Living with plague: Lessons from the Soviet Union's antiplague system

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Zoonoses, such as plague, are primarily animal diseases that spill over into human populations. While the goal of eradicating such diseases is enticing, historical experience validates abandoning eradication in favor of ecologically based control strategies (which reduce morbidity and mortality to a locally accepted risk level). During the 20th century, one of the most extensive plague-eradication efforts in recorded history was undertaken to enable large-scale changes in land use in the former Soviet Union (including vast areas of central Asia). Despite expending tremendous resources in its attempt to eradicate plague, the Soviet antiplague response gradually abandoned the goal of eradication in favor of plague control linked with developing basic knowledge of plague ecology. Drawing from this experience, we combine new gray-literature sources, historical and recent research, and fieldwork to outline best practices for the control of spillover from zoonoses while minimally disrupting wildlife ecosystems, and we briefly compare the Soviet case with that of endemic plague in the western United States. We argue for the allocation of sufficient resources to maintain ongoing local surveillance, education, and targeted control measures; to incorporate novel technologies selectively; and to use ecological research to inform developing landscape-based models for transmission interruption. We conclude that living with emergent and reemergent zoonotic diseases—switching to control—opens wider possibilities for interrupting spillover while preserving natural ecosystems, encouraging adaptation to local conditions, and using technological tools judiciously and in a cost-effective way.

disease ecology | *Yersinia pestis* | USSR history | eradication programs | disease control programs

Zoonoses, diseases transmitted to humans from animals, remain important public health problems, especially in medically underserved, poor populations living in close contact with animals (1, 2). Control of these diseases may be hampered by lack of knowledge about the ultimate source: how the disease is maintained in its wildlife reservoir. Preventing the spillover of zoonoses into nearby human populations can be challenging even when the reservoir species are known, due to the complex ecology of endemic natural disease systems. Plague, caused by the bacterium *Yersinia pestis*, is a classic example of such a zoonotic disease (3). Although we often think of plague as a historical curiosity that was transmitted by rats and fleas, plague is currently active around the world, mainly in persistent endemic foci, and it is primarily a wildlife disease, not one of humans (4). The causative agent *Y. pestis* is susceptible to antibiotics and a vaccine against it exists (5, 6), but plague persists despite determined efforts to eradicate it. The WHO estimates that 3,248 people contracted bubonic plague in Asia, Africa, and the Americas between 2010 and 2015 (7). For over a century, scientists have focused on central Asia and eastern Asia as the ancient homelands of plague, the disease's primary foci. From there, trade routes spread *Y. pestis* around the world, including to the western United States (where plague has now become established in secondary endemic foci).

Endemic plague foci occur in environments as diverse as steppes, meadows, deserts, and high mountain

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ranges, from temperate zones to the tropics. Dozens of different rodent species, many of which dig burrows and form large colonies, serve as reservoir hosts that maintain enzootic plague within these endemic foci (3). *Y. pestis* has been detected in over 280 species and subspecies of fleas associated with rodent colonies in these areas (8). While the factors constraining where plague reservoirs may exist are not fully known (9), certain rodent species appear to be cornerstone hosts for the disease (10). In our current understanding, plague persists within these ecosystems in a continuous exchange of *Y. pestis* between rodent individuals, with fleas as the main vector (11). Plague is generally only present among a small percentage of the individuals within a rodent population but can flare up into epizootics (wild rodent epidemics) (12, 13). When and where such epizootics occur depends on the spatial and seasonal patterns of the host and vector species present (their distribution, breeding season, hibernation, etc.) and the direct and indirect influence of climate fluctuations on the various rodent and flea population densities (12, 14) (Fig. 1).

Under conditions of high rodent and flea density, the bacterium may spread efficiently through rodent populations from burrow to burrow across the landscape into new territories (15). However, when conditions deteriorate and rodent density decreases, the fleas crowd onto the remaining rodents. The flea density per rodent may increase to such high levels that infected fleas spill over to less-preferred hosts (16) such as peridomestic rodents, domesticated mammals, or humans. Humans are usually dead-end hosts, but under certain conditions the disease may spread, either through ectoparasites (17) or via inhalation (pneumonic plague) (18), thus potentially giving rise to human outbreaks of plague. Understanding this complex ecology is crucial to controlling plague and to deciding how to best allocate limited resources to prevent wildlife diseases from spilling over into human populations.

