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REVIEW ARTICLE

The Animal Origin of Major Human Infectious Diseases: What Can Past Epidemics Teach Us About Preventing the Next Pandemic?

Guha Dharmarajan[1,*], Ruiyun Li[2], Emmanuel Chanda[3], Katharine R. Dean[4], Rodolfo Dirzo[5], Kjetill S. Jakobsen[2], Imroze Khan[6], Herwig Leirs[7], Zheng-Li Shi[8], Nathan D. Wolfe[9], Ruifu Yang[10] and Nils Chr. Stenseth[2,*]

Abstract

Emerging infectious diseases are one of the greatest public health challenges. Approximately three-quarters of these diseases are of animal origin. These diseases include classical zoonoses maintained in humans only via transmission from other vertebrates (e.g., rabies) and those initiated by a successful one-off zoonotic event (host-switch) in conjunction with efficient human-to-human transmission (e.g., H1N1 influenza). Here, we provide a systematic review, in conjunction with a meta-analysis and spatial risk modeling, to identify the major characteristics of past epidemics of animal origin and predict areas with high future disease emergence risk. Countermeasures against future pandemics of animal origin must focus on several key mechanisms. First, the eco-epidemiological contexts favoring spillover events must be clearly establish. Second, pathogen surveillance must be scaled up, particularly in taxa and/or eco-geographic areas with high disease emergence risk. Third, successful spillover risk must be mitigated through proactive strategies to interrupt animal-to-human transmission chains. Fourth, to decrease epidemic potential and prevent epidemics from becoming pandemics, improved source identification and real-time spatial tracking of diseases are crucial. Finally, because pandemics do not respect international borders, enhancing international collaboration is critical to improving preparedness and response.

Key words: disease ecology, emerging infectious disease, pathogen, parasite, zoonoses

INTRODUCTION

Human history has been punctuated by many pandemics, including the bubonic plague (14th century), the Spanish flu (20th century), HIV/AIDS (20th and 21st centuries), and coronavirus disease 2019 (COVID-19). Having infected more than 238 million people and caused more than 4.8 million deaths since its emergence in December 2019 [1] (Fig 1), COVID-19 has underscored the devastating, long-lasting societal and economic consequences of emerging infectious diseases. Particularly alarmingly, the risk of novel disease emergence in human populations is increasing because of the confluence of numerous drivers of global environmental change, including those associated with climate,

Edited by:
Wei Wang, Jiangsu Institute of Parasitic Diseases, China

Reviewed by:
Cao Chen, National Institute for Viral Disease Control and Prevention, China
Aaron Irving, Zhejiang University-University of Edinburgh Institute, China
The third reviewer chose to remain anonymous.

***Corresponding authors:**
E-mail: guha.dharmarajan@krea.edu.in (GD); n.c.stenseth@mn.uio.no (NS)

[1]Division of Science, School of Interwoven Arts and Sciences, Krea University, Sri City, Andhra Pradesh, India
[2]Centre for Ecological and Evolutionary Synthesis, Department of Biosciences, University of Oslo, Oslo, Norway
[3]Communicable and Non-Communicable Diseases Cluster, World Health Organization Regional Office for Africa, Brazzaville, Republic of Congo
[4]Norwegian Veterinary Institute, Oslo, Norway
[5]Department of Biology and Woods Institute for the Environment, Stanford University, Stanford, CA, USA
[6]Department of Biology, Ashoka University, Sonepat, India
[7]Evolutionary Ecology Group, Department of Biology, University of Antwerp, Wilrijk, Belgium
[8]CAS Key Laboratory of Special Pathogens, Wuhan Institute of Virology, Wuhan, China
[9]Metabiota, 425 California Street, Suite 1200, San Francisco, CA, USA
[10]State Key Laboratory of Pathogen and Biosecurity, Beijing Institute of Microbiology and Epidemiology, Beijing, China

