A call to action: Understanding land use-induced zoonotic spillover to protect environmental, animal, and human health

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Abstract

The rapid, global spread and human health impacts of SARS-CoV-2, the agent of COVID-19 disease, demonstrates humanity's vulnerability to zoonotic disease pandemics. Although anthropogenic land use change is known to be the major driver of zoonotic pathogen spillover from wildlife to human populations, the scientific underpinnings of land use-induced zoonotic spillover have rarely been investigated from the macro-ecology perspective. We call on colleagues to advance our knowledge of land use implications for zoonotic disease emergence. A wide range of disciplinary cosmologies, approaches, and tools are needed to identify the environmental triggers of spillover and inform the decisions needed to protect public health by reducing spillover risk as a biosecurity priority. We call for a mechanistic focus on the zoonotic pathogen "infect-shed-spill-spread" cascade and review the relevant literature, elucidating the current biases and information gaps. We also consider the opportunities for better instituting the necessary scientific collaboration, primary technical challenges, and policy and management issues that warrant particular attention.

Main

More than 70% of emerging zoonoses, infectious diseases that are transmitted from animals to humans, originate in wildlife[1]. The rapid, global spread and human health impacts of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the agent of COVID-19 disease) have led to calls for far greater controls on wildlife commerce and consumption. These measures, though warranted in high-risk situations, should be complementary to regulatory reforms to address land use change—the primary driver of pathogen transmission from wildlife to humans[2], a process known as zoonotic pathogen spillover[3]. When political and financial capital are wisely invested in measures to protect the health of ecosystems and their wildlife inhabitants, human health is a return on investment.

Land use change—which we regard as all anthropogenically-induced ecosystem change, in any ecosystem—operates through various mechanisms from local to regional scales to induce environmental stressors that: a) determine the abundance and distribution of wildlife, b) shape the dynamics of wildlife exposure to pathogens and susceptibility to pathogen infection, c) drive pathogen shedding from wildlife, and d) create novel contact opportunities facilitating pathogen spread between species (spillover), ultimately leading to human infection and further spread[2,4]. Hereafter, we refer to this “infect-shed-spill-spread” cascade simply referred to as land use-induced spillover. In Figure 1, we further describe and emphasize the heterogeneity inherent in this process. Note that while the term “shed” generally refers to the release of a pathogen into the environment, we use the term broadly to indicate the release of pathogen from the host in a manner that facilitates exposure of another mammal (e.g., shedding into saliva that could come into contact with a human or other animal through a bite wound or release of pathogen through slaughter[3]).

While the linkages between land use and wildlife disease dynamics are well recognized in concept, the scientific underpinnings have rarely been investigated from the macro-ecology perspective. As a result, there is neither a philosophy of managing land use so as to minimize zoonotic disease emergence, nor sufficient data to advance such a practice. A focused, applied research effort at the interface of landscape ecology,wildlife immunology, and disease ecology is required to develop an operational understanding of land use consequences for wildlife and human health. The results of this work are urgently needed to develop an integrated, holistic set of science-based policy and management measures enlightened by COVID-19 and other epidemics that effectively and cost-efficiently minimize zoonotic disease risk by preventing the ecological conditions that trigger the events that lead to zoonotic pathogen spillover.

Here we call on colleagues across the fields of environmental, wildlife, and human health to forge the interdisciplinary collaborations urgently needed to advance our knowledge of land use implications for zoonotic disease emergence. We call for a mechanistic focus on the zoonotic pathogen “infect-shed-spill-spread” cascade and review the relevant literature, elucidating the current biases and information gaps. We also consider opportunities for better instituting the necessary collaboration, as well as the primary technical challenges to progress. We conclude by discussing applications for policy and management decision making, noting issues that warrant particular attention.