New technologies, such as gene drives or predictive genomic screening, are often touted as a solution to disease problems with the potential for eradication (total elimination of naturally caused human cases) (19, 20). However, setbacks encountered by disease eradication and elimination schemes over the past century—including a large-scale Soviet effort to purge its republics of endemic plague—starkly remind us that many such diseases require long-term multifaceted policies and programs, and even then eradication can fail. However, global campaigns by philanthropists and health organizations to eradicate diseases still capture the imagination, asserting that new technologies are the keys to success (21). The "technological imperative"—applying new technologies (such as genomics) because they are available and exciting—has encouraged eradication thinking for at least a century (22). As Holmes et al. (23) note, however, a reliance on predictive genomic screening is both exorbitantly expensive and potentially ineffective, while more modest goals of screening vulnerable human populations hold much more promise with fewer unintended consequences (such as species extinction and disrupted ecosystems) (24–26). This is not to advocate ignoring new tools; rather, we evaluate them as practical components of disease control systems. For example, landscape genetics methods, which leverage already-available satellite data, track the movements of disease-carrying insects (27–29). This tool works because it is inexpensive, provides data integral to

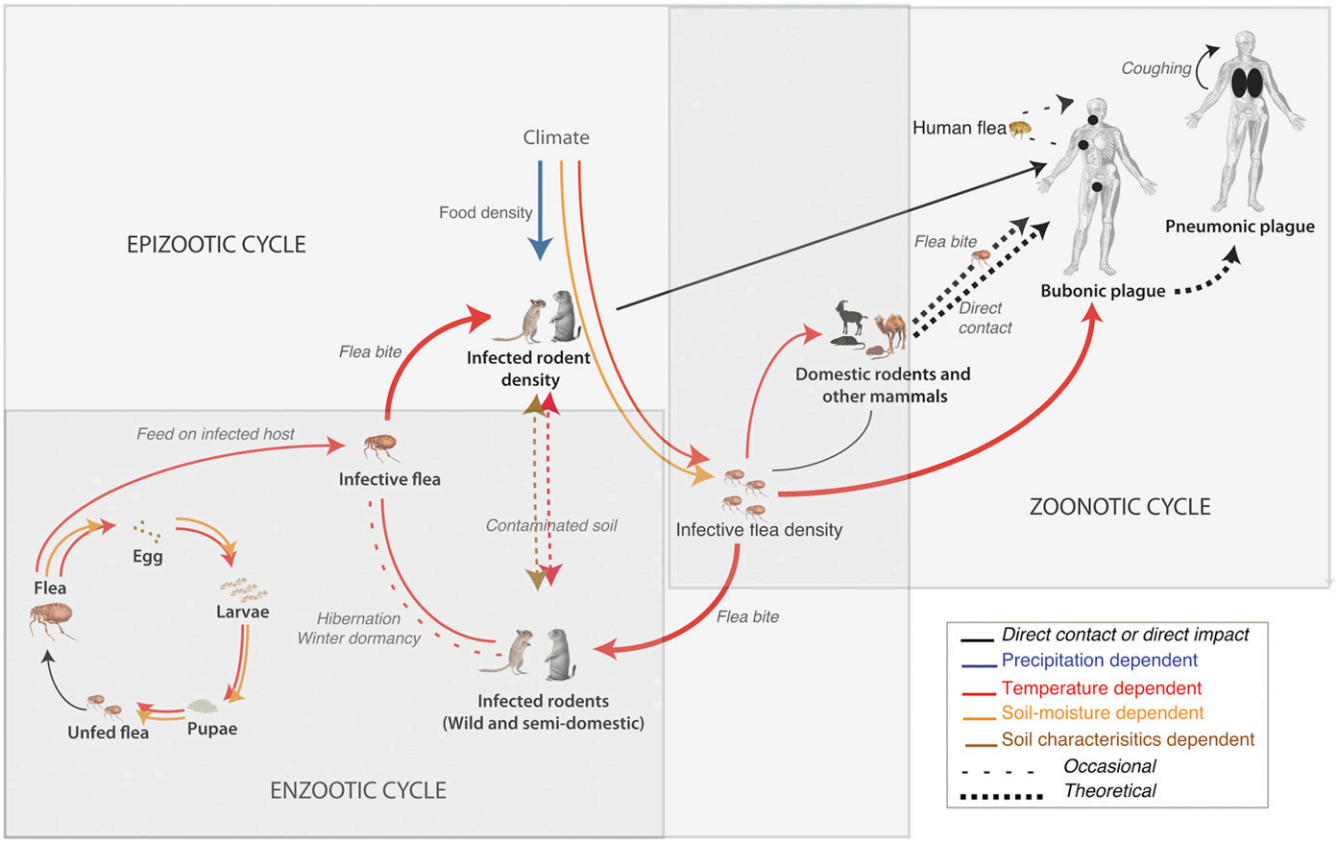

Fig. 1. Influences on plague enzootic, epizootic, and zoonotic cycles. The host–vector–plague system is sensitive to multiple external influences (see the key) in many of the lifecycle steps that are relevant in plague for the transitions from the enzootic to the epizootic and finally the zoonotic cycle. Reprinted with permission from ref. 11, which is licensed under CC BY 4.0.

surveillance and a broader ecological assessment, and does not disrupt ecosystems.

