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REPORT OF THE SCIENTIFIC TASK FORCE ON PREVENTING PANDEMICS

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Report of the Scientific Task Force on Preventing Pandemics

Convened by the Harvard Global Health Institute and the Center for Climate, Health, and the Global Environment at Harvard T.H. Chan School of Public Health

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Executive summary and key findings

No one wants to endure another pandemic the likes of COVID-19. Yet, the likelihood of another such pandemic occurring may be greater than ever. How to prevent the next pandemic was the core question addressed in the following report. The Scientific Task Force on Preventing Pandemics convened by the Harvard Global Health Institute and the Center for Climate, Health, and the Global Environment at Harvard T.H. Chan School of Public Health evaluated the latest research on what forces contribute to pathogen spillover, what actions are warranted to curtail this risk, and what more we must learn to make wiser investments directed at forestalling another pandemic.

The report contains key findings and recommendations for research and action to inform pandemic prevention. The task force found that evidence strongly establishes spillover of viruses from wildlife into people, sometimes via livestock, as the root cause of pandemic risk. Spillover of the viruses currently understood to have pandemic potential occurs from land use change, and in particular the destruction of tropical forests, expansion of agricultural lands, especially near human settlements, livestock and farmed wildlife intensification, and wild animal hunting and trade.

While vaccines, drugs, tests, and healthcare system strengthening are critical to contain disease outbreaks once they occur, they do not address spillover or fully address pandemic risk. At the same time, spillover prevention activities such as tropical forest conservation afford many benefits, including carbon sequestration which is more important than ever given the findings of the Intergovernmental Panel on Climate Change's Sixth Assessment Report.

Key findings of the report include:

- Infectious pandemic risk originates predominantly from spillover of viruses from wildlife into people, sometimes via farmed animals.
- Viral discovery in wild animals has uncovered thousands of viruses from viral families that contain zoonoses, yet millions of unknown viral species remain.
- Land use change, wild animal hunting, wildlife trade, and animal farming are primary drivers of viral zoonotic spillover.
- Forest conservation activities can reduce risk of zoonotic disease spread.
- Current investments in addressing drivers of spillover are small in comparison to the direct economic losses from COVID-19, even when these are annualized over a century.

No more than $4 billion are spent each year worldwide on spillover prevention activities, whereas COVID-19 alone has resulted in an estimated global GDP loss of US$4 trillion dollars, or roughly $40 billion per year for a century.

The task force recommends actions directed at spillover prevention that include greater investments in forest conservation, especially in the tropics; better biosecurity around livestock and wild animal farms; and establishment of One Health Platforms that work to reduce spillover risk. The report also recommends that current investments in strengthening healthcare systems and One Health platforms in low- and middle-income countries be leveraged to jointly advance conservation, animal and human health, and spillover prevention.

The report makes clear that more must be learned to optimize where and when investments in spillover prevention interventions are made. The effectiveness of interventions has been assessed in small studies, but it must be evaluated at scale, and with full consideration of their economic, ecological, and social welfare impacts. More research can help pinpoint where viral zoonoses with high pandemic risk may be most likely to emerge and how to better curtail risk of spillover within wildlife trade. Viral discovery in wildlife can help inform where spillover prevention activities should be focused while also benefiting wildlife conservation.

The report will be distributed widely to high-level decision makers and leaders of private, non-profit and philanthropic organizations as well as government and UN agencies. The task force report is intended to serve as scientifically sound reference for the many important discussions taking place globally about the steps needed to greatly reduce the chances of a future pandemic.

Introduction and scope

Preventing another pandemic with the magnitude of COVID-19 is of paramount importance to every human concern. To date, most attention and financing to address future pandemics has been directed towards pandemic preparedness. These include vaccine and drug development, better human health surveillance, and healthcare system strengthening. As critical as these actions are, they do not fully address a root cause of pandemic risk: the spillover of pathogens between animals and people.

The need to consider actions that prevent spillover as a key objective in pandemic prevention has been underscored by the difficulties in containing COVID-19. Even with the unprecedented short interval between disease emergence and vaccine availability and availability of testing, the disease continues to spread, aided by the evolution of variants that are more contagious, political divisions, and the spread of misinformation.

Furthermore, reliance on post-spillover interventions must be considered in light of rapid global loss of biological diversity and an unstable climate. Vaccines, drugs, and tests neither buffer against these drivers of infectious disease emergence, nor do they address their potential to damage human health and welfare more broadly. However, actions directed at spillover prevention, such forest conservation, offer the potential to reduce pandemic risk, avoid more expenditures on post-spillover containment, and reduce damages from climate change.

The Harvard Global Health Institute (HGHI) and the Center for Climate, Health, and the Global Environment at Harvard T.H. Chan School of Public Health (Harvard Chan C-CHANGE) have convened a Scientific Task Force with the objective of creating a report that summarizes scientific findings pertinent to pathogen spillover as a root cause of pandemic risk, identifying research needed to better characterize spillover risk and generating solution-oriented recommendations to prevent pathogen spillover.

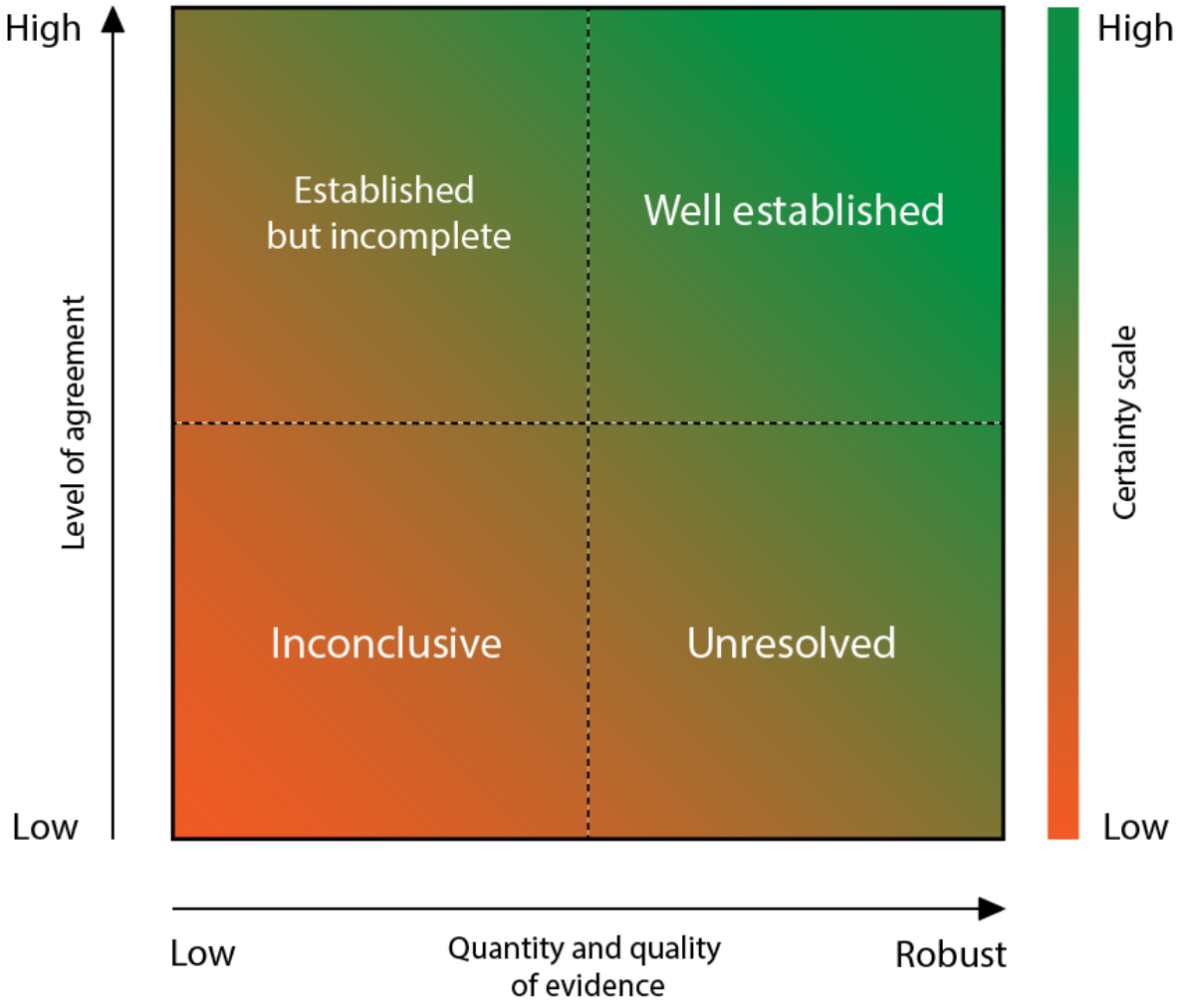
The Task Force's scope of work is limited to considering science that bears upon emerging pathogens most likely to cause rapid and global societal disruption. This puts out of scope antimicrobial resistance, for example, even though antimicrobial resistant organisms pose a major threat to human health around the world. The report also does not evaluate evidence pertaining to bioterrorism.

This project was conducted between May 10, 2021 and August 6, 2021. Task force members contributed to the creation of a report outline based upon the objectives above. When the outline was finalized, semi-systematic literature reviews were conducted to identify peer-reviewed research studies that provide the substance of the

report's sections. Based on these studies and the expertise of the task force members, key messages and unknowns were identified. Each key message was given an evidence grade to provide a qualitative assessment of confidence (see below).

Evidence Grading

This report uses an evidence grading framework adopted from the Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services (IPBES).



Specific findings in this report are given with the following labels indicating a qualitative assessment of confidence:

Well established (WE) – comprehensive meta-analysis or other syntheses/multiple independent studies that agree.

Established but incomplete (EI) – general agreement although only a limited number of studies exist but with no comprehensive synthesis, or the studies that do exist imprecisely address the question.

Unresolved (UR) – multiple independent studies exist but conclusions do not agree.

Inconclusive (IC) – existing as or based on a suggestion or speculation; no or limited evidence.