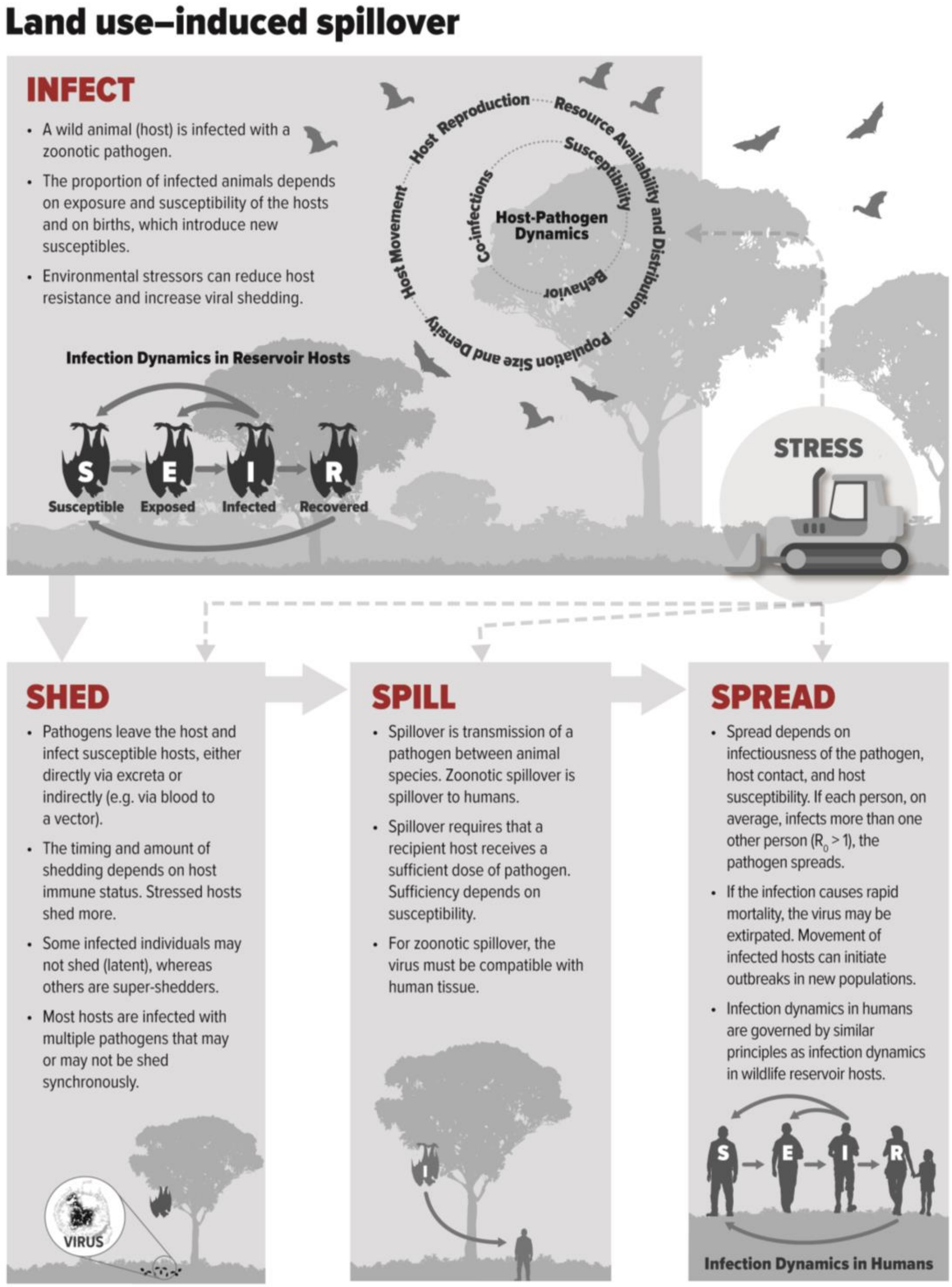

Fig. 1 Land use-induced spillover. Infect: Infection dynamics in the reservoir host are driven by the life-cycle of infection within and among hosts (susceptible-exposed-infected-recovered [SEIR] dynamics) that may include waning immunity, latency, or re-infections. The degree and distribution of infection are also driven by host susceptibility and co-infections, reproduction, and the myriad of factors that determine the spatial and temporal dynamics of host populations. Environmental stress affects almost every driver of infection dynamics.

Shed: The release of pathogen from the infected reservoir host may occur through shedding into the environment such as through respiratory secretions, urine, or feces, but can also occur through slaughter, butchering, and preparation of reservoir hosts for consumption, or through an animal bite (usually arthropods or mammals). Environmental stress influences pathogen excretion, especially when hosts are persistently or latently infected.

Spill: Zoonotic spillover is the passage of a pathogen from a vertebrate animal to a human. To establish a zoonotic infection, the human must receive an infectious dose through an appropriate route and the pathogen must overcome a series of within-human barriers, including receptor binding and the innate immune response.

