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Exploring and Mitigating Plague for One Health Purposes

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Abstract

Purpose of Review—In 2020, the Appropriations Committee for the U.S. House of Representatives directed the CDC to develop a national One Health framework to combat zoonotic diseases, including sylvatic plague, which is caused by the flea-borne bacterium *Yersinia pestis*. This review builds upon that multisectoral objective. We aim to increase awareness of *Y. pestis* and to highlight examples of plague mitigation for One Health purposes (i.e., to achieve optimal health outcomes for people, animals, plants, and their shared environment). We draw primarily upon

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examples from the USA, but also discuss research from Madagascar and Uganda where relevant, as *Y. pestis* has emerged as a zoonotic threat in those foci.

Recent Findings—Historically, the bulk of plague research has been directed at the disease in humans. This is not surprising, given that *Y. pestis* is a scourge of human history. Nevertheless, the ecology of *Y. pestis* is inextricably linked to other mammals and fleas under natural conditions. Accumulating evidence demonstrates *Y. pestis* is an unrelenting threat to multiple ecosystems, where the bacterium is capable of significantly reducing native species abundance and diversity while altering competitive and trophic relationships, food web connections, and nutrient cycles. In doing so, *Y. pestis* transforms ecosystems, causing "shifting baselines syndrome" in humans, where there is a gradual shift in the accepted norms for the condition of the natural environment. Eradication of *Y. pestis* in nature is difficult to impossible, but effective mitigation is achievable; we discuss flea vector control and One Health implications in this context.

Summary—There is an acute need to rapidly expand research on *Y. pestis*, across multiple host and flea species and varied ecosystems of the Western US and abroad, for human and environmental health purposes. The fate of many wildlife species hangs in the balance, and the implications for humans are profound in some regions. Collaborative multisectoral research is needed to define the scope of the problem in each epidemiological context and to identify, refine, and implement appropriate and effective mitigation practices.

Keywords

Plague; *Yersinia pestis* ; United States; Flea; Invasive species

Introduction

In 2017, the Centers for Disease Control and Prevention (CDC), U.S. Department of Agriculture (USDA), and U.S. Department of the Interior held a "One Health Zoonotic Disease Prioritization Workshop for the United States." Plague, caused by the flea-borne bacterium *Yersinia pestis*, was prioritized as a zoonosis of national concern. Similarly, the Government of Uganda, CDC, U.S. Agency for International Development, and Preparedness and Response Project identified plague as a zoonosis of national concern in Uganda [1]. Previously, the World Health Organization described plague as a significant re-emerging zoonotic threat in Madagascar [2]. In all cases above, partners (from federal, state, local, tribal, and territorial groups), non-profit and private sectors, and the public were invited to collaborate on projects aiming to increase the understanding of plague ecology and mitigation measures. A greater understanding of the impacts of *Y. pestis* on ecosystem function and integrity, and interactions with multiple stressors, including climate change, land use, and biodiversity loss, should facilitate efforts to mitigate plague for One Health purposes (i.e., to achieve optimal health outcomes for people, animals, plants, and their shared environment) [3]. This review builds upon that multisectoral objective.

A Brief History of Plague and Its Introduction to North America

From an evolutionary perspective, *Y. pestis* (Enterobacteriaceae) might be considered a newly evolved pathogen [4]. It adapted to flea-borne transmission only ~ 3000–6000

years ago [5]. Most evidence suggests *Y. pestis* originated in Asia [6] and subsequently spread broadly to become a scourge of human history across much of Earth [7]. Here, we concentrate on *Y. pestis* in the Western US, where the pathogen is classified as a tier 1 biological agent on the U.S. Health and Human Services and USDA Select Agents and Toxins list. Since, in recent decades, the majority of human plague cases are reported from East and Central Africa and Madagascar [8, 9], we also draw upon research from Madagascar and Uganda for a more encompassing current view of the bacterium's far-reaching influence.

In the early 1900s, *Y. pestis* was introduced to North America on trading ships carrying flea-infested rats to seaports of Louisiana, Texas, California, and Washington [10, 11]. Continued introductions and brief associations with commensal rats and fleas were mostly eliminated through inspection and sanitation of quarantined wharf ships and urban sanitation/rodent control [12]. In 1903, health researchers in California suspected that *Y. pestis* was present in California ground squirrels (*Otospermophilus beecheyi*), and in 1908, the pathogen was also found in peridomestic rats, other free-ranging rodents, and flea vectors [13, 14]. Eradication of *Y. pestis* proved to be difficult to impossible due to its presence in multiple host and flea species [7, 10, 15–17]. *Y. pestis* quickly naturalized itself among native mammal and flea species of the Pacific coast and interior California [18]. Over time, *Y. pestis* invaded areas > 2000 km eastward, expanding to multiple regions and ecosystems. Mammalian hosts, flea vectors, soil characteristics, weather, and climate played influential roles in expansion to the 100th meridian in the USA [19–23]. Similar scenarios of maritime *Y. pestis* invasion apply to its invasion of Africa [8, 24].

In a seminal book on ecological invasions, Elton [25] describes the spread of *Y. pestis* in the Western US as akin to invasions by other introduced organisms. Kugeler et al. [26] characterized three distinct eras of human plague in the USA: common but restricted outbreaks occurring in populous Pacific port cities from 1900 to 1925, rapid geographic expansion among wildlife with a falling number of human cases from 1926 to 1964, and sporadic annual human cases, primarily in the rural Southwest combined with continued spread among wildlife from 1965 to 2012 (a trend continuing today, with an annual average of seven confirmed human plague cases). The scenario is different in other areas. From 2006 to 2015, about 97% of reported plague cases (11,247 of 11,598) were reported from Madagascar, the countries of Democratic Republic of the Congo (DRC), Tanzania, and Uganda [8, 9, 27].