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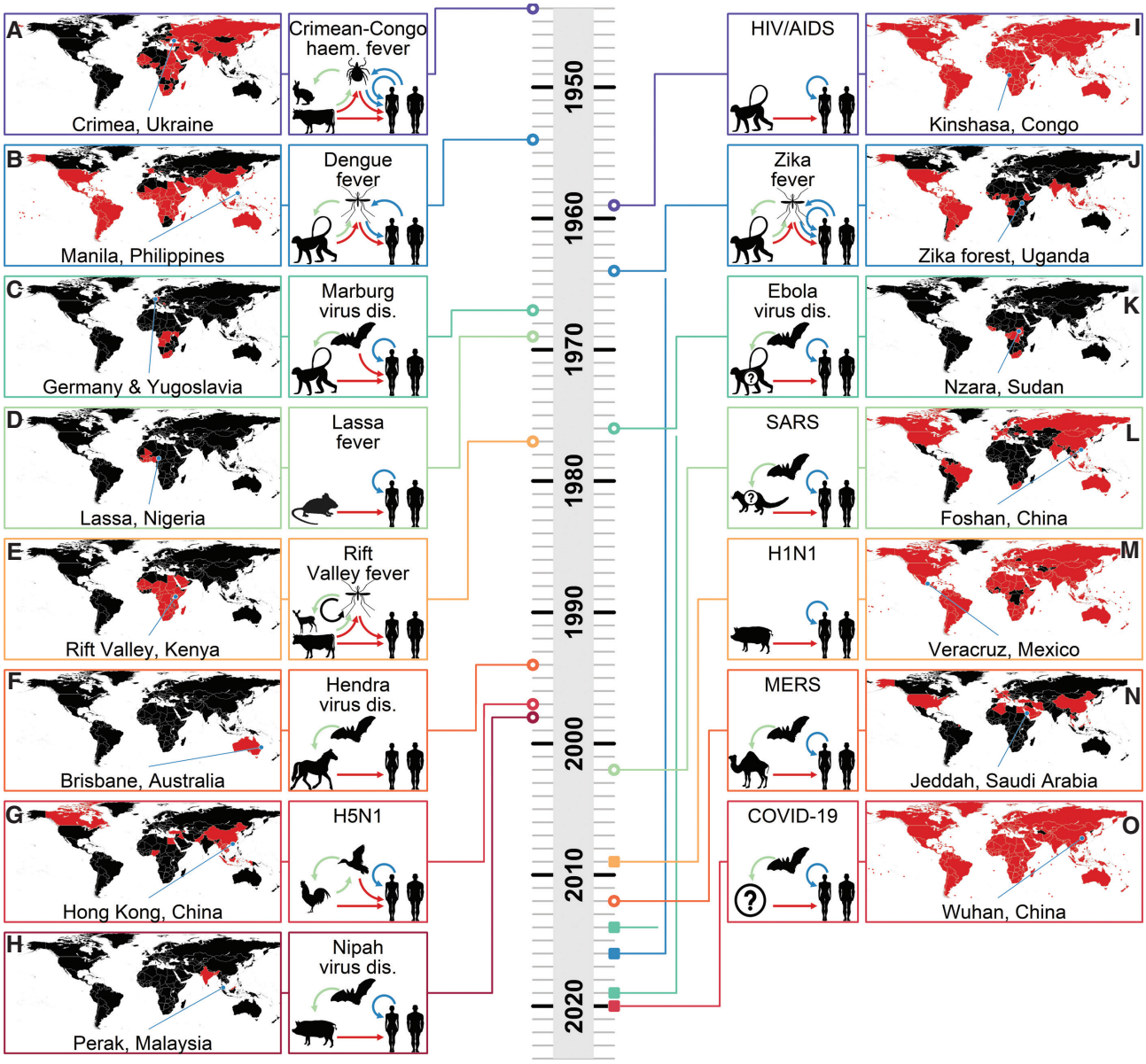