Chapter 1: Recent pandemic infections

1.1 Overview of Recent Pandemic Infections

The World Health Organization defines a pandemic as, “an epidemic occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people.” [1a]

1.2 Trends in Emergence

1.2.A Infectious pandemic risk originates predominantly from spillover of viruses from wildlife into people, sometimes via farmed animals. (WE)

1.2.B Emerging infectious disease events are increasing in frequency over time. (EI)

Emerging infectious diseases (EIDs) have been increasing in frequency over the past five decades.[2,3] EIDs are predominantly zoonoses that spread from animals to humans.[4,5] 50% of EIDs originate in wildlife, with that proportion increasing in recent decades.[6] Among all pathogen types, viruses are the most likely to cause disease emergence and have greatest pandemic risk.[7–11] 1.67 million unknown viral species from key zoonotic viral families are projected to exist in animal reservoirs. Of these unknown viruses, between 631,000 and 827,000 may have zoonotic potential.[12]

[a] What defines a pandemic differs among authoritative agencies, such as the World Health Organization, the U.S. Centers for Disease Control, and reference texts, such as the International Epidemiology Association's Dictionary of Epidemiology. For the purposes of this report, we generally refer to pathogens with pandemic potential, which we mean as the potential to infect large numbers of people across many nations and continents.

Chapter 2: What are the sources of viral spillover?

2.1 Animals of Interest for Pathogen Spillover

2.1.A Wildlife with close association to people are most likely to be the source of spillover. (WE)

2.1.B Bats are more permissive hosts to viruses and may be able to tolerate highly pathogenic viruses. (EI)

Certain animal taxa, as well as domesticated animals, have been identified as harboring more zoonotic viruses. Bats, rodents, and primates have been found to harbor a higher proportion of zoonotic viruses than other groups of species.[13–18]

Bats are reservoirs for a diversity of viral groups associated with human disease, including coronaviruses (SARS), paramyxoviruses (Nipah), filoviruses (Ebola) and rhabdoviruses (rabies).[15] Bats may have an exceptional ability to host viruses without presenting clinical disease, which makes them an ideal reservoir host for viruses. This may result from their unique immune response to infection which mitigates clinical disease while clearing the virus.[19]

Wild rodents have been found to be a major source of spillover for arenaviruses (Lassa) and bunyaviruses (Hanta),[16] while primates have been the primary reservoir for zoonotic retroviruses (e.g., HIV) spillover.[18,20]

Mollentze and Streicker (2020) found that the proportion of viruses that infect humans varies minimally across reservoir taxonomic orders. Their results suggest that the number of human-infecting viruses increases proportionately to the total number of viruses maintained by each reservoir group. This is in turn explained by the number of animal species within each group.[13,21] Rodents and bats, for example, collectively comprise 60% of all mammalian diversity.

Animals associated with zoonotic viruses have been less likely to be threatened with extinction and more resilient to human impacts, such as land use change, pollution, and invasive species.[13,22] More abundant and generalist species that adapt to humanized environments generally have more opportunity for contact with livestock and people. Among threatened wildlife species, those with population reductions owing to exploitation and loss of habitat may be more likely to share viruses with humans.[13]

Similar to findings of spillover in wild animals, the number of viruses shared between domesticated animals and humans scales with livestock abundance. Domesticated animals also share more zoonotic viruses with humans than those known at present in wild animals.[13,21]

Wild aquatic birds maintain a large, genetically diverse pool of influenza A viruses, which can supply novel genetic material for genetic shift in influenza viruses in mammals and, ultimately, humans.[23] Low pathogenic avian influenza (LPAI) viruses have been isolated from at least 105 wild bird species of 26 different families. Birds of wetlands and aquatic environments constitute the major natural LPAI virus reservoir.[24] LPAI can convert to highly pathogenic avian influenza (HPAI) through relatively minor genetic changes. HPAI outbreaks have occurred across the globe in the past few decades, including the highly pathogenic Asian avian influenza A(H5N1) virus. H5N1 was first detected in 1996 among geese in China and in humans the following year during a poultry outbreak in Hong Kong. It has since been detected in poultry and wild birds in more than 50 countries in Africa, Asia, Europe, and the Middle East.[25]

Chapter 3: Which viruses are most likely to cause pandemics?

3.1 Mode of Transmission

3.1.A. Zoonotic viruses of pandemic potential are more likely to be transmitted by respiratory aerosols than arthropods at a global scale. (EI)

Non-segmented, non-vector-borne viruses with relatively low host mortality have been found to have the highest likelihood of transmissibility among humans.[26,27] Conversely, Johnson et al. found that approximately 40% of zoonotic viruses required arthropod vectors for transmission to humans, with vectors providing an effective transmission bridge of diseases from animals that do not normally contact humans.[16]

While respiratory transmission may be the mode of transmission most likely to result in a pandemic, the rapid spread of Zika virus, which moved from the eastern to the western hemisphere from 2013-2015, indicates the potential of widespread transmission of vector borne viral zoonoses.

HIV also underscores that sexual transmission can result in a pandemic, especially from a retrovirus with a long latency period between infection and onset of disease symptoms.

3.2 Host Plasticity

3.2.A Viruses with high host plasticity are more likely to spill over and have broader geographic spread. (EI)

Viruses capable of infecting a greater diversity of hosts may have higher likelihood of emergence[11] and greater pandemic potential.[16]

Among coronaviruses, risk of emergence associates with the ability of a virus to infect different species of mammals. Among bats, a natural reservoir for alpha and beta coronaviruses (SARS, MERS and COVID-19 are caused by beta-coronaviruses), host switching by coronaviruses may be common, with Asian and African coronaviruses showing greater host plasticity than those found in Latin America. Given that host plasticity may predict pandemic risk, coronavirus spillover in Asia and Africa may be more probable than spillover in South America, though the mechanisms underlying differences in viral host plasticity and its consequences are not well understood.[28]

3.3 Viral Transmissibility in Humans

Zoonotic viruses that are genetically adapted to spread among humans are more likely to cause outbreaks following spillover. COVID-19 mutations during its global spread led to variants that were significantly more transmissible than the original viral strained recognized in China. Zoonotic viruses that do not efficiently spread among people are less likely to cause pandemics.

3.4 Key Unknowns

1. Can specific viral attributes, such as their genomes, be used to predict spillover risk, host plasticity and pandemic potential?
2. Can viral genomes inform approaches to viral discovery, that may, for instance, identify viruses previously thought to be of low human disease risk?
3. Does viral discovery research in wild animals increase spillover risk?

Chapter 4: Where will the next pandemic most likely begin?

4.1 Hotspot Analysis

Predicting where the next pandemic may emerge can be done through determining emergence hotspots based on historical emergence data. Jones et al. analyzed a database of all known emerging infectious diseases to quantify the likelihood of a region to source an emerging infectious disease that originates in wildlife. This analysis identified hotspots globally but especially in parts of East Africa, South Asia and South East Asia.[29]

Other approaches to hotspot analysis have yielded different results. Keesing et al. used historical emergence data classified by drivers and location of emergence events and found that the most emergence events for zoonotic infectious diseases in humans from 1940–2005 occurred in the United States.[22] A review of all outbreaks reported to the World Health Organization between 1996 and 2009 found that 53% of all emerging infectious disease outbreaks occurred in Africa.[30]

One limitation of hotspot analysis based on historical emergence is that reporting bias can play a major role in shaping understanding of past events. Adjusting for reporting bias, as Allen et al. and others have done, is important for reliable outputs.[3]

Analysis on historical emergence may also neglect areas where disease ecosystems are primed for emergence but one or a few factors necessary for zoonotic disease transmission have not yet been set in motion. Several studies have begun to apply observed traits of disease ecosystems prone to emergence in identifying future hotspots.

Allen et al., for example, found that tropical regions in North America, Asia, Central Africa, and regions in South America have extensive areas of predicted emerging infectious disease occurrence, while areas of high population outside the tropics, such as cities in Europe, the United States, Asia, and Latin America also may be high risk (see Figure 1).[3]

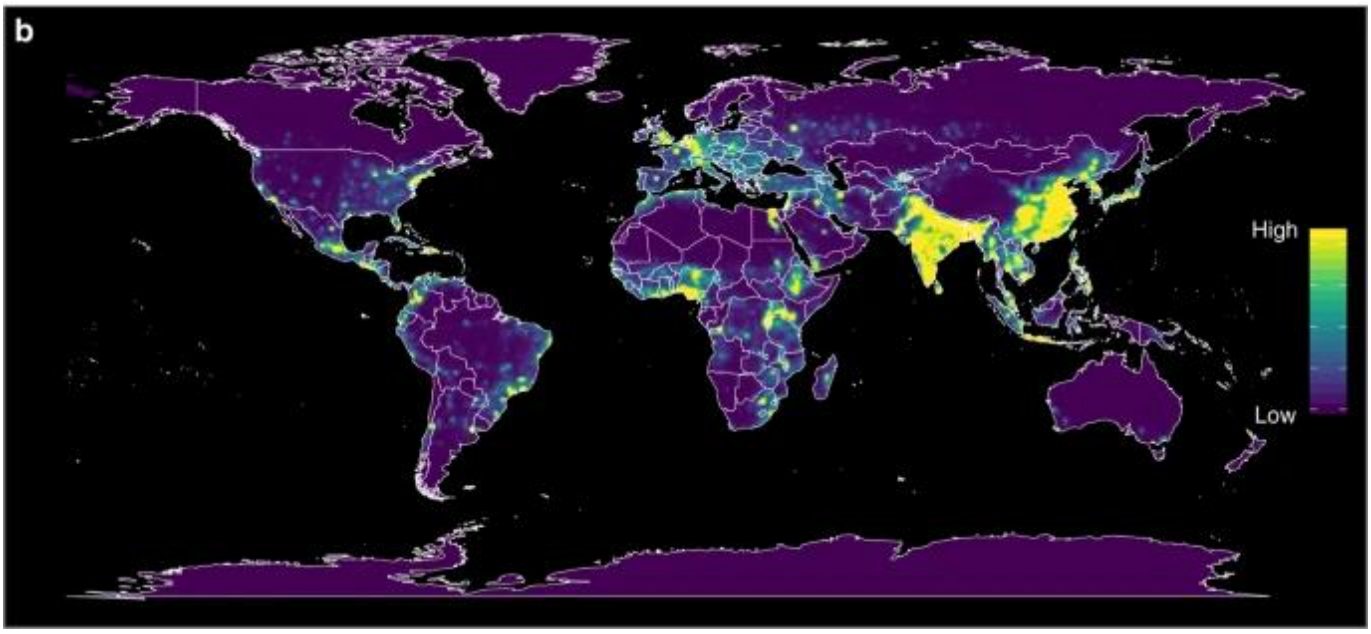


Figure 1. Heat maps of predicted relative risk distribution of zoonotic EID events. (CC License from Allen et al. *Nature Communications*. Volume 8, Article number: 1124 (2017)). (*Note: Allen et al. hotspot predictions are affected by limited data in several regions, including, e.g., the Amazon.*)

Olivial et al. estimated the largest number of 'missing zoonoses' (i.e., where zoonoses might appear based upon modeled expectation) among carnivores and even-toed ungulates in eastern and southern Africa; bats in South America, Central America and parts of Asia; primates in specific tropical regions in Central America, Africa, and southeast Asia; and rodents in pockets of North and South America and Central Africa.[14] "Missing viruses" for all mammals were modeled to occur in northeast Asia, Greenland, peninsular Malaysia, and parts of western Asia and Patagonia. Their analysis of viruses was limited by large parts of the tropics with limited data on mammal viral reservoirs.