Spread: A pathogen that can infect and spread among humans with an $R_0>1$ may, in the right circumstances, establish sustained human-to-human transmission.

Stress: Any type of anthropogenic land use change (acute or chronic stressor) may be sufficient to trigger spillover for a particular species in certain circumstances. We need to better understand these dynamics *in situ* in order to be able to prevent spillover.

Land Use-Induced Spillover

A person's risk of contracting a disease from wildlife depends on the degree and distribution of pathogen infection and shedding in wildlife populations, alongside the patterns of human-wildlife interaction[3]. This zoonotic infect-shed-spill-spread cascade is the fundamental process for zoonoses spillover[3], yet most studies intended to better inform spillover prevention—important as they are—work around the margins of the issue. For example, genetic characterization of wildlife viruses in nature, and improvements in disease detection in human communities, are essential but insufficient to prevent spillover events[5,6].

We propose land use-induced spillover as a priority arena for interdisciplinary focus to mobilize existing data, fill vital information gaps, and guide disease prevention measures. In particular, we call for timely, innovative investigations into land use influences on the biology and dynamics of zoonotic pathogens with the aim of preventing spillover into human populations by fostering landscape immunity, the ecological conditions that, in combination, maintain and strengthen the immune function of wild species within a particular ecosystem. This includes fostering the environmental conditions that promote animals behaving and moving across the landscape in ways that do not bring them into proximity to humans, or don't cause them to be aggregated into small spaces that produce disease outbreaks. The crux of this work is inquiry into the complex interactions between land use and disease dynamics: What are the ecological conditions that lead to: a) high prevalence of zoonotic pathogens in wildlife populations, b) wildlife shedding pathogens c) spillover of these pathogens into other species, ultimately humans, and d) further pathogen spread through the human population?

For an animal-origin virus like SARS-CoV-2 to result in a human epidemic or pandemic, an animal must, in the hierarchical sequence, become infected with a virus and shed live virus in sufficient quantities and circumstances for a viable pathogen to then spread to susceptible humans either directly or through intermediary animals or vectors[3]. Our call to scientific inquiry is based on the premise that we can identify and foster the ecosystem conditions that strengthen and maintain the immune function of inhabiting species thereby preventing periods and places of high prevalence that can initiate the infect-shed-spill-spread cascade. This paradigm recognizes that the mechanisms by which zoonotic pathogens cause human disease are far more complex than the mere act of human contact with infected animals in nature, under propagation (e.g., food and fur farms), or in commerce (e.g., distribution facilities, wildlife markets[3]). Avoiding further pandemics requires understanding the causal hierarchy of pathogen transmission from wildlife to humans (Fig. 2).