Plague Epidemiology

Yersinia pestis remains a significant hazard to human health. Following the onset of symptoms, septicemic and pneumonic plagues are almost 100% fatal within 1 to 4 days without appropriate antimicrobial treatment [28, 29]. With early detection and diagnosis, some treatment protocols are highly effective (e.g., streptomycin) [7]. Strains of *Y. pestis* carrying resistance plasmids, or strains capable of acquiring resistance plasmids via horizontal gene transfer from other Enterobacteriaceae, remain an enduring threat [30–32]. Likewise, the emergence of more adaptive changes is anticipated due to natural selection and, perhaps, artificial experimentation in laboratories [33–35].

Ecological Consequences of Plague

Globally, *Y. pestis* transmission imposes extraordinary ecologic and evolutionary consequences. *Yersinia pestis* mostly circulates among rodents and their fleas, but there is potential for spillover to several sympatric mammal species including carnivores, lagomorphs, and insectivores such as Eulipotyphla, raising concerns for wildlife conservation [36]. The bacterium can infect and kill nearly all susceptible mammals [6, 36, 37] as it spreads rapidly during occasional but repeated epizootic outbreaks [38–40], colonizes new habitats [8, 19], and persists and kills hosts between epizootics [41–46]. *Yersinia pestis* has a demonstrated ability to transform ecosystems in the Western US by reducing native species abundance and diversity, altering competitive and trophic relationships, undercutting food web connections, distorting nutrient cycles, reducing ecosystem resilience, and depopulating imperiled species [18, 36, 38, 48]. As discussed 20 years ago [36] and still applicable today, *Y. pestis* has received little attention in ecological reviews of non-native organisms (see [49] for a recent exception). New research suggests *Yersinia* murine toxin (Ymt) facilitates spillover among a variety of mammals, highlighting opportunities for ecological disruptions [50]. Earlier *Y. pestis* strains lacking Ymt may have circulated mostly among brown rats (*Rattus norvegicus*) and their fleas [50]. Acquisition of Ymt via horizontal gene transfer [51] expanded the range of hosts considerably [50] and enhanced bacterial survival in fleas [52], helping *Y. pestis* to become a sweeping threat.

We view *Y. pestis* as an influential ecological entity of conservation concern and One Health importance [18, 36, 42, 47, 48, 53–57]. In this review, we aim to raise awareness of *Y. pestis*. We discuss the following topics, with citations and case examples for illustration: (1) descriptions of epizootic and enzootic plague manifestations, (2) mechanisms of *Y. pestis* transmission by fleas and the evolution of hypervirulence to mammalian hosts, (3) “shifting baselines syndrome” caused by *Y. pestis*, and (4) an update on methods and tools for plague mitigation. We conclude by briefly discussing the need for more research on plague across varied ecosystems.

Epizootic and Enzootic Plague

The literature commonly lacks explicit definitions of ecological phenomena associated with plague, which may hinder scientific progress. In this review, we consider *Y. pestis* transmission rates to occur along a continuum. We have defined epizootic plague (mainly in studies of prairie dogs, which are highly susceptible) as outbreaks resulting in the deaths of ≥ 90% of hosts in a given population over a defined geographic area and within a short time span (often months; e.g., [50]). In a dichotomous classification, enzootic plague includes all slower *Y. pestis* transmission rates affecting lesser proportions of hosts [50, 54] often on smaller spatial scales and over longer time intervals. Definitions may vary by region or local rodent community, particularly in regions with species thought to be less susceptible to *Y. pestis*, and context-specific definitions are perhaps useful. This practical classification of *Y. pestis* transmission is defined by differential mortality with spatial and temporal limitations. In this sense, epizootic plague defines the high mortality end of a spectrum and enzootic plague encompasses a large range of lesser transmission and host mortality rates [58]; what is considered enzootic conditions in some regions may be considered epizootic in others.

Epizootics as we have defined them in prairie dogs, for instance, might be rare or absent in some mammal communities [58], and perceptions may lead to differing mitigation strategies. From a public health perspective, for instance, the threshold for epizootic transmission (and therefore increased risk of transmission to the public) may be much lower than for prairie dog systems. In the Sierra Nevada Mountains of California, numerous rodent species of variable susceptibility are involved in the enzootic maintenance and epizootic transmission of *Y. pestis*. Epizootic mortality (as defined here) is rarely detected partly because of complex variations in rodent density, diversity, and susceptibility (and other factors), but any transmission significantly above the baseline is considered epizootic and may need to be mitigated to decrease a risk of transmission to the public.

One of the most striking aspects of *Y. pestis* is its ability to spread explosively during epizootics [55]. These generative, fulminating events [59] kill enormous numbers of susceptible animals in an area, or multiple areas connected epidemiologically, sometimes in quick succession, for instance within days, weeks, or months [14, 39]. These epizootic periods represent times when humans are at greatest risk of acquiring plague infection. In addition, at least some *Y. pestis* transmission and host mortality can occur during longer periods of enzootic plague, when a lack of obvious mortality in some cases makes it seem as if *Y. pestis* has disappeared [55]. The bacterium actually persists or is maintained in a "plague triad" including hosts and their fleas [41] with potential roles for soils, amoebas, and other factors in bacterial maintenance [55]. How *Y. pestis* persists during enzootic periods and what triggers transitions to epizootics are debated; adaptive strategies for *Y. pestis* to persist during enzootic periods and to spread rapidly during epizootics were reviewed previously in the literature [60, 61]. Although the mechanism by which *Y. pestis* persists during inter-epizootic periods is largely unknown, from a public health perspective, early recognition of plague epizootics is paramount to reducing plague morbidity and mortality.

