Interventions to Reduce Risk for Pathogen Spillover and Early Disease Spread to Prevent Outbreaks, Epidemics, and Pandemics

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The pathogens that cause most emerging infectious diseases in humans originate in animals, particularly wildlife, and then spill over into humans. The accelerating frequency with which humans and domestic animals encounter wildlife because of activities such as land-use change, animal husbandry, and markets and trade in live wildlife has created growing opportunities for pathogen spillover. The risk of pathogen spillover and early disease spread among domestic animals and humans, however, can be reduced by stopping the clearing and degradation of tropical and subtropical forests, improving health and economic security of communities living in emerging infectious disease hotspots, enhancing biosecurity in animal husbandry, shutting down or strictly regulating wildlife markets and trade, and expanding pathogen surveillance. We summarize expert opinions on how to implement these goals to prevent outbreaks, epidemics, and pandemics.

The pathogens that cause most emerging infectious diseases in humans originate in animals, particularly wildlife, and then spill over into humans. Emerging infectious diseases, including pandemic influenza, Ebola, mpox, and HIV/AIDS, have had profound effects on humanity (*1*). SARS-CoV-2, the virus that causes COVID-19, also likely emerged in humans through spillover (*2*,*3*). Land-use change, animal husbandry, and commercial wildlife markets and trade create opportunities for spillover, and climate change is further increasing the risk for infectious disease emergence (*4*).

The ecologic disruption caused when land with intact ecosystems is converted for purposes such as agriculture increases contact between humans, domestic animals, and wildlife, providing opportunities for spillover. Among ecosystem types, clearing and degradation of tropical and subtropical forests likely carries the highest risk for spillover (*5*,*6*). Forest clearing and degradation brings humans to the forest edge, increasing opportunities for humans and domestic animal contact with wildlife and subsequent pathogen transmission (*6*–*9*). Forest clearing and degradation also causes loss of biodiversity, which disrupts and decreases natural species assemblages and favors animals that can survive near humans, which often are animals associated with zoonotic pathogens, such as bats and rodents (*10*). In addition, those wildlife species might experience physiologic stress from habitat disruption, increasing

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their risk of becoming infected with or shedding viruses (*8*). Furthermore, commercial exploitation of wildlife through markets and trade often increases when previously intact forests are opened (*11*). The subsequent admixture of wildlife and domestic animals creates further opportunities for spillover and potential for viral recombination.

Spillover events combined with the interconnectedness of the modern world will accelerate the frequency of outbreaks, epidemics, and pandemics unless underlying spillover drivers are addressed (*12*). Unfortunately, spillover prevention has largely been sidelined in discussions on reforming global approaches to pandemics during the rebuilding from COVID-19 (*13*). Instead, most discourse, often couched as prevention, focuses on postspillover interventions, such as outbreak response, health system strengthening, and vaccine development (*14*,*15*). Such interventions are essential but are not prevention; on their own, postspillover interventions are insufficient to safeguard against the catastrophic threats posed by pandemics. Even when outbreaks are rapidly identified, postspillover interventions can be unsuccessful. Furthermore, timely and effective vaccines and therapeutics might not be available for every future disease. In addition, vaccine and therapeutic effectiveness at the population level can be hampered by supply and distribution challenges, especially in low-income countries, and limited uptake resulting from disinformation and personal beliefs (*16*).

All of those factors point to the urgent need to invest in interventions to prevent spillover and to curb early disease spread among domestic animals and humans. Doing so would be consistent with One Health, an integrated, unifying approach to sustainably balance and optimize the health of humans, animals, and ecosystems (*17*).

We summarize expert opinions on how interventions to reduce risk for spillover and curb early disease spread can be implemented. The interventions we describe fall into 5 categories: stop clearing and degradation of tropical and subtropical forests, improve health and economic security of communities living in emerging infectious disease hotspots, enhance biosecurity in animal husbandry, shut down or strictly regulate wildlife markets and trade, and expand pathogen surveillance at interfaces between humans, domestic animals, and wildlife.