FIGURE 1 | Major diseases of animal-origin affecting human health.
A timeline of emergence of diseases of animal-origin which are considered to be a threat to global health or which require urgent research as identified by the World Health Organization, including: (a) Crimean-Congo hemorrhagic fever; (b) Dengue fever; (c) Marburg virus disease; (d) Lassa fever; (e) Rift Valley fever; (f) Hendra virus disease; (g) Highly Pathogenic Asian Avian Influenza A subtype H5N1; (h) Nipah virus disease; (i) HIV/AIDS; (j) Zika fever; (k) Ebola virus disease; (l) Sudden Acute Respiratory Syndrome (SARS); (m) Influenza A virus subtype H1N1; (n) Middle East Respiratory Syndrome (MERS); (o) Coronavirus Disease 2019 (COVID-19). For each disease the year of initial identification (round symbols on time line) or declaration of a public health emergency of international concern (square symbols on time line) are shown. The spatial extent of each disease is also given as a map highlighting with areas where transmission is reported (red areas) and the location from where the pathogen was first reported (blue symbol). Also, depicted are the major routes of transmission in the zoonotic source population (green arrows), primary zoonotic event (red arrows) and mode of maintenance in the human population (green arrows). Diseases include those that are strictly zoonotic and maintained in the human population only through transmission from a vertebrate animal host (e.g., Rift Valley fever and Hendra virus disease), diseases that are primarily maintained by zoonotic spillover but which can also be transmitted directly between humans (e.g., Ebola/Marburg virus diseases and MERS), and diseases of animal-origin which show very efficient human-to-human transmission (e.g., HIV infection, H5N1/H1N1 influenza). Several diseases are suspected to be of zoonotic origin but the vertebrate animal reservoir remains unconfirmed (e.g., Ebola virus disease, SARS and COVID-19). See Supplemental Material for references to source information used to produce the figure.

land-use (e.g., urbanization), and the agricultural industry (e.g., large commercial animal farms). Moreover, this risk is aggravated by the ever-increasing resistance to antimicrobial drugs and insecticides used for disease vector control [2,3], and the growing potential for the rapid spread of diseases with increased global transport [4–7].

From a public health perspective, because approximately three-quarters of all emerging infectious diseases are caused

by pathogens originating from domestic or wild animal species [8], concerns regarding the threat of human infectious diseases of animal origin have grown. These pathogens vary considerably in terms of the conditions favoring spillover events and the resultant public health consequences. For example, strictly zoonotic diseases cannot be maintained in human populations without new spillover events from a vertebrate reservoir, because human-to-human transmission does not occur (e.g., echinococcosis, toxoplasmosis, and rabies). Other infections, such as bubonic plague (caused by *Yersinia pestis*), Lyme disease (caused by *Borrelia burgdorferi*), and West Nile fever (caused by the West Nile virus) are transmitted by arthropod vectors but do not show long-term human-to-human transmission. Other diseases are primarily maintained in human populations through spillover from vertebrate reservoirs, but do show rare (e.g., hantavirus disease and hepatitis-E infection) or inefficient (e.g., pneumonic plague) human-to-human transmission. Finally, some diseases are initiated by a successful one-off zoonotic event (host-switch) with such efficacious rates of long-term human-to-human transmission that a new human pathogen is created *de facto*, and the original animal reservoir is no longer essential to maintaining recurring infections in humans. Many recent emerging infectious diseases have been caused by pathogens whose ancestors were maintained in vertebrate reservoirs but now are efficiently transmitted between humans via aerosol/respiratory droplets (e.g., H1N1 influenza), exchange of bodily fluids (e.g., HIV/AIDS), or arthropod vectors (e.g., Zika virus fever). Although SARS-CoV-2 may also be a virus of animal origin, the actual source of the virus in human populations remains enigmatic [9]. Interestingly, many modern human pathogens have zoonotic origin. One classical example of such a disease is measles, which probably diverged from rinderpest approximately 900 years ago [10]. Additionally, human malaria caused by both *Plasmodium falciparum* and *P. vivax* is the result of successful historical host switching between African apes and humans [11]. Currently, macaque monkeys are a major reservoir of *P. knowlesi,* an important emerging human malaria pathogen in parts of southeast Asia [12,13].