In the plague literature, host species have sometimes been characterized as enzootic "maintenance" and/or epizootic "amplifying" hosts [62]. Effectively, *Y. pestis* might be maintained by sustained transmission among partially resistant enzootic hosts and their fleas and occasionally spread to more highly susceptible epizootic hosts that, along with their fleas, allow for *Y. pestis* amplification and epizootic or sustained enzootic spread. Although this dichotomy seems reasonable, evidence for separate enzootic and epizootic cycles is perhaps unconvincing, and epizootics may represent periods of greatly increased transmission among the same hosts and fleas that support *Y. pestis* during enzootic periods [6] (additional review in [60]).

Epizootic outbreaks can be apparent among some conspicuous, susceptible rodents or populations, especially diurnal, colonial sciurids such as prairie dogs (*Cynomys* spp.) and ground squirrels, or rats in urban and rural settings [54, 63]. The outbreaks are sometimes (but not always [64]) accompanied by detection of *Y. pestis* in hosts, carcasses, and/or fleas. In contrast, due to the sequestered activity of enzootic plague, slow declines in host densities are typically not appreciated until late in the process, if at all, and *Y. pestis* is even more difficult to detect [42, 54]. Species declines from enzootic plague are more likely to be

incorrectly attributed to familiar causes such as concurrent habitat destruction, hunting, food scarcity, and climatic events [65].

Ecologists and epidemiologists agree epizootic plague is a real phenomenon, whereas the concept of enzootic plague is debated. Colman et al. [66] suggested confirmation of enzootic plague, as defined here, would require detection of *Y. pestis* with specific PCR assays, particularly those targeting multiple regions of the *Y. pestis* genome (e.g., the *pla* and *F1* genes), in the absence of host mortality of epizootic proportions as defined by ≥ 90% mortality criterion. Tests on multiple targets are important because the *pla* gene is not specific to *Y. pestis*, and the presence of any one marker is not assured. During a 3-year capture-mark-recapture study of 4 prairie dog species on 58 plots in 7 western states [67], *Y. pestis* was positively detected via PCR testing of *pla* and *F1* genes from prairie dog carcasses (16 plot-year cases) and/or fleas (15 plot-year cases) collected from plots lacking epizootic declines (Table 1). Detection in host carcasses was defined as “confirmed plague” [67]. Thus, under Colman et al.’s [66] recommendations, which might be considered stringent given *Y. pestis* must be detected [64, 68, 69], our definition of enzootic plague seems reasonable, even for purported amplifying hosts like prairie dogs. Additional support for the concept of enzootic plague comes from experiments involving vaccination (direct support) and flea control measures and intensive monitoring and testing of fleas and hosts (indirect support) with highly susceptible mammals (prairie dogs [54]; black-footed ferrets, *Mustela nigripes* [42]; woodrats, *Neotoma* spp. [70]; ground squirrels, *Urocitellus* spp.; and yellow-pine chipmunks, *Neotamias amoenus* [57]; see also [21, 45, 71]). Regular serological surveillance of rodents and carnivores, combined with evaluation of other indicators of plague activity (e.g., carcasses, flea data, evidence of burrow abandonment), can provide useful information to determine the suspected magnitude (i.e., enzootic or epizootic) and/or extent of plague activity in an area [43].

Put simply, accumulating evidence demonstrates that flea-borne *Y. pestis* can actively kill hosts in the presence or absence of epizootic outbreaks regardless of how epizootic is defined [45, 72]. This general concept is not new (e.g., [73]), and experiences in California demonstrate that it is not uncommon to see mortality (e.g., *Y. pestis* positive host carcasses) in highly and moderately susceptible rodent species without evidence of obvious population declines [43].

Flea-Borne *Yersinia pestis* Transmission and Hypervirulence

Generally speaking, fleas are a “key” to *Y. pestis* transmission [17, 74–78], though other modes of transmission occur (e.g., inhalation of respiratory droplets or consumption of infectious carcasses [6, 22]). At least half of the *Y. pestis* life cycle occurs in the flea, which is another site of refuge, replication, gene sharing, and adaptation [77, 78]. Multiple lines of evidence demonstrate that flea-borne transmission predominates, particularly with rodent hosts [4, 76, 79–81]. Field experiments during enzootic and epizootic periods are revealing; in many cases, if flea populations are controlled with the use of insecticides, *Y. pestis* transmission is reduced or eliminated, thereby retaining or increasing host survival and population densities [42, 47, 54, 57]. For more on this topic, see also [82, 83].

