

Reducing the threats of rodent-borne zoonoses requires an understanding and leveraging of three key pillars: disease ecology, synanthropy, and rodentation

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Rodents have co-existed with humans for centuries, and frequently exchange pathogens. Historically, rodent-driven plague outbreaks scoured the Old World, resulting in substantial human mortality. Although such pandemics have not occurred for centuries, serious threats from rodent-borne infections, such as the global emergence of mpox, still exist. Moreover, endemic and emerging rodent infections continue to cause substantial human morbidity and mortality in low-income and middle-income countries. Efforts by the medical community to control rodent-borne zoonoses primarily focus on treating or preventing symptoms in humans using biomedical interventions (eg, vaccination). Such approaches are geared towards preparedness and response but are insufficient for prevention. In this Personal View, we identify three key pillars that drive rodent-borne zoonotic spillover: ecology of rodent infections; use of human habitation by rodents (synanthropy); and the influence of humans on the ecological proliferation of rodents in our landscape (rodentation). The challenge is to leverage these pillars as entry points for interventions, to prevent spillover and reduce disease burden. Given shortcomings of rodent culling, we advocate for integrated countermeasures that are socially and ecologically grounded, apply systems thinking, and leverage emerging technologies to prevent spillover driven by persistent human–rodent interactions and global change.

Introduction

Zoonotic infections cause frequent but unpredictable disease outbreaks. These outbreaks can range from isolated cases to pandemics such as influenza, plague, and COVID-19. Zoonotic infections arise in humans when pathogens spill over from non-human vertebrate hosts. Rodents are an important source of zoonotic pathogens, including viruses (eg, monkeypox virus, hantaviruses, arenaviruses), bacteria (eg, *Leptospira* spp, *Borrelia* spp, *Rickettsia* spp), fungi (eg, *Histoplasma capsulatum*, *Coccidioides* spp), and parasites (eg, *Toxoplasma* spp, *Echinococcus* spp). Some pathogens traditionally considered human-specific, such as hepatitis A viruses, several endemic coronaviruses, and smallpox, likely originated in rodent species.^{1–3} Mpox, caused by an orthopoxvirus closely related to smallpox, is believed to have spilled over from rodents in central and west Africa.⁴ Previously, mpox caused self-limiting outbreaks, but of late, mpox has triggered several sustained epidemics of human-to-human transmission across multiple countries.⁵ This emergence, coupled with ongoing risks from other rodent-borne zoonoses, warrants the timely consideration of disease dynamics and the interventions needed for public health.

Rodents are the most abundant and diverse mammalian order on Earth and inhabit all continents, including regions of the sub-Antarctic.⁶ Rodents occupy a wide range of habitats, and many taxa readily adapt to environmental disturbance and anthropogenic settings. Rodentia harbours the highest number of zoonotic host species and pathogens among all mammalian orders, and three times greater than that of Chiroptera (bats).^{7,8}

Zoonotic diseases are generally classified into three groups based on the extent of human-to-human transmission following spillover.⁹ Rodent-borne zoonoses, wherein the pathogen spills over and infects a single human host with no secondary transmission ($R_0=0$; stage II), include Sin Nombre virus and *Borrelia burgdorferi*. Stage III zoonoses involve those with self-limiting, subcritical transmission, where the basic reproduction number R_0 is between 0 and 1 and results in stuttering chains of transmission without sustained spread (eg, Lassa virus). Stage IV pathogens include those with efficient onward transmission ($R_0>1$) after spillover (eg, monkeypox virus during the 2022 epidemic). Naturally, R_0 in the reservoir determines the force of zoonotic infection, but does not directly correlate with R_0 observed in humans, where transmissibility is generally reduced, presumably owing to biological differences.¹⁰

The degree of human-to-human transmission potential determines the intervention strategies applied to reduce human exposure to an infection. When R_0 is less than 1, human burden is associated with the rate of pathogen spillover; therefore, prevention is invariably focused on reducing human exposure to infected animals.¹¹ When R_0 is more than 1, outbreaks expand exponentially in the human population (eg, SARS-CoV-2), requiring primary prevention through proactive interventions to mitigate initial spillover, alongside secondary measures to reduce morbidity and human-to-human transmission.¹² After spillover, secondary measures involve biomedical interventions such as human vaccination, which focus on reducing human morbidity and mortality. These reactive

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Panel 1: Definitions of key terms

Hosts

Species capable of supporting a microorganism in their body or cells; their importance in disease dynamics varies depending on their role.

Reservoir host: A host species that maintains a pathogen endemically and acts as a source of infection for other species

Bridging host: A host that has an important role in transmitting infections among species (eg, when a virus is passed to humans from wildlife via a domestic animal)

Amplifying host: A host in which a pathogen multiplies rapidly to high levels, thus increasing the transmission among species

Dead-end host: A host that can become infected with a pathogen but does not lead to further transmission to susceptible hosts

Basic reproduction number (R_0)

The average number of new cases infected by a single infected host in a susceptible population; typically restricted to transmission within a single host species. The point at which R_0 is greater than 1 is the threshold for sustained transmission. The R_0 for a reservoir host is different and invariably greater than that for the human host.

Rodentation

Rodent proliferation in terms of abundance and spatial distribution, along with changes in rodent diversity, in response to human activities that alter rodent resource availability and predation pressure across a landscape

Spillover

The interspecific transmission of a pathogen from one animal species to another (often human) in which the infection was not previously endemic

Synanthropy

The tendency for certain undomesticated wildlife to live in close proximity to and benefit from human settlements and their habitat modification

Zoonosis

Any infectious disease transmissible to humans from vertebrate animals under natural conditions

public health responses can slow transmission, but cannot fully prevent outbreaks owing to delays in response and the exponential nature of the spread.

How can we reduce the spillover of pathogens from rodents to humans? Spillover is an ecological process, and its effective control requires an understanding of the interactions among rodents, humans, and their shared environment. In this Personal View, we advocate for a cohesive, transdisciplinary approach to disease prevention that addresses the root drivers of rodent-borne spillovers at the ecological, sociological, and public health levels. This strategy adopts a proactive approach and preventive framework rather than a reactive one. We address this issue by establishing a knowledge structure that delineates three ecological pillars driving rodent-borne zoonoses in humans: the ecological dynamics of rodent-borne diseases; the association between rodents and human habitation (synanthropy); and the influence of human activities on shaping the ecological proliferation of rodents in the landscape (rodentation; panel 1). Our ability to control the abundance of rodent reservoirs living close to humans remains rudimentary. Therefore, these three pillars lead us to address three fundamental questions. How can we reduce the threat of rodent-borne outbreaks through primary spillover prevention? Which ecological aspects of rodent-borne infections can assist in effectively preventing spillovers? Which technologies and techniques can be used

to increase the effectiveness, ecological sustainability, and cultural acceptability of interventions for spillover prevention?