Host switching events leading to the creation of a new human pathogen can occur directly from the original animal reservoir (e.g., non-human primates in the case of HIV) or via an intermediate step with amplification/adaption (e.g., recombination) in other species, including domestic animals (e.g., domestic swine for H1N1 influenza) [14]. Although any zoonotic disease can have serious public health consequences, the risk of a pandemic is greatly enhanced after efficient human-human transmission is established. The currently high connection among human populations [15] further facilitates the geographical spread of novel viruses, particularly respiratory syndrome diseases such as COVID-19 [1]. The potential for geographical spread of novel viruses in human populations is exemplified by the emergence of respiratory syndrome diseases in the 21st century, particularly coronaviruses, such as those causing sudden acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19 (Fig 1). Epidemics of these diseases have shown rapid spatial and temporal spread. For example, SARS (2002–2003) affected countries across five continents (Africa, Asia, Australia, Europe, and North America), MERS (2012–2020) affected four continents (Africa, Asia, Europe, and North America), and COVID-19 has spread to all continents [1].

To mitigate the persistent threat of emerging and re-emerging diseases, several global health security frameworks have been established, such as the International Heath Regulations [16]. These frameworks aim to protect individuals and societies from acute public health events and to support global preparedness and responses to emerging infectious diseases [17]. For example, in the past few decades, the World Health Organization (WHO) has declared six Public Health Emergencies of International Concern—health emergencies that "potentially require a coordinated international response" [16]. Five of the six have been associated with pathogens of animal origin: the H1N1 influenza virus in 2009, Ebola virus in 2014 and 2018, Zika virus in 2016, and SARS-CoV-2 in 2020 (Fig 1). To advance the ability to fight future pandemics, identifying the major characteristics, sources and conditions for emergence of previous diseases of animal origin is critical. To this aim, we performed a systematic review in conjunction with a meta-analysis and spatial modeling to identify the major characteristics associated with past epidemic outbreaks of animal origin and to predict areas with high future disease emergence risk (details on the methods used to identify, extract, and analyze these data are described in the Supplementary Online Materials).

DISCUSSION

Key drivers of pathogen spillover

The initial transmission of pathogens originating from animals to humans requires specific ecological barriers to be overcome (Fig 2). The transmission route acts as an initial barrier by limiting the pathogens that humans can encounter from specific vertebrate animals. Zoonotic diseases can be maintained in human populations through transmission of a pathogen from a vertebrate animal host through various routes [4], including direct contact with infected animal tissues or body fluids through wounds or abraded skin; animal bites and scratches (e.g., *Brucella abortus* and rabies virus); indirect contact with a contaminated environment or fomites (e.g., *Burkholderia pseudomallei* and *Leptospira interrogans*); airborne transmission via aerosols or dust particles (e.g., MERS-COV and H1N1 influenza viruses); oral transmission (e.g., *Toxoplasma gondii* and *Giardia spp.*); and vector-borne transmission (e.g., *Yersinia pestis* and *Borrelia burgdorferi*). Diseases of animal origin with efficient human-to-human transmission can also initially enter the human population through any of the routes described above. However, zoonotic events introducing infections into humans may result from unusual transmission routes that differ from the normal transmission route in the animal reservoir as well as the normal transmission route in humans. For example, HIV is efficiently transmitted