There are two main mechanisms of flea-borne *Y. pestis* transmission [4]. The first mechanism, termed early-phase transmission [84], can occur when a newly infected flea next feeds on a naïve host. In this scenario, within a few hours after fleas ingest blood from a host with high numbers of *Y. pestis*, the bacteria coalesce into multicellular aggregates that localize to the proventriculus, a valve in the flea foregut [76, 85]. These forming bacterial masses can be sufficient to interfere with blood flow into the midgut during the next feeding event, resulting in backflow of blood mixed with dislodged *Y. pestis* into the bite site [76, 85]. This early transmission phenomenon following a short extrinsic incubation period (≤ 4 days post-infection) was originally called mass transmission because it depends on several infected fleas feeding simultaneously on the same host, though early-phase transmission has also been demonstrated for a single flea [86–89]. It was long assumed to be due to mechanical transmission via contaminated mouthparts. However, *Y. pestis* survives for only a few hours on flea mouthparts [90], and so is probably nonviable by the next feeding attempt. Several lines of evidence suggest that the early-phase mechanism involves regurgitation from a fouled foregut [76, 85]. Early-phase transmission potential is significantly lower in subsequent feeds [60, 91], presumably because the initial proventricular obstruction is transient; incoming blood during the first post-infection feed eventually flushes most of the bacterial mass out of the proventriculus back into the midgut [4, 16, 88]. Thus, infectiousness typically wanes over the first few days following the flea's infectious feeding on a highly bacteremic host and may not recur unless the flea takes another infectious blood meal [60, 91].

The second phase of transmission ensues after *Y. pestis* establishes a cohesive biofilm in the proventriculus that is refractory to being flushed back into the midgut during blood feeding. This mode is referred to as proventricular biofilm-dependent transmission or, more familiarly, the "blocked flea model" of transmission [92]. As the biofilm grows and consolidates, it interferes with normal blood feeding and eventually completely blocks the passage of blood into the midgut. Complete blockage typically does not develop until 7 to 21 days or later after infection but can occur as early as 5 days [4]. Blocked fleas are unable to feed to repletion, if at all, but persistently probe and strenuously attempt to feed throughout the few days before they starve to death [92]. The altered, sustained feeding behavior of a blocked flea is a significant multiplier of transmission probability [4].

Unlike many arthropod-borne pathogens, which rely on a single vector species, *Y. pestis* is a generalist, able to infect and be transmitted by many different flea species via the mechanisms described above. The transmission potential of its many different flea vector species varies considerably, which is evident for both modes of transmission [16, 93]. This, together with the varying degrees of susceptibility of its many different wild rodent hosts, contributes to the complex ecology of plague. Notably, some important flea vector species do not develop proventricular blockage readily, leading to proposals that early-phase transmission is more important in some host populations (reviewed recently in [94]). Quantitative estimates of blockage rates have been based on different experimental conditions, making comparisons problematic and sometimes leading to discordant conclusions [93]. Chronic infectivity and subsequent blockage are sensitive to infectious dose and blood source [95]. Furthermore, the relative importance of early-phase vs. blockage-dependent mechanisms following a single infectious blood meal has yet to

be systematically evaluated for any flea species. These significant unknowns merit further research [16].

Nonetheless, both modes of transmission are fairly inefficient requiring a large number of fleas to sustain epizootic transmission [84, 96]. During epizootics, as hosts die of infection, the average number of fleas per remaining host typically increases [58], thus increasing the efficiency of transmission during both phases of infection. During both enzootic and epizootic periods, the need for blocked fleas to attempt multiple blood feeding opportunities increases the overall rates of transmission by individual fleas. Together, early phase and blocked flea transmission combine to extend the infectious period of individual infected fleas, but the rate of *Y. pestis* spread in a mammal population or community is dependent on contact rates between fleas and hosts.

Plague endemicity and transmission rates might be explained by host and flea diversity, for instance with multiple flea species, of varying host preferences, facilitating persistence and transmission [17]. Moreover, flea physiology and feeding preferences may influence local transmission rates [4]. Differences in digestive tract physiology, foregut anatomy, and feeding frequency likely contribute to the varying degrees of vector competence among flea species [16, 88, 93]. Recently, it has been recognized that the source of host blood affects the prevalence of infection and *Y. pestis* loads in fleas [97]; subsequent work showed that the biochemical characteristics of host blood is important, independent of any factors intrinsic to the flea [95]. Host blood with a poorly soluble hemoglobin molecule, such as rat and guinea pig blood, is digested more slowly by fleas and correlates with a phenomenon termed post-infection esophageal reflux [95, 97]. When fleas are infected using rat blood, the proventricular is colonized more aggressively and infected blood is found in the esophagus within a day after an infectious blood meal [95]. In this case, the proventricular obstruction is more resistant to dislodgement, and *Y. pestis* is already present in the esophagus, which can enhance regurgitative early-phase transmission [95]. Because post-infection esophageal reflux helps to stabilize proventricular colonization, *Y. pestis* may quickly develop a protective biofilm, producing overlap with the second phase of transmission in fleas.

Fleas are integral to the process, but they are not especially efficient at transmitting *Y. pestis* [96]. In many cases, the dose of *Y. pestis* needed to infect an individual flea is high (ID_{50} = 4.8×10^3 *Y. pestis*), at least partly because *Y. pestis* does not adhere to or invade the midgut epithelium and may be eliminated rapidly through peristalsis and excretion in flea feces [96]. Consequently, it seems fleas must feed on a mammalian host with terminal septicemia to become infected (e.g., > 10^8 *Y. pestis*/ml peripheral blood [96]). Moreover, if flea infection occurs, the number of *Y. pestis* colony-forming units (CFUs) transmitted per individual blocked flea bite is highly variable (0 to > 1000 CFUs and transmission rate of ~ 40 to 50% for *Xenopsylla cheopis* [96]) even though infected fleas may contain 4.8×10^5 or more *Y. pestis* organisms. The transmission rate of individual early-phase fleas infected using rat blood is ~ 5 to 10% [94]; the number of CFUs transmitted per flea has not been determined but appears to be even lower than for blocked fleas [93, 95]. Inefficient flea infection and transmission of few *Y. pestis* (or fewer than needed) reduces transmission efficiency.