Research and knowledge of rodent-borne zoonoses

Taxonomically, rodent-borne zoonotic pathogens are considerably diverse and include viruses, bacteria, protozoans, and helminths that can be directly or indirectly transmitted (panel 2). Indirectly transmitted infections include major vector-borne diseases, which are nearly all tick-borne (panel 2). Rodents also contribute to the complex lifecycles of zoonotic parasites such as trematodes. Several human infections, including schistosomiasis and trichinellosis, do not qualify as true rodent-borne zoonoses but involve rodents as sufficient, although not necessary, components of the transmission cycle. Even within a pathogen genus, the relative role of rodents can vary between subtypes. For example, among *Leptospira* species, some serovars are rodent specialists, whereas others use rodents as alternative hosts or not at all.¹⁶

When zoonoses are identified, research initially tends to focus on human pathogenesis, epidemiology, therapeutics, and public health response, whereas spillover dynamics and ecological context tend to be neglected (figure 1. For search strategy and selection criteria see appendix pp 2–5).^{9,49}

See Online for appendix

Panel 2: Examples of directly and indirectly transmitted rodent-borne zoonotic diseases

Directly transmitted rodent-borne zoonotic diseases

Lassa fever

- Infection dynamics: Lassa fever is a viral haemorrhagic fever endemic in west Africa with an estimated 897 000 human cases, 54 000 hospital admissions, and 18 000 deaths annually.¹³ Lassa fever has low but sustained transmission in humans and a basic reproduction number (R_0) that is often close to 1. In 2016, WHO classified Lassa fever as a priority disease with high epidemic potential.¹⁴
- Role of rodents: *Mastomys natalensis* is the primary host reservoir,¹⁵ although other species appear to be competent hosts as well.¹⁴ Knowledge about the role of the community of rodent species in the amplification and maintenance of Lassa virus, and the hosts responsible for transmission to humans, is important but lacking. Most associated rodent species are synanthropic, and the incidence of infection in rodent hosts is higher in habitats modified by human activity.¹⁶
- Interventions: Currently, vaccines are in phase 2 of development, and diagnostic testing remains challenging in endemic regions.¹⁷ Rodent control to reduce abundance near people is used in Nigeria and Sierra Leone, despite inefficient campaigns that were trialled in Guinea.¹⁸ An opportunity exists for more ecological trials to reduce the movement of rodents and exposure of people. Public health interventions are focused on education and rat-proofing food, trapping in homes, and avoiding rat consumption.

Mpox

- Infection dynamics: Mpox is a zoonotic viral disease endemic to west and central Africa. Recognised since 1958, the incidence of the disease in humans is rising as mpox capitalises on the niche vacated by smallpox vaccination.^{19,20} Traditionally, mpox cases were primarily caused by animal-to-human transmission in endemic areas, with occasional transmission between humans. Since 2022, human-to-human transmission has increased in multiple viral clades, linked primarily to sexual transmission and leading to more than 100 000 confirmed cases across 122 countries.⁵
- Role of rodents: Monkeypox virus infects various animals, with high seropositivity in rodents such as giant pouched rats (*Cricetomys* spp) and rope squirrels (*Funisciurus* spp).²¹ Further studies are needed to identify rodent hosts that transmit the virus. Zoonotic transmission occurs through close contact with animals, often through hunting and butchery. One hypothesis to explain the increase in the incidence of clade I mpox is that as hunting depletes the larger edible species and biodiversity falls, hunters switch their efforts to rodents, increasing human-rodent contact and facilitating spillover.²²
- Interventions: Given the cross-reaction among different poxviruses, vaccination against smallpox provides protection against mpox and is recommended to prevent human-to-human transmission. Although vaccines against mpox are increasingly available globally, they are not widely available in Africa, where primary transmission has been neglected. Reducing exposure to reservoir species is the main form of spillover prevention, although a clear opportunity exists to restore ecological biodiversity, reduce viral amplification, and hence, reduce exposure.

Hantavirus syndromes

- Infection dynamics: Old-World orthohantaviruses, including Hantaan, Dobrava, Puumala, and Seoul viruses, cause more than 150 000 annual cases of haemorrhagic fever with renal syndrome in Asia and Europe, with a fatality rate of 0.1–10%, depending on the virus. New-World orthohantaviruses, including Sin Nombre and Andes viruses, have caused more than 5000 cases of hantavirus pulmonary syndrome since their discovery in the 1990s, with a fatality rate of 30–40% in North and South Americas. There is no human-to-human transmission of these hantaviruses, with the exception of the Andes virus from South America.
- Role of rodents: Each human case of hantavirus syndrome arises from contact with rodent urine, faeces, saliva, and their aerosols. Understanding disease dynamics in rodents and the ecological changes that lead to increases in the rodent reservoir are important for predicting human infection. For example, the abundance of *Peromyscus* sp deer mice (host of Sin Nombre virus) and *Clethrionomys glareolus* bank voles (host of Puumala virus) fluctuates widely,^{23,24} and during periods of high abundance, spillover to humans is increased.^{25–27}
- Interventions: There is no universally accepted vaccine or specific treatment for hantavirus syndromes. Current interventions include ad hoc outreach and education on rodent proofing and safe cleaning of rodent faeces from human habitation. The assumption is that emergence is event-based, in which case predicting *Peromyscus* growth rates based on climatic effects on resources could identify new ecological means of intervention.

Vector-borne zoonotic diseases from rodents

Lyme disease

- Infection dynamics: Lyme disease is transmitted by a tick vector, *Ixodes* sp. Lyme disease is the most frequently reported notifiable zoonotic disease in North America and Europe, with more than 750 000 global cases annually. In North America, all infections are associated with one species of bacteria (*Borrelia burgdorferi*), whereas in Europe, many other species are responsible.²⁸ Most affected individuals recover quickly after treatment, but some individuals experience post-treatment Lyme disease syndrome, potentially

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Panel 2 (continued from previous page)

due to immune system dysregulation, neural network alterations, or secondary co-infections.²⁹ No human-to-human transmission occurs, and human cases occur primarily after being bitten by a nymphal tick.

- Role of rodents: The proportion of infected nymphs depends on the infection status and host species that the larval stage feeds upon. Rodents play a crucial role as hosts for the larval ticks, which in turn drive the abundance of infected nymphal ticks, facilitating transmission. Habitat fragmentation and spatial aggregation of resources for *Peromyscus* deer mice, such as acorn masts, can increase the abundance of rodent hosts and facilitate disease transmission in North America.^{30,31} Note that adult female ticks require a large mammal species, usually a deer species, to complete the lifecycle, and deer are often a necessary part of vector maintenance.
- Interventions: Control measures include avoidance of tick bites through the use of acaricides, protective clothing, fencing to keep deer out of yards, and rodent trapping. Innovative proposals include using acaricide-treated cotton rolls to treat mice and using guinea fowl as tick predators. Ecological interventions encourage more non-amplifying hosts, and in North America, *Peromyscus* rodents or the ticks on them are controlled. One study used permethrin-treated bait boxes to attract and treat *Peromyscus* so that they did not transmit Lyme disease, and such treatment resulted in fewer infected questing ticks,³² although permethrin is heavily restricted in Europe, and these findings have not been replicated at scale. No human vaccine is available for Lyme disease.