4.2 Key Unknowns

1. How much will past emergence predict future emergence given changes in biodiversity, human population and demographics, and cultural change (e.g., wild meat consumption and hunting practices)?
2. How valid are modelling approaches to predict emergence that rely on adjustments for reporting bias and limited data on viral reservoirs?

Chapter 5: What are the drivers of viral spillover?

Human activities and their resultant changes to ecosystems that affect how species interact, including interactions among wildlife, livestock, and microbes, as well as greater contact among wildlife, livestock, people, and their pathogens drive viral spillover and disease emergence.[31]

5.1 Land Use Change

5.1.A. Land use change has been a primary driver of viral zoonotic spillover. (WE)

Land use-change is a primary driver of zoonoses.[32] Between 1960 and 2019, land use change has affected almost one third of the global land area.[33]

Roughly half of global zoonotic infectious disease in humans have resulted from changes in land use, changes in agricultural and food production practices, or through wildlife hunting.[22] While spillover risk may be greatest in places where land conversion is well underway, the largest epidemics appear to occur at the extremes of land conversion.[9] In tropical regions, disease emergence may especially relate to land clearing for agricultural purposes.[3]

Land use change alters the abundance and diversity of animals in a disease ecosystem as well as their interactions with each other and people. This, in turn, can influence the prevalence of pathogens within a disease ecosystem and the interfaces for contact between species (Figure 2).[34] These consequences of land use change do not uniformly promote disease emergence.[35]

Pathogen spillover has been found to occur more often from species that have increased in abundance due to human actions, such as forest clearing.[13] This effect may in part result from some zoonotic reservoir species having faster life history characteristics (i.e., short gestation length, large litters, low neonate body mass, and a young age at sexual maturity) than mammals overall, and investing more in greater reproductive output than long-term survival.[36] A notable exception to this is bats, which have longer life spans, especially for their size.

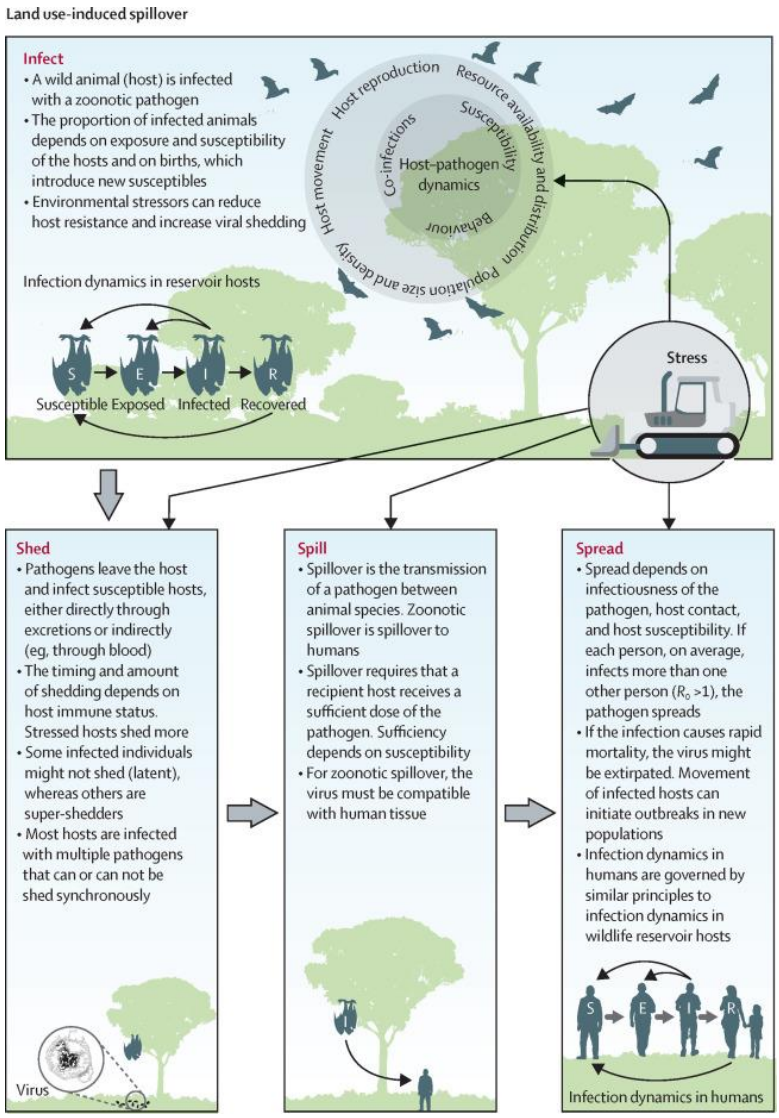


Figure 2. Land use-induced spillover. Used with permission from Plowright et al. (2021).[34]

5.1.2 Deforestation

One of the most common types of land use change contributing to zoonotic spillover is deforestation. Deforestation has been linked to increases in zoonotic disease outbreaks in tropical countries, along with reforestation in temperate countries.[37] During deforestation, species that survive (or thrive) tend to be less sensitive to human disturbances and are thus the ones most able to infect humans or livestock.[38]

As examples, following deforestation in the Americas and at regional and land levels in Central America, rodent reservoirs for Hantavirus Pulmonary Syndrome increased.[31]

Olivero et al. found that increased probability of Ebola outbreaks in humans occurred in sites linked to recent deforestation.[39]

Reforestation and afforestation may contribute to disease emergence risk.[37] An example of this may be the emergence of Lyme disease in North America in new growth forests, though in this instance, forest fragmentation and human driven changes in reservoir species populations have been major contributors to disease incidence.[40]

5.1.3 Agricultural Development

5.1.3.A Expansion of agricultural lands, especially near human settlements, has been linked to disease emergence and amplification. (EI)

Since 1940, agricultural drivers have been found to be associated with greater than 50% of zoonotic infectious diseases that emerged in humans.[41]

Agricultural expansion can promote human and farmed animal encroachment into wildlife habitats and bring humans and livestock into closer proximity to wildlife and vectors. These actions can disturb wildlife habitats and lead to reduced biodiversity, which may create spillover pathways.[41,42] About 22% of the land area within biodiversity hotspots, which often overlap with emerging disease hotspots, is threatened by agricultural expansion.[38]

Agricultural development often accompanies the redistribution of fresh water. Dams, reservoirs, and irrigation networks often increase with agriculture while wetlands often decrease. This redistribution of fresh water is associated with the spread of vectors and hosts of human pathogens.[43] For example, Aswan High Dam in Egypt and its irrigation network was associated with a rise in mosquito vectors and mosquito-borne disease lymphatic filariasis.[44] Similarly, dam and irrigation construction in Sri Lanka and India led to increases in malaria.[43,45]

With a growing human population and persistent food insecurity in many countries, the need to grow more food is evident. To address these needs while preventing further destruction of nature and disease emergence, greater investments in sustainable intensification of agriculture and in the prevention of crop and food waste are needed to reduce biodiversity losses, conserve water resources, and prevent further land use change while promoting food security and economic welfare.[46,47]

5.2 Livestock Intensification

5.2.A Livestock and farmed wildlife intensification creates environments favorable for increased zoonotic spillover. (EI)

Domesticated animal husbandry or farmed wildlife can serve as reservoirs for potential zoonotic pathogens. In intensified systems, farm animals are often reared in dense populations with low genetic diversity and in close contact with humans, favoring increased viral transmission. These animals can act as intermediate or amplifier hosts in which pathogens can evolve and spillover to humans.[42]

An example of the links between agricultural intensification and spillover can be found in the first-known outbreak of Nipah virus 1998. Disease spread was driven by intensification of the pig industry in an area already populated by Nipah virus-infected fruit bats.[42] Fruit grown close to pig enclosures allowed Nipah virus spillover from bats to pigs. The density and continuous introduction of new susceptible pigs that were born on the farm fueled the outbreak. The virus spilled from pigs into people and infected pigs that were moved off the farm spread the disease to other pigs and people in the country.