Poor flea vector efficiency coupled with the need for fleas to imbibe highly bacteremic blood to reliably become infected [77, 98] may provide the evolutionary explanation for *Y. pestis*' high virulence (i.e., host killing capacity [96, 99]). Reliance on the blood-feeding flea for transmission has naturally selected for *Y. pestis* strains that produce an aggressive infection and high virulence in mammals [76, 100]. Host deaths encourage live infectious fleas to quest for new hosts, resulting in more host deaths, host-seeking by more "flocking" fleas, and further host deaths, and so forth, perpetuating *Y. pestis* transmission and epizootic spread in a positive feedback cycle [58] with varying degrees of plague mortality among host species and populations of differing density/susceptibility and flea communities/densities.

In some cases, as an epizootic subsides, plague dynamics transition into the largely occult, enzootic phase, during which *Y. pestis* is perhaps "hiding in plain sight," is often undetected [42, 54], even with targeted surveillance [101], while killing hosts or even "cooling off" when few to no live fleas or (perhaps preferred) hosts are available (e.g., persisting in soils, or even plants or amoebas, or host carcasses, or moving elsewhere on the landscape [55, 60, 61, 102–105]. Inapparent, latent long-term infections have often been documented within rodent populations, and fleas may also assist in maintaining prolonged prevalence of *Y. pestis* in locales [60, 61, 106, 107]. Where and how *Y. pestis* persists during such periods is poorly understood and a top research priority. When conditions allow in some host species or mammal communities, or a trigger is pulled or a match is sparked, so to speak, yet another epizootic event may ensue and endure until conditions dampen transmission rates back to enzootic proportions (the latter of which might actually be the modus operandi of *Y. pestis* [58]). In essence, the effects of *Y. pestis* are perhaps unrelenting. Yet, human perceptions of plague's far-reaching influence on natural ecosystems may shift over time.

Yersinia pestis and Shifting Baseline Syndrome

"Any measure of change in a natural ecosystem must be grounded upon a well-defined natural standard or benchmark against which potential changes are measured and evaluated in relation to natural variation in the system" ~ Dayton et al. [108].

The definition of a meaningful benchmark of abundance or distributions is perhaps impossible for *Y. pestis*-susceptible mammal species. Humans had already caused significant ecologic change before *Y. pestis* invaded the Western US, for instance, and the invasion itself preceded collections of benchmark data for many species. Thus, the effects of plague can only be measured relative to an already altered state. This sort of scenario allows for shifting and sliding ecologic benchmarks and baselines.

Pauly [109] was perhaps the first scientist to use the term shifting baseline syndrome, in relation to fisheries, defining the syndrome as occurring because each new generation of fisheries scientists accepts as a baseline the conditions that occurred at the beginning of their careers, and they use this baseline to evaluate changes. As ecosystems change over time, past ecosystem states are sometimes forgotten. Consequently, the baseline used shifts, perhaps to a more and more degraded state [110].

Yersinia pestis may be contributing to a shifting baseline syndrome. In this context, we discuss prairie dogs, which can serve a noticeable role in amplifying *Y. pestis* in the grasslands of western North America [18]. Independent estimates place total prairie dog occupancy around 40 million ha in the early 1900s [111]. *Yersinia pestis* was detected among prairie dogs in 1932 [112] and thereafter devastated their populations [18]. The impacts to prairie dogs have been profound [111]. Admittedly, however, estimates of prairie dog densities before European settlement and the invasion of *Y. pestis* are incomplete [113].

Prairie dogs are classified into two subgenera, each ecologically unique [114, 115]. Neither subgenus exhibits functional resistance to *Y. pestis* [36, 116]. Opportunities for *Y. pestis* transmission might be reduced in colonies of prairie dogs from the "white-tail" subgenus *Leucocrossuromys* (*Cynomys gunnisoni*, *Cynomys leucurus*, and *Cynomys parvidens*) which typically occur at lower densities, and in more fragmented distributions within colonies, than prairie dogs in the "black-tail" subgenus *Cynomys* (in particular, black-tailed prairie dogs [117]). If a host species maintains low densities and patches of hosts are spatially isolated, *Y. pestis* may spread more slowly [117], suggesting *Leucocrossuromys* prairie dogs would experience plague epizootics less frequently or at different scales. Similar arguments have been proposed for rodents on other continents [118, 119].

Nevertheless, members of the white-tail subgenus of prairie dogs are substantially affected by *Y. pestis*. For example, between 1984 and 1997, plague nearly extirpated Gunnison's prairie dogs (*C. gunnisoni*) from the Moreno Valley, New Mexico [117], and between 1941 and 1977 plague eliminated them from South Park, Colorado [120]. *Yersinia pestis* has persisted in white-tailed prairie dogs (*C. leucurus*) near Meeteetse, Wyoming, since at least 1984 or 1985 [36]. *Yersinia pestis* is repeatedly detected (during targeted studies) in colonies of Utah prairie dogs (*C. parvidens*) throughout much of their range and is considered one of the primary threats to this listed species [18, 54].

If prairie dogs or other mammals persist on landscapes under the influence of *Y. pestis*, their colonies (or subpopulations) often become smaller and more isolated and may exist as "metapopulations" [121, 122]. Occupancy patterns may include extinctions followed by recolonization of some, but not all sites in a manner consistent with plague [123, 124]. The white-tailed subgenus of prairie dogs is often characterized as having patchy distributions of populations at low densities compared to black-tailed prairie dogs, but we cannot assess whether this phenomenon was historically normal, or a result of decades of persistent plague. Before *Y. pestis*' arrival, both *Leucocrossuromys* and *Cynomys*, while ecologically different, might have occurred at similar densities and distributions in regions with comparable rates of primary production and predation [125].