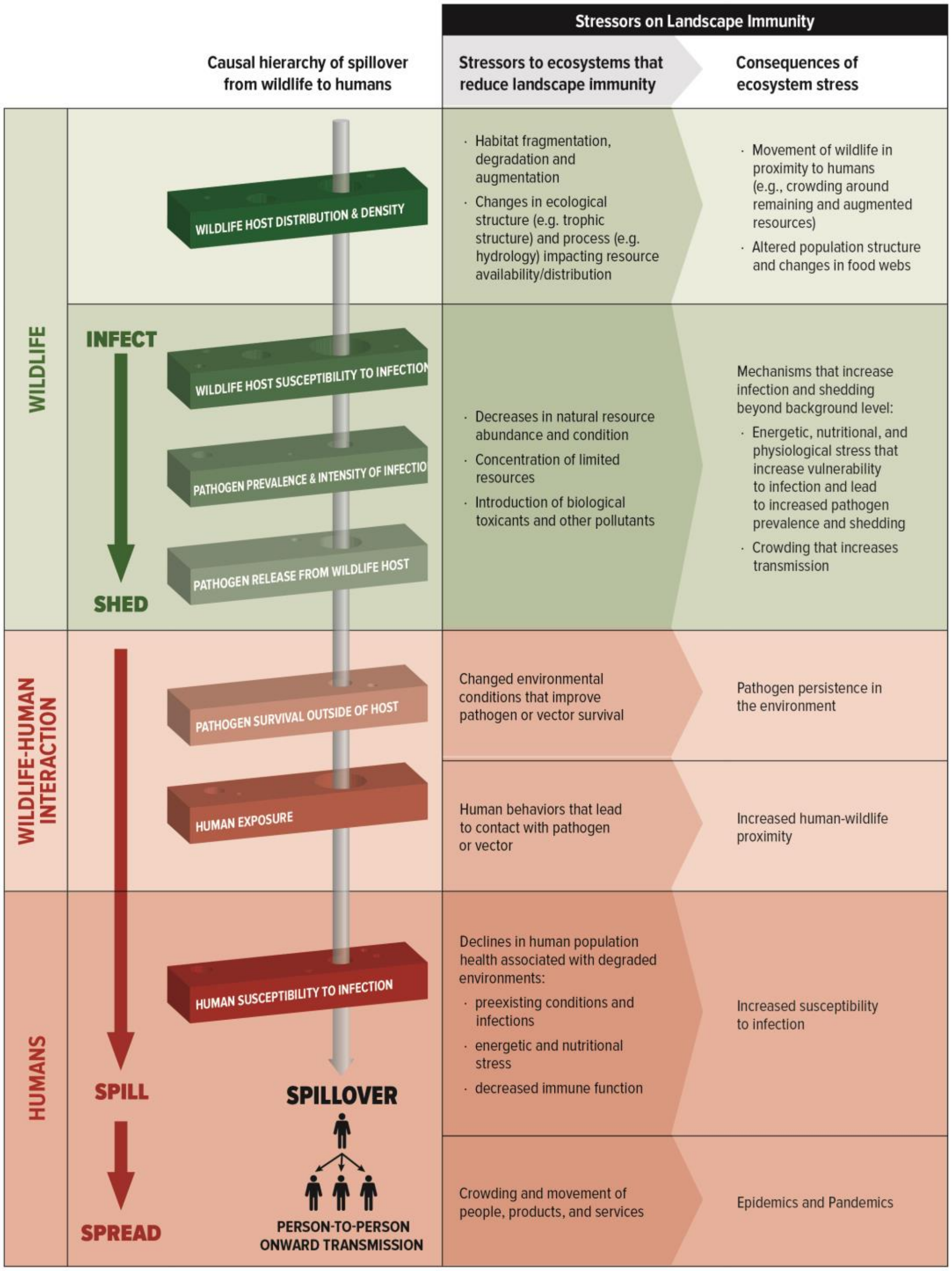

Fig. 2 The zoonoses spillover cascade: loss of landscape immunity as the pandemic trigger. Landscape immunity drives the distribution of spillover risk by determining where animals are, where they are infected, how intensively they are infected, and how intensively they are shedding at any point in space and time. The dynamics of wildlife-human proximity and interaction drive human exposure. Human behavior and connectivity facilitates onward transmission. All of these processes occur within a landscape context.

Studies of the infect-shed-spill-spread paradigm would seek to identify the origins and controls for the ecological conditions that cause high pathogen prevalence and shedding, ranging from anthropogenically-induced shifts in land use that influence wildlife immunity and pathogen survival to factors driving hyper-abundance of animals that result in high contact rates and generate outbreaks, such as feeding on human-provisioned resources (e.g., agricultural crops)[7]. With regard to spread, further investigation is needed into the drivers and controls for landscape-level factors influencing dynamics of proximity—the spatiotemporal land use parameters that determine the risk of human zoonoses infection via interaction with wildlife. From the most comprehensive perspective, this work would explore how the ecological conditions associated with various land uses influence the entirety of the infect-shed-spill-spread cascade from micro- to meta-scales across time and space.

In recent decades, zoonoses such as Ebola virus, influenza A (H1N1) pdm09 virus, influenza A (H7N9) virus, Middle East respiratory syndrome coronavirus (MERS-CoV), Hendra virus, and Nipah virus[3,8,9], have aptly demonstrated the interdependence of human, animal, and ecosystem health and that local land use decisions can have large-scale socio-economic consequences. Integrative concepts such as One Health emerged to address the human and animal health connections inherent in zoonotic disease[10,11]. Our proposal for an interdisciplinary focus on the infect-shed-spill-spread paradigm fits within and complements these and other dimensions of the One Health concept by, for example, including wildlife health as an essential component of global disease prevention and employing transdisciplinary approaches to investigate animal-to-human transmission[12,13]. To clarify the relatedness of One Health principles and practices to the proposed arena of inquiry, we provide definitions in Table 1 (Supplementary Material), which can serve as the foundation for a shared vocabulary. In Table 2 (Supplementary Material), we provide relevant references and the groundwork for a focused research agenda. Table 2 illustrates that studies to quantify the causal links between habitat change, physiological stress, susceptibility, and pathogen shedding are relatively rare, largely from the physiological rather than landscape science perspective, and limited in their spatial replication, range of possible immune assays, and insights into whether immune phenotypes are protective. Table 2 lays the foundation for an online, open-access database of research into land use-induced spillover processes.