Large, high-density poultry and pig farms contribute to pandemic influenza risk. These animals each carry influenza virus strains that can swap genomic segments and create novel influenza strains with pandemic potential in people.[48] Poultry and pork production has grown rapidly, especially in low and middle income countries where production may double or more in the next decade.[49]

Models of livestock production have shown a trend towards intensification, particularly in regions where coronavirus host diversity (e.g., horseshoe bats) is greatest, including in China and South Asia.[50] Among other livestock and farmed wild animal operations, coronaviruses have been detected in rodents on the majority of wildlife farms in Viet Nam and were found in Malayan porcupines and bamboo rats raised on wildlife farms for human consumption.[17]

Domesticated species are more likely to share zoonotic viruses with humans, with eight times more zoonotic viruses in a given domesticated mammal species compared to wild mammalian species. As a group, domesticated mammals host 50% of the zoonotic virus richness but represent only 12 species.[13] The top 10 mammalian species with the highest number of viruses shared with humans included eight domesticated species, including pigs, cattle, horses, sheep and goats.[13,42]

As industrial food-animal production becomes more common in low- and middle-income countries, agricultural intensification may increase the risk of zoonotic disease emergence and spread.[35]

5.3 Urbanization

5.3.A Urbanization has been associated with zoonotic disease emergence. (EI)

Rapid, unplanned urbanization contributes to land use change and may create conditions that promote disease emergence, including high population density and poor living conditions.[51,52] Urbanization can provide favorable conditions for disease reservoirs to thrive and diseases to spread, such as rodent-borne leptospirosis.[35] Leptospirosis has emerged with urbanization and burgeoning rat populations around the world and become a leading cause of zoonotic morbidity.[53]

Urban locations may also provide high-risk interfaces where humans and urban-acclimated wildlife hosts are in close contact. For example, northern latitude vertebrate reservoirs in city parks and gardens (such as hedgehogs, rats, and squirrels) present known zoonotic risks and usually live in high densities in close proximity to people.[31] In South America, the presence of sand fly vectors and large feral dog populations in cities increase risk for outbreaks of canine and human visceral leishmaniasis.[31,54]

In 2020, 56.2% of the global human population lived in urban settings.[55] By 2030, 60% of people may be urban dwellers, and cities are expected to increase in size and number as the human population grows.[56] Despite the growing relevance of urbanization to land use change, the demographic, environmental, and local factors underpinning transmission risk for zoonotic pathogens in urban areas is limited, particularly in the urban global South.[52]

5.4 Wild Animal Hunting and Consumption

5.4.A Wild animal hunting and consumption are drivers of zoonotic viral spillover. (EI)

Wild animal hunting and consumption has been associated with many viral disease outbreaks. HIV, for example, is believed to have emerged from hunting of nonhuman primates for food in central African forests.[57] Other retroviruses have spilled into people through hunting and consumption of wild primates.[58,59] Close to 8% of nonhuman primate wild animal meat from the Democratic Republic of Congo has been found to be infected with Simian-T-lymphotropic virus,[60] and an increased risk of simian foamy virus

was found in people preparing nonhuman primates for consumption.[61] A substantial proportion of wild monkeys in Cameroon are infected with simian immunodeficiency viruses, and humans who hunt and handle bushmeat are exposed to genetically divergent viruses.[62] Wild animal consumption has also contributed to outbreaks of Ebola in Gabon and the Republic of Congo.[42,63]

In coastal populations, terrestrial wild animal hunting and consumption may depend on coastal seafood abundance. Brashares et al. found there to be a direct link between fish supply and subsequent bushmeat demand in villages which illustrates bushmeat's role as a dietary staple in the region.[64]

5.5 Wildlife Trade

5.5.A Wildlife trade creates interfaces for spillover and zoonotic disease transmission. (EI)

Wildlife trade can facilitate close contact between wildlife and humans,[13] and wildlife trade and risks of zoonotic disease emergence seem to be strongly associated.[65] Wildlife trade has led to several emerging disease outbreaks, including monkeypox virus, SARS coronavirus and heartwater disease of cattle.[31,66,67] In Laos, wildlife traded in local markets is believed to have facilitated transmission of 36 zoonotic agents.[68] Retroviruses, such as simian foamy virus, and herpesviruses have also been found in illegally imported wildlife products in the United States.[69]

Some mammals in trade may be more likely to carry zoonotic diseases. For example, 26.5% of the mammals in the wildlife trade harbor 75% of known zoonotic viruses. Primates, ungulates, carnivores, and bats host 132 (58%) of 226 known zoonotic viruses in present wildlife trade and, thus, pose significant zoonotic disease risks.[65]

Risk for zoonotic spillover has been found to grow across the chain of wildlife trade. In a study that examined field rats, the odds of coronavirus RNA detection significantly increased along the supply chain from rats sold by traders to rats sold in large markets to rats sold and served in restaurants.[17]

Wildlife trade has grown in the last few decades. International legal wildlife trade has increased in value 200% since the 1980s and 500% since 2004, although a portion of this increase may be due to enhanced captive breeding and ranching. The United States is a leading consumer of legally traded wildlife globally, importing 10-20 million individual wild animals each year.[31]

The global illegal trade in wildlife is estimated to be worth US$7–23 billion per year, or nearly 25% of the value of the legal market.[70]

5.6 Cultural Practices

5.6.A Cultural practices and preferences strongly influence the likelihood of wild animal hunting, consumption, and trade. (EI)

Culturally informed preferences strongly influence wildlife hunting, consumption and trade among people around the world.[71–73] Cultural influences shape demand for wildlife used for food, as pets, medicines, and for decorative purposes.[74] For example, in parts of China, eating wild animals can be a symbol of wealth, and wildlife meat is often thought to be more natural and nutritious than meat from farmed animals.[75] In Iquitos, Peru, wild animals are most often captured for eating, which can offer an important source of nutrients and fats, particularly for those inhabiting rural rainforest areas.[76]

5.7 Affluence and Wildlife Consumption

5.7.A Economic status influences spillover risk and its effect depends on local cultural norms. (WE)

Affluence may promote wild animal consumption in more urbanized areas but has the opposite effect in more rural ones.[77] In China, higher income, better educated males were found to be most likely to consume wild animals.[78] In contrast, in Madagascar, wildlife consumption and anemia risk were associated with household income, with households at the highest income levels being least dependent on wildlife consumption compared to low-income households.[79] A wildlife use survey conducted in Ghana, Cameroon, Tanzania, and Madagascar found that wealthier households consume more bushmeat when situated nearer urban areas, but the opposite pattern was observed in more isolated areas.[77] Wildlife hunting and consumption was also found to increase when alternative livelihoods collapse, but only for those living near harvestable wildlife.[77]

At the global trade level, national economic inequality has been found to influence wildlife trade. The wild animal trade network was more highly connected when wealth inequality between participating nations/territories was greater, and there were also found to be fewer links in the global trade network when average national and per capita wealth were higher.[80]

5.8 Climate Change

5.8.A Climate change creates conditions that can increase or decrease disease emergence risk depending on the disease ecosystem. (UR)

As the world continues to warm, disease reservoirs and their habitats are shifting their ranges. Climate change produces alterations to ecosystems that will affect where and how reservoirs live because of new temperature and precipitation regimes, food supplies, and the presence or absence of predators, as examples.

In a review of 40,000 species across the world, roughly half were found to already be on the move as a result of changing climate conditions.[29] Modeling by Carlson et al. predicts that by 2070, range-shifting mammal species will aggregate at high elevations, in biodiversity hotspots, and in areas of high human population density in Asia and Africa. These aggregations were estimated to result in the sharing novel viruses between 3,000 and 13,000 times.[81]

Along with species migrations, climate change is forecast to shrink suitable habitats.[82] Habitats with smaller areas may promote spillovers via more encounters between wildlife and humans.[83] Shrinking habitats and nectar availability for bats, for example, have pushed bats to seek alternative food sources in urban and peri-urban areas.[84]

Climate change may also decrease host habitat suitability or, through its effects on species survival and biodiversity loss, increase risk of disease spread through contributing to the success of generalist reservoirs able to survive under a wide range of conditions.

5.9 Key Unknowns

1. What are the mechanisms that underlie the association between urbanization and spillover?
2. What are the mechanisms that underlie the association between deforestation and non-vector borne viral emergence?
3. How frequently does viral spillover occur in rural settings? How does the frequency change with environmental disturbance?
4. Will greater affluence along with unplanned urbanization promote increased wildlife product demand and associated spillover risk?
5. How does climate change influence the prevalence of known infectious diseases and the prospects for new pathogen emergence?

Chapter 6. What are the interfaces of zoonotic viral spillover?

Each of the drivers of spillover identified above increase the likelihood of human-animal contact. Interfaces between humans and animals can be targeted to reduce the opportunity for spillover.

6.1 Forest Edge

6.1.A Zoonotic spillover occurs frequently in forested landscape with many edges. (EI)

Forest edges, created when forests are cleared, are key interfaces for human-wildlife encounters and spillover.[9] Forest edges create new pathways through forests and increase contact points between humans and pathogen-carrying species. Length of edge habitat correlates with interspecies contact rates and increases pathogen sharing between wildlife and humans.[9] Bloomfield et al. found that increased edge density around households significantly increased the likelihood of human to non-human primate contact.[85]

Forest edge may have particular importance to coronavirus spillover. Horseshoe bat reservoirs of coronavirus are more likely to inhabit areas in China with greater forest fragmentation and adjacent livestock farms,[50] which may at least in part explain why China is a hotspot for coronavirus emergence.

6.2 Wildlife Markets

6.2.A Wildlife markets facilitate viral spillover from animals to humans. (EI)

Wildlife markets are particularly apt for facilitating zoonotic virus spillover, as live animals may be kept near each other with poor hygiene standards and high human contact creating opportunities for viral spillover between animals and humans. These markets are popular in parts of Asia. A majority of urban Chinese consumers may prefer to purchase food in wildlife markets because they believe these markets offer them fresher meat.[86]

Wild animal markets have been sources of several widespread infectious disease outbreaks. A SARS virus outbreak in 2002 that killed 774 people is believed to have originated from masked palm civets sold in wildlife markets in China.[87] Live bird markets have also been associated with emergence of avian influenza.[88] Wild animal meat sold

in both rural and urban markets in places such as western Africa and South Asia have also led to infections by Ebola, Hendra virus, and other pathogens.[89]

Viruses from wildlife that are transmitted at high-risk interfaces, such as wildlife markets, were also found to have higher host plasticity.[16] As incomes increase, and wet markets persist in many parts of the world, demand for higher-risk animal protein is projected to increase.[89]

6.3 Animal Farms

6.3.A Animal farms are a key interface for viral zoonotic spillover. (EI)

Among human pathogens, more than one-third also infect domesticated animals and roughly one-quarter infect domesticated animals and wildlife.[90] Livestock operations have been the sources of viral zoonoses. High density pig farms enabled rapid pig-to-pig transmission of Nipah virus in Malaysia that eventually spilled into agricultural workers.[91] SARS-CoV-2 infected mink farms in Denmark and resulted in several human infections.[92] Coronavirus rapidly spreads through Dutch mink farms, triggering culls to prevent human infections. Several studies have also reported higher seroprevalence in farm workers of pandemic H1N1/09 influenza, hepatitis E, and avian influenza H5 and H7 compared with the general public.[93,94]

Chapter 7: What can be done to prevent viral zoonotic spillover?

