Landscape immunology: Understanding land use influences on zoonotic spillover and public health

Authors: Raina K. Plowright[1]†*, Jamie K. Reaser[2,3,4]†, Harvey Locke[5], Stephen J. Woodley[6], Jonathan A. Patz[7], Daniel Becker[8], Gabriel Oppler[2] and Gary M. Tabor[2]*.

Affiliations:

[1] Montana State University, Bozeman, MT, USA.

[2] Center for Large Landscape Conservation, Bozeman, MT, USA.

[3] George Mason University, Fairfax, VA, USA.

[4] University of Rhode Island, Providence, RI, USA.

[5] Beyond the Aichi Targets Task Force IUCN World Commission on Protected Areas and Yellowstone to Yukon Conservation Initiative, Banff, CAN.

[6] IUCN World Commission on Protected Areas, Quebec, CAN.

[7] University of Wisconsin, Madison, WI, USA.

[8] Indiana University, Bloomington, IN, USA.

† Authors contributed equally as co-leads.

*Correspondence to: raina.plowright@montana.edu; gary@largelandscapes.org.

Abstract

The rapid, global spread and human health impacts of SARS-CoV-2, the agent of COVID-19 disease, demonstrate 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 the pathogen "infect-shed-spread paradigm" have rarely been investigated. We propose, describe, and justify "landscape immunology" as an applied, interdisciplinary field to advance our knowledge of land use implications for zoonotic disease emergence. Landscape immunology will identify the environmental triggers of spillover and inform the decisions needed to protect public health by reducing spillover risk as a biosecurity priority. We frame the terminology and base of knowledge for the field, elucidating the current biases and information gaps. We also consider the collaborative scientific opportunities presented by the new field, primary technical challenges to field establishment, 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, terrestrial and otherwise—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 susceptibility to pathogen infection, c) drive pathogen shedding from wildlife into the environment, and d) create novel contact opportunities facilitating pathogen spread between species[2,4]; hereafter simply referred to as the "infect-shed-spread paradigm". While the linkages between land use and wildlife disease dynamics are well recognized in concept, the scientific underpinnings have rarely been investigated. 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.

We call for a focused, applied research effort at the interface of landscape ecology and wildlife immunology in order 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 propose, describe, and justify a new interdisciplinary field to advance our knowledge of land use implications for zoonotic disease emergence. We provide supplementary information that frames the terminology and current base of knowledge for the field, elucidating the current biases and information gaps. We consider the collaborative scientific opportunities presented by the new field, as well as the primary technical challenges to field establishment. We conclude by discussing applications for policy and management decision making, noting issues that warrant particular attention.

Landscape Immunology Described

A person's risk of contracting a disease from wildlife depends on the degree and distribution of pathogen infection and shedding in wildlife populations, as well as the patterns of human-wildlife interaction[3]. This zoonoses infect-shed-spread paradigm 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 the next pandemic[5,6].

We propose "landscape immunology" as a new interdisciplinary field to mobilize existing data, fill vital information gaps, and guide disease prevention measures. We define landscape immunology as the study of land use influences on the biology and behavior of zoonotic pathogens with the aim of preventing spillover into human populations. The crux of landscape immunology 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) shedding of pathogens into the environment, and c) spread of pathogens to susceptible humans?

For an animal-origin virus like SARS-CoV-2 to result in a human epidemic or pandemic, an animal must, in 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]. Landscape immunology is based on the premise that we can identify and foster the ecosystem conditions that strengthen and maintain the immune function of inhabiting species ("landscape immunity") thereby preventing periods and places of high prevalence that can initiate the infect-shed-spread cascade. It 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 wildlife to human pathogen spillover (Fig. 1).

Landscape immunology seeks 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 density-dependent factors resulting from the hyper-abundance of animals attracted to human-provisioned resources (e.g., agricultural crops)[7]. With regard to spread, landscape immunology investigates 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, landscape immunology explores how the ecological conditions associated with various land uses influence the entirety of the infect-shed-spread paradigm from micro- to meta-scales across time and space.