The historic structure and functioning of plague-affected ecosystems can be partially restored if the disease is effectively and operationally managed for conservation purposes [125]. However, shifting baseline syndrome and the resulting moving target, sometimes of reduced expectations [108], may stimulate proposals for management actions that maintain an altered state. In some cases, it has been argued that mammals of the Western US, including prairie dogs, should be managed in a manner that promotes metapopulation structure, because metapopulations sometimes persist under plague pressure (depending

on specific details of those metapopulations [121]). For instance, focus areas of mammal conservation might be identified as areas with sufficient numbers and distributions of colonies to be considered a metapopulation. At least two points are important to the application of such an approach:

1. Metapopulation approaches in this context assume that the underlying subpopulations operate independently [126]. As discussed in the next section, climatic patterns create spatial synchrony in the occurrence of plague epizootics, sometimes over broad landscapes in the Western US [40, 127], thereby forcing multiple mammal subpopulations or populations into plague outbreaks during the same general timeframe [61, 128–130]. This synchrony limits the applicability of the metapopulation concept when used in the context of plague mitigation. The fates of mammals in neighboring areas are often correlated [129, 131, 132].

2. Even if mammals can sustain metapopulations under pressure from *Y. pestis*, their densities can be chronically reduced by plague [36, 54, 133]. Repeated bouts of extinction and recolonization may allow for continued taxonomic representation of such mammal species, but the corresponding habitat fragmentation, continued oscillations in abundance, and chronically struggling subpopulations subjected to enzootic plague can inhibit them from serving their ecologic functions, sometimes as keystone species or ecosystem engineers [18, 134].

There are also flaws inherent to implied (or unintentional) arguments for the creation of fragmented metapopulations of mammals at low densities. These arguments fail to recognize that in many cases, spatial isolation does not necessarily reduce the vulnerability of mammalian hosts to *Y. pestis* [120, 121, 128, 135] nor do low host densities [58]. In fact, with prairie dogs, evidence suggests *Y. pestis* persists on or very near their colonies, perhaps eliminating any spatial isolation. Indeed, once *Y. pestis* invades an area, it appears to locally persist in many cases [44, 46] but can remain undetected. It is also likely that the inter-colony habitats are occupied by other rodent species that may maintain plague. Moreover, habitat constraints reduce connectivity among subpopulations, thereby reducing the rate at which mammals recolonize extirpated sites, especially in the case of smaller and relatively sedentary species of limited dispersal capabilities [126]. There is evidence to suggest some rodent subpopulations may evolve some, or perhaps locally strong, resistance to *Y. pestis* [136–138], but opportunities for such adaptive responses are reduced for less dense and more genetically isolated subpopulations [116]. Furthermore, isolated populations are more vulnerable to extirpation due to additional threats such as unusual weather patterns, fire, and high predation pressure, which are occurring with increasing frequency and intensity as the climate changes [126].

The metapopulation and isolation strategies illustrate contradictions and trade-offs. Plague converts some mammal populations (e.g., of some rodents) into fragmented metapopulations, thereby creating smaller, more isolated subpopulations that are chronically affected, and in some cases, extirpated by *Y. pestis* [47, 54, 123, 124, 132]. In fact, patchy distributions of highly *Y. pestis*-susceptible territorial hosts might even favor long-term *Y. pestis* maintenance [45, 70, 124, 139].

Integrated Plague Mitigation Toolbox

Generally speaking, plague might be managed under an Integrated Pest Management strategy, with *Y. pestis* defined as the pest [140]. Ecological disruptions caused by *Y. pestis* and the complexity of interactions make simple silver-bullet solutions mostly unattainable. Available methods and tools for plague mitigation are numerous, and their efficacy varies by context, sometimes widely. In any given system, plague mitigation is facilitated by an increased understanding of the particular hosts and fleas involved [141–147].

The goals of plague mitigation vary widely. From a public health perspective, the primary objectives are to recognize epizootics prior to the onset of human cases, or to understand where humans were exposed to *Y. pestis* to prevent subsequent infections, primarily through a combination of education, habitat manipulation, and limited use of insecticides for flea control [41]. In Uganda, for instance, where human health is of primary interest, the goal typically is not to eradicate *Y. pestis* or even to prevent epizootics, but rather to disrupt transmission to humans [147]. In the Western US, *Y. pestis* has a vast geographic range and surveillance is commonly focused on areas where human contact with infected fleas and rodents is elevated (e.g., popular campgrounds [43, 148]).

Following the recognition of increased transmission, an epizootic among rodents, or human plague cases, public education assists in increasing awareness of *Y. pestis*, transmission pathways, rodent die-offs, and effective mitigation strategies that prompt people to alter their behavior in ways to reduce exposure [147, 149, 150]. Community education also helps to emphasize the importance of seeking care rapidly if plague symptoms occur [151, 152]. Including One Health messages can improve public health outcomes and conservation ethic [153]. Vector control is implemented on a limited basis when the potential for human contact with infectious fleas justifies use [149, 154]; for instance, in California, flea control is typically conducted when *Y. pestis* has been detected in areas with increased human risk (e.g., campgrounds) and flea densities are greater than one flea per rodent. Effective antibiotics are available for human treatment, notwithstanding the importance of quick diagnosis, response, and treatment [7, 155]. Improvements in spatial and climate modeling and mapping of potential exposure sites aid in targeting limited public health resources dedicated to plague prevention [156].