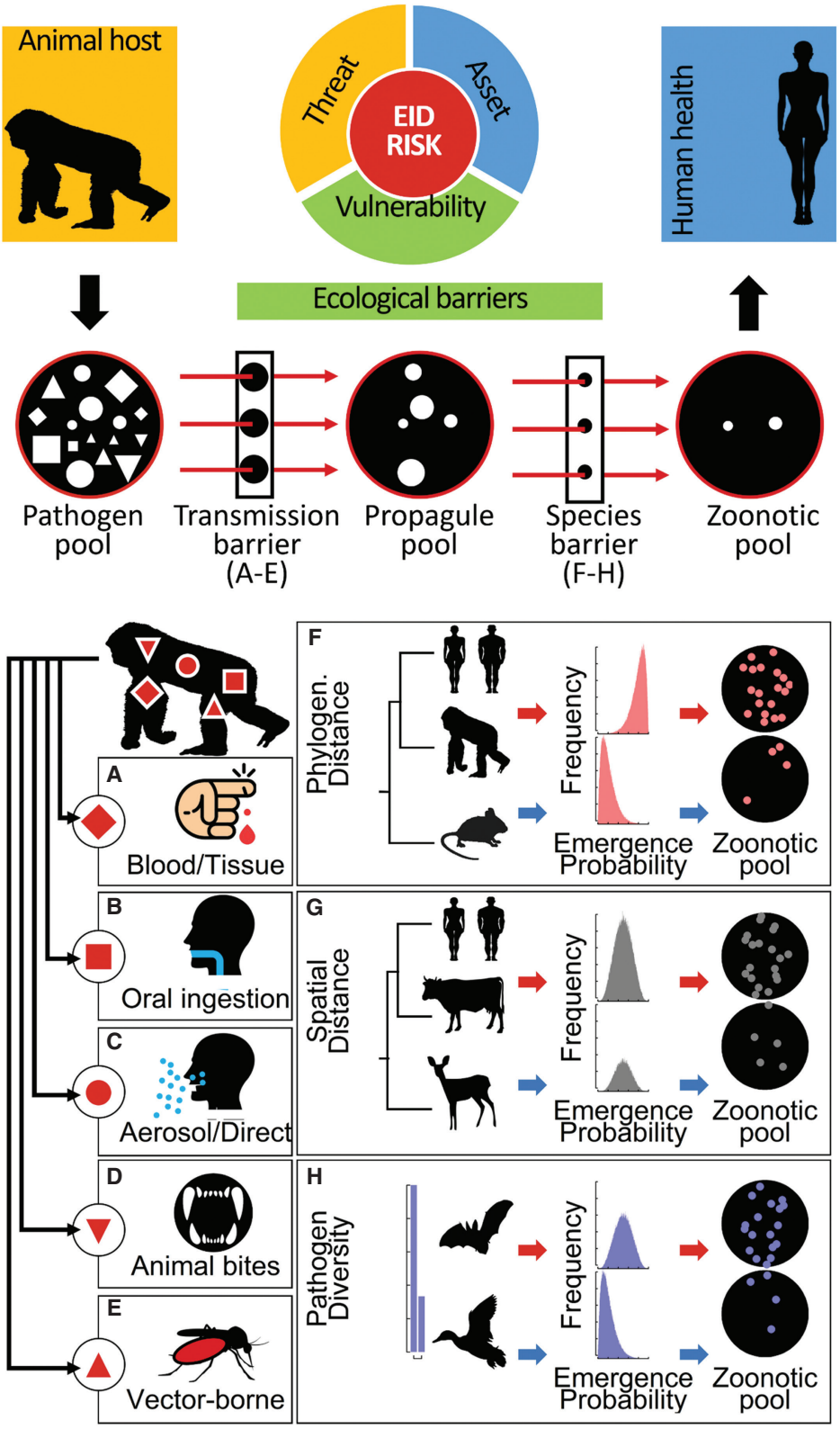

FIGURE 2 | An eco-evolutionary risk assessment framework of zoonotic disease emergence.
Risk of zoonotic disease emergence (EID risk) can be viewed as a function of threats (the animal host and pathogen pool), vulnerabilities (the ecological barriers that pathogens need to overcome to emerge in human populations) and the focal asset (i.e., human health). To emerge a pathogen first needs to overcome transmission barriers, which depend on the pathogen transmission route, and include: (A) Direct contact; (B) Indirect contact; (C) Airborne transmission; (D) Oral ingestion; (E) through bites of arthropod vectors. The pathogen then has to overcome species barriers, which can be influenced by: (F) Phylogenetic distance between the animal species and humans; (G) Spatial distance between the animal species and humans; (H) Pathogen diversity hosted by the animal species. In each panel, the histograms indicate the overall pool of pathogen propagules hosted by the animal with pathogens with higher risk of emergence in humans being depicted by increased numbers. The zoonotic pool indicates the sample of propagule pool that can emerge in humans, and is affected by the overall frequency of the pathogen in the propagule pool and the pathogen's risk of emergence.

through sexual contact among humans, but the original spillover was likely to have occurred through repeated exposure of humans to simian immunodeficiency virus through cuts received during butchering meat or contact with the blood of infected wild primates [18-20]. Similarly, plague is transmitted among rodents and from rodents to humans by flea bites or sometimes the consumption of infected meat [21,22]; however, human-human transmission occurs through pneumonic transmission or lice [23].