7.1 Preventing Deforestation

7.1.A Forest conservation activities can reduce risk of zoonotic disease spread. (UR)

Deforestation is the largest component of land use change and is associated with spillover. However, deforestation programs have rarely been assessed for effects on spillover and disease emergence. An intervention aimed at expanding health care access and use for communities living near a national park in rural Borneo utilized clinic discounts to offset costs historically met through illegal logging. The study found an approximately 70% reduction in deforestation was achieved compared to a modeled control. A dose–response was observed between forest loss and engagement with health care across communities bordering the park, where the greatest logging reductions were adjacent to the most highly engaged villages.[95]

7.2 Wild Animal Consumption

7.2.1. Wild animal consumption restrictions

After infectious disease outbreaks that arise from spillover related to wild animal consumption, governments often impose restrictions on wild animal consumption. In response to the COVID-19 pandemic, China's Standing Committee of the National People's Congress adopted an unprecedented decision to ban the consumption of almost all wild animals.[96] Despite promising legislative steps, such as enhancing the regulation of wildlife farms and markets, there remain concerns about the long-term effectiveness of the ban as similar interventions have been short-lived or had problematic consequences.[97] For example, palm civets were temporarily banned in China after the 2003 SARS outbreak, but the ban was reversed because of pressure from wildlife farmers and traders who suffered severe economic impacts.[96] Another example was the West African "bushmeat ban" during the 2013-2016 Ebola epidemic, which created a host of problems, including entrenching distrust towards outbreak responders and exacerbating pre-existing tensions within villages.[98]

7.2.2. Behavior change

Many initiatives address spillover risk among people at high risk because of occupation or avocation (e.g., working in wet animal markets, recreational hunters), cultural norms,

or who are subsistence wild animal consumers. In the Brazilian Amazon, a before-after control-intervention design assessed social marketing (an information campaign and community engagement) with and without an economic incentive (discount coupons for chicken) on wild meat consumption. Coupons increased chicken consumption but did not reduce wild meat consumption. Social marketing without the price incentive reduced wild meat consumption by ~62%.[99]

In Singapore, 2000 individuals were engaged in a behavior change intervention to reduce consumption of an endangered antelope (Saiga) used in Traditional Chinese medicine. Consumption decreased somewhat more in the intervention group, but sellers identified price and availability as predominant drivers of purchases and reduction of high-usage consumer frequency was not significant at the population level.[100]

In a cohort of 168 North Tanzanian individuals, a radio show intervention, including a 15-minute narrative drama and 45 minutes call in with experts, was found to not be effective in reducing bushmeat consumption.[101] One group theorized that utilizing Confucianist, Daoist, and Buddhist belief messaging in targeted campaigns could effectively change the behavior of end consumers in the East Asia illegal wildlife trade.[102]

Thomas-Walters et al. caution that sifting from the reductionist approach of limiting supply to another of limiting demand may not be optimal to prevent wild meat consumption.[103] Conservationists may benefit from public health and international development experience in applying systems thinking. Strategic approaches to protecting endangered species should account for interactions between economic, demographic, and cultural factors in wildlife trade.[103]

7.3 Wild Animal Trade

7.3.A Evidence based interventions to prevent viral spillover in wild animal trade are limited. (EI)

The OIE conducted a literature review that included an assessment of risks in wildlife trade. The authors found that research did not clearly identify the most vulnerable points in the wildlife trade supply chain nor the most effective interventions to reduce the risk of disease emergence.[104] There remains a dearth of systematic evaluations of risk management strategies, policies, or practices that are effective and efficient in reducing emerging diseases from wildlife trade. [104]

7.4 Early Detection and Viral Discovery

7.4.1 Global pathogen surveillance in humans, livestock and wildlife – a One Health approach

To improve detection of disease emergence, early warning systems that detect new viral spillover have been advocated.[105] Carroll et al. propose a global, risk-based, multisectoral viral surveillance network would focus on detecting new “high consequence” viruses in humans and animals in hotspots for emerging risks.[105] Gardy et al. advocate for a similar pathogen surveillance system that couples genomic diagnostics with epidemiology to create an “open, global, digital pathogen surveillance system.”[106]

7.4.2 Viral discovery in wild animals

7.4.2.A Viral discovery in wild animals has uncovered thousands of viruses from viral families that contain zoonoses, yet millions of unknown viral species remain. (EI)

The Global Virome Project has been proposed to discover potentially zoonotic viruses in wild animals, with the goal of identifying the bulk of viral zoonoses and providing genomic data that could accelerate public health responses to outbreaks.[12] The USAID Emerging Pandemic Threats (EPT) PREDICT project serves as a partial template for a broader viral discovery program. PREDICT was designed to evaluate the feasibility of preemptively mitigating pandemic threats.[12] PREDICT discovered more than 1000 viruses from viral families that contain zoonoses, including viruses involved in recent outbreaks.[12,106]

However, there remains a projected 1.67 million unknown viral species from key zoonotic viral families that exist in animal reservoirs. Of these unknown viruses, between 631,000 and 827,000 are expected to have zoonotic potential.[12]

7.4.3 Wild animal products in trade

7.4.3.A Disease surveillance in wildlife trade within commercial markets and other trade systems can prevent disease emergence. (UR)

A pilot project to establish surveillance methodology for zoonotic agents in confiscated wildlife products utilized pathogen screening and identified retroviruses and herpesviruses in nonhuman primate samples collected at several international airports. The results of the project demonstrated that illegal animal importation into the United

States could be a pathway for pathogen emergence, and implementation of disease surveillance of wildlife trade could help facilitate prevention of disease emergence.[69] Levinson et al. also emphasize that to be effective, wild animal disease surveillance should focus on diseased and healthy animals to maximize zoonotic virus discovery.[107]

7.4.4. Livestock surveillance

7.4.4.A Livestock surveillance varies by host and geographic region and does not capture the extent of viruses circulating in livestock. (WE)

Global livestock surveillance activities prioritize the monitoring of specific animal viruses, such as the avian influenza (HPAI) viruses H5 and H7 subtypes in poultry, but allow for animal influenza viruses, and possibly other zoonotic viruses, to circulate globally unmonitored.[108]

No centralized global data repository for circulating animal influenza strains is available. Voluntary surveys of veterinary health officers have been used to estimate levels of surveillance globally.[108] For example, in 2014, a survey of national animal influenza surveillance programs was conducted to assess the capacity to detect influenza viruses with zoonotic potential in animals at regional and global levels.[109] The survey collected information on 587 animal influenza surveillance system components for 99 countries. All but five countries (from Africa, Europe, and the Americas) indicated having several surveillance system components in place, each with different attributes. However, less than 1% of these components were aimed at detecting influenza viruses with pandemic potential. Those countries that sought to detect influenza viruses with pandemic potential did so exclusively in domestic pigs.[109]

In an analysis of influenza virus surveillance of swine and domestic poultry, 78% and 49% of areas at high risk for influenza virus spillover in Southeast Asia, Eastern Europe, Central America, and sub-Saharan Africa lacked adequate influenza virus surveillance in swine and domestic poultry, respectively.[108]

Where surveillance is present, it can be effective at identifying and addressing disease emergence. The US Department of Agriculture's IAV-S Surveillance Program conducts voluntary surveillance of Influenza A Virus in swine. Between 2010 and 2021, the program tested over 120,000 samples from 33,000 swine. Over that time period, over 10,000 cases were identified as positive for IAV-S.[110]

In low- and middle-income countries, innovative approaches have been taken for animal health surveillance. A mobile phone-based surveillance system was found to be

effective for reporting disease events by communities in rural Kenya. Livestock illness events were 14.8 times more likely to be reported through the mobile phone-based surveillance system when compared with the routine household visits.[111]

7.5 Wildlife and Domesticated Animal Vaccination

7.5.A While vaccination of wildlife and domesticated animals has the potential to protect humans against zoonoses, drawbacks to vaccine deployment and implementation have limited their use. (UR)

Vaccination of domesticated and wild animals has the potential to protect humans against zoonoses by indirectly interrupting transmission in cases where animals are amplifying hosts or directly by preventing pathogen spread from infected animals to humans.[112] A Hendra Virus vaccine has been deployed to reduce disease in horses, which can also truncate the viral transmission chain from bats to horses to humans.[113] Rabies eradication has been pursued in Latin America and the Caribbean through dog vaccination as well.[114,115]

Vaccination of animals can be expensive, difficult to implement and hampered by vaccine supplies too limited to achieve disease control. For example, oral vaccination of vampire bats has been proposed to reduce rabies spillover, and while vaccination has been successful for canine rabies control, no commercial vaccine is available for rabies control in vampire bats.[115]

7.6 Ecological Interventions

7.6.A While ecological interventions may offer effective, sustainable solutions to preventing spillover, better understanding is needed to implement such approaches in many disease ecosystems. (EI)

Sokolow et al. suggest that ecological interventions are potentially underused approaches to finding effective, long-lasting solutions that reduce spillover, have minimal environmental damage, and can be complementary to conventional approaches. Ecological interventions that prevent spillover include employing natural enemies to control disease, which may be more effective and less costly than culling and have additional environmental benefits.[115]

As an example of an effective ecological intervention, requiring fruit trees to be planted a minimum distance from pig sties in order to reduce bat to pig transmission has prevented outbreaks of Nipah virus in Malaysia.[116] In Bangladesh, limiting bat access to

date palm sap that is drip-collected is another ecological intervention that can reduce Nipah virus spillover through drinking contaminated date palm sap. However, widespread adoption of this approach across Bangladesh has been difficult to achieve.[115]

Wetlands can provide a buffer between livestock and wildlife and mitigate spillover. Wu et al. examined how outbreaks of highly pathogenic avian influenza (HPAI) H5N1 are related to the degree of protection given to waterfowl habitats in China. They found that protecting lakes and wetlands reduced the probability of avian influenza spillover to poultry by wild waterfowl.[117]

Chapter 8: What scale of investment is warranted and what is the return on investment?