Stop Clearing and Degradation of Tropical and Subtropical Forests

Multiple approaches can be used to address spillover caused by tropical and subtropical forest clearing and degradation. Integrated policies with increased enforcement aim to remove incentives for deforestation while respecting rights of Indigenous Peoples and local communities (IPLCs). Brazil successfully demonstrated this approach in the Amazon Basin. In 2004, the government of Brazil, working with international donors, provided sufficient funds to put into action policies that resulted in a 70% reduction in annual deforestation (*18*). After 2012, policy enforcement weakened and deforestation rose, demonstrating that sustained commitment is crucial for success. Agricultural production increased while the policy was in effect, suggesting reduced deforestation did not affect economic development (*18*–*20*). Of note, nearly 50% of intact forests in the Amazon Basin are in Indigenous territories, and deforestation rates on these lands are lower than elsewhere (*21*).

Regulatory and market-based measures can establish standards that affect international supply and demand for products and lead to decreased deforestation. For instance, Europe is considering restricting imports of commodities such as soybeans, beef, cocoa, and palm oil if production is linked to deforestation (*22*). In an example of market-based measures, >30 financial institutions with trillions of US dollars in assets have pledged to end investment in activities linked to deforestation (*23*).

Payment for ecosystem services gives landholders incentives to maintain or increase forest cover on their lands, thus enhancing levels of ecosystem services provided by those forests (*24*). Success of this strategy has varied across implementation sites; better outcomes might be achieved by focusing on local or regional scales, using in-kind contributions rather than cash payments, and emphasizing equity (*24*).

Community-designed interventions provide local services, such as healthcare, to IPLCs living within and near forests to minimize reliance on deforestation to generate income. For example, communities in Indonesian Borneo were heavily engaged in local illegal logging partly because of high healthcare costs (*25*). When supported to design their own solutions, IPLCs chose to build a medical center and start an alternative livelihood program (*25*). After those solutions were put in place over a decade, at a total cost of US $5.2 million, the percentage of households relying on illegal logging decreased by 90%, forest regrowth increased by 21,000 hectares, and US $65 million in carbon loss was averted (*25*). Similar models have been successfully replicated in Madagascar and Brazil.

Improve Health and Economic Security of Communities Living in Emerging Infectious Disease Hotspots

In many emerging infectious disease hotspots, little intact forest remains, and spillover events occur because dense human and domestic animal populations live closer to wildlife and commercial activities might involve intentional (e.g., wildlife trade) or unintentional contact with wildlife (*26*). Such areas make up only 4% of global area (10% of tropical area), but account for 60% of global spillover risk (*26*). Thus, community-designed interventions to decrease human and domestic animal contact with wildlife probably represent the best means to reduce virus spillover in these areas. Many communities in emerging infectious disease hotspots lack access to healthcare, sustainable livelihoods, food security, and education (*27*). Improving health and economic security are often high priorities for these communities, creating alignment between local needs and global pandemic prevention priorities.

Actions to reduce local risk for zoonotic diseases can be simple. For example, Nipah virus infection risk can be reduced by covering the shaved areas of palm tree trunks and sap vessels, thus preventing contamination with excrement of bats that feed on these palms (*28*). Where contact cannot be eliminated, improved practices, such as better sanitary practices during wildlife butchering, can minimize spillover (*29*).

Community-designed interventions to reduce human–wildlife contact and decrease spillover risk have not been widely implemented. However, projects in several countries, such as in Indonesia (as described in the previous section) and in Uganda, show that changing relationships between communities, forests, and wildlife are possible and beneficial (*25*,*30*). A project in Manombo Rainforest, Madagascar, aims to put in place community-designed conservation initiatives and collect metrics over 10 years to assess effects on biodiversity and wildlife and human health (A. Emerson et al., unpub. data). More projects specifically targeting spillover risk in emerging disease hotspots are needed as proofs of concept (*31*). Such pioneering projects should include measurement of spillover within target communities to enable thorough outcome assessments (*32*).

Enhance Biosecurity in Animal Husbandry

The World Organisation for Animal Health (WOAH) defines biosecurity in animal husbandry as "a set of management and physical measures designed to reduce the risk of introduction, establishment and spread of animal diseases, infections or infestations to, from and within an animal population" (*33*). Several zoonotic viruses, including highly pathogenic avian influenza A(H5N1) virus, 2009 pandemic influenza A(H1N1) virus, Nipah virus, and Middle East respiratory syndrome coronavirus (MERS-CoV), have emerged from wildlife reservoirs into humans via commercial animal industries (*5*,*34*–*36*).