In recent decades, zoonoses such as Ebola, influenza A virus (H1N1) pdm09, Influenza H7N9, 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]. Landscape immunology 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 landscape immunology, we provide definitions in Table 1 (Supplementary Material), which can serve as the foundation for a landscape immunology communication toolkit. In Table 2 (Supplementary Material), we provide relevant references and the groundwork for a research agenda for landscape immunology. Table 2 illustrates that studies to quantify the causal links between habitat change, physiological stress, susceptibility, and pathogen shedding are notably rare and limited in their spatial replication, scope of possible immune assays, and insights into whether immune phenotypes are protective.

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 investigated[13]. We, therefore, suggest a conceptual framework for landscape immunology to guide such inquiries (Fig. 1). To place the general concepts conveyed in the figure in a specific context, and because bats have been identified at the beginning of the infect, shed and spread sequence of several zoonotic diseases including COVID-19, we offer the example of pathogen spillover from bats to humans:

A) Wildlife Distribution and infection: Bat distribution, abundance, and density are determined by resource availability. 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 (e.g., migration) and seek critical resources in human-dominated landscapes (e.g., feeding on agricultural plants and roosting in parks or in buildings)[8,14]. Accordingly, likelihood and intensity of bat infection changes with the host population distribution, with bats that are stressed (e.g., nutritionally deprived or crowded around resources) being more likely to become infected.

B) Pathogen Shedding: Environmental stress also influences the likelihood of bats to shed pathogens into the environment[15,16]. For example, in Australia, acute nutrient deprivation is thought to cause Pteropodid bats to shed multiple zoonotic viruses in extreme, brief, and spatially restricted pulses[17,18]. However, there is a paucity of research on how bat immune systems function during shedding in response to stress. One theory is that bats are persistently infected with some zoonotic viruses but only shed these viruses when immunocompromised, much like humans shed herpesvirus through cold sores when stressed[18].

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 raiding crops in a village, or being slaughtered by a hunter, human exposure is more likely[4]. Land use also influences pathogen survival outside of the host. For example, in Bangladesh, Nipah virus survives well in date palm sap, collected for human consumption. If infected bats consume the sap, humans who drink the sap can be exposed to high viral doses[19]. 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].

Landscape immunology 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, and immune defense 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 pathogen dynamics as influenced by landscape factors[13,24,25].

Research funding for interdisciplinary studies is notoriously lacking[26,27]. Nevertheless, programs such as the National Science Foundation’s Coupled Natural-Human Systems program[28] are increasingly making it feasible for multi-facted infectious disease studies. Investments in landscape immunology studies 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[29]. Also, while surveillance of diseases in humans 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.

Landscape immunology will 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 species in specific contexts. As is the case for all biodiversity studies, landscape immunology 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[18]. 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.

Landscape Immunology Justified

Consideration of landscape immunology as a new field 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 humans, the specific area of interface for these disciplines as relates to the zoonoses infect-shed-spread paradigm is relatively unconceptualized and, therefore, grossly under-resourced. Landscape immunology as an explicitly recognized interdisciplinary field 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.

Landscape immunology 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 epizootics of 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 outputs of landscape immunology 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 landscape immunology from intellectual, technical, and policy perspectives that can only be driven by a bold call to fill a vital scientific niche.

Landscape Immunology 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[30]. 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[31]. 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 (e.g., https://ghsagenda.org/, accessed 13 May 2020).

Increasingly, risk evaluation is mandated by international, national, and sub-national policies to improve measures to prevent potentially harmful organism from entry across jurisdictional borders and/or introduction into novel ecosystems[32,33]. 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, 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 slaughter and a subsequent outcry by conservation organizations to focus on the societal drivers of the pandemic rather than the wildlife pathogen hosts[34].

These and other advances in landscape immunology 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. Landscape immunology 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 landscape immunology research findings into practical measures to prevent zoonotic spillover will be slow and largely fortuitous. In 2002, Reaser et al.[35] 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[36]. It fails to raise awareness of or provide a framework for addressing land use policy and management as a fundamental aspect of zoonoses prevention.