8.1.A Current investments in addressing drivers of spillover are small in comparison to the direct economic losses from COVID-19, even when these are annualized over a century. (EI)

The COVID-19 pandemic resulted in an estimated global GDP loss of 4.5% in 2020 or nearly US$4 trillion.[118] Although the probability of a pandemic may have grown in recent decades, If COVID-19 is a 1/100-year event, this translates into US$40 billion per year over the next century, without accounting for the time value of money.

Global investments in preventing spillover likely amount to no more than US$4 billion a year. Each year, roughly US$2 billion are spent on forest conservation.[119] The World Bank estimated that US$260 million is spent each year on wildlife trafficking.[120] The budgets of organizations charged with monitoring the legal wildlife trade have modest budgets for the scope of legal trade. The US Fish and Wildlife Service has ~US$8 million.[121] The budget for OIE, which is primarily concerned with diseases of domesticated animals, is US$35 million.[122] No organization conducts routine systematic surveillance of wildlife. Government sponsored research programs have conducted viral surveillance in wildlife. Grants for these programs such as PREDICT as well as proposed budgets for the Global Virome Project[123] amount to on the order of US$100 million.

A recent analysis suggests that the costs of addressing spillover in emergence hotspots through forest conservation and One Health approaches would amount to US$22 to US$31 billion per year, a fraction of the economic and mortality costs of responding to these pathogens once they have emerged.[124]

Chapter 9: Sustainability of interventions

The effectiveness of initiatives to address deforestation, wildlife trade and hunting, and other drivers of spillover depends heavily on the continuity of effort to achieve them. Unsteady funding streams, political upheaval, competing changing priorities, and cultural practices can all upend progress on reductions in the drivers of spillover risk.

As a recent example of how progress in one driver of emergence, land use change, can be halted, consider conservation of the Amazon in Brazil. Rates of deforestation in the Brazilian Amazon fell approximately 70% between 2005-2012 due to public policies combined with public and private actions.[125] A change in government has resulted in rapid acceleration in deforestation such that rates of deforestation have hit decadal highs in 2020.[126]

Chapter 10: Key recommendations for research and action

Recommendations for research

1) Establish the effectiveness of spillover prevention interventions, including those focused on forest conservation, wildlife hunting and trade, and biosecurity around farms.

2) Assess the economic, ecological, and social welfare impacts of interventions aimed at reducing spillover as well as their long-term viability. Economic analyses should include cost benefit analysis that considers the full scope of benefits that can come from spillover prevention.

3) Refine identification of emergence hotspots for viral zoonoses and include assessments of pandemic drivers, including aspects of governance, travel, and population density.

4) Continued viral discovery in wildlife to ascertain the breadth of potential pathogens and improve understanding of genotype-phenotype associations that can enable assessments of the pandemic potential of novel viruses or strains of known pathogens.

Recommendations for investment priorities

1) Conserve tropical forests, especially in relatively intact forests as well as those that have been fragmented, to address spillover risk.

2) Improve biosecurity for livestock and farmed wild animals and remove spillover interfaces, especially when animal husbandry occurs amid or adjacent to large or rapidly expanding human populations.

3) Improve surveillance for emerging pathogens in wildlife trade.

3) Consistent with recommendations from the IPBES workshop on biodiversity and pandemics, establish an intergovernmental partnership to address spillover risk from wild animals to livestock and people that includes organizations such as FAO, WHO, OIE, UNEP, CITES and Wildlife Enforcement Networks.

4) Establish and fully support One Health Platforms or Coordination Committees within national governments to help coordinate spillover prevention.

5) Promote workforce development that includes training multiple disciplines on One Health approaches to pandemic prevention, including One Health research, surveillance and spillover prevention strategies and policies.

6) Leverage investments in healthcare system strengthening and One Health platforms in low- and middle-income countries to jointly advance conservation, animal and human health, and spillover prevention.

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References

1 Kelly H. The classical definition of a pandemic is not elusive. *Bull World Health Organ* 2011; **89**. DOI:10.2471/BLT.11.088815.

2 Daszak P, Keusch GT, Phelan AL, Johnson CK, Osterholm MT. Infectious disease threats: A rebound to resilience. *Health Aff* 2021; **40**: 204–11.

3 Allen T, Murray KA, Zambrana-Torrelio C, *et al.* Global hotspots and correlates of emerging zoonotic diseases. *Nat Commun* 2017; **8**: 1–10.

4 Chan EH, Brewer TF, Madoff LC, *et al.* Global capacity for emerging infectious disease detection. *Proc Natl Acad Sci* 2010; **107**: 21701–6.

5 Taylor LH, Latham SM, Woolhouse MEJ. Risk factors for human disease emergence. *Philos Trans R Soc B Biol Sci* 2001; **356**: 983–9.

6 Jones KE, Patel NG, Levy MA, *et al.* Global trends in emerging infectious diseases. *Nature* 2008; **451**: 990–3.

7 Smith KF, Goldberg M, Rosenthal S, *et al.* Global rise in human infectious disease outbreaks. *J R Soc Interface* 2014; **11**. DOI:10.1098/rsif.2014.0950.

8 Grange ZL, Goldstein T, Johnson CK, *et al.* Ranking the risk of animal-to-human spillover for newly discovered viruses. *Proc Natl Acad Sci* 2021; **118**: e2002324118.

9 Faust CL, McCallum HI, Bloomfield LSP, *et al.* Pathogen spillover during land conversion. Ecol. Lett. 2018; **21**: 471–83.

10 Morse SS, Mazet JAK, Woolhouse M, *et al.* Prediction and prevention of the next pandemic zoonosis. Lancet. 2012; **380**: 1956–65.

11 Woolhouse MEJ, Gowtage-Sequeria S. Host Range and Emerging and Reemerging Pathogens - Volume 11, Number 12—December 2005 - Emerging Infectious Diseases journal - CDC. *Emerg Infect Dis* 2005; **11**: 1842–7.

12 Carroll D, Daszak P, Wolfe ND, *et al.* The Global Virome Project. *Science (80-)* 2018; **359**. DOI:10.1126/science.aap7463.

13 Johnson CK, Hitchens PL, Pandit PS, *et al.* Global shifts in mammalian population trends reveal key predictors of virus spillover risk. *Proc R Soc B Biol Sci* 2020; **287**. DOI:10.1098/rspb.2019.2736.

14 Olival KJ, Hosseini PR, Zambrana-Torrelio C, Ross N, Bogich TL, Daszak P. Host and viral traits predict zoonotic spillover from mammals. *Nature* 2017; **546**: 646–50.

15 Letko M, Seifert SN, Olival KJ, Plowright RK, Munster VJ. Bat-borne virus diversity, spillover and emergence. Nat. Rev. Microbiol. 2020; **18**: 461–71.

16 Kreuder Johnson C, Hitchens PL, Smiley Evans T, *et al.* Spillover and pandemic properties of zoonotic viruses with high host plasticity. *Sci Rep* 2015; **5**: 14830.

17 Huong NQ, Nga NTT, van Long N, *et al.* Coronavirus testing indicates transmission risk increases along wildlife supply chains for human consumption in Viet Nam, 2013-2014. PLoS One. 2020; **15**. DOI:10.1371/journal.pone.0237129.

18 Sintasath DM, Wolfe ND, LeBreton M, *et al.* Simian T-lymphotropic virus diversity among nonhuman primates, Cameroon. *Emerg Infect Dis* 2009; **15**: 175–84.

19 Irving AT, Ahn M, Goh G, Anderson DE, Wang L-F. Lessons from the host defences of bats, a unique viral reservoir. *Nat 2021 5897842* 2021; **589**: 363–70.

20 Santos AF, Cavalcante LTF, Muniz CP, Switzer WM, Soares MA. Simian foamy viruses in central and South America: A new world of discovery. Viruses. 2019;

11. DOI:10.3390/v11100967.
21 Mollentze N, Streicker DG. Viral zoonotic risk is homogenous among taxonomic orders of mammalian and avian reservoir hosts. *Proc Natl Acad Sci U S A* 2020; **117**: 9423–30.
22 Keesing F, Belden LK, Daszak P, *et al.* Impacts of biodiversity on the emergence and transmission of infectious diseases. *Nature* 2010; **468**: 647–52.
23 Zhang X, Cunningham FL, Li L, *et al.* Tissue Tropisms of Avian Influenza A Viruses Affect Their Spillovers from Wild Birds to Pigs. *J Virol* 2020; **94**: 847–67.
24 Olsen B, Munster VJ, Wallensten A, Waldenström J, Osterhaus ADME, Fouchier RAM. Global Patterns of Influenza A Virus in Wild Birds. *Science (80-)* 2006; **312**: 384–8.
25 Asian Avian Influenza A (H5N1). Centers Dis. Control Prev. 2018; published online Dec 12. https://www.cdc.gov/flu/avianflu/h5n1-virus.htm (accessed Aug 4, 2021).
26 Walker JW, Han BA, Ott IM, Drake JM. Transmissibility of emerging viral zoonoses. *PLoS One* 2018; **13**: e0206926.
27 Geoghegan JL, Senior AM, Giallonardo F Di, Holmes EC. Virological factors that increase the transmissibility of emerging human viruses. *Proc Natl Acad Sci U S A* 2016; **113**: 4170–5.
28 Anthony SJ, Johnson CK, Greig DJ, *et al.* Global patterns in coronavirus diversity. *Virus Evol* 2017; **3**: 12.
29 Jones KE, Patel NG, Levy MA, *et al.* Global trends in emerging infectious diseases. *Nature* 2008; **451**: 990–3.
30 Chan EH, Brewer TF, Madoff LC, *et al.* Global capacity for emerging infectious disease detection. *Proc Natl Acad Sci* 2010; **107**: 21701–6.
31 Daszak P, Amuasi J, das Neves CG, *et al.* Workshop Report on Biodiversity and Pandemics of the Intergovernmental Platform on Biodiversity and Ecosystem Services. Bonn, 2020 DOI:10.5281/zenodo.4147317.
32 Loh EH, Zambrana-Torrelio C, Olival KJ, *et al.* Targeting Transmission Pathways for Emerging Zoonotic Disease Surveillance and Control. *Vector-Borne Zoonotic Dis* 2015; **15**: 432–7.
33 Winkler K, Fuchs R, Rounsevell M, Herold M. Global land use changes are four times greater than previously estimated. *Nat Commun 2021 121* 2021; **12**: 1–10.
34 Plowright RK, Reaser JK, Locke H, *et al.* Land use-induced spillover: a call to action to safeguard environmental, animal, and human health. *Lancet Planet Heal* 2021; **5**: e237–45.
35 White RJ, Razgour O. Emerging zoonotic diseases originating in mammals: a systematic review of effects of anthropogenic land-use change. *Mamm Rev* 2020; **50**: 336–52.
36 Plourde BT, Burgess TL, Eskew EA, Roth TM, Stephenson N, Foley JE. Are disease reservoirs special? Taxonomic and life history characteristics. *PLoS One* 2017; **12**: e0180716.
37 Morand S, Lajaunie C. Outbreaks of Vector-Borne and Zoonotic Diseases Are Associated With Changes in Forest Cover and Oil Palm Expansion at Global Scale. *Front Vet Sci* 2021; **8**: 661063.
38 Baudron F, Liégeois F. Fixing our global agricultural system to prevent the next