Rodent control is not commonly implemented as a means of plague control. As discussed previously, thinning of native rodent populations is unlikely to be effective in plague mitigation. In fact, this sort of approach has proven ineffective many times [155]. However, thinning of rodent populations might be deemed an appropriate means of preventing human exposure to infected rodents and fleas, particularly in domestic or peridomestic settings where invasive rodent species pose multiple risks to human health (e.g., *Rattus* spp.: [157, 158]) or at recreational sites (e.g., campgrounds). Even so, multiple trap types may be required to capture and remove (or kill) rodents [147, 158] and connectedness of the landscape might prove to be an impediment [159]. Moreover, rodent control without prior or concurrent flea control encourages infectious fleas to quest from carcasses to susceptible hosts and, discouragingly, thinning of rat densities may lead to increased host movement, facilitating *Y. pestis* spread and higher disease prevalence [7]. Habitat

modification, including reducing food or refuge for rodents in and around human habitations and public use areas (e.g., campgrounds and trails), is often recommended as a prevention strategy [28]. Judicious application of insecticides (e.g., limiting application to areas when and where epizootics have been confirmed) can limit costs and potentially slow the evolution of insecticide resistance in fleas; targeting such response activities may be guided by monitoring rodent populations for epizootics [150].

In the context of wildlife conservation, the goal of plague mitigation is to prevent epizootics and dampen or eliminate enzootic transmission [47]. Effective mitigation necessitates targeted intervention with insecticides or vaccines for individual and/or population protection. Injectable F1 or F1-V (*Y. pestis* antigen) vaccines have shown good efficacy in target species [42, 57, 70]. Unfortunately, such applications remain time and labor intensive for large-scale use and reagents are limited in supply. Hence, these vaccines have been mostly limited to experimental uses, such as proof-of-concept studies [160], but also were very effective for targeted investigations of plague effects on host populations [42, 57, 70]. F1-V fusion protein, however, has been used widely to protect black-footed ferrets [42, 161] and requires trapping and injection which can be effectively completed, for instance as demonstrated by annual trapping and vaccination efforts at a ferret reintroduction site in South Dakota [162].

A new raccoonpox-vectored oral bait vaccine that stimulates production of similar antigens has thus far shown limited promise in protecting prairie dogs from plague [47, 67, 69, 163]. Seasonality in the timing of oral baiting and other factors may have partially influenced the results [164]. Also, attaining sufficient overall immunity in the field may be unlikely in some systems, because the vaccine is ineffective with plague-susceptible deer mice (*Peromyscus maniculatus*), which are largely ubiquitous [165] but with potentially varying roles in plague ecology across the Western US [166]. In addition, only a portion of target rodent populations become vaccinated due to imperfect bait uptake and other factors [167]. Finally, new additions of nonvaccinated juveniles occur in years with successful reproduction [69].

When using host plague vaccines, protection relies on hosts developing functionally protective antibodies against *Y. pestis* antigen(s). Assuming the vaccine has no effect on flea populations (as found, for instance, with prairie dogs and the oral vaccine noted above [69, 168]), flea populations may remain unrestrained, which may allow for continued *Y. pestis* transmission to unvaccinated hosts (which could remain abundant). To illustrate this point, consider the oral vaccine experiment noted above. Over 5000 flea pools combed from live-trapped prairie dogs were tested for *Y. pestis* via PCR assays (*pla* and *F1* genes). In total, 39 of 64 (61%) *Y. pestis*-positive flea pools were collected from sites treated with the vaccine [168]; overall, *Y. pestis* was more prevalent among flea pools on plots treated with the vaccine than on plots treated with placebo baits (chi-square $P = 0.0782$), an interesting trend given inherent difficulties with *Y. pestis* detection noted previously.

Investigating a wide range of potential plague control methods could support the goal of meeting unique applications and challenges, with economic, social, public health, and ecological sustainability as important considerations. Arguably, the most effective approach to plague mitigation may involve flea vector control. Even small decreases in vector survival

and abundance can cause large reductions in transmission [169]. Chemical insecticides have been employed for flea control with varying success in varied applications historically [24, 170–172]. In some cases, these insecticides are mainstays of public health and conservation action plans [28, 162, 173]. For applications in wildlife habitat over large areas, the timing [174], dose [175], and duration of efficacy [176] can affect costs and remain important considerations. Adding to these concerns is recent evidence demonstrating that repeated applications of insecticides can lead to resistance in fleas, manifested as shorter periods of efficacy, leading to increased costs and, in some cases, mammal population losses or limitations on the compounds that can be used effectively to prevent human plague cases [177–179].

Insecticide application methods for rodents historically have included baited insecticide dusting boxes and dispensing tubes, and infusing ("dusting") insecticide directly into burrows [171, 180–183]. Agents proven effective in some contexts include synthetic pyrethroids, organochlorines, and carbamates [54, 154, 184, 185]. Chitin-inhibiting insecticides (fluazuron, pyriproxyfen, and lufenuron) have also been tested on fleas with good initial effect in some cases [186–188] but had little residual action. Recently, fipronil, a GABA receptor antagonist, has gained some favor for field applications in edible bait form [176, 189–193]. Compared to other agents tested, fipronil allows higher initial (1st hour) flea engorgement rates after application, facilitating uptake by, and suppression of, blood feeding adult fleas [194]. Fipronil resistance has not yet been identified in the field (though *Ctenocephalides felis* cat fleas may exhibit some cross-resistance to dieldrin and fipronil [195]). Data suggest fipronil and metabolites excreted in host feces may have prolonged effects on larval flea life stages [176]. In addition to potential mammal toxicity from over-exposure to insecticides, secondary effects to the local biota remain a potential downside of burrow and host applications of chemical insecticides (label specifications and other use limitations help to reduce non-target effects). Additional means of flea control, such as insect pathogenic fungi, may be of value but require further study [140]. With any tool, the scale, scope, and targeted species may dictate the effectiveness of mitigation measures.