Management Considerations

Even though human transformation of nature has reached unprecedented levels[37], we reduce the risk of future pandemics by addressing the land use stressors influencing the zoonotic infect-shed-spread paradigm. In practice, landscape immunity corresponds to ecological integrity[38]. 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 erodes the barriers to zoonotic spillover (Fig. 1). Ideally, landscape immunology will help identify practical, context-specific land use metrics and measures to enhance landscape immunity and thus reduce the risk of zoonotic disease transfer 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[39]. In looking at the type and extent of human impacts, the risk of pathogen spillover varies considerably by landscape condition[12,40]. 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[41]. 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[42].

Because interaction and connectivity among species and the environment define the essence of all life on the planet, promoting landscape connectivity is a conservation priority at local to global levels[43]. 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, landscape immunology can serve as a new integrative path forward to safeguard natural systems and human health as a biosecurity priority. As a new interdisciplinary field, landscape immunology can catalyze the research necessary to identify the triggers for zoonotic disease spillover 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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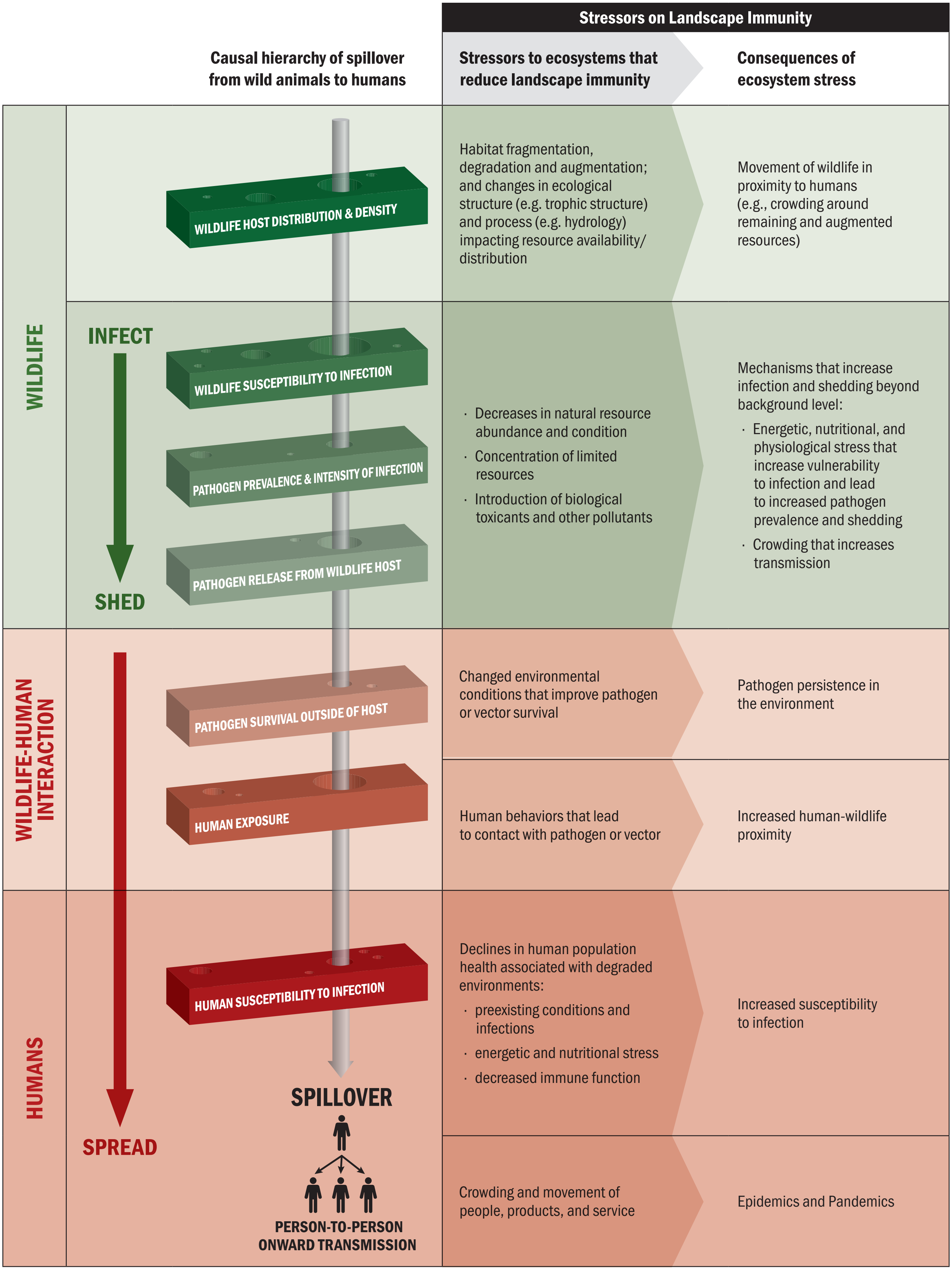
Figures and supplemental information