One continually developing technology, vaccination, has been a successful part of control for several wildlife and environmental diseases. However, vaccination has played a limited role in plague control, in part because the most widely used plague vaccines are based on live *Y. pestis* cultures, cause adverse effects in a relatively large proportion of people vaccinated, and at best offer only 10 to 12 mo of immunity (5). While various live plague vaccines have in the past been used, or are still currently in use for routine vaccination of military personnel and some populations living in plague-endemic areas, these vaccines are contraindicated in some subpopulations (immunosuppressed and young children, for example) and revaccination must be performed to maintain immunity (30, 31). Newer molecular-component vaccines, approved for use and being tested in clinical trials (32, 33), may improve this situation, but human vaccination alone will not eliminate or even control plague in endemic areas. Along with safe and efficacious vaccines, ongoing ecological surveillance and intervention as discussed below for plague are the keys to preventing spillover and outbreaks of endemic zoonotic diseases.

Central Asia contains dozens of active plague foci in desert, mountain, and steppe biomes. Plague spillover continues occasionally in these areas. Central Asia is an example of how to live with endemic zoonoses: in this case, maintaining long-term ecological intervention to reduce human infections in the face of plague persistence. The current system derives from the historic Soviet-era Anti-Plague Institute (API) eradication program. In the mid-20th century, thousands of API-directed scientists and workers used the latest chemical technologies and "laborious methods" to study and liquidate populations of plague-carrying rodents, including the great gerbil (*Rhombomys opimus*), midday jird (*Meriones meridianus*) and tamarisk jird (*Meriones tamariscinus*), and jerboas (*Dipodidae* spp.) (34). Plague-infected flea species found on these host animals included *Xenopsylla gerbilli minax, Xenopsylla hirtipes, and Xenopsylla skrjabini* (35). Predator species carrying infected fleas or (ingested) rodents included raptors, owls, snakes (especially *Erix miliaris*), foxes (*Vulpes Vulpes*), and even monitor lizards (*Varanus griseus*) (36–39). Predator species may contribute substantially to the geographic spread of plague (40). The original goal of eradication addressed this complex ecology (and political necessity) by mandating a complete elimination of plague in rodents, predators, fleas, and humans (and often the destruction of rodent and insect populations) over vast areas. However, even this centrally controlled and well-funded campaign failed to eradicate endemic plague permanently.

Even if it had succeeded, this type of large-scale campaign is unlikely to be replicated today given different political configurations, technologies, and priorities. However, the Soviet eradication campaign's enduring legacy is a wealth of ecological knowledge and a system of targeted surveillance and control that has, over time, dramatically reduced human cases in the primary endemic foci of Kazakhstan and other former central Asian Soviet socialist republics (Fig. 2). The Kazakh Scientific Center for Quarantine and Zoonotic Diseases (KSCQZD), the Alma-Ata API's successor, provides a good example of ongoing efforts to control plague in rural areas where people are exposed through habitation, work, or recreation. Restricting humans from traversing or living in such areas is not feasible. Instead, control is better accomplished by monitoring endemic areas, tracking epizootics, and minimizing animal–human transmission where plague-infected animals naturally occur. The KSCQZD's antiplague activities are split into two branches: education and vaccination of at-risk humans and interrupting ecological transmission from infected animals to humans

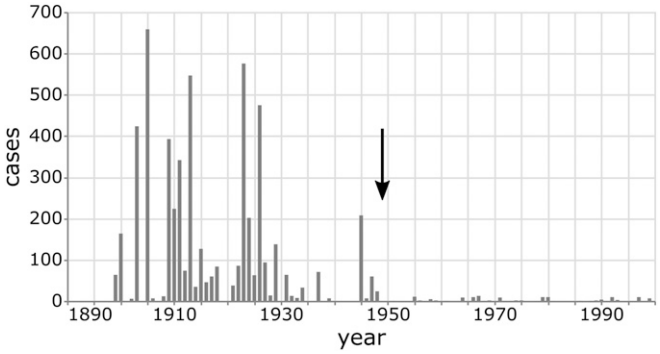

Fig. 2. Reported human plague cases over time in Kazakhstan. Arrow indicates the start of the eradication campaigns in central Asia in 1949, which reduced the number of cases from hundreds to a handful of plague cases per year. The figure is based on data from ref. 31. The inventory of epidemic and epizootic manifestations of plague in the territory of the Russian Federation and nearby areas from 1876 to 2016 [in Russian]. Saratov.