Plague

- Infection dynamics: *Yersinia pestis*, the causative agent of plague, has been identified in ancient DNA samples from 5300 BCE. Many plague pandemics have since been reported, with the most recent pandemic in the mid-19th century, which spread along shipping routes.³³ Plague outbreaks continue to occur in several countries, including the Democratic Republic of the Congo, Madagascar, Peru, and the USA.³⁴ The clinical manifestations of plague are varied, potentially associated with the route of infection, and are in order of prevalence: bubonic, septicemic, and pneumonic plague. Other clinical symptoms, such as plague meningitis and ocular plague, are rare.³⁵
- Role of rodents: Rodents are important reservoirs of the plague bacterium, which exists in a complex ecological system.^{36,37} 48 species of rodents act as reservoirs for *Y. pestis* in endemic foci, and all but eight rodent species make burrows in which the plague can persist under favourable conditions. Flea vectors transmit *Y. pestis* among reservoir populations during feeding, thus promoting transmission and sporadic outbreaks in human populations.³⁸ In Kazakhstan, climate factors such as warmer springs and wetter summers increase infection rates in the primary rodent host, the great gerbil (*Rhombomys opimus*), most likely due to increased flea activity and survival.³⁹ Similar conditions might have contributed to previous pandemics and are expected in the future due to climate change.³⁶
- Interventions: Interventions include improved diagnostic capacity, antibiotic therapy, and post-exposure prophylaxis in situations wherein adequate personal protective equipment is not available.⁴⁰ The US Centers for Disease Control and Prevention recommends pre-exposure vaccination in a few examples, such as those including work with antimicrobial-resistant strains and emergency disaster response in enzootic locations.⁴¹ Rodent control as interventions to reduce the risk of plague outbreaks have been trialled in Madagascar,⁴² whereas flea control has been successfully used in Kazakhstan.⁴³

Tick-borne encephalitis

- Infection dynamics: The causative agent of tick-borne encephalitis is a flavivirus transmitted by *Ixodes* ticks that is distributed across northern and central Europe and also central Asia.⁴⁴ The reported incidence of approximately 12 000 cases per year is most likely an underestimate.⁴⁵ Louping ill virus is a closely related virus and part of the tick-borne virus complex that shows cross-reactivity with tick-borne encephalitis virus and does not overlap in distribution.
- Role of rodents: Rodents play a key role in amplifying the tick-borne encephalitis virus, often through non-viraemic transmission. Detailed studies of the main rodent reservoir, the yellow-necked mouse (*Apodemus flavicollis*), show that most transmissions occur among sexually mature male mice with a large body mass, and these individuals have a major influence on human risk.⁴⁶ In contrast, rodents have no role in the transmission of the Louping ill virus, but the virus is sustained by mountain hares (*Lepus timidus*) and the process of non-viraemic transmission.⁴⁷
- Interventions: Prevention is non-specific, including the use of acaricides and protective clothing to prevent bites. Vaccination of woodland workers has been effective in Austria. Ecological interventions that reduce the ratio of amplifying to non-amplifying hosts can be effective, as observed in the case of the Louping ill virus in Scotland.⁴⁸

For example, during the global outbreaks of mpox, control focused on vaccination and behavioural modification to reduce human-to-human transmission. However, few measures were introduced to prevent mpox spillover from rodents in endemic regions, even though most outbreaks appeared to have resulted from multiple spillover events originating from different viral lineages.⁵⁰ Further

investigation is required to identify rodent species that serve as reservoirs for monkeypox virus, although some evidence suggests that rope squirrels and pouched rats are likely candidates.^{22,51}

In contrast to mpox, the role of rodents in driving the emergence of hantavirus pulmonary syndrome in the USA (panel 2) was discovered soon after identifying the causal

agent (Sin Nombre virus). Although knowledge of the Sin Nombre virus and its rodent reservoir hosts was new to Western medicine during the 1993 Four Corners hantavirus outbreak,⁵² relevant indigenous knowledge had existed for decades. Navajo elders had long associated outbreaks with increased rainfall, which in turn increased piñon nut production and the number of mice.⁵³ Such knowledge has been historically underutilised during outbreak research and response.

Analysing the research timelines of rodent-borne diseases (figure 1) reveals a recurring pattern: research effort increases rapidly in response to human infection and outbreaks, but is not reflected across the rodent, viral, and human factors that shape infection. In the case of epidemic mpox ($R_0 > 1$), rodent-related research remained minimal, whereas in the case of hantavirus, which involves no onward human-to-human transmission ($R_0 = 0$), research was more proportionally directed towards the reservoir host. Improved understanding of rodent ecology and disease dynamics could help to prevent spillover and reduce human disease burden across a broad range of rodent-borne zoonoses (panel 2).

Pillars of rodent-borne zoonotic spillover

Spillover can be conceptualised as a series of dynamic interactions in which the pathogen percolates from reservoir hosts to humans through several ecological, social, and biological barriers.⁵⁴ This process is shaped by the dynamics of the rodent populations, pathogen characteristics, human behaviour, and the environmental context. Viewing spillover of rodent-borne zoonoses as a socioecological system provides clarity about how actions in one component might generate intended or unintended effects elsewhere in the dynamic system through feedback mechanisms (figure 2). For instance, these feedback loops show that human-induced environmental changes shape rodent population dynamics, driving rodent movement into human habitations. The feedback loops also highlight how intervening to prevent spillover could unintentionally reduce the ecosystem services provided by rodents, such as wild meat availability. Recognising these complex interactions among humans, rodents, and the environment is central to developing interventions that minimise unintended consequences while enhancing benefits for food, environmental, and global health security. Effective control of rodent-borne zoonoses requires an integrated approach that considers social and ecological factors shaping rodent disease ecology, synanthropy, and rodentation. We address these themes in the following section, within a framework that we call the pillars of emergence of rodent-borne zoonoses.

Pillar 1: rodent disease ecology

Several core aspects of rodent biology have resulted in rodents becoming successful reservoir hosts for zoonotic pathogens. Primarily, most rodent species have a high reproductive potential. Female rodents generally reach

