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Vaccines for Conservation: Plague, Prairie Dogs & Black-Footed Ferrets as a Case Study

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Abstract: The endangered black-footed ferret (*Mustela nigripes*) is affected by plague, caused by *Yersinia pestis*, both directly, as a cause of mortality, and indirectly, because of the impacts of plague on its prairie dog (*Cynomys* spp.) prey base. Recent developments in vaccines and vaccine delivery have raised the possibility of plague control in prairie dog populations, thereby protecting ferret populations. A large-scale experimental investigation across the western US shows that sylvatic plague vaccine delivered in oral baits can increase prairie dog survival. In northern Colorado, an examination of the efficacy of insecticides to control fleas and plague vaccine shows that timing and method of plague control is important, with different implications for long-term and large-scale management of *Y. pestis* delivery. In both cases, the studies show that ambitious field-work and cross-sectoral collaboration can provide potential solutions to difficult issues of wildlife management, conservation and disease ecology.

Keywords: *Yersinia pestis*, black-footed ferret, prairie dog, wildlife vaccine, plague control, wildlife disease and conservation

INTRODUCTION

Part of the appeal of working on the ecology of infectious wildlife diseases is the applied nature of the research: how does transmission occur within the host population? What are the health impacts upon individuals, and/or effects on a host population's resilience or conservation status? And if the pathogen can be transmitted to humans, how do people and wildlife populations interact and what are the conditions that cause zoonotic spillover?

These issues are embodied in the case of prairie dog ecology. Although now sometimes regarded as an animal iconic of the United States' Great Plains, prairie dogs have borne the brunt of persecution campaigns throughout the twentieth century, when they were considered a pest that competed for cattle forage or acted as an impediment to land settlement (Lockhart et al. 2006). Despite poisoning, habitat loss and recreational shooting, of the four species in the USA—black-tailed (*Cynomys ludovicianus*), white-tailed (*C. leucurus*), Gunnison's (*C. gunnisonni*), and Utah (*C. parvidens*)—only the Utah prairie dog is listed as threatened by the US Fish and Wildlife Service (https://ecos.fws.gov/ecp/).

Simultaneously, prairie dog populations have been heavily impacted by the arrival of an invasive pathogen, the bacterium *Yersinia pestis,* which causes plague in human and animal populations. Most famous for the Black Death in medieval Europe, *Y. pestis* was introduced to the USA in Pacific ports circa 1900 and spread eastward. During outbreaks on prairie dog colonies, 95–100% of individuals may die from plague (Pauli et al. 2006; Salkeld et al. 2016).

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Figure 1. A black-footed ferret (*Mustela nigripes*) preying upon a black-tailed prairie dog (*Cynomys ludovicianus*). Ferrets measure approximately 18–24 in. long, and are 1½ to 2½ pounds in weight; adult prairie dogs are 14–17 in. in length, and 1½ to 3lbs in weight. Photo: Mike Lockhart.

The relevance of prairie dogs, disease and conservation becomes more pressing when considering the endangered black-footed ferret (*Mustela nigripes*). The black-footed ferret is a near-obligate predator of prairie dogs—the rodents comprise the majority of their diet (Fig. 1), and the ferrets use the prairie dog burrow complexes for shelter (Biggins et al. 2006). Without a suitable prey base, black-footed ferrets fail to thrive, and the decline in prairie dog populations during the 20th century resulted in deterioration of ferret populations. As prophesied by Seton (1929, cited in Biggins et al. 2011), "Now that the big Demon of Commerce has declared war on the Prairie-dog, that merry little simpleton of the Plains must go … and with the passing of the Prairiedog, the Ferret, too, will pass." Indeed black-footed ferret populations terminally waned, the species was listed as endangered under the 1973 Endangered Species Act, and seemingly went extinct in the wild before the US Fish and Wildlife Service had been able to approve a recovery plan in 1978 (Biggins et al. 2006).

However, in 1981, a happy accident in Meeteetse, north-western Wyoming, presented conservationists with a remnant wild population of ferrets. The population was discovered when John Hogg's ranch dog Shep presented the rancher with a dead ferret, and Mr. Hogg remembered:

"We took it down to a taxidermist in town here, and he said, 'Oh my God, you got a ferret.' And I said, 'What the hells' that?' Ha, ha, I didn't know what it was." (Preston 2016).