(41). Both depend on ongoing ecological research and on maintaining epidemiological surveillance.

Here we draw on several decades of plague studies, interviews, records kept by scientists from the Soviet APIs (42), and a rare gray-literature newsletter, "Interesting Stories of the Anti-Plague System," that included much unpublished data (43). Together these sources point to how we can best live with plague in the places where it is permanently entrenched, as a model for other endemic zoonoses. Current practices are the result of a historical process during which antiplague strategy shifted from wholesale eradication to plague control. That process enables us to identify the most important ecological factors in plague persistence and to argue against spending scarce resources on expensive technologies that promise to eradicate it. We also briefly compare the descriptive epidemiology and control strategies deployed in central Asia (plague's ancient homeland) with those of the western United States (where *Y. pestis* invaded and became endemic only during the 20th century) (44).

From Eradication to Control: Different Models

Global eradication schemes have had two notable successes (smallpox and rinderpest, both viruses with well-defined transmission pathways and effective vaccines), but eradication has proven elusive for other diseases with more complex ecologies (45). Global public health experts have classified antidisease schemes into categories, from "disease extinction" and "eradication" to "elimination of infection," "elimination of disease," and "control" (46). Control differs from the other categories because it reduces morbidity and mortality to a "locally accepted level," rather than aiming to reduce disease incidence and/or human infections to zero (whether locally or globally) (47). Control has been less attractive because human and animal cases may still occur, continued intervention efforts seem endless and costly, and it does not seize politicians' and funding agencies' attention. However, a brief exposition of an eradication campaign that enjoyed optimal resources and conditions, yet failed, argues forcefully in favor of control over extinction, eradication, or elimination.

Between 1917 and 1991, one of the most extensive endemic plague-eradication efforts in recorded history was undertaken in the Union of Soviet Socialist Republics (USSR) to enable large-scale changes in land use (such as mining and agricultural development). Eradication meant zero human plague cases and eliminating endemic plague by destroying the ecological systems

that enabled *Y. pestis* to survive and circulate in vast regions. These centrally planned eradication campaigns, coordinated by the APIs, began in the 1920s with ecological and serological surveys to identify infected and susceptible rodent host populations and predators (48–50), key species of the flea vectors (51), and the roles of burrow microhabitats and soil (52, 53) in maintaining endemic plague. Public health workers and scientists attempted to "sanitize" or "liquidate"—the terms used at the time—all wild rodent and flea populations by engaging tens of thousands of local people to place poisons (such as chloropicrin, zinc phosphide, or carbon disulfide) manually into each burrow entrance and by using airplanes to spray vast regions with dichlorodiphenyltrichloroethane (DDT) during the 1950s and 1960s (34, 48, 54). Animals resistant to poison baits (such as marmots) were gassed, snared, or shot (55).

The economic expense of these efforts is unknown but must have been astronomical; the chemical methods alone were "costly," especially when carried out over such vast areas (56). The goal was "complete purges of animal-infested territories" through poisoning, burning all vegetation, and finally plowing up wild rodent colonies (57), to "keep districts free from plague. . .by decreasing the number of sources of future epizootics" (58). This goal dovetailed well with Soviet plans to make the steppes productive, including Nikita Khrushchev's "Virgin Lands" initiative (1953–1964) in which workers plowed up over 30 million hectares of grassland and dug massive irrigation works (59). Remaking this landscape on a vast scale required removing primary plague foci.