Although the land use parameters that affect human health have been broadly conceptualized[2], how landscape conditions and processes influence the immune function and pathogen dynamics in wildlife across space and time is rarely robustly investigated[13]. We, therefore, suggest a conceptual framework to guide inquiries into the land use induce spillover processes (Fig. 2). To place the general concepts conveyed in the figure in a specific context, we offer below the example of pathogen spillover. We have chosen to illustrate these points using a bat to human transmission model because bats have been identified at the beginning of the infect, shed and spread sequence of several zoonotic diseases, including COVID-19, and bat pathogen dynamics are among the best studied within the landscape change context. However, such proceses are broadly applicable across other wildlife that can serve as zoonotic pathogen reservoirs, including primates, rodents, ungulates, carnivores, and a diverse range of birds:

A) Wildlife Distribution and Infection: Bat distribution, abundance, and density are determined by resource availability, princiapllay food and the availability of mates and roosting sites. The destruction and fragmentation of bat habitat limits key resources, such as food and roost sites.

Bats may thus be forced to change behavioral norms, for example forgoing nomadism to seek critical resources in human-dominated landscapes such as feeding on agricultural plants and roosting in parks or in buildings[8,14]. Accordingly, the likelihood and intensity of bat infection changes with the host population distribution, as bats that are stressed (e.g., nutritionally deprived or crowded around resources) are thought to be more likely to become infected[15].

B) Pathogen Shedding: Environmental stress likely also influences whether bats shed pathogens into the environment[16,17]. For example, in Australia, acute nutrient deprivation is thought to cause Pteropodid bats to have reduced ability to control pathogens and they shed multiple zoonotic viruses in extreme, brief, and spatially restricted pulses[18,19]. However, there is a paucity of research on bat immune function during shedding in response to stress. Currently, the parsimonious explanation is that bats are persistently infected with some zoonotic viruses, such as henipaviruses, but only shed these viruses when immunocompromised, much like humans shed herpesvirus through cold sores when stressed[19].

C) Pathogen Spread. Wildlife-human interaction is a key determinant of spillover. If a bat sheds virus in a remote wilderness, no human will be affected. If that same bat sheds virus while foraging on fruit trees in a village, or being slaughtered for human consumption, human exposure is more likely[4]. Finally, multiple environmental factors shape human susceptibility to zoonotic infections and the likelihood of onward transmission. The factors driving human susceptibility and transmission mirror the factors driving wildlife susceptibility and transmission (e.g., body condition, crowding), whereas human population size and connectivity determine the spatio-temporal scale of resulting epidemics, with the largest epidemics predicted to occur at extremes of land conversion[4].

We believe the proposed research agenda can catalyze an organizing framework for further collaborative study among scientific, human health, and conservation institutions. Such partnerships should focus on fundamental information gaps and help address two of the most limiting factors to putting the field in practice: a lack of scientific tools and research funding (Table 2, Supplementary Material). Many current tools that measure wildlife immune status are difficult to apply and interpret, and are impractical for the large sample sizes expected in field-based, spatiotemporal monitoring[13,20]. Investment is needed in reagents, such as monoclonal antibodies to assess immunity in non-model species[21], experiments to validate biomarkers of susceptibility and shedding in high-risk host-pathogen systems[22], and application of 'omics' approaches to develop new immunological tools[22,23]. Moreover, characterizing the relationships between land use, environmental conditions, immune defense, and infection dynamics requires field studies with broad spatial and temporal replication[13]. Thus, there is a need for a focused initiative to sample wildlife populations over space and time to characterize infection dynamics as influenced by landscape factors[13,24,25]. Like the calls for a Global Immunology Observatory for humans[26], the study of wildlife reseroirs of zoonotic pathogens should be an international priority that leads to mechanistic understanding of zoonotic spillover.