The local population numbered over 100 individuals. Tragically, in the 1980s, local prairie dog populations were depleted by plague, and the ferrets were probably afflicted by plague and canine distemper virus, such that the species was restricted to 18 captive individuals by 1987 (Williams et al. 1988; Biggins et al. 2006). Subsequently, 15 of the 18 ferrets bred in captivity, and their careful management has resulted in over 8500 descendants, with reintroduction to the wild at 28 locations, and approximately 300 individuals surviving in the wild (black-footed ferret.org). Nonetheless, plague still presents a threat as it reduces prairie dog populations in areas where the ferrets have been reintroduced, and also affects the ferrets themselves (Williams et al. 1994; Matchett et al. 2010).

Combating Infectious Disease in Wildlife Populations

Given this conundrum, i.e., how to maintain a species of rare carnivore in the wild given its predilection for a prey base that succumbs to a mutually-deadly disease, researchers have struggled with how to combat a notoriously complex disease system. Vitally, the successful intervention must be viable at an ecologically meaningful scale (Tripp et al. 2017).

Three main control interventions are available. Fleas are the predominant vector of *Y. pestis* during outbreaks, and "dusting" with insecticides can suppress flea populations in prairie dog burrows (Seery et al. 2003; Tripp et al. 2009, 2016; Fig. 2). Second, an injectable vaccine protective against plague has been tested and used successfully in black-footed ferrets, and beginning in 2008, all captive-born ferrets released into the wild have been given two doses of the F1–V vaccine to protect them against plague. In Montana, vaccinated captive-reared ferrets have higher survival rates than controls (Matchett et al. 2010). A third approach is oral vaccination of prairie dogs to provide resistance to plague, which has the benefits of preserving

Figure 2. Colorado Parks & Wildlife technicians "dusting" a prairie dog colony with insecticide. Photo: Dan Tripp, Colorado Parks & Wildlife.

the ferret's prey base and reduce *Y. pestis'* force of infection of plague to the ferrets (Biggins et al. 2011; Abbott et al. 2012).

All methods have their drawbacks (Abbott et al. 2012). The impact of insecticide dusting upon invertebrates is indiscriminate, insect populations may develop resistance, the technique is labor-intensive and the timing of application is key, i.e., dusting may fail to halt outbreaks if applied too late (Abbott et al. 2012; Tripp et al. 2016). Vaccination of ferrets requires recapture of naïve, born-in-the-wild individuals, and does not protect the prairie dog prey base from the disease. And until recently, the feasibility and sustainable success of administering oral vaccine to wild prairie dog populations was unknown.

Field-Testing the Sylvatic Plague Vaccine

In this issue, and in forthcoming EcoHealth editions, some of these challenges have been addressed by field studies that directly examine the use of vaccine baits. Spanning 29 study sites across seven western states, Rocke et al. (2017) examined relative abundance and apparent survival of prairie dogs on plots that had been provided the sylvatic plague vaccine (Fig. 3), and compared these metrics with placebo plots. Prairie dog populations receiving sylvatic plague vaccine exhibited better abundance and survival than animals on placebo plots. And when plague was active, even though vaccine-treatment did not completely prevent mortality, survival was markedly higher on the treatment plots compared to placebos, with juvenile animals exhibiting a stronger response.

Tripp et al. (2017) examined prairie dog populations treated with insecticide dusting *or* sylvatic plague vaccine (compared with controls) at a black-tailed prairie dog colony complex in northern Colorado (Soapstone–Meadow Springs). Insecticidal and vaccine treatments did indeed mitigate plague's impacts upon the prairie dog populations. As in the larger geographic investigation (Rocke et al. 2017), neither intervention provided complete protection from plague transmission and mortality, and the efficacy of both depended on the timing of application. Burrow dusting offers more immediate protection by killing fleas and breaking at least some transmission pathways and can be used in the event of suspected plague activity. Vaccine application also suppressed outbreaks, though the difference in survival was most obvious when plague was active a year *after* vaccination. As a colony complex, prairie dog populations were more resilient and had greater ability to recover when management alleviated the outbreak.

This work provides evidence that disease management techniques offer the potential to protect target host populations—whether those of the threatened black-footed ferret, or to prevent host species from becoming listed as threated or endangered, e.g., Gunnison's prairie dogs.