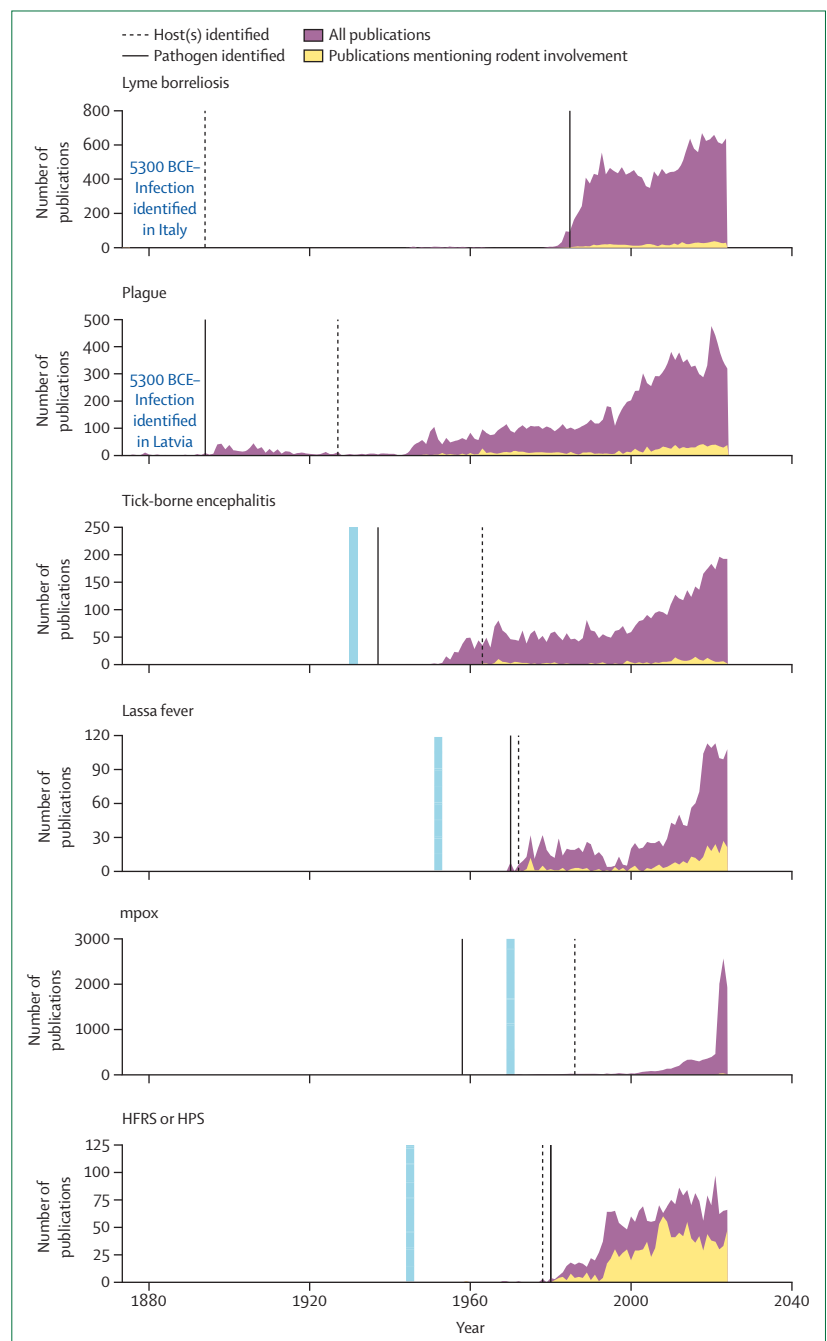


Figure 1: Timelines of research on rodent-borne zoonoses

Bibliometric timelines for six rodent-borne disease systems in relation to when the first human case was reported (indicated by blue shaded area or blue text in each graph), the causative agent was first identified (solid vertical line), and the reservoir host was identified (broken vertical line) (for search criteria, see appendix pp 2–5). The area in purple shows the total number of annual publications relative to those mentioning rodent involvement in the disease system (yellow). Note that the y-axis scale varies on each panel. HFRS=haemorrhagic fever with renal syndrome. HPS=hantavirus pulmonary syndrome.

reproductive maturity at a young age; they can conceive shortly after parturition, and produce numerous offspring per litter in short intervals.⁵⁵ For example, *Mastomys natalensis*, the primary reservoir for Lassa virus, is

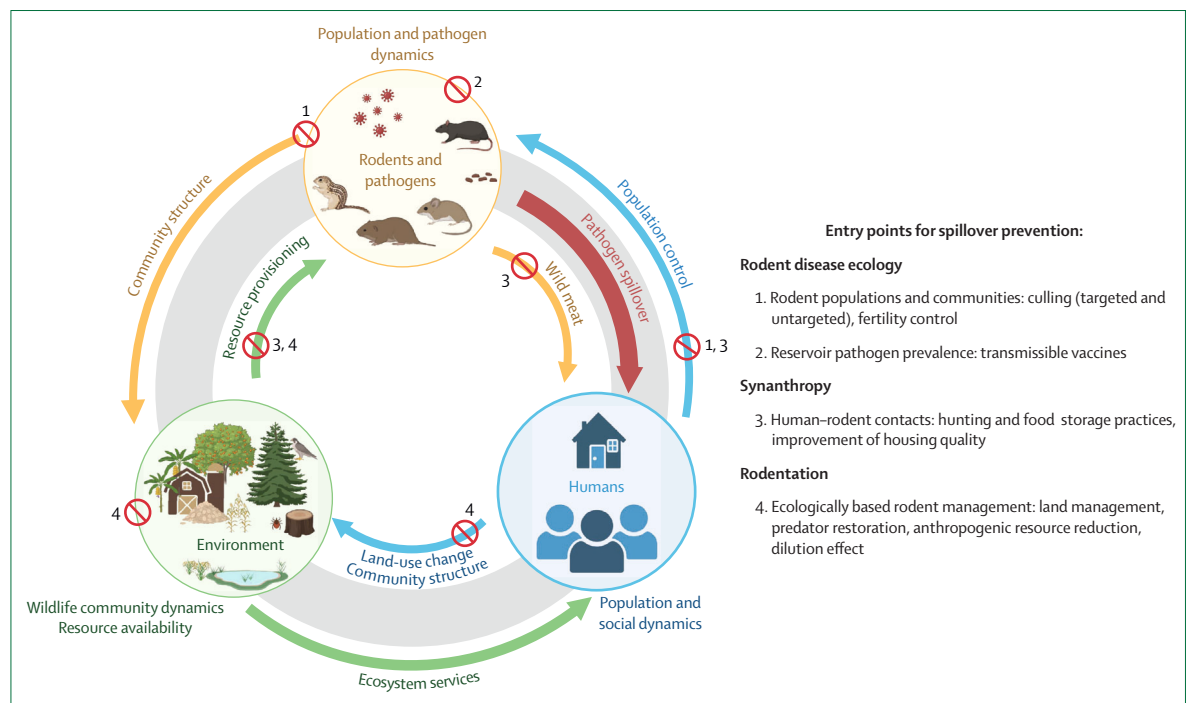


Figure 2: Rodent-human-environment interactions and intervention points

A conceptual model highlighting interactions and feedback between rodent ecology (gold), human behaviour (blue), and the ecological context (green). Arrows indicate the human-rodent-environment interactions that have immediate and downstream effects on rodent-borne zoonotic spillover. For example, human settlement and land-use change shape the ecological community, particularly predator and resource availability, which modulate rodent populations, dynamics, and the likelihood of spillover to humans. Red circles indicate opportunities for disease control that disrupt upstream interactions affecting spillover and provide entry points for control. Figure created with BioRender.com.

highly fecund and capable of producing four or more large litters annually, with an average of 11 offspring per litter, but occasionally as many as 22.⁵⁶ As a result, rodent populations increase rapidly, and these high population growth rates can facilitate rapid pathogen transmission.

One hypothesis to explain why rodents are important hosts for zoonoses proposes that the high reproductive capacity and short life expectancy are associated with reduced investment in immunocompetence; therefore, infections are not effectively neutralised. Evidence supporting this hypothesis is available but sparse and requires further investigation. For example, comparisons among *Peromyscus* species indicated that the species did indeed show variation in their innate response to bacteria, and this variation in their innate response was inversely related to their acquired immune responses but was not associated with their reproductive rates.⁵⁷

The high reproductive rates of rodents can result in multi-annual cyclic fluctuations, wherein the peaks in rodent abundance coincide with zoonotic disease outbreaks, often with a time lag.^{23,25} In Finland, major tularemia outbreaks caused by the bacterium *Francisella tularensis* were preceded by periods of high abundance of voles (*Microtus agrestis* and *Clethrionomys glareolus*).⁵⁸ Inter-annual and intra-annual patterns of Nephropathia epidemica in humans (caused by the Puumala virus) in Europe are similarly predicted by the overall abundance or density

of bank voles (*C glareolus*) or the density of infected bank voles.^{25–27} In the Four Corners region of USA, hantavirus outbreaks were associated with El Niño events, when excess food resources led to high rodent abundance.²⁵ These patterns indicate that rodent density often corresponds with elevated spillover risk and can serve as predictive indicator for human exposure.