Fig. 1: 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.

Supplementary Materials:

Tables S1-S2



	Causal hierarchy of spillover from wild animals to humans	Stressors on Landscape Immunity	
		Stressors to ecosystems that reduce landscape immunity	**Consequences of ecosystem stress**
WILDLIFE	WILDLIFE HOST DISTRIBUTION & DENSITY	Habitat fragmentation, degradation and augmentation; and changes in ecological structure (e.g. trophic structure) and process (e.g. hydrology) impacting resource availability/ distribution	Movement of wildlife in proximity to humans (e.g., crowding around remaining and augmented resources)
WILDLIFE INFECT SHED	WILDLIFE SUSCEPTIBILITY TO INFECTION PATHOGEN PREVALENCE & INTENSITY OF INFECTION PATHOGEN RELEASE FROM WILDLIFE HOST	· Decreases in natural resource abundance and condition · Concentration of limited resources · Introduction of biological toxicants and other pollutants	Mechanisms that increase infection and shedding beyond background level: · Energetic, nutritional, and physiological stress that increase vulnerability to infection and lead to increased pathogen prevalence and shedding · Crowding that increases transmission
WILDLIFE-HUMAN INTERACTION	PATHOGEN SURVIVAL OUTSIDE OF HOST	Changed environmental conditions that improve pathogen or vector survival	Pathogen persistence in the environment
WILDLIFE-HUMAN INTERACTION	HUMAN EXPOSURE	Human behaviors that lead to contact with pathogen or vector	Increased human-wildlife proximity
HUMANS	HUMAN SUSCEPTIBILITY TO INFECTION	Declines in human population health associated with degraded environments: · preexisting conditions and infections · energetic and nutritional stress · decreased immune function	Increased susceptibility to infection
HUMANS SPREAD	SPILLOVER PERSON-TO-PERSON ONWARD TRANSMISSION	Crowding and movement of people, products, and service	Epidemics and Pandemics

Fig. 1: 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.

Supplementary Materials for

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†Authors contributed equally as co-leads

[1] Montana State University, Bozeman, MT, USA.
[2] Center for Large Landscape Conservation, Bozeman, MT, USA.
[3] George Mason University, Arlington, VA, USA;
[4] University of Rhode Island, Providence, RI, USA.
[5] Beyond the Aichi Targets Task Force IUCN World Commission on Protected Areas and Yellowstone to Yukon Conservation Initiative, Banff, CAN.
[6] IUCN World Commission on Protected Areas, Quebec, CAN.
[7] University of Wisconsin, Madison, WI, USA.
[8] Indiana University, Bloomington, IN, USA.

Correspondence to: raina.plowright@montana.edu; gary@largelandscapes.org

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Tables S1 to S2

Table S1.