Figure 3. A Gunnison's prairie dog (*Cynomys gunnisoni*) eating an oral bait containing sylvatic plague vaccine. The sylvatic plague vaccine (SPV) is a recombinant raccoon poxvirus engineered to express two protective *Y. pestis* antigens, F1 and a truncated V protein (Rocke et al. 2014). The vaccine is integrated into an oral bait format that is attractive and palatable to prairie dogs (using an edible polymer and peanut butter). A biomarker (rhodamine B) is added, and allows researchers to determine the extent to which animals are actually eating the bait by examining and hairs and whiskers under a fluorescence microscope, where the marker fluoresces red. Photo: Dan Tripp, Colorado Parks & Wildlife.

The Importance of Collaborative Field-Work

Other lessons are apparent from the prairie dog plague work. The author affiliations for this work include federal, state and local stake-holders, demonstrating that large, collaborative teams can work together to achieve innovative solutions to difficult questions. Indeed, without cross-sectoral partners, the results would be less likely to have the same relevance across scales.

An under-appreciated aspect of this type of research is the hugely demanding field-work requirements. Over the course of the 3-year study, over 10,000 prairie dog individuals were captured and recaptured; over 10,000 pools of fleas were tested for *Y. pestis*. These data fail to represent the actual field conditions: carrying vast numbers of heavy traps across wind-blown, sunburnt, cactus-infested landscape filled with prairie dog holes, lurking rattlesnakes and black-widow spiders. Interpretations of disease ecology research on wild populations must always be cognizant of the logistic demands and efforts involved, which have implications for our state of knowledge, e.g., do surveillance efforts for disease outbreaks really encompass the time, space and numbers required for the full picture to emerge?

Furthermore, plague outbreaks are often regarded as sporadic and unpredictable, and thus it requires a certain amount of luck to be able to compare management options in actual circumstances of plague. The researchers incorporated this element of happenstance by designing their surveillance at a grand scale (i.e., the seven states, and 29 study sites). Interestingly, plague activity was observed or suspected in 12/26 paired plots (Rocke et al. 2017), and across all of the insecticide/vaccine blocks in northern Colorado (Tripp et al. 2017). This prompts the hypothesis that perhaps plague activity is not as sporadic as commonly thought; active field-based surveillance will continue to provide data on the spatiotemporal aspects of plague ecology and transmission.

When *Y. pestis* does become active in prairie dog colonies, it does so with little deference to carefully designed monitoring experiments. Thus, plague occurred on some of the sites before Tripp et al. (2017) could properly measure survival in one particular triplicate. As Tripp et al. (2017) comment: "Plague's emergence … preceded or coincided with the beginning of our study, confounding survival analyses." This echoes the sentiments of the mammalogist Robert Burns, who wrote in 1785: "the best-laid plans of mice and men often go awry" (actually he wrote "The best laid schemes o' mice an' men/Gang aft a-gley."). Disease ecologists strive to understand the emergence and spread of wildlife and zoonotic pathogens, but it is worth remembering that field-work can be messy and unpredictable, even while Pasteur's old saw "Chance favors the prepared mind" holds true.

Implications

The research by Rocke et al. (2017) and Tripp et al. (2017) examining the potential for intervention in plague transmission dynamics to enable prairie dog population sustainability, stability and recovery is heartening. However, key questions still remain. Can this management option actually succeed in increasing ferret survival and resilience at reintroduction sites? How long does immunization from the sylvatic plague vaccine last in wild populations, and how often must the oral bait vaccine be applied to protect the prairie dog populations? And is the scale that is required to dampen plague transmission at a landscape level achievable for management purposes given logistical and financial constraints (Corro et al. 2017)? Nevertheless, this research can act as a model study for other efforts that are attempting to intervene in wildlife disease transmission cycles by developing oral bait application programs, e.g., European badgers (*Meles meles*) and bovine TB (*Mycobacterium bovis*) (Gormely et al. 2017; Gowtage et al. 2017), as well as to allow insight by comparing the idiosyncrasies of different pathogen systems, e.g., the rabies virus and endangered Ethiopian wolves (*Canis simensis*) (Sillero-Zubiri et al. Sillero-Zubri et al. 2016).

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