In comparison, no such centralized eradication scheme was carried out in the United States, where locally determined land use predominated. Plague arrived in North America circa 1900 in Los Angeles, San Francisco, and other port cities. Local and state public health officials, collaborating with the US Public Health Service and university-based scientists, recognized the importance of preventing *Y. pestis* from spreading beyond ports of entry. The local eradication-and-containment strategy succeeded in places like New Orleans, Louisiana and Galveston, Texas (60). [The same was true in Australia, where a combination of strict quarantine, mandatory fumigation, rat killing, and concrete walls managed to contain plague (61).] Despite equivalent efforts in California, containment failed due to the presence of almost-ideal ecological factors: high urban and ex-urban rodent contact rates, variably susceptible wild rodent and flea species, and a congenial climate. By 1935, containment had shifted to county-by-county control (facilitated by sporadic state and federal investment, never on the Soviet scale) (4, 60). By the 1960s plague had become established in secondary endemic foci throughout the western United States, newly entrenched in wild burrowing rodents in several states. In contrast to its long-standing presence in central Asia, plague's geographic expansion into the interior United States demonstrated an epidemiological pattern similar to an exotic invasive plant or animal: early success in port cities, then a quiescent period of geographic spread, and then, in ecologically appropriate areas, consistent endemic/enzootic cycles with sporadic human cases in rural areas (44). North American secondary plague foci now function similarly to primary foci in central Asia, where the history of eradication and control campaigns provides some object lessons on how to minimize human cases in populations that must live or work in endemic plague areas.

In the Soviet hinterlands, plague-eradication campaigns looked successful at first, but within periods of 5 to 20 y ecological surveys of plague foci again found burrows containing rodents, fleas, and *Y. pestis*, demonstrating the resilience of the endemic plague ecosystem (62). For example, scientists cited plague-eradication campaigns begun in the 1930s in southwest Russia as models of success. However, by the 1950s and early 1960s, rodents and plague had returned on the eastern side of the Volga River and in the Kalmyk autonomous area (63–65). Plague's resilience meant that even full-out interventions failed to reduce infected fleas and wild animals to zero and failed to prevent future recurrences. Fenyuk (66) cautioned that "single campaigns" were not sufficient to "liquidate the foci"; the "disinfection" of endemic plague foci had to be repeated for several years. In the Kyzyl Kum area, Stogov (67) estimated that endemic plague could not be eradicated unless >90% of all gerbils were killed. Iakolev (68) noted that gerbil population density in this area nonetheless recovered from eradication campaigns in about 3 to 4 y under favorable climatic and food conditions. Moreover, scientists increasingly worried about the use of carcinogenic, toxic, and long-lasting chemicals such as DDT and the exposure of people and nontarget animals (57, 69).

Human plague cases did significantly decrease by the 1950s, but not to zero. In 1959, B.N. Pastukhov notified the WHO that "since about 1928, when plague control measures began to be developed on a large scale, there have been no cases of plague in human beings in the USSR" (70). Pastukhov's assertion hid the truth. As seen in Fig. 2, plague nonetheless persisted in Kazakhstan and other areas of the USSR. Soviet plague researchers could not publish information about epizootics until 1956 and were forbidden to discuss human cases at any time (71). Once reported to Moscow, plague cases and outbreaks (in animals and humans) did not appear in media or WHO reports because, as one former high-ranking official remembered, "the totalitarian state was concerned about its respectable image" (72). Therefore, Union-level data about plague (and other "sensitive" diseases) in both animal and human populations were systematically underreported, underscoring the manner in which science was subverted to political ends.

By the 1970s, although eradication of plague was still the ostensible goal for the Soviet APIs, practices had shifted toward management and control of plague (73). Fig. 3 shows a generalized timeline of changes in strategies, especially in Kazakhstan. The shift from eradication to control included increased emphasis on managing flea densities. This made epidemiological sense: By reducing vector densities in the ecosystem, tangible reductions in the transmission of plague, frequency of epizootics, and the risk of human spillover were achieved, even without complete rodent eradication. The availability of chlorinated hydrocarbons (such as DDT) after the Second World War made vector control achievable. As DDT became less effective and its dangers more apparent, however, scientists shifted to using other compounds by the 1980s. Draconian interventions, such as burning vegetation and plowing up rodent colonies, were largely abandoned. By 1990, eradication practices such as widespread rodent extermination had also been abandoned in favor of a preventive regime built around predictive modeling, surveillance, education of local people, and vector control (34).

The history of the antiplague campaigns in the former USSR also warns us to be critical of eradication claims and the official data that were used to support them. Union-level data during Soviet days were often subject to political pressures and thus biased to some degree. However, this does not generally apply to regionally curated data: The KSCQZD and Kazakh antiplague stations hold decades of continuous plague surveillance data collected by trained and dedicated scientists and specialists (74, 75). Using the Soviet-era data most productively today requires that they also be subject to scholarly historical analysis (76), including documentary investigation into the external social, cultural, and political factors influencing scientific work in a given place and time; semistructured or open interviews of participants

(or their successors); full integration of both ecological/biological and human social data for a given dataset; notation of problems with datasets; and close collaboration with scientists using these datasets. Historical analysis is key to analyzing change over time in disease patterns and responses.