Research funding for interdisciplinary studies is notoriously lacking[27,28]. Nevertheless, programs such as the National Science Foundation's Coupled Natural-Human Systems[29] are increasingly making it feasible for multi-facted infectious disease studies. Investments in studies addressing the infect-shed-spill-spread cascade would magnify the value of the investments already made in programs like the Emerging Pandemic Threats PREDICT program that aimed to identify and map wildlife pathogens with zoonotic potential[30]. Also, while surveillance of human pathogens is essential for detection and control once an outbreak has occurred, human infection comes late in the causal chain of zoonotic disease emergence; broader prevention is possible by addressing the upstream stressors from ecological disruption that set the wildlife disease process in motion.

Studies of land use-induced zoonotic spillover should explore whether zoonotic disease emergence must largely be considered unpredictable due to data shortfalls or if we can develop sufficient prediction and thus management capacities for certain host-viral systems in specific contexts. As is the case for all biodiversity studies, the proposed work is hampered by the lack of baseline data on wildlife and their associated pathogens in native and introduced ranges. Organisms are in constant interplay with other species and their environment. Therefore, when species occurrence and biological data are available, they must be considered with respect to a chain of land use consequences: impacts on geophysical parameters which influence resource type and abundance; which in turn have implications for species diversity, abundance, and density at the population level; as well as animal nutrition and physiology which, among other things, regulate immune function and within-host processes following pathogen exposure at the individual level[19]. A further challenge is the ability of scientists to access and integrate relevant data across disciplines and information platforms. Investments need to be made to accelerate information tools and system interoperability.

The Call to Action Justified

Consideration of land use-induced zoonotic spillover processes as an interdisciplinary priority is justified from technical perspectives, as well as strategic pragmatism. Although there are existing fields of science focused on landscape ecology, as well as the immunology and epidemiology of wildlife and human infections, the specific area of interface for these disciplines as relates to the the mechanics of spillover from wildlife to humans is relatively unconceptualized and, therefore, grossly under-resourced. Recognizing the proposed work as an explicit arena for scientific inquiry will enable the rapid synthesis of ideas and approaches across disparate areas of technical investigation and practice. Only by exploring beyond the margins of current disciplinary boundaries can scientists develop the necessary questions and tools to discover and describe what hasn't thus far garnered their attention.

It is our hope that the proposed work will not only address a currently unoccupied inquiry "niche" that must be filled in order to make urgently needed scientific findings available for land use policy and management decisions, it will provide a framework for immediate action. Worldwide, modern epidemics of zoonotic disease, COVID-19 most recently, have awakened policy makers and land use managers to the lack of information available to guide decision making aimed at protecting human health from wildlife-based zoonoses. The critical need for science-based information that unpacks the causal mechanisms linking environmental stressors to zoonotic pathogen spillover has been recognized and demands for action-informing data are being voiced globally by various policy, research, and funding entities, including the Convention on Biological Diversity's Subsidiary Body on Scientific, Technical and Technological Advice, the Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services, and the US Agency for International Development.

All of these initiatives, as well as those that will certainly be added to the list, desperately need the knowledge derived from a better understanding of the zoonotic pathogen infect-shed-spill-spread paradigm in order to direct well-informed and cost-efficient decisions on behalf of human, animal, and environmental health. Preventing future zoonotic pandemics requires us to make the substantial, highly-focused investments in the proposed work from intellectual, technical, and policy perspectives that can only be driven by a bold call to fill a vital scientific niche.

Research Findings Applied

Policy Considerations

A comprehensive approach to biosecurity considers the risks that potentially harmful organisms pose to a wide range of assets, including the environment and human health[31]. A growing number of countries, Australia and New Zealand as examples, are developing broad biosecurity frameworks that cut across environmental, agriculture, and human health sectors[32]. Fostering landscape immunity should thus be regarded as a biosecurity imperative and actions taken to maintain and enhance landscape immunity as part of the national and global security agenda.