COVID-19: *https://doi.org/101177/0030727020931122* 2020; **49**: 111–8.
39 Olivero J, Fa JE, Real R, *et al.* Recent loss of closed forests is associated with Ebola virus disease outbreaks. *Sci Rep* 2017; **7**: 1–9.
40 Kilpatrick AM, Dobson ADM, Levi T, *et al.* Lyme disease ecology in a changing world: consensus, uncertainty and critical gaps for improving control. *Philos Trans R Soc B Biol Sci* 2017; **372**: 20160117.
41 Rohr JR, Barrett CB, Civitello DJ, *et al.* Emerging human infectious diseases and the links to global food production. Nat. Sustain. 2019; **2**: 445–56.
42 Jones BA, Grace D, Kock R, *et al.* Zoonosis emergence linked to agricultural intensification and environmental change. *Proc Natl Acad Sci U S A* 2013; **110**: 8399–404.
43 Amerasinghe FP, Indrajith NG. Postirrigation Breeding Patterns of Surface Water Mosquitoes in the Mahaweli Project, Sri Lanka, and Comparisons with Preceding Developmental Phases. *J Med Entomol* 1994; **31**: 516–23.
44 Harb M, Faris R, Gad AM, Hafez ON, Ramzy R, Buck AA. The resurgence of lymphatic filariasis in the Nile delta. *Bull World Health Organ* 1993; **71**: 49.
45 Tyagi BK, Chaudhary RC. Outbreak offalciparummalaria in the Thar Desert (India), with particular emphasis on physiographic changes brought about by extensive canalization and their impact on vector density and dissemination. *J Arid Environ* 1997; **36**: 541–55.
46 Muller A, Schader C, El-Hage Scialabba N, *et al.* Strategies for feeding the world more sustainably with organic agriculture. *Nat Commun 2017 81* 2017; **8**: 1–13.
47 Garnett T, Appleby MC, Balmford A, *et al.* Sustainable Intensification in Agriculture: Premises and Policies. *Science (80-)* 2013; **341**. DOI:10.1126/science.1234485.
48 Walters MJ. Birds, Pigs, and People: The Rise of Pandemic Flus. *Seven Mod Plagues* 2014; : 151.
49 OECD-FAO Agricultural Outlook 2020-2029. OECD, 2020 DOI:10.1787/1112C23B-EN.
50 Rulli MC, D'Odorico P, Galli N, Hayman DTS. Land-use change and the livestock revolution increase the risk of zoonotic coronavirus transmission from rhinolophid bats. *Nat Food 2021 26* 2021; **2**: 409–16.
51 Gottdenker NL, Streicker DG, Faust CL, Carroll CR. Anthropogenic Land Use Change and Infectious Diseases: A Review of the Evidence. Ecohealth. 2014; **11**: 619–32.
52 Ahmed S, Dávila JD, Allen A, Haklay M (MUKI), Tacoli C, Fèvre EM. Does urbanization make emergence of zoonosis more likely? Evidence, myths and gaps: *https://doi.org/101177/0956247819866124* 2019; **31**: 443–60.
53 Costa F, Hagan JE, Calcagno J, *et al.* Global Morbidity and Mortality of Leptospirosis: A Systematic Review. *PLoS Negl Trop Dis* 2015; **9**: e0003898.
54 Thomaz-Soccol V, Gonçalves AL, Piechnik CA, *et al.* Hidden danger: Unexpected scenario in the vector-parasite dynamics of leishmaniases in the Brazil side of triple border (Argentina, Brazil and Paraguay). *PLoS Negl Trop Dis* 2018; **12**: e0006336.
55 Buchholz K. How has the world's urban population changed? World Econ. Forum. 2020; published online Nov 4. https://www.weforum.org/agenda/2020/11/global-

continent-urban-population-urbanisation-percent (accessed Aug 4, 2021).
56 The World's Cities in 2016 – Data Booklet (ST/ESA/ SER.A/392). 2016 https://www.un.org/en/development/desa/population/publications/pdf/urbanization/the_worlds_cities_in_2016_data_booklet.pdf (accessed Aug 4, 2021).
57 Sharp PM, Hahn BH. Origins of HIV and the AIDS Pandemic. *Cold Spring Harb Perspect Med* 2011; **1**: a006841.
58 Kazanji M, Mouinga-Ondémé A, Lekana-Douki-Etenna S, *et al.* Origin of HTLV-1 in Hunters of Nonhuman Primates in Central Africa. *J Infect Dis* 2015; **211**: 361–5.
59 Switzer WM, Qari SH, Wolfe ND, Burke DS, Folks TM, Heneine W. Ancient Origin and Molecular Features of the Novel Human T-Lymphotropic Virus Type 3 Revealed by Complete Genome Analysis. *J Virol* 2006; **80**: 7427–38.
60 Ahuka-Mundeke S, Mbala-Kingebeni P, Liegeois F, *et al.* Identification and molecular characterization of new simian T cell lymphotropic viruses in nonhuman primates bushmeat from the democratic Republic of Congo. *AIDS Res Hum Retroviruses* 2012; **28**: 628–35.
61 Switzer WM, Tang S, Ahuka-Mundeke S, *et al.* Novel simian foamy virus infections from multiple monkey species in women from the Democratic Republic of Congo. *Retrovirology* 2012; **9**: 100.
62 Peeters M, Courgnaud V, Abela B, *et al.* Risk to human health from a plethora of Simian immunodeficiency viruses in primate bushmeat. *Emerg Infect Dis* 2002; **8**: 451–7.
63 Leroy EM, Rouquet P, Formenty P, *et al.* Multiple Ebola Virus Transmission Events and Rapid Decline of Central African Wildlife. *Science (80-)* 2004; **303**: 387–90.
64 Brashares JS, Arcese P, Sam MK, Coppolillo PB, Sinclair ARE, Balmford A. Bushmeat hunting, wildlife declines, and fish supply in West Africa. *Science (80-)* 2004; **306**: 1180–3.
65 Shivaprakash KN, Sen S, Paul S, Kiesecker JM, Bawa KS. Mammals, wildlife trade, and the next global pandemic. *Curr Biol* 2021; published online July 7. DOI:10.1016/J.CUB.2021.06.006.
66 Peiris JSM, Guan Y, Yuen KY. Severe acute respiratory syndrome. Nat. Med. 2004; **10**: S88–97.
67 Bell D, Roberton S, Hunter PR. Animal origins of SARS coronavirus: Possible links with the international trade in small carnivores. In: Philosophical Transactions of the Royal Society B: Biological Sciences. 2004: 1107–14.
68 Greatorex ZF, Olson SH, Singhalath S, *et al.* Wildlife trade and human health in Lao PDR: An assessment of the zoonotic disease risk in markets. *PLoS One* 2016; **11**. DOI:10.1371/journal.pone.0150666.
69 Smith KM, Anthony SJ, Switzer WM, *et al.* Zoonotic viruses associated with illegally imported wildlife products. *PLoS One* 2012; **7**. DOI:10.1371/journal.pone.0029505.
70 The World Bank. Illegal logging, fishing, and wildlife trade: the costs and how to combat it. Washington D.C., 2019.
71 Morsello C, Yagüe B, Beltreschi L, *et al.* Cultural attitudes are stronger predictors of bushmeat consumption and preference than economic factors among urban Amazonians from Brazil and Colombia. *Ecol Soc Publ online Nov 18, 2015* |