Accepting Plague Persistence

The shift from eradication to control was possible because of enhanced ecological understanding of the complete plague system and acceptance of plague as a disease of endemic wildlife. Spillover to humans is more likely with epizootics, which occur only at particular rodent and flea species' density thresholds (77, 78). Humans are exposed through flea bites and direct contact (eating, skinning, or butchering infected animals). Urban areas near endemic foci may experience transmission to commensal rodents and the spillover to humans may escalate through direct (pneumonic) and possibly indirect (human ectoparasites) transmission (16, 17). The historical Soviet data strongly suggest that for successful control we should focus on four attributes of plague ecology: flea vector species' distributions and densities, understanding the role of the burrow in plague persistence, the interplay between multiple rodent and flea species and their resistance to *Y. pestis*, and the role of landscape-level features in plague epizootics. This is validated by recent work using niche modeling, which found that plague cases occurred only where host animal ranges overlapped with "plague niches" whose locations depended on nonhost factors such as vector (flea species) distribution (79).

Flea Distribution and Density. Flea species differ in their *Y. pestis* transmission capability, efficiency, and temporality. In southeastern Kazakhstan, *X skrjabini, X. hirtipes*, and *X. gerbilli minax* become quickly blocked by *Y. pestis* biofilm aggregates in their guts, leading to intensive feeding behaviors on multiple hosts that make them rapid transmitters of plague (mediated by individual host-vector interactions) (80). By contrast, *Coptopsylla* spp. (becoming active in the autumn as *Xenopsylla* goes dormant) are slower transmitters (8). Fleas may exhibit different transmission potentials even at the subspecies level: In the United States, *Oropsylla tuberculate cynomuris* has been found to transmit *Y. pestis* three times more efficiently than does the closely related *Oropsylla hirsuta* (81). The relative abundance of these different flea subspecies may contribute to epizootic potential in specific areas. Plague persistence in foci and spillover transmission can be interrupted by reducing flea abundance, especially if locally present flea species maintain *Y. pestis* without vectoring (some infected flea species live much longer than acutely infected hosts) (15, 82). Soviet scientists also cataloged flea species, such as *X. gerbilli* spp., that feed on multiple hosts (*R. opimus*, *Meriones* spp., and rats); the distribution and density of such flea species may determine *Y. pestis* circulation among hosts (83, 84). Certain flea species may also facilitate cross-species mammalian transmission: One study found *Y. pestis*-infected *X. skrjabini* on great gerbils, foxes, weasels, and steppe polecats in a single test area, for example (85). In the United States, *Pulex simulans* functions as a cosmopolitan feeder (and probably spreader) (86). Reducing flea densities became a cornerstone of Soviet policy in 1959, when Pastukhov outlined the new official antiplague program that combined flea and rodent eradication to "give prospects of a more rapid sanitation of natural foci and the final eradication of the plague epizootics" (70).

That goal proved elusive, however. Between the 1940s and 1970s, scientists reported increasing insect resistance, mammalian toxic effects, and environmental persistence of chlorinated hydrocarbon insecticides (87, 88). These problems stimulated a search for alternative insecticides. In Kazakhstan, for example, antiplague scientists shifted first to pyrethrins, then more recently to fipronil (a phenylpyrazole that disrupts insects' central nervous systems without affecting mammals) (89). Recent attempts to deploy fipronil in treated grain baits have shown effective reductions of flea vectors on individual mammalian hosts (90). With recent studies highlighting the role of climate on flea abundance (86, 91), ongoing surveillance of species-specific vector densities and distributions is a crucial component of endemic plague control.

Burrow Ecology. A focus on flea control rather than rodent eradication also led to an interest in how the burrow environment influenced plague persistence. Fleas can become relatively dormant if conditions are poor (92); others, most notably *Xenopsylla*, overwinter in the burrows. Some flea species (*Citellophilus tesquorum*, for example) can harbor *Y. pestis* for up to 18 mo (93, 94), making them potential key sources of plague persistence. Soviet scientists have investigated the roles of burrow microhabitats and soil in maintaining plague at least since the 1960s (52, 95), finding, for example, that *Y. pestis* persisted in the detritus of deeper burrows even after host abandonment (93). Great gerbil burrows vary in depth up to 3 m, and the depth is critical to flea survival, with shallow burrows less favorable for fleas (96, 97). Burrows in sandy soil and those surrounded by vegetation may be more likely to contain plague-bearing fleas (9). Using PCR assays (98), *Y. pestis* can be more sensitively detected in burrow-collected fleas, and flea species more likely to contribute to plague persistence locally