Summary and Conclusions

The host range of *Y. pestis* is impressive. A recent (albeit under) estimate included 354 mammal species worldwide, 279 of which are rodents [196]. Epizootics have been documented in many rodent taxa of the Western US (e.g., prairie dogs, chipmunks, woodrats, and ground squirrels [55]). More than half the rodents of conservation concern in North America have ranges overlapping the invasive range of *Y. pestis* [36]. Persistent enzootic mortality is expected for many species (including and in addition to rodents) and has been detected in multiple published experiments (e.g., three prairie dog species [54]; black-footed ferrets [42]; Mexican woodrats, *Neotoma mexicana* [56, 70]; yellow-pine chipmunks, *Neotamias amoenus*; northern Idaho ground squirrels, *Urocitellus brunneus*; and Columbian ground squirrels, *Urocitellus columbianus* [57]). Significantly, there are multiple reasons to believe the effects of enzootic plague were underestimated in these controlled field experiments [57, 70]. In certain areas (e.g., California) where detection of enzootic/epizootic mortality is often cryptic, long-term serological surveillance of rodents

and carnivores is an important tool used by public health agencies to evaluate local/regional changes in *Y. pestis* activity.

The implications of plague could be profound for a variety of host species that play critical roles in *Y. pestis* maintenance and spread, but also susceptible spillover hosts that play less critical roles. For example, spillover hosts might include lagomorphs (e.g., *Sylvilagus* rabbits and *Ochotona* pikas). Ostensibly, the phrase spillover host might seem to suggest the effects of plague are minimal, or even entirely fortuitous for such species. However, persistence of *Y. pestis* in some hosts is not only costly for those hosts but also associated spillover species that are susceptible but perhaps inconsequential to disease maintenance [70]. Low or moderate rates of mortality, even due to enzootic plague as defined herein, may substantially alter ecosystem function and structure over the long term [70].

From a top-down trophic level perspective, *Y. pestis* is a tertiary "predator" [197] that reduces prey biomass for other predators. The bacterium also directly kills a variety of carnivores, with unknown population effects in most cases (e.g., Canadian lynx, *Lynx canadensis* [198]) but with known significant effects in others (e.g., black-footed ferrets [42]). Widespread detection of *Y. pestis* among carnivores is commonly used by state and local public health agencies to inform or direct targeted surveillance activities. Bevins et al. [38] documented *Y. pestis* exposure in 18 wildlife species of the Western US from 2015 to 2018 (44,857 samples), including coyotes (*Canis latrans*), bobcats (*Lynx rufus*), and black bears (*Ursus americanus*), with *Y. pestis* detections in every state of the contiguous Western US.

Y. pestis is an invasive killer of a variety of mammals, and an ecosystem transformer throughout much of the Western US and abroad, with attendant One Health implications [33, 149, 199, 200]. Expanded research is needed to identify and quantify the effects of *Y. pestis* on a variety of host species and populations, to identify the roles of different flea species in plague cycles, and to determine how plague perturbations may cascade or "vortex" through ecosystems [201], causing widespread, unrelenting conservation challenges. In this context, scientists might be considered "detectives" (sensu [202]) and partial "justice" may involve increased recognition and awareness of *Y. pestis* and the devastation and perturbations it causes. Increased awareness may lead to more informative research and effective mitigation measures, favoring a beneficial feedback cycle that counters the destructive, pernicious positive feedback cycles *Y. pestis* imposes on wildlife. Eradication of plague is difficult to impossible, but effective mitigation is achievable. Identification of species and ecosystems negatively impacted by *Y. pestis*, and their unique ecologies, can allow for strategic mitigation and risk reduction approaches aimed at improving the resilience of these populations to this and other population-level stressors. This treatise functions to stimulate thinking and innovation on this front, for the enhancement of individuals, subpopulations, metapopulations, and populations of all species involved, and humans, wildlife communities, and ecosystems broadly.

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Table 1

Prairie dog population responses and levels of suspected *Y. pestis* circulation on plots with *Y. pestis*-positive host carcasses or flea pools during a 3-year capture-mark-recapture study of 4 prairie dog species on 58 plots in 7 western states [67]

Prairie dog population response[a]	Level *Y. pestis* circulation[b]	Sample type tested for *Y. pestis*[c]	No. plot-years *Y. pestis* detected[d]
Increase, stable, or < 50% decline	Enzootic	Host carcasses	5
		Flea pools	10
50–89% decline	Enzootic	Host carcasses	11
		Flea pools	5
≥ 90% decline	Epizootic	Host carcasses	9
		Flea pools	0

[a] Change in catch-per-unit effort (*n* is the number of unique animals captured/number of trap days)

[b] Suspected *Y. pestis* circulation (≥ 90% decline = epizootic, < 90% = enzootic)

[c] Samples tested for *pla* and *F1* genes using PCR

[d] Sampling unit = individual trapping plots by year