Improving biosecurity in animal husbandry requires management measures, such as quarantining new animals and vaccinating animals against endemic disease, and physical measures, such as enclosures that separate farm animals from each other and from wildlife (*37*). However, backyard flocks and large-scale commercial industrial systems face challenges in implementing biosecurity (*38*). Standard biosecurity recommendations are rarely tailored for extensive production systems in resource-limited settings, and translating recommendations into local languages requires time and knowledge of local perceptions of disease (*37*,*38*). Commercial industrial systems require major investments in biosecurity measures to counteract zoonotic disease transmission risks posed by raising a high density of genetically homogeneous, single-age animals, especially when animal welfare is suboptimal (*39*).

In addition to biosecurity challenges, humans also have major effects on disease incursion into and spread within backyard and commercial industrial systems. Underfunded animal health and extension services, which contributes to ineffective livestock disease surveillance, and chronic household food insecurity (i.e., lack of regular access to sufficient safe and nutritious food), drive risky husbandry practices and household food choices such as consumption of sick animals or animals that died of disease (*40*,*41*). Two global institutions mandated to oversee animal disease prevention and control recognize these challenges: the Food and Agriculture Organization of the United Nations (FAO) and WOAH. In April 2022, FAO and WOAH signed an agreement with the World Health Organization and the United Nations Environment Program to sustainably balance and optimize the health of humans, animals, plants, and the environment and released the One Health Joint Plan of Action to improve prevention, prediction, detection, and response to health threats (*42*,*43*). This partnership will require engagement and support from national and local agencies and organizations.

Biosecurity could be greatly enhanced through investments in public and private animal health services, identification of animal illnesses of public health concern by animal holders, and interventions to address these (*26*,*44*). Benefits of this approach include decreased pathogen transmission between wildlife and domestic animals, enhanced disease surveillance sensitivity via increased producer trust in services, fewer greenhouse gas emissions through efficiency, and improved food security (*37*,*40*,*45*,*46*). This approach is fully compatible with the described community-designed interventions and could be implemented by the same project teams, saving costs. Emerging infectious disease hotspots are among the highest priority areas for reducing spillover risk associated with animal husbandry. Therefore, community-designed interventions and animal husbandry projects should be integrated into any One Health pandemic prevention framework.

Controlling vaccine-preventable diseases in domestic animals also should be prioritized. Vaccination benefits communities and domestic animals through reduced illness and death from vaccine-targeted disease. Vaccination also reduces the spread of emerging infectious diseases because diagnosis can be delayed when emerging infectious diseases have similar clinical signs to vaccine-preventable diseases. For example, identification of highly pathogenic avian influenza in chickens frequently is delayed in areas with low Newcastle disease vaccination rates (*45*,*47*). Similarly, control for outbreaks of African swine fever (ASF), a disease with no effective vaccine, is hampered by low vaccination rates against classical swine fever (CSF) because the diseases have similar clinical signs, making ASF differentiation difficult in herds not vaccinated against CSF (*48*). In China, a 2019 pork shortage caused by ASF might have increased consumer demand for wildlife, thereby increasing the risk of pathogen spillover (*2*).

Shut Down or Strictly Regulate Wildlife Markets and Trade

Legal and illegal wildlife markets and trade pose a high risk for emergence, amplification, and transmission of zoonotic pathogens, as observed with mpox virus, SARS-CoV-1, and probably SARS-CoV-2 (*2*,*3*,*5*). Wildlife trade is driven by demand for animals as food and pets and for skins, traditional medicines, and ornaments. For pandemic prevention, the primary focus should be live and freshly butchered wild birds and mammals because those pose the highest risk for spillover. Furthermore, prevention should focus on commercial wildlife markets and trade but should prioritize the rights of IPLCs, who are often dependent on wildlife for food and livelihoods. Addressing wildlife markets and trade that lead to pathogen spillover will require investments in 4 areas.

First, policy reform to restrict or close legal commercial wildlife markets and trade is needed. New legislation and amendments to existing laws should aim to end the sale of live and freshly butchered wild birds and mammals for commercial purposes; such reforms are consistent with recommendations released in 2021 by the World Health Organization (*49*). Several countries have taken these steps. For example, China banned farming, hunting, trading, and consuming terrestrial wildlife in the context of COVID-19 in February 2020 (*50*). In March 2020, Gabon banned sale and consumption of pangolins and bats (*51*).