Landscape immunology terms framework

Term	**Definition**	**Source**
Biosecurity	A strategic and integrated approach to analyzing and managing relevant risks to human, animal and plant life and health and associated risks for the environment	International Food Safety Authorities Network, Biosecurity: An integrated approach to manage risk to human, animal and plant life and health. *INFOSAN Information Note* (2010).
Conservation physiology	An integrative scientific discipline applying physiological concepts, tools, and knowledge to characterizing biological diversity and its ecological implications; understanding and predicting how organisms, populations, and ecosystems respond to environmental change and stressors; and solving conservation problems across the broad range of taxa (i.e. including microbes, plants, and animals).	S. J. Cooke, L. Sack, C. E. Franklin, A. P. Farrell, J. Beardall, M. Wikelski, S. L. Chown, What is conservation physiology? Perspectives on an increasingly integrated and essential science. *Conserv. Physiol.* **1** (2013), doi:10.1093/conphys/cot001.
Disease ecology	Study of the population-level patterns and dynamics of infectious diseases—how transmission, prevalence, and consequences of disease change in space and time; how interactions between pathogens, hosts and environment drive these changes; why pathogens cross species barriers; and how control strategies can reduce disease transmission and prevalence.	K. Wilson, A. Fenton, D. Tompkins, *Wildlife Disease Ecology: Linking Theory to Data and Application* (Cambridge University Press, 2019). P. J. Hudson, A. P. Rizzoli, B. T. Grenfell, J. A. P. Heesterbeek, A. P. Dobson, *Ecology of Wildlife Diseases* (2002).
Ecoimmunology	Field of study that aims to explain variation in individual immune phenotypes and to understand their fitness consequences.	A. B. Pedersen, S. A. Babayan, Wild immunology. *Mol. Ecol.* **20**, 872–880 (2011).

		G. E. Demas, D. A. Zysling, B. R. Beechler, M. P. Muehlenbein, S. S. French, Beyond phytohaemagglutinin: assessing vertebrate immune function across ecological contexts. *J. . Anim. Ecol.* **80**, 710–730 (2011).
Ecological resilience	Ecological capacity for renewal in a dynamic environment.	L. H. Gunderson, Ecological Resilience—In Theory and Application. *Annu. Rev. Ecol. Syst.* **31**, 425–439 (2000).
Environmental stress	Adverse abiotic or biotic conditions that increase physiological stress of an organism over long time spans and can cause immunosuppression.	K. Acevedo-Whitehouse, A. L. Duffus, Effects of environmental change on wildlife health. *Phil. Trans. R. Soc. Lond. B.: Biol. Sci*. **364**, 3429–3438 (2009).
Landscape epidemiology	Describes how the temporal dynamics of host, vector, and pathogen populations interact spatially within a permissive environment to enable transmission. It also aims at understanding the vegetation and geologic conditions that are necessary for the maintenance and transmission of a particular pathogen.	N. N. Emmanuel, N. Loha, M. O. Okolo, O. K. Ikenna, Landscape epidemiology: An emerging perspective in the mapping and modelling of disease and disease risk factors. *Asian Pac. J. Trop. Dis.* **1**, 247–250 (2011). R. S. Ostfeld, G. E. Glass, F. Keesing, Spatial epidemiology: an emerging (or re-emerging) discipline. *Trends Ecol. Evol.* **20**, 328–336 (2005).
Landscape immunology	Interdisciplinary, applied field that identifies and manages the landscape-level stressors that influence immune function of wildlife inhabiting those landscapes and	Herein

	the dynamics of proximity of wildlife and people	
Landscape immunity	A condition of ecosystems that strengthens and maintains the immune competence of inhabiting species in order to prevent zoonotic pathogen contraction, shed, and spread to humans.	Herein
Macroecology	The study of large-scale patterns in animal abundance, diversity, and distributions	K.J. Gaston, T.M. Blackburn, *Patterns and Processes in Macroecology* (2000)
Macroimmunology	Expands ecoimmunology into macroecological approaches that aim to identify broad spatial patterns in defense	D. J. Becker, G. F. Albery, M. K. Kessler, T. J. Lunn, C. A. Falvo, G. Á. Czirják, L. B. Martin, R. K. Plowright, Macroimmunology: The drivers and consequences of spatial patterns in wildlife immune defence. *J. Anim. Ecol.* **89**, 972–995 (2020).
One Health	A collaborative, multisectoral, and transdisciplinary approach (working at the local, regional, national, and global levels) with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment.	E. P. J. Gibbs, The evolution of One Health: a decade of progress and challenges for the future. *Vet. Rec.* **174**, 85–91 (2014).

Table S2.