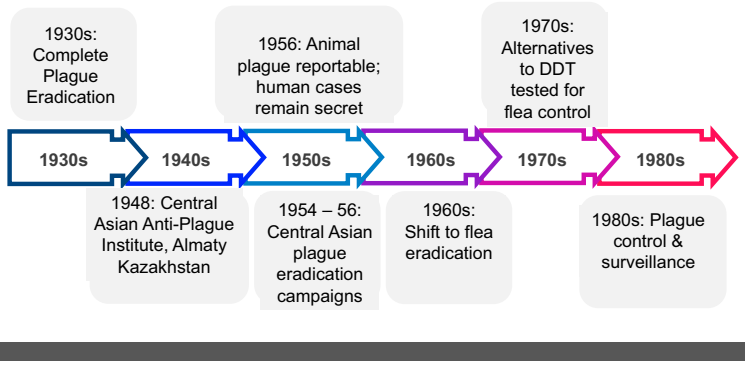

Fig. 3. Timeline of shift from plague eradication (blue) to control (red), USSR. Central Asian antiplague activities are highlighted. Demonstrates timing of shifts from rodent eradication to vector control, and from DDT to nonchlorinated hydrocarbon residuals, and increasing use of surveillance data in predictive models.

can be identified. Work on flea behavior in the context of rodent ecology, including selection of microhabitats within burrows, would be a potentially fruitful area for future research.

Host Diversity and Behavior. How does the local composition and social behavior of rodent species influence plague control? In the former USSR, 15 rodent species are considered main plague host reservoirs, but many other rodent populations coexist with these main hosts (10). While it is unclear what traits make a rodent population a suitable main plague host—the rodent species itself is not a sufficient determinant (43)—one hypothesis is that main plague host populations are characterized by a heterogeneous susceptibility to the disease and a long duration of infection in some ill individuals (65). Another is social behavior (most main plague hosts are social or facultatively social species). Social species facilitate transmission more effectively than solitary ones through direct contacts and colony-mediated spatial distributions (96). Together these traits facilitate both the survival of the plague host species and of the disease and assessing them are important host surveillance goals. Cost-effective detection tools used to identify human cases, such as lateral flow strip-testing, may be adaptable for identifying exposed surviving primary host animals (99–101). Secondary plague host species, some of which are highly susceptible, may have an amplifying effect on the spread of the disease during epizootics, or others may enable plague persistence (102). Furthermore, secondary species' habitat ranges can serve as a bridge between plague reservoir hosts and peridomestic rodents, thus putting humans at risk. Secondary plague hosts are characterized by a low resistance to plague (with little heterogeneity within their populations) (8, 103). Control efforts must include assessment of the temporal population dynamics and habitat range of both primary and secondary hosts to accurately estimate epizootic risk in a particular area.

Landscape/Population Ecology. Landscape-level features are crucial in promoting or inhibiting epizootics. As noted above, many of the rodents harboring plague live in burrow colonies, often with complex spatial and population dynamics that can only be appreciated at a broad geographic scale (7, 13, 104). Burrows can be drivers of disease in several respects (14, 75). They often contain multiple individuals, which allows longer-term interactions and potentially greater contact rates. Species using complex burrow systems also may exhibit greater philopatry, which in turn alters the spread of infection from one burrow system to another. In *R. opimus*, dispersal between colonies is common; one study in Uzbekistan found that 42.8% of female great gerbils and 100% of males switched colonies at least once during a year (105), potentially spreading *Y. pestis*. An enhanced potential for plasticity of social organization in complex burrow systems also yields different potential for dispersal and hence transmission of disease. Soviet researchers recognized the contributions of spatial structure to plague, noting that female kinship, shared burrows, and male-biased dispersal would contribute to high contact rates and plague persistence at low host abundance (57, 106–108). More recently, Wilschut et al. (96, 97) conducted a survey in Kazakhstan of great gerbil colonies (whose burrow systems include multiple branching tunnels that can occupy an area of 20 to 60 m^2). They then created landscape objects from satellite images which were linked to plague data from 1949 to 1995. Burrow distribution was nonrandom, associated with greener areas, and the direction of plague outbreaks were aligned with burrows and their connections. This method of tracking great gerbil dispersion with freely available data promises to guide efficient on-ground surveillance.