Pillar 2: synanthropy

In addition to functioning as effective reservoir hosts, rodents are frequently synanthropic, and human exposure to rodent-borne pathogens is high. The rise of synanthropic rodents began with the development of agriculture and permanent human settlements approximately 15 000 years ago.⁵⁹ The house mouse (*Mus musculus*) originated in Asia and the Middle East and adapted to a commensal lifestyle,⁶⁰ whereas the black rat (*Rattus rattus*) originated in southern India, reached Mesopotamia 4000 years ago, and spread throughout the Roman Empire 2000 years later.⁶¹ The brown rat (*Rattus norvegicus*), although historically commensal in East Asia, spread globally during European imperial expansion between the 16th and 19th centuries.⁶²

Synanthropy is not necessarily a species-specific trait. Some species show synanthropy seasonally or at small geographical scales.⁶³ For example, *M natalensis* are prominent agricultural pests across sub-Saharan Africa, but the extent of synanthropy varies seasonally and spatially. In

west Africa, *M natalensis* have been observed to move between agricultural and domestic environments seasonally,⁶⁴ whereas in east Africa, the species appears less associated with domestic environments, potentially due to regional agricultural practices.⁶⁵ Similarly, in Madagascar, movement of *R rattus* between domestic and agricultural spaces fluctuates in response to agricultural activities, with implications for plague transmission.⁶⁶

Spillover from synanthropic rodents to humans occurs through indirect exposure to contaminated food, water, fomites, and aerosolised dust particles; or directly, by contact with infected rodents and their bodily fluids. Indirect transmission is typically associated with housing quality, food storage, and pest management. For example, housing structure affects rodent infestation in the context of Lassa fever, wherein rats frequently enter houses and urinate on people, household items and surfaces, and stored or left-over food, which some cannot afford to discard.⁶⁷ Women and girls are considered highly susceptible in these settings, due to the social differentiation in domestic tasks.⁶⁸

Direct human–rodent contact occurs through hunting for food, trade, cultural practices, or pest control, and often results in less frequent but higher-dose exposures. Rodents have long provided a source of wild meat, particularly for children.^{69–71} Indeed, children often specialise in hunting small and ecologically resilient animals, and rodent hunting can be an important part of boyhood identity.^{71,72} Hunting and consumption of rodents is also a biological control mechanism for rodent pests, and can be important for food security, medicine, and cultural heritage.^{69,73,74} For example, a putative mpox reservoir (*Cricetomys* spp) is used in traditional medicine to treat yellow fever in Nigeria, illustrating how cultural practices involving rodents could facilitate zoonotic exposure (Friant S, unpublished).

The human–rodent interface, and human capacity to adapt to risks from synanthropic rodents, is socially determined. Structural drivers (ie, social, economic, and political) such as poverty manifest at local scales through factors such as housing structure, food storage, hygiene and sanitation, and rodent hunting. Unlike other zoonotic hosts, synanthropic rodents are frequently perceived as unavoidable elements of daily life, with people expressing a sense of resignation or powerlessness towards their presence, describing them as unavoidable housemates.⁷⁵ This perception is reflected in the discrepancy between levels of complaint regarding rodents and the limited individual or collective action to manage them in households, granaries, or cultivated areas.⁶⁸

Pillar 3: rodentation

When human activities alter the environment and biodiversity in an area through processes such as hunting, climate disruption, habitat conversion, and fragmentation, a general pattern emerges. Predators and large-bodied herbivores are typically extirpated first, followed by declines in medium-sized species, ultimately leaving small mammals, including rodents, to dominate the altered

landscape.^{76,77} Rodents readily exploit disturbed and edge habitats associated with urban or agricultural ecosystems, capitalising on anthropogenic resource provisioning, such as food concentrations in fixed storage sites. These sites buffer rodent populations against climatic and external disturbances that affect the natural resource availability.^{63,78,79} This pattern of mutual encroachment, in which humans facilitate the proliferation of rodents by altering the landscape and its ecological communities, is referred to as rodentation (figure 3).

Rodentation often reduces the rodent diversity in favour of synanthropic species (figure 3A). Most synanthropic rodents act as reservoirs for zoonotic pathogens, and human land-use practices appear to systematically favour rodent host species over non-hosts.^{63,78,79} Invasive synanthropic rodents can introduce novel zoonoses or modify the dynamics of endemic ones. For example, in western Uganda, the introduction of *R rattus* was followed by an increase in human plague outbreaks. Before the 1960s, *Yersinia pestis* was maintained among native rodents and shrews via flea vectors. The displacement of native domestic pests by *Rattus* in the 1960s has been proposed to have contributed to the subsequent increase in human plague outbreaks.⁸⁰ Conversely, invasive rodents could also reduce the incidence of specific diseases. For example, one theoretical model proposes that an increase in *R rattus* populations reduces *M natalensis* populations and the subsequent spillover risk of Lassa fever.⁸¹

Rodentation influences population dynamics by concentrating food in fixed storage sites and altering predation pressure through both the loss of wild predators and the introduction of domestic ones (figure 3B). Resource provisioning from humans can provide buffers against climate and external disturbances that affect the natural resource availability and influence rodent population fluctuations, with implications for transmission risk.⁶³ For example, in east Africa, *M natalensis* breed seasonally on monoculture plantations, with peaks following the rainy season, likely linked to new vegetation and crop growth in extensively cultivated agricultural land.⁸² In west African villages, where subsistence agriculture and stored food remain accessible year-round, *M natalensis* populations appear to present more stable patterns of fecundity and reduced population fluctuations.⁸³ Rodentation has direct implications for zoonotic exposure risk. For example, experimental exclusion of large wildlife in east Africa resulted in increased rodent abundance, and consequently, higher *Bartonella* prevalence and vector density, which elevated the transmission risk to humans.⁸⁴

Interventions to reduce spillover

Disease ecology and rodent-focused interventions

Conventional approaches to controlling spillover of rodent-borne zoonotic diseases prioritise reducing rodent density, based on the assumption that transmission rate increases with host density. This reduction is typically achieved through culling. Methods vary in effectiveness and

