North American red foxes via rewilding in the form of applied veterinary biomedical engineering to achieve rabies immunity via gene drive. This project is proposed in a first trial species in one region (and then one continent) as a representative pilot project which could culminate in global rabies virus eradication.

Prior to this paragraph, the omission of any scientific species name for 'red' foxes (whose common naturally occurring colour morphs also include silver and cross, with an even-broader colour palette achieved by artificial selection in captive-bred foxes) has been entirely intentional and perhaps even necessary, given the current dispute on red fox speciation (Dugatkin and Trut 2017, Statham et al. 2014). Notably, it is debated whether North American red foxes are now a distinct species from red foxes elsewhere on Earth (Statham et al. 2014, Wozencraft 2005). While one widely held view is that all red foxes (including various colour morphs, such as silver and cross) are of the single biological species concept *Vulpes vulpes*, featuring 45 subspecies worldwide per Wozencraft (2005), including numerous distinct subspecies spanning North America, Mark J. Statham and Benjamin N. Sacks of the Mammalian Ecology and Conservation Unit and Veterinary Genetics Laboratory at the University of California Davis as well as their co-authors conclude on the basis of extensive genetic research that the 'most fundamental genomic division' amongst red foxes occurs at the Bering Strait (the erstwhile Beringia land bridge) following the 400 ± 139 kya (kiloyears ago; thousands of years ago) origin of the North American (Nearctic) clade of red foxes, such that the North American red fox is best considered to have undergone peripatric speciation into a distinct species, *Vulpes fulva* (Baker and Harris 2004, Dugatkin and Trut 2017, Henry 1986, Statham et al. 2014). Based on multiple maps from these cited sources, the contemporary North American red fox geographic range includes virtually all of Alaska, all of Canada and nearly all of the lower 48 States, except for a few gaps in the extreme south-western parts of the US adjoining the Mexican border and Baja California Peninsula (Henry 1986, Macdonald and Sillero-Zubiri 2004). Such generic maps showing a largely filled-in continent fail to address the risk that these red foxes will have animal control called on them if they dare venture deep into North American suburbs or cities during daylight hours, although their general time preference is crepuscular, with peak activity at dawn and dusk (AAAnimal Control Trappers 2020, Hemmington 1997, Henry 1986).

Phylogenetically speaking, within tribe Vulpini (an intermediate taxonomic level between the family Canidae and the genus *Vulpes* corresponding to the ‘true foxes’), while arctic foxes (*Vulpes lagopus*) share overlapping habitats with North American red foxes (*Vulpes vulpes* or *Vulpes fulva*; contested) in both Alaska and Canada, it seems likely that arctic foxes as a rabies reservoir could only be directly impacted by a separate arctic fox gene drive in another project beyond the scope of this initial proposal (Hueffer and Murphy 2018, Macdonald and Sillero-Zubiri 2004, Statham et al. 2014, Wozencraft 2005). Critically, fox breeders have confirmed that captive-bred AI hybrids of the red fox and the arctic fox (photographs available at reference) are viable yet sterile:

There have been reports of hybrid fox kits occurring in the wild, but such matings (arctic x red) are not a common occurrence as the two species are natural enemies in the wild, with red foxes often killing and eating arctic fox kits as well as competing with them for food and territory. Hybrid foxes can come in several different colour mutations, depending on the colouration of the red and arctic parents. Hybrid foxes are quite uncommon in the exotic pet trade. They are born sterile, meaning they cannot reproduce (Anonymous 2020).

However, patterns in sea ice surrounding eastern North America allowed an arctic fox to migrate from Spitsbergen, Norway to Ellesmere Island, Canada over 2,000 miles in 76 days (Fuglei and Tarroux 2019, The Wildlife Society 2020). It cannot be ruled out that a North American red fox might successfully leave North America via the reverse journey, due to lack of research in this specific area (Kim et al. 2014). Thus, options for a self-limiting gene drive system such as daisy drives, homing modification drives, homing suppression drives, underdominance drives, toxin-antidote drives, killer-rescue drives and split drives alongside monitoring the spread for follow-up changes if needed, as described by Esvelt, Wang and others, would be an essential part of population genetic monitoring of red and arctic foxes in North America and worldwide (Bier 2022, Esvelt 2020a, Noble et al. 2019, Wang et al. 2022).

With respect to raw calculations of resource allocation, with even non-heritable human rabies vaccination costing $750 per capita in the US, it may be orders of magnitude less expensive to use gene drives in red foxes and then all other wild mammal rabies reservoirs to eradicate the rabies virus entirely, as opposed to vaccinating over 8 billion humans (and counting, given that traditional rabies vaccination is not heritable) at a comparable per capita expense to yield the same ‘zero zoonotic rabies cases in humans’ and ‘better human-wildlife co-existence’ outcomes that could conceivably be reached without altering any non-human animals, albeit at an exorbitant cost to achieve global vaccination of humans against rabies (Shlim 2015).

In closing, reframing the bioethics issues of gene drive from solely anthropocentric concerns to the broader issues of animal ethics and deep ecology that rewilding entails, the following passage from Beston (1928) as quoted in the vegan documentary *Earthlings* by Monson and Phoenix (2005) may illuminate an alternative worldview:

We need another and a wiser and perhaps a more mystical concept of animals. Remote from universal nature and living by complicated artifice, man in civilisation surveys the creatures through the glass of his knowledge and sees thereby a feather magnified and the whole image in distortion. We patronise them for their incompleteness, for their tragic fate of having taken form so far below ourselves. And therein we err and greatly err. For the animal shall not be measured by man. In a world older and more complete than ours, they move finished and complete, gifted with extensions of the senses we have lost or never attained, living by voices we shall never hear. They are not brethren, they are not underlings; they are other nations, caught with ourselves in the net of life and time, fellow prisoners of the splendour and travail of the earth.

If Beston is correct that wildlife species are indeed other nations, then perhaps it is an ‘idea whose time has come’ for a novel foreign aid programme to continue the struggle to eradicate a notorious zoonotic disease for multiple ecological downstream benefits that could accrue to both wild mammal rabies reservoirs and those urbanites who seek to live in a post-rewilding North America alongside charismatic, sometimes approachable urban mesocarnivore neighbours, as well as recovering native bird populations.

Key results

Since rabies causes afflicted animals to lose their fear of humans and has a near 100% fatality rate in humans once symptoms occur, it is an ideal first disease to target for eradication by using gene drive to spread immunity in the wild mammal reservoir populations harbouring this virus, making rewilding more feasible. Animals may avoid vaccine-laden bait when alternative food sources are abundant, as in the case of some suburban/urban habitat niches.

Conclusions

Heritable rabies immunity may improve the ecology of urban and suburban habitats given the potential for red foxes to keep invasive feral cat populations in check in these ecosystems. This intervention represents a novel endeavour that may be applied to zoonotic diseases present in other wild populations, working towards healthier, more harmonious ecosystems. Using medical and veterinary resources to prevent disease in not only humans, but also wild non-human animals, represents progress within the compassionate conservation ethic for minimising wildlife suffering in the course of ecological management decisions.

Implications

This research concerning a rabies immunity gene drive in North American red foxes explores how spreading heritable, population-wide immunity to zoonotic diseases can reduce the risk of human-wildlife conflict and assist in safer (sub)urban rewilding as a win-win for animals suffering from infectious diseases and humans at risk of contracting these zoonotic diseases.

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Conflicts of interest

The authors have declared that no competing interests exist.

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