These ecological approaches to plague persistence, combined with modeling and statistical inference of outbreak potential, can be used to help predict shifts in targeted enzootic foci by increasing surveyable surface area without increasing resource costs. Indeed, efforts to create "risk maps" from annual surveillance data have been tested in the Pre-Balkash plague focus, although problems with the model used included high rates of false-positive predictions (109, 110). Incorporating the ecological data we highlighted earlier, such as flea density, will maximize the usefulness of this model to field surveillance teams by reducing false positive risk predictions. Adding a thorough understanding of the ecology of plague and the sensitivity of its actors to climate fluctuations are the keys to integrating modeling tools with the ground-level work currently done by plague control centers.

Accepting plague persistence also means being attentive to conservation to maintain healthy ecosystems. Plague-reservoir species, such as *R. opimus*, may promote ecosystem resilience and should not be eradicated. Resilient ecosystems include communities of organisms whose interactions sustain one another in the system and diminish disruptions to it; endemic diseases can shape populations and communities (111). In our case study, healthy burrowing rodent populations function as "ecosystem engineers," enhancing steppe soils, influencing the nitrogen content, and creating a "fertile island" effect (112, 113). Annihilating rodent populations not only destroys this effect but also temporarily encourages starving fleas to seek new hosts (including humans and domesticated animals), facilitating the transmission of the disease. Thus, pathogens and attempts to regulate them can threaten biodiversity (114), loss of biodiversity may increase risk of disease transmission (115), and climate change may amplify that risk (116).

Conclusion

As the old saying goes, "those who do not understand history are doomed to repeat it." Ecologically complex endemic zoonoses such as plague resist eradication efforts, and several social and biological lessons follow from the experience of Kazakh and Soviet scientists in the ancient plague foci of central Asia. Over time, Soviet antiplague policies abandoned eradication in favor of control, with emphasis on developing basic knowledge of plague ecology in local areas. Switching to control opens wider possibilities for interrupting spillover while preserving natural ecosystems, encourages us to adapt to local conditions, and uses technological tools judiciously and in a cost-effective way. Finally, using history as a guide reminds us that political and social influences will always affect scientific work and public policy and must be factored into successful disease control programs.

Once our focus shifts from eradication to control, we are better equipped to respond to existing, emerging, and reemerging diseases in wildlife systems that naturally spill over into humans. Interrupting transmission is essential when disease cannot be eliminated from the environment, either because we lack the necessary knowledge and tools to control a newly emergent disease or because some diseases (like plague) are highly resilient to eradication. Surveillance, vector control, and preventive-measures education are the cornerstones of a generic endemic disease control system. Local infrastructure in place to rapidly respond to new spillover events is essential, rather than waiting for outbreaks to occur and then developing a response. On a practical level, it is important to support less-glamorous but necessary needs such as vehicles and pumps that are often neglected in favor of alluring new technologies. Resource-intensive schemes such as ambitious sequencing efforts (for example) can come at the expense—literally—of practical results (23). We do not

advocate eschewing novel technologies but instead argue for their selective incorporation in the context of basic ecological knowledge about endemic disease systems.

The history of antiplague work in central Asia suggests several avenues for further research on plague in endemic foci (including established secondary foci such as those in the western United States). First, since fleas are the key to plague transmission, better understanding of variation in flea species' behavior in different types of burrows, on different host rodent species, and over seasonal and shorter-scale variation is essential (82, 83, 92, 117). Second, more landscape-level models and other efforts to understand patterns of rodent and flea dispersal and its influence on disease outbreaks should prove productive and predictive for transmission interruption (75, 104). Third, more attention should be paid to how resistance to *Y. pestis* varies among and within rodent species (8, 118). This is of particular interest in the context of recent efforts to develop oral vaccines for rodents that carry plague (119), since species may differ in the degree to which such vaccines are effective.

Practical decisions and policy should be based on solid scientific knowledge, historical and current, in social context. Today, most plague cases occur in Africa, where secondary endemic foci are in the process of becoming established due to close proximity between wildlife, domestic rodents, and people. Along with the factors advocated above, attention to urban and rural resources for protecting people from vector bites (such as improved housing) and containment of *Y. pestis* spread is essential. Changing demographics and development in central Asia due to the Chinese-sponsored Belt and Road Initiative and infrastructure improvements in Africa means that more travelers will be exposed to endemic disease foci and can quickly move infections and vectors into new territories. It is therefore essential that monitoring and control networks collaborate to quickly detect and act upon the opportunistic spread of endemic diseases.

While we must accept the persistence of plague and other zoonotic wildlife diseases, living with them requires a coordinated response of ecologists, public health officials, and people who are cognizant of the lessons of history. In our opinion, such an approach will be much more likely to reduce the overall human burden from wildlife spillover of diseases than single-disease-focused eradication attempts.

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