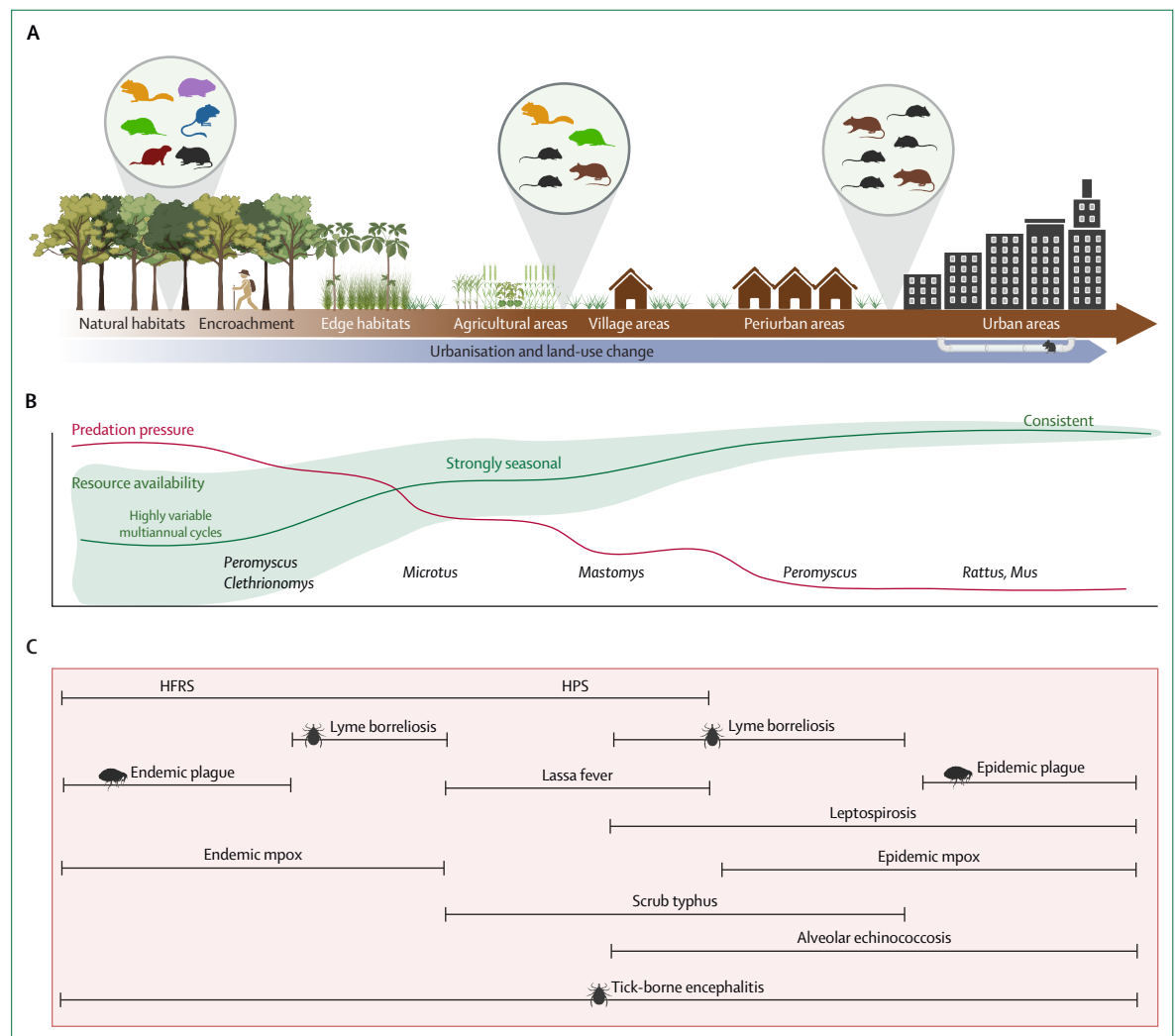


Figure 3: Rodentation and zoonotic spillover with anthropogenic change

(A) Rodentation, a process of mutual encroachment by rodents and humans that is driven by anthropogenic land-use change, leads to declines in rodent biodiversity and increases in the abundance of synanthropic species. (B) Key drivers of rodentation are changes in resource availability and predation pressure in increasingly urbanised environments. (C) Different rodent-borne zoonotic diseases occur at characteristic ranges of locations across the gradient of native vegetation to urban environments. Figure created with BioRender.com. HFRS=haemorrhagic fever with renal syndrome. HPS=hantavirus pulmonary syndrome.

sophistication, ranging from basic kill traps, poison baits, and domestic predators to fumigation and anticoagulants. However, culling of rodents can have inconsistent or counterintuitive effects on pathogen prevalence within rodent populations and on spillover risk. For example, the use of anticoagulant baits might increase environmental contamination before rodent death and delay mortality, thereby elevating blood-borne exposure risk. Culling can also have additional, unintended negative effects, such as the death of non-targeted hosts (including their predators) through the bioaccumulation of rodenticides.⁸⁵

Effectively reducing transmission through culling requires not only an understanding of rodent population dynamics, specifically density dependence and compensation, but also that of community composition and dispersal. Culling is often the easiest and most efficient way to control

infection risk, for example, by targeting efforts when rodents seasonally disperse into human settlements. However, reservoir host culling can also lead to increased dispersal that promotes viral transmission, particularly during outbreaks, as observed in the case of the Sin Nombre virus.^{86,87} In Guinea, an increased infection rate of Lassa virus was observed among rodents after intensive culling, potentially due to density-dependent reproductive compensation and an influx of susceptible individuals.¹⁸ These findings highlight the importance of consistent rodent control; without regular culling, populations quickly rebounded to their pre-intervention size.^{18,88} Such rapid rebound complicates management in rural, low-resource settings where rodenticides are not widely accessible.

Rodent control via culling might not be beneficial for tick-borne diseases, since the abundance of ticks is not

necessarily determined by rodent abundance, but by the abundance of larger mammalian hosts, such as deer, that the adult female ticks feed on. Furthermore, the random culling of rodents might be minimally effective in reducing the risk of exposure to humans when a small proportion of the specific types of individuals in the population account for more than 90% of the transmission events⁴⁶ (panel 2). Some tick-borne pathogens transmit through non-viraemic routes, where virus is transmitted between ticks co-feeding on a shared host (eg, tick-borne encephalitis virus-Eur, Louping ill virus, Thogoto virus).⁴⁷ In this case, when the number of rodent hosts is low or reduced, the number of ticks per host increases, thereby intensifying non-viraemic transmission, such that the risk of spillover can increase with reduced rodent density.⁸⁹

Considering these challenges, approaches are now being developed such that they are either complementary to culling or replace culling altogether. Some of the novel techniques that could help to improve interventions aimed at managing disease within rodents (figure 2) are summarised in panel 3.

Synanthropy and managing the human–rodent interface

Social and behavioural change campaigns seek to influence human behaviours and social norms to reduce disease exposure. These campaigns are a main stay of many rodent intervention strategies and seek to disrupt points of contact between humans and rodents, often through risk communication, reducing indirect exposure through improved food and grain storage, enhanced sanitation, and discouragement of hunting and consumption of rodents serve as core components. Effective implementation requires attention to the sociodemographic and structural determinants that shape high-risk contacts,⁶⁸ thereby creating exposure disparities that complicate public health interventions.

Health messaging that ignores the lived experiences of people can erode public trust and become counter-productive, as observed with the wild meat bans during the Ebola outbreak in west Africa.⁹⁵ Hunting and consumption of rodents in endemic regions often yield benefits that can outweigh perceived disease risks, including improved food security, pest control, and crop yields.^{69,70,96} Indeed, rodents represent an accessible, protein-rich food source, particularly for children. Although children have been identified as index cases for multiple zoonotic infections, including Ebola virus disease, Lassa fever, and mpox,^{72,97,98} they are largely excluded from health research and educational campaigns.

Where synanthropic rodents affect households and agricultural systems, control measures are more effective when aligned with community needs. In a four-year chemical intervention targeting Lassa fever, participants welcomed improved protection of food and personal belongings; however, outcomes depended on village-wide cooperation.⁸⁸ Another campaign codeveloped with communities promoted rat-proofing using locally available

materials,⁹⁹ thereby reducing barriers to adopting positive health practices. These cases highlight the value of participatory approaches and the need for community monitoring to enhance effectiveness and sustain impact.

Fragmentation across regulatory and health sectors complicates behavioural change implementation.¹⁰⁰ Strategies to reduce human–rodent contact might not be effective when they conflict with cultural practices and other established conservation and food security strategies. For example, rodents are promoted as sustainable wild meat and as farming species, including giant pouched rats (*Cricetomys* spp) and cane rats (*Thryonomys* spp), despite the links between wildlife farming and zoonoses such as coronaviruses and influenza viruses. Rodent control intersects with agricultural, environmental, and human health, which will require coordination across multiple sectors and levels. As highlighted in the Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services (IPBES) report on invasive species,¹⁰⁰ effective responses to biological invasions such as rodentation require integrated, multisectoral governance strategies that go beyond individual behaviour change to address structural drivers of vulnerability.

Vulnerability-based approaches that emphasise community engagement are essential for addressing rodent-borne zoonotic spillover. Such approaches can enhance local agency and improve intervention uptake when aligned with community needs.¹⁰¹ However, the long-term effectiveness of these approaches is constrained by structural and institutional factors beyond individual behaviour, including material limitations, shifting institutional priorities, and dependence on external support. Without sustained structural investment, the responsibility for managing rodent-related risks falls disproportionately on affected communities, potentially undermining trust in policy makers and health officials. To enhance resilience and reduce zoonotic spillover, intervention frameworks should account for socioecological feedbacks linking human activity, environmental transformation, and rodent population dynamics (figure 2), and be supported by governance systems that enable social and behavioural change. Spillover prevention strategies that integrate rodent ecology with participatory, cross-sectoral collaboration are more likely to succeed.