Second, legislation and enforcement need to reflect efforts to address illegal wildlife markets and trade. Law enforcement, judicial, and other agencies mandated to stop illegal activities and bring criminals to justice should have budgets for staffing, equipment, training, enforcement, and judicial activities. In addition, they should have sufficient legal mandates to use all available investigative approaches and be held to the highest integrity standards to eradicate corruption. Although pathogen spillover is indifferent to the legality of individual animals in trade, increased vigilance to combat wildlife trafficking remains a priority.

Third, programs focusing on local communities and the rural poor need to be implemented to reduce dependence on wildlife markets and trade for income. Partnerships between local communities and governments will be crucial to provide incentives for robust and sustainable income streams that do not depend on wildlife markets and trade.

Fourth, to end the purchase and desirability of live wild birds and mammals, government leaders and experts need to lead behavior change efforts that apply behavioral science, psychology, economics, and social marketing best practices. Civil society and academia have capacity to find solutions. Several projects are underway, but more effective and sustainable efforts could benefit from public institutions leading or co-leading scale-up programs. In numerous countries, wildlife consumption, especially in urban centers, is not required for food security; rather, wildlife is consumed as a luxury, as a status symbol, or for perceived health reasons. In China, the price for wildlife is generally 2- to 5-fold higher than for pork, the most common animal protein source in the country, and even higher for exotic, endangered, or illegally obtained species (*52*,*53*). Reducing urban demand for wildlife will have a positive effect on IPLCs by reducing economic incentives to those supplying the trade and leaving more wildlife for IPLC subsistence needs.

A strategy to ensure recognition and support of IPLC rights is vital, but that support must not be used as a smokescreen to continue business-as-usual in commercial markets and trade.

Expand Pathogen Surveillance at Interfaces between Humans, Domestic Animals,and Wildlife

Pathogen surveillance platforms that include coordinated multisectoral efforts can increase their effectiveness (*54*). In this context, pathogen surveillance refers to various ongoing active and passive systems for collecting and reporting data on exposures or infections at the human or animal population level; the frequency and severity of disease caused by a given pathogen; and the evolution of microbes circulating in natural reservoirs and additional hosts (*55*). Integrated surveillance systems provide insights into zoonotic pathogens, such as Ebola virus, in their ever-changing natural reservoirs, as well as data on spillover into domestic animals and humans, which can inform targeted pandemic prevention, preparedness, and response strategies (*56*,*57*). For example, 25 years of data showed that Hendra virus spillover from bats to horses increased during periods of environmental stress; this finding provides evidence for using forest restoration as an ecologic countermeasure to reduce future spillovers (*58*).

Systematic wildlife surveillance will require substantial veterinary medical capacity and massive strengthening of multisectoral, decentralized, laboratory networks to support molecular and serologic screening of animal and human samples. Laboratory-based surveillance should include pathogen-specific molecular and serologic diagnostic assays and unbiased high-throughput screening tools (*59*,*60*). As whole-genome sequencing platforms and near real-time genomic sequencing for examining viral evolution and epidemiology become more common and field applicable, investments in bioinformatics capacity to analyze genomic data will become increasingly vital.

For humans, data can be extracted from several primary sources, including health information systems, sentinel surveillance sites, and repeated standard household surveys, to monitor for pathogen emergence. Such systems could be extended to wild and domestic animal populations. Many human febrile illnesses in low-income countries never reach the health system and are not thoroughly evaluated; thus, many viral infections are never diagnosed (*61*,*62*). Routine diagnostic systems for traditionally undiagnosed illnesses could be improved by increasing libraries of pathogens found in wild and domestic animal populations. However, limited access to diagnostic testing is not just confined to low-income countries; even countries like the United States experienced challenges that hampered disease control efforts during the COVID-19 pandemic and mpox epidemic (*63*,*64*).

Mounting evidence suggests that zoonotic pathogen spillover occurs more frequently than previously known. A study of exposure to batborne SARS-related coronaviruses suggested that ≈66,000 persons are infected with SARS-related coronaviruses annually in South and Southeast Asia (*65*). High rates of pre–COVID-19 SARS-related coronavirus exposure also were observed in Sierra Leone (*66*). This evidence underscores the need to improve surveillance for zoonotic pathogens that have pandemic potential.