Landscape immunology data challenges, data needs, cases studies and limitations on inference

<table>
<tr><th colspan="2">Data challenges and needs</th></tr>
<tr><th>Data challenge</th><th>Critical need</th></tr>
<tr><td>Studies examining mechanistic links among habitat change, physiological stress, immunity, and infection outcomes in wildlife studies are rare, especially for reservoir host species (<i>1–3</i>).</td><td>Measures of stress response (glucocorticoid hormones) and immunity, as well as infection state and shedding intensity, are needed across habitat gradients in reservoir hosts like bats.</td></tr>
<tr><td>Although many ecoimmunology studies sample multiple wildlife populations, few address anthropogenic drivers and most have low spatial replication, especially when sampling wildlife over large extents (<i>4</i>).</td><td>Spatial (and temporal) studies that sample reservoir hosts across different environmental conditions to statistically link environmental stressors with immune changes, likelihood of infection, and intensity of pathogen shedding.</td></tr>
<tr><td>Ecoimmunology studies often measure only one or very few metrics, but single, general immune measures cannot provide insight into whether metrics correlate with protection (<i>5</i>).</td><td>Determining protective immune measures (those that decrease susceptibility and shedding) requires temporal and spatial replication or experimental manipulations (<i>5</i>).</td></tr>
<tr><td>Ecoimmunology studies are limited by a lack of reagents to measure immune components in non-model species, although some reagents can be adapted from domestic animals (<i>6</i>).</td><td>Genomics and transcriptomics can allow designing primers to quantify expression of immune genes relevant to key pathogens (<i>7</i>, <i>8</i>). Sequencing and bioinformatics are costly and gene expression does not always correlate with functional signaling proteins.</td></tr>
<tr><td>A heightened immune state of wild animals can indicate a stronger immune defense or a recent (or active) infection, and it is typically difficult to interpret such data in field systems without robust measurements of both (<i>9</i>).</td><td>Experimental validations can help develop immunity biomarkers for field studies. This captive approach was recently used for house sparrows, where expression of key cytokines indicated high West Nile virus resistance (<i>10</i>).</td></tr>
<tr><th colspan="2">Examples of studies linking ecological integrity, wildlife physiology, and the infection-shed-spread paradigm of reservoir hosts, alongside key limitations on inference</th></tr>
<tr><th>Ecological integrity and susceptibility to infection</th><th>Limitations</th></tr>
<tr><td>Urban habituation of wildlife is associated with immune impairment (<i>11</i>)</td><td>Few urban studies link immunity and susceptibility</td></tr>
</table>

Mercury exposure in wildlife is linked with weaker immune response (*12*, *13*)	Functional measures but specific to one pathogen or antigen
Wildlife at the latitudinal limits of their geographic range may have increased susceptibility (*14–18*)	Sampling is often temporally asynchronized, and spatial replication is generally low
Primates experiencing nutritional stress had higher cortisol and were more likely to be infected (*19*)	No habitat gradient, immunity not quantified
Meta-analysis suggests deforestation is generally associated with more physiological stress, weaker immunity, and greater infection prevalence (*20*)	Immune measures are general and restricted to leukocytes
Ecological integrity and pathogen shedding	**Limitations**
Spatial patterns in immunoglobulins predicted spatial intensity of nematode shedding in red deer (*21*)	Fine-scale sampling but across a small spatial extent
Habitat fragmentation is associated with poor condition, few leukocytes, high chronic stress, and higher odds of astrovirus shedding in bats (*22*, *23*)	Generally small spatial scale, immune measures are general
Bats experiencing nutritional stress and poor condition during a food shortage had higher prevalence of Hendra virus antibodies (*24*)	No habitat gradient, no spatial or temporal replication, immunity not quantified
Multiple viruses were shed by bats in an extreme and synchronized shedding pulse (*25*)	Environmental stress was hypothesized as the underlying driver, but physiological and immunological data were not collected
Wild ungulates experiencing nutritional stress were in poor body condition and shed more parasites (*26*)	No habitat gradient, immunity not quantified
Experimental increases in glucocorticoid hormones amplify viremia and infectious periods in birds (*27*)	Captive experiment, not linked to habitat

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