Rodentation and vision for socioecological management

A forward-looking approach to preventing rodent-borne zoonoses should move beyond narrow, proximate control strategies towards integrated ecological and social interventions that reshape the broader interactions with the environment that shape human–rodent interfaces. We propose a framework that draws on principles from public, agricultural, and environmental health. Approaches such as ecological countermeasures and landscape immunity^{102–104} are promising for spillover prevention and have been developed primarily in the context of bat-borne diseases. Conversely, ecological rodent management is promising for rodent control, but it does not focus explicitly

Panel 3: Examples of developing technologies that could be used in the management of rodent disease ecology (pillar 1) for spillover prevention

Immune contraceptives

Fertility control using immune contraceptives is considered both humane and more species-specific than culling or using poisons.⁹⁰ Several fertility control agents have been identified, including synthetic steroids and plant extracts such as triptolide. Challenges include efficient and cost-effective delivery to a sufficient proportion of the rodent population, developing species-specific formulations with minimal side-effects for other species, and overcoming logistical challenges. The humane aspect of this technology could allow for increased buy-in.

Transmissible vaccines

Large-scale distribution of vaccine baits has been successful in limiting rabies in the USA and even eliminating rabies in Europe. However, achieving sufficient levels of vaccination coverage in synanthropic rodent species via systematic vaccination of individuals would be challenging, particularly with the high demographic turnover of rodent species. A self-disseminating transmissible vaccine could overcome these logistical constraints. Indeed, a transmissible vaccine has been proposed to control pathogen prevalence in the reservoir of Lassa fever. Mathematical simulations indicate that transmissible vaccines could have a substantial impact on decreasing the prevalence of the infection in rodents while concomitantly reducing human exposure;^{91–93} however, identifying suitable viral vectors and developing vaccines for the target system remain a challenge.

Gene drive

Genetic engineering of heritable genes throughout a population could include targeting female fertility, disrupting zygote viability, and creating a synthetic sperm-killing gene drive that could eradicate mice by eliminating females. Although gene drive is yet to be used to control rodent populations, simulation models indicate that island populations of rodents could be eradicated within a few years.⁹⁴ Nevertheless, although gene drive technology shows good promise, issues remain with safety and containment, resistance development, and ethical and regulatory concerns.

RNA interference

RNA interference could be used to silence genes that are essential for rodent growth, development, or reproduction, or alternatively, crucial to viral lifecycles. This intervention could be delivered through baits, transgenic crops that express double-stranded RNA that could target rodent genes, or through the use of modified viruses to deliver double-stranded RNA. Efficiency could be improved by targeting multiple genes. Such approaches are considered more environmentally friendly than chemical rodenticides and could gain traction with communities. However, challenges remain, such as ensuring efficient uptake and spread in rodents, optimising double-stranded RNA stability and persistence, and testing biosafety concerns.

Electronic rodent repellents

Devices that emit ultrasonic sounds, inaudible to humans but irritating to rodents, could be useful in deterring rodents. The principal function of the devices would be to drive rodents away from rich resources or human habitation, thus reducing exposure; however, this approach could be limited by the fact that ultrasonic waves cannot penetrate walls. More rigorous testing is still needed to establish the effectiveness of such devices, although we suspect that if successful, this low-cost approach would appeal to farmers and others.

on disease management.¹⁰⁵ Together, these approaches prioritise ecological strategies such as habitat management, restoration of predator–prey dynamics, and reduced anthropogenic resource provisioning.

Ecological management of rodent-borne diseases requires identifying spillover mechanisms and understanding the environmental conditions under which outbreaks occur. Although knowledge about the climatic drivers that precede rodent-borne zoonotic outbreaks is increasing (eg, Lassa fever, plague, and hantavirus pulmonary syndrome), solutions often arise when the mechanisms of action are elucidated. One illustrative example linking mechanisms to climate drivers comes from detailed, long-term studies on bat-borne Hendra virus in eastern Australia, where La Niña was identified as a predictor of outbreaks based on its role in the modulation of reservoir behaviour and viral shedding through the availability of nectar from flowering trees. This mechanistic understanding has led to more refined predictions of spillover in time and space.^{106,107} This study, although on bats, illustrates the importance of long-term dynamic monitoring of multiple spillover events. In rodents, the 1993 Sin Nombre hantavirus outbreak in the Four

Corners region followed El Niño-driven vegetation growth, a corresponding rise in *Peromyscus* mouse populations, and repeated spillover events, suggesting underlying mechanisms.²⁵ The ability to generate similar predictions for rodent-borne disease systems would help to guide primary spillover prevention. For example, acorn abundance serves as an indicator of human risk of Lyme disease nearly two years in advance, given its association with the abundance of white-footed mice.³⁰

One potentially important ecological approach to spillover prevention is the reconstruction of biodiverse ecological communities to protect human health. In any host community, some species are more competent hosts than others and amplify the pathogen, whereas other species are incompetent dead-end hosts and do not transmit or spread the virus. Within a community of host species, the ratio of amplifying to non-amplifying hosts considerably affects the basic reproduction number (R_0) of the pathogen in the whole system, and hence, the exposure risk to humans; this relationship is central to the dilution effect.¹⁰⁸ This effect is particularly relevant with tick-borne infections that have a limited number of bites (transmission events), such that when a tick bites a non-competent or

dead-end host, no onward transmission happens. For example, in Lyme disease, *Peromyscus* mice are both an important amplifying host and the most ecologically resilient host. As biodiversity falls in fragmented habitats, the ratio of amplifying to non-amplifying hosts increases, concomitantly increasing disease risk for humans. This finding suggests that retaining a high abundance of non-amplifying hosts, or reducing the abundance of amplifying hosts, are ecological interventions that will reduce the risk of exposure of humans to infections such as Lyme disease or tick-borne encephalitis. Although trapping can be focused on specific types of rodents, some level of by-kill, and hence, new targeted technologies (such as those proposed in panel 3) need to be developed.

Management of anthropogenic resources and restoration of predator–prey dynamics offer additional opportunities for intervention. Synchronised planting in agricultural settings has the potential to reduce rodent breeding periods by extending fallow periods,¹⁰⁵ whereas nest box programmes to increase native owl populations¹⁰⁹ could contribute to landscapes of fear that deter rodent activity.¹¹⁰ However, adoption of such strategies can be constrained by local beliefs, such as associations of owls with witchcraft in some communities, highlighting the need to ground ecological strategies in local cultural contexts.¹¹¹ Both cost-effectiveness and cultural acceptability are crucial to the success of ecological rodent management. For example, in the Afro-Malagasy context, traditional approaches such as poison are often preferred due to the perceived short-term effectiveness.¹¹¹ Community-driven practices, such as fire-breaks and weeding to reduce rodent habitat in Nigerian rice fields (Harden C, unpublished data), illustrate the value of incorporating community knowledge into scalable interventions. Long-term, data-informed strategies such as the eradication of invasive coypu (*Myocastor coypus*) in the UK have been successful in part due to both ecologically and socially informed trapping.¹⁰⁵ Similar integrative approaches could prove effective for managing rodent-borne zoonoses. Given the complementary principles and objectives, broader initiatives such as agroforestry, biodiversity conservation, and urban sanitation hold key but underexplored potential for reducing rodent-borne zoonoses. Such preventive ecological countermeasures are more cost effective than containing threats after they emerge.^{49,112}

Future directions: research agenda

In this section, we seek to identify the research needs required to effectively harness ecological principles and develop more successful approaches for controlling rodent-borne zoonotic diseases.