Increasingly, risk evaluation is mandated by international, national, and sub-national policies to improve measures to prevent potentially harmful organism from entry across jurisdicational borders and/or introduction into novel ecosystems[33,34]. In order to minimize the risk of future zoonotic epidemics, research is urgently needed to deepen our understanding of: a) what land use parameters are associated with low, medium, and high risk of zoonotic pathogen infection, shedding, spillover, and spreading in a specific context; b) what are the land use management options to minimize risk; and c) how can these risk management options be communicated in a manner that institutes the lowest risk land use practices fit to context. Since these risk management options will include various actions to reduce human-wildlife interaction, careful consideration needs to be made to promote biophilia rather than biophobia. Risk communication that instills disrespect or fear of wildlife could facilitate even greater human-wildlife conflict. For example, COVID-19 has greatly increased fear of bats worldwide, resulting in their mass culling events and a subsequent outcry by conservation organizations to focus on the societal drivers of the pandemic rather than the wildlife hosts[35].

These and other advances in the study of the land use factors that influence the infect-shed-spill-spread paradigm will help us understand and demonstrate how investments in landscape conservation provide returns for human health, as well as climate change, international trade, sustainable development, environmental justice and other policy issues associated with human well-being. The proposed work can help place, focus, and operationalize land use planning and protected area initiatives in the biosecurity context. However, unless new biosecurity initiatives are coordinated through a comprehensive policy strategy, the transfer of research findings into practical measures to prevent zoonotic spillover will be slow and largely fortuitous. In 2002, Reaser et al.[36] recommended a broad set of U.S. policy measures focused on wildlife disease prevention that have not yet been institionalized. Most recently, the World Health Organization, Food and Agriculture Organization, and World Organization for Animal Health collaborated in the development of a guide for addressing zoonotic disease at the national level[37]. The guide fails to raise awareness of or provide a framework for addressing land use policy and management as a fundamental aspect of zoonosis prevention.

Management Considerations

Even though human transformation of nature has reached unprecedented levels[38], we can reduce the risk of future pandemics by addressing the land use stressors influencing the zoonotic infect-shed-spill-spread paradigm. In practice, landscape immunity corresponds to ecological integrity[39]. Landscapes with high levels of ecological integrity such as structural intactness and connectivity, native biotic diversity and abundance, and generative trophic system relatedness and function provide biosecurity. Any land use practice that reduces ecological integrity and resilience erodes the barriers to zoonotic spillover (Fig. 2). Ideally, a focus on the infect-shed-spill-spread paradigm will help identify practical, context-specific land use metrics and measures to enhance landscape immunity and thus reduce the risk of zoonotic pathogen spillover to humans.

Minimizing anthropogenic habitat fragmentation and penetration, and minimizing the perimeter of habitat edges, should be one of the first principles in landscape management to reduce wildlife zoonoses risk[40]. In looking at the type and extent of human impacts, the risk of pathogen spillover varies considerably by landscape condition[12,41]. Penetrating the world's last large wild areas creates one set of risks, landscapes which are semi-wild with strong edge effect create a different set of risks[4], and intensely transformed landscapes with high human population density present an even greater suite of risks[42]. Thus, a practical approach is to organize conservation and distancing measures aimed at sustaining landscape immunity by the Three Global Conditions for Biodiversity Conservation and Sustainable Use framework[43].

Because interaction and connectivity among species and the environment define the essence of all life on the planet, promoting ecological connectivity is a conservation priority at local to global levels[44]. Conservation policy and practice must holistically navigate two realities: 1) that intact and connected nature is vital for the health of the biosphere and 2) human livelihood is derived from social contact that comes about through commerce, travel, and socio-cultural traditions. A challenge for land managers is navigating this "connectivity paradox". Land use decision makers need to simultaneously consider how to maintain and enhance landscape immunity while meeting the increasing demands for infrastructure expansion.

Conclusion

COVID-19 has taught us that humanity is highly vulnerable to zoonotic disease pandemics. Fragmented landscapes and fragmented solutions increase this vulnerability. As the planet succumbs to a variety of cumulative stresses on ecological systems, the infect-shed-spill-spread paradigm and associated studies of landscape immunity can serve as a new integrative path forward to safeguard natural systems and human health as a biosecurity priority. As a new focused arena for interdisciplinary study, investigations of the infect-shed-spill-spread paradigm can identify the factors that reduce landscape immunity and inform the policy and management decisions that must be taken to protect public health by proactively minimizing spillover risk. Scientists have a moral obligation to prioritize inquiry that serves the public good and, as necessary, challenge long-held disciplinary boundaries in order to do so. At this time, it is imperative that the relevant institutions mobilize the political, cultural, and financial encouragement.

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Supplementary Materials:

Tables S1-S2

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