Discussion

COVID-19 and mpox exposed inadequacies in current domestic and global approaches to pandemics and their prevention. A narrow window of time for reform exists before the next crisis of zoonotic origin takes hold (*14*,*15*). History suggests that the most likely source of the next pandemic will be spillover of a novel virus from wildlife directly into humans or into domestic animals and then humans (*1*). Therefore, we must address underlying drivers of pathogen spillover to prevent outbreaks.

We have provided a nonexhaustive set of interventions to reduce risk of spillover. Pandemic prevention is a global imperative and must be addressed as such. Programs funded by high-income countries and focused on bilateral aid remain critical, but no country should carry the costs alone when the stakes are so high. Programs like the US Agency for International Development (USAID) Emerging Pandemic Threats PREDICT program (2009–2020) have transformed zoonotic disease prevention efforts by strengthening local workforce and laboratory capacity to detect and respond to known and unknown zoonotic viral threats (*67*). USAID continues to invest in spillover prevention in priority countries through projects to develop a One Health workforce via university networks in Asia and Africa and develop interventions to stop spillover at key high-risk human-animal interfaces. Despite the focus on spillover prevention, these programs are subject to changes in governmental priorities and are not funded at a scale that can sufficiently address the global threat. An integrated global pandemic prevention (prespillover) and preparedness (postspillover) strategy would cost US ≈$20–$50 billion annually from all sources (*14*,*68*). Published research indicates that the pandemic prevention (prespillover) initiatives we describe can be achieved for US ≈$20 billion per year globally, representing a fraction of the trillions of dollars, and millions of lives, lost from COVID-19 (*30*).

Addressing the drivers of spillover will have benefits beyond pandemic prevention, including mitigating climate change, preventing biodiversity loss, enhancing basic human health, respecting human rights, and promoting sustainable development (*10*). Thus, as the World Bank Pandemic Fund and the World Health Assembly pandemic accord both take shape, the activities we describe must be included (*13*). The UN climate summit commitment of billions of dollars to help end deforestation in >100 countries by 2030 is promising (*23*), and health outcomes should be prioritized to maximize impacts and minimize the risk for failure seen with prior commitments. Irrespective of high-level governance agreements, compliance on the ground will require active engagement by communities that believe the proposed measures will make a positive difference in their lives.

In practice, One Health is often narrowly applied to public health approaches after spillover has occurred. To stop future waves of accelerating and intensifying outbreaks, epidemics, and pandemics, the global community needs to broaden One Health approaches and embrace initiatives to prevent spillover (*69*). Addressing the multitiered complexities of spillover events, nature, and human behavior will require stacked safeguards before and after the point of spillover to decrease the risk for future pandemics. Thus, the One Health approach for pandemics requires coordination, collaboration, and major new resources across human health, animal health, environmental, and food safety agencies (*70*).

Preventing spillover is an issue of equity. Focusing only on postspillover interventions signals that the global community is tolerant of outbreaks in the most resource-limited settings, as long as those outbreaks do not grow into epidemics or pandemics. Preventing outbreaks will save lives in some of the world's most vulnerable regions, which will help ensure equitably distributed health benefits.

A robust research agenda will be essential for examining causal links between the interventions we propose and subsequent spillover reductions. Available evidence suggests that these interventions will have meaningful effects on reducing the probability of spillover events (*5*). However, to date, few large-scale programs focus on spillover prevention and evaluate efficacy of interventions; more large-scale implementation is needed to build an evidence base to show how investments in addressing the drivers of spillover lead to lower spillover risk. Nonetheless, we already know enough to act now, and the Precautionary Principle (https://unesdoc.unesco.org/ark:/48223/pf0000139578) dictates that we must.

Zoonotic pandemic risk is heightened by humanity's broken relationship with nature. The actions we describe will reduce the risk of spillover and early disease spread and address pandemics, climate change, biodiversity loss, and inequity. Evidence for these actions existed before COVID-19, but no action was taken. However, as we emerge from the acute phase of the current pandemic, we can take actions to prevent the next pandemic. We cannot undo the past, but we must do better in the future.

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