doi105751/ES-07771-200421 2015; **20**. DOI:10.5751/ES-07771-200421.
72 Bachmann ME, Junker J, Mundry R, *et al.* Disentangling economic, cultural, and nutritional motives to identify entry points for regulating a wildlife commodity chain. *Biol Conserv* 2019; **238**: 108177.
73 Friant S, Paige SB, Goldberg TL. Drivers of Bushmeat Hunting and Perceptions of Zoonoses in Nigerian Hunting Communities. *PLoS Negl Trop Dis* 2015; **9**: e0003792.
74 What Drives Demand for Wildlife? A Situational Analysis of Consumer Demand for Wildlife Parts and Products in China, Thailand and Vietname Based on a Literature Review. 2017 https://www.usaidwildlifeasia.org/resources/reports/inbox/what-drives-demand-for-wildlife (accessed Aug 4, 2021).
75 Zhang L, Yin F. Wildlife consumption and conservation awareness in China: a long way to go. *Biodivers Conserv 2014 239* 2014; **23**: 2371–81.
76 D'Cruze N, Galarza FER, Broche O, *et al.* Characterizing trade at the largest wildlife market of Amazonian Peru. *Glob Ecol Conserv* 2021; **28**: e01631.
77 Brashares JS, Golden CD, Weinbaum KZ, Barrett CB, Okello G V. Economic and geographic drivers of wildlife consumption in rural Africa. *Proc Natl Acad Sci U S A* 2011; **108**: 13931–6.
78 Zhang L, Hua N, Sun S. Wildlife trade, consumption and conservation awareness in southwest China. *Biodivers Conserv* 2008; **17**: 1493–516.
79 Golden CD, Fernald LCH, Brashares JS, Rasolofoniaina BJR, Kremen C. Benefits of wildlife consumption to child nutrition in a biodiversity hotspot. *Proc Natl Acad Sci* 2011; **108**: 19653–6.
80 Liew JH, Kho ZY, Lim RBH, *et al.* International socioeconomic inequality drives trade patterns in the global wildlife market. *Sci Adv* 2021; **7**: eabf7679.
81 Dunne D. Q&A: Could climate change and biodiversity loss raise the risk of pandemics? Carbon Br. 2020; published online May 15. https://www.carbonbrief.org/q-and-a-could-climate-change-and-biodiversity-loss-raise-the-risk-of-pandemics (accessed Aug 4, 2021).
82 Nunez S, Arets E, Alkemade R, Verwer C, Leemans R. Assessing the impacts of climate change on biodiversity: is below 2 °C enough? *Clim Chang 2019 1543* 2019; **154**: 351–65.
83 Rodó X, San-José A, Kirchgatter K, López L. Changing climate and the COVID-19 pandemic: more than just heads or tails. Nat. Med. 2021; **27**: 576–9.
84 Plowright RK, Eby P, Hudson PJ, *et al.* Ecological dynamics of emerging bat virus spillover. Proc. R. Soc. B Biol. Sci. 2014; **282**. DOI:10.1098/rspb.2014.2124.
85 Bloomfield LSP, McIntosh TL, Lambin EF. Habitat fragmentation, livelihood behaviors, and contact between people and nonhuman primates in Africa. *Landsc Ecol 2020 354* 2020; **35**: 985–1000.
86 Zhong S, Crang M, Zeng G. Constructing freshness: the vitality of wet markets in urban China. *Agric Hum Values 2019 371* 2019; **37**: 175–85.
87 Magouras I, Brookes VJ, Jori F, Martin A, Pfeiffer DU, Dürr S. Emerging Zoonotic Diseases: Should We Rethink the Animal–Human Interface? *Front Vet Sci* 2020; **7**: 582743.
88 Chen Y, Liang W, Yang S, *et al.* Human infections with the emerging avian

influenza A H7N9 virus from wet market poultry: clinical analysis and characterisation of viral genome. *Lancet* 2013; **381**: 1916–25.
89 Wu T. The socioeconomic and environmental drivers of the COVID-19 pandemic: A review. *Ambio 2021 504* 2021; **50**: 822–33.
90 Cleaveland S, Laurenson MK, Taylor LH. Diseases of humans and their domestic mammals: pathogen characteristics, host range and the risk of emergence. *Philos Trans R Soc London Ser B Biol Sci* 2001; **356**: 991–9.
91 Looi L-M, Chua K-B. Lessons from the Nipah virus outbreak in Malaysia. 2007.
92 Enserink M. Coronavirus rips through Dutch mink farms, triggering culls to prevent human infections. *Science (80-)* 2020; published online June 9. DOI:10.1126/SCIENCE.ABD2483.
93 JP G, JH L, LB P, *et al.* The animal-human interface and infectious disease in industrial food animal production: rethinking biosecurity and biocontainment. *Public Health Rep* 2008; **123**: 282–99.
94 MJ G, C G, DB W, GW B, DG R, PS T. The potential role of concentrated animal feeding operations in infectious disease epidemics and antibiotic resistance. *Environ Health Perspect* 2007; **115**: 313–6.
95 Jones IJ, MacDonald AJ, Hopkins SR, *et al.* Improving rural health care reduces illegal logging and conserves carbon in a tropical forest. *Proc Natl Acad Sci U S A* 2020; **117**: 28515–24.
96 Koh LP, Li Y, Lee JSH. The value of China's ban on wildlife trade and consumption. *Nat Sustain 2021 41* 2021; **4**: 2–4.
97 Roe D, Dickman A, Kock R, Milner-Gulland EJ, Rihoy E, 't Sas-Rolfes M. Beyond banning wildlife trade: COVID-19, conservation and development. *World Dev* 2020; **136**: 105121.
98 Bonwitt J, Dawson M, Kandeh M, *et al.* Unintended consequences of the 'bushmeat ban' in West Africa during the 2013–2016 Ebola virus disease epidemic. *Soc Sci Med* 2018; **200**: 166–73.
99 Chaves WA, Valle DR, Monroe MC, Wilkie DS, Sieving KE, Sadowsky B. Changing Wild Meat Consumption: An Experiment in the Central Amazon, Brazil. Conserv. Lett. 2018; **11**: e12391.
100 Doughty H, Milner-Gulland EJ, Lee JSH, Oliver K, Carrasco LR, Veríssimo D. Evaluating a large-scale online behaviour change intervention aimed at wildlife product consumers in Singapore. *PLoS One* 2021; **16**: e0248144.
101 Veríssimo D, Schmid C, Kimario FF, Eves HE. Measuring the impact of an entertainment-education intervention to reduce demand for bushmeat. *Anim Conserv* 2018; **21**: 324–31.
102 Thomas-Walters L, Cheung H, Lee TM, Wan AKY, Wang Y. Targeted values: The relevance of classical Chinese philosophy for illegal wildlife demand reduction campaigns. *People Nat* 2020; **2**. DOI:10.1002/pan3.10127.
103 Thomas-Walters L, Veríssimo D, Gadsby E, Roberts D, Smith RJ. Taking a more nuanced look at behavior change for demand reduction in the illegal wildlife trade. *Conserv Sci Pract* 2020; **2**: e248.
104 Stephen C, Berezowki J, Carmo, Pedro L, Friker B, Miguel Maximiano Alves de Sousa F, Vidondo B. A rapid review of evidence on managing the risk of disease emergence in the wildlife trade. Paris, 2021.

105 Carroll D, Morzaria S, Briand S, *et al.* Preventing the next pandemic: the power of a global viral surveillance network. *BMJ* 2021; **372**: n485.
106 Yi S, Lin S, Li Y, Zhao W, Mills GB, Sahni N. Functional variomics and network perturbation: connecting genotype to phenotype in cancer. *Nat Rev Genet 2017 187* 2017; **18**: 395–410.
107 Levinson J, Bogich TL, Olival KJ, *et al.* Targeting surveillance for zoonotic virus discovery. *Emerg Infect Dis* 2013; **19**: 743–7.
108 Berger KA, Pigott DM, Tomlinson F, *et al.* The Geographic Variation of Surveillance and Zoonotic Spillover Potential of Influenza Viruses in Domestic Poultry and Swine. *Open Forum Infect Dis* 2018; **5**. DOI:10.1093/OFID/OFY318.
109 Dobschuetz S. Von, Nardi M De, Harris KA, *et al.* Influenza surveillance in animals: what is our capacity to detect emerging influenza viruses with zoonotic potential? *Epidemiol Infect* 2015; **143**: 2187–204.
110 Influenza A Virus in Swine Surveillance Information. USDA Anim. Plant Insp. Serv. 2020; published online Aug 5. https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/sa_animal_disease_information/sa_swine_health/ct_siv_surveillance/ (accessed Aug 4, 2021).
111 Thumbi SM, Njenga MK, Otiang E, *et al.* Mobile phone-based surveillance for animal disease in rural communities: Implications for detection of zoonoses spillover. *Philos Trans R Soc B Biol Sci* 2019; **374**. DOI:10.1098/rstb.2019.0020.
112 Monath TP. Vaccines against diseases transmitted from animals to humans: A one health paradigm. Vaccine. 2013; **31**: 5321–38.
113 Middleton D, Pallister J, Klein R, *et al.* Hendra virus vaccine, a one health approach to protecting horse, human, and environmental health. *Emerg Infect Dis* 2014; **20**: 372–9.
114 Vigilato MAN, Clavijo A, Knobl T, *et al.* Progress towards eliminating canine rabies: policies and perspectives from Latin America and the Caribbean. *Philos Trans R Soc B Biol Sci* 2013; **368**. DOI:10.1098/RSTB.2012.0143.
115 Sokolow SH, Nova N, Pepin KM, *et al.* Ecological interventions to prevent and manage zoonotic pathogen spillover. Philos. Trans. R. Soc. B Biol. Sci. 2019; **374**. DOI:10.1098/rstb.2018.0342.
116 Pulliam JRC, Epstein JH, Dushoff J, *et al.* Agricultural intensification, priming for persistence and the emergence of Nipah virus: a lethal bat-borne zoonosis. *J R Soc Interface* 2012; **9**: 89–101.
117 Wu T, Perrings C, Shang C, *et al.* Protection of wetlands as a strategy for reducing the spread of avian influenza from migratory waterfowl. *Ambio 2019 494* 2019; **49**: 939–49.
118 OECD. OECD Economic Outlook, Volume 2021 Issue 1. Paris: OECD, 2021 DOI:10.1787/edfbca02-en.
119 New York Declaration on Forests Progress Assessment. For. Declar. https://forestdeclaration.org/goals (accessed Aug 4, 2021).
120 Wright EM, Bhammar HM, Gonzalez Velosa AM, Sobrevila C. Analysis of International Funding to Tackle Illegal Wildlife Trade. 2016 https://documents.worldbank.org/en/publication/documents-reports/documentdetail/695451479221164739/analysis-of-international-funding-to-tackle-illegal-wildlife-trade (accessed Aug 4, 2021).

121 The United States Department of Interior Budget Justifications and Performance Information Fiscal Year 2020: Fish and Wildlife Service. 2020.
122 Strategy. World Organ. Anim. Heal. https://www.oie.int/en/who-we-are/strategy/ (accessed Aug 4, 2021).
123 Imagine a World Free From Pandemic Threats. Glob. Virome Proj. https://www.globalviromeproject.org/support-gvp (accessed Aug 4, 2021).
124 Dobson AP, Pimm SL, Hannah L, *et al.* Ecology and economics for pandemic prevention. *Science (80-)* 2020; **369**. DOI:10.1126/science.abc3189.
125 Nepstad D, McGrath D, Stickler C, *et al.* Slowing Amazon deforestation through public policy and interventions in beef and soy supply chains. *Science (80-)* 2014; **344**: 1118–23.
126 Silva Junior CHL, Pessôa ACM, Carvalho NS, Reis JBC, Anderson LO, Aragão LEOC. The Brazilian Amazon deforestation rate in 2020 is the greatest of the decade. *Nat Ecol Evol 2020 52* 2020; **5**: 144–5.