Rodent disease ecology

Understanding rodent population dynamics is hindered by gaps in knowledge about rodent dispersal, as most studies rely on small-scale trapping grids. Although rodents disperse into human settlements and seasonally transmit infections, traditional mark–recapture methods primarily

estimate survival and abundance but miss key traits such as dispersal and individual fecundity. Calibrated index methods, combining mark–recapture with activity indices, and occasionally satellite imagery, offer some insights, but often do not identify rodent sources.^{113,114} Ethical concerns also arise when capturing and releasing potentially infected rodents near human dwellings. Emerging technologies, such as miniaturised radio collars and drones, could facilitate the tracking of movement patterns and exposure risks across space and time.

Reservoir hosts require more thorough investigation, particularly in recognising that communities of amplifying rodent species might collectively contribute to pathogen maintenance, with varying degrees of public health relevance. Throughout this paper, we have highlighted mpx as one such example in which the reservoir host(s) remain undetermined. Notably, the fact that some cohorts within a population (eg, age, sex, and immune status) could be driving the infection dynamics also needs to be considered.

Laboratory mouse models have advanced immunological research, but they do not fully reflect wild contexts. Innovations such as organ-on-a-chip technologies could enhance our understanding of complex immune interactions among rodent hosts exposed to diverse pathogen communities. Laboratory mice do not represent the immunological phenotypes of wild mouse populations; therefore, rewilding strategies have been used to expose laboratory-reared mice to natural infections and improve the translational validity of experimental findings.¹¹⁵

Research examining the ecological and social consequences of rodent culling is needed across systems. Targeting rodents alone can often be ineffective when culling does not have community support, or does not consider the larger ecosystem dynamics of rodent populations and their pathogens.¹⁸ For example, culling or removing rodents might increase movement, physiological stress, and pathogen shedding, thereby elevating human exposure risk.

Synanthropy

The relative contributions of direct and indirect human–rodent contact to pathogen spillover are difficult to disentangle across many disease systems. A stronger empirical basis for pathogen dose–response relationships would improve the design of targeted and culturally responsive interventions.

Rodent reservoirs could paradoxically improve and threaten food security in regions where they are not only an important part of local diets but also major pests that destroy crops and food stores. Understanding the consequences of interventions that restrict rodent hunting for consumption and pest control is important for minimising barriers to implementation and maximising co-benefits.

Research and intervention planning should integrate participatory approaches that engage affected

communities. For example, in regions where perceived disease risk is low but rodent-related damage and food losses are substantial, interventions might be more successful when their co-benefits for agricultural health and food security are well understood and communicated. Such approaches align disease control efforts with local priorities and thus enhance the ability for effective and sustained intervention.

Rodentation

Rodents are adapted to human habitats and are most likely to adapt to our countermeasures. Anticipating evolutionary responses will be necessary to maintain the long-term effectiveness of any new drugs or technologies. Just as insects have adapted to human control efforts (eg, insecticide-treated bed nets), rodents will also most likely adapt to human control efforts, albeit over longer time scales. To ensure the sustainability of interventions, the evolutionary responses of rodents to control measures need to be anticipated and accounted for.

How anthropogenic change interacts with rodent predation to shape the risk of zoonoses is unclear. Human activity reduces native rodent predators, whereas other predators (eg, red kites, red foxes) persist in urban settings. Humans and domesticated animals (eg, dogs, cats) also function as rodent predators, but these roles are rarely considered in ecological studies. The human influence on these dynamics and the subsequent effects on zoonotic transmission require more direct investigation.

Although the introduction of management practices guided by the dilution effect is attractive, the dilution effect needs to be first tested experimentally at scale, by changing the ratio of amplifying to non-amplifying hosts.⁴⁸

Development of public health systems

In addition to the socioecological approaches outlined in this Personal View, several health systems research, development, and intervention strategies exist to support spillover prevention at the source and foster resilience beyond outbreak response.

Prospective epidemiological and ecological studies in humans, rodents, and livestock will help to characterise the baseline burdens and distribution patterns of rodent-borne diseases and facilitate early detection. This baseline understanding is crucial for identifying high-risk areas and populations and for guiding intervention development, including vaccine strategies.

Programmes that focus on vulnerability to rodents and rodent-borne diseases by reducing rodent infestations, such as improved housing, food and grain storage, and sanitation, should also address structural factors (eg, improved livelihoods) to ensure programme sustainability.

Governance of human–rodent interactions via hunting, trade, and land use will need to be coordinated with

environmental (eg, conservation, forestry), agricultural, and urban planning sectors.

Conclusions

Rodent-borne zoonoses have caused substantial morbidity and mortality throughout human history, as illustrated by mpox, the global spread of which has prompted two public health emergencies of international concern since 2022. Threat reduction, for both endemic and emerging rodent-borne diseases, requires understanding the ecological mechanisms driving spillover and applying these insights for prevention. In this Personal View, we highlight three key pillars—rodent-borne disease ecology, synanthropy, and rodentation—that distinguish rodent-borne diseases from other zoonoses and present unique challenges and opportunities for proactive spillover prevention. These pillars reorient focus toward interventions suited to a rapidly changing, human-dominated planet, where spillovers are embedded within broader socioecological systems.

Limitations of traditional trap-and-kill strategies for disease prevention have become increasingly evident. A more effective approach requires a socioecological perspective that identifies spillover mechanisms alongside the dynamic feedbacks between human and rodent ecologies. These systems are characterised by complex, often non-linear feedback loops, which can be perturbed by changes in climate, land-use patterns, or shifts in human behaviour that often trigger rapid responses in rodent populations, and in turn, the risk of spillover. Historical patterns of rodentation provide valuable insights into these dynamics. Long-standing and adaptive practices, such as land clearing for food production, have repeatedly shaped human–rodent interfaces that facilitate disease emergence.¹¹⁶ Conversely, practices such as clean farming appear to reduce rodent abundance and associated health risks, suggesting that human-driven improvements in land and food system management could be leveraged to mitigate threats of future spillover. However, key knowledge gaps remain. Clarifying the underlying mechanisms driving these interactions, including how social and environmental changes influence temporal patterns of infection in rodents, human disease incidence, and intervention effectiveness, is an urgent research priority.

Given the uniquely close association between rodents and humans, prevention of rodent-borne zoonoses requires strategies that are grounded in both social and ecological systems. Such strategies include adopting emerging rodent control technologies embedded within an ecological framework, alongside community-based interventions that address local vulnerabilities, behaviours, and structural drivers. Social scientists will be key partners in testing and adapting interventions, and participatory approaches can help to identify barriers and opportunities overlooked by top-down strategies. Ultimately, prevention of rodent-borne zoonoses requires interventions targeting

prespillover processes within their socioecological contexts. This approach, we argue, offers the most potential to reduce the societal burden of rodent-borne zoonoses and build more resilient communities.

Contributors

All authors contributed to the conceptualisation of this paper. SF, JM, ADL, CH, DS, EF-C, NG, ONB, AD, and PJH contributed to the writing and visualisation of the original draft, and the reviews and editing of the manuscript. LM, KV, and JOL-S also contributed to the visualisation. ONB contributed to the writing of the original draft. RG, HH, NI, GHP, DR, NCS, KV, and JOL-S and contributed to the review and editing of the manuscript.

Declaration of interests

We declare no competing interests.

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