For a novel pathogen to emerge in humans from another vertebrate species, the pathogen must also successfully overcome the species barrier (Fig 2). Although host switching events are inherently stochastic, past zoonoses have revealed that animal species with a high risk of harboring potentially zoonotic pathogens are characterized by at least one of three key features. First, hosts that are phylogenetically related are more likely to share pathogens [24-26]. Thus, non-human primates (specifically great apes) are a major source of potential zoonotic diseases [24,27,28], and 21% of non-human primate species (77/365) have been identified as hosts [6] for zoonotic pathogens. This increased risk of pathogen sharing between humans and non-human primates is likely to be driven by the underlying coevolutionary relationships between primates and their pathogens [29-31].

Second, spatial overlap with humans appears to be an even more important driver than phylogenetic proximity in influencing the extent of pathogen sharing between humans and non-human primates [32]. Indeed, species in close contact with humans are more likely to be sources of emerging zoonotic pathogens, because a higher frequency of interspecific contacts leads to greater pathogen transmission risk. High contact rates with domestic animals, which are regularly near humans, are also expected [33]. The number of diseases that these species share with humans increases with the time after domestication [34]. Additionally, synanthropic species (e.g., brown rats, *Rattus norvegicus*) have been estimated to be 15 times more likely to be sources of emerging infectious diseases than other species [35]. Critically, recent evidence has demonstrated that hosts that tend to thrive in human-modified landscapes also tend to harbor a higher diversity of zoonotic pathogens [36]. This relationship is likely to be driven by specific traits (e.g., fast pace of life) that increase susceptibility to infection and facilitate survival in human-dominated landscapes [36].

Third, the risk of emergence of novel pathogens is expected to be greater with increasing diversity of the pathogens harbored by a particular species [25]. This relationship occurs because a diverse "zoonotic pool" [37] has a higher probability of harboring specific pathogen lineages that can potentially infect humans (with or without additional mutations). A recent study has revealed that the zoonotic viral diversity of a particular taxonomic order is proportional to the total viral richness, which in turn depends on the species richness of the order [31]. Thus, the two most specious orders of mammals, Rodentia (2020 species) and Chiroptera (1100 species), harbor the highest proportion of zoonotic viruses [6,28,33]. Rodents and bats can transmit various viruses (e.g., Ebola, Hendra, Nipah, and Lassa fever viruses) and bacteria (e.g., *Y. pestis* and *Francisella tularensis*). Thus, these two taxa are of special interest from a human disease perspective, because of the diversity of pathogens that they harbor [28,38-45] and because they commonly are found in human-modified landscapes [36].

Importantly, host and vector ecology and host physiology (e.g., immune strategies) can regulate the genetic diversity of pathogens [46] and thus the zoonotic risk posed by a host species [43,47-49]. For example, the transmission efficiency of plague (*Y. pestis*) appears to be affected by the bacterium's ability to form a biofilm blockage in the flea gut, thus causing fleas to bite more frequently. This extended flea phenotype is caused by selection for mutations in the *rpoZ* gene in the bacterium under wet and cold climate conditions [45]. Another critical aspect affecting the "zoonotic pool" is the type (i.e., genetic variability) of pathogens harbored by a specific host species. For example, the standing genetic variation (associated with population size) and mutation rate of the pathogen critically affect the risk of a zoonotic event. Thus, RNA-viruses, which mutate more rapidly than DNA-viruses, can adapt more rapidly to a novel host [50,51]. Interestingly, pathogen evolution rates may themselves be affected by host immune responses, and increased selection for mutations can evolve under stressful environments of immunity accelerating the rate of adaptation [52,53]. For example, the stomach bacterium *Helicobacter pylori* produces mutation bursts during the acute phase of infection, which facilitate faster adaptation against host immunity [54].

What will drive the next pandemic of animal origin?

An understanding of past zoonoses enables informed predictions to be made regarding where the next pandemic of animal origin is likely to originate. For example, climate is recognized to critically influence disease dynamics in multiple ways. Climate can affect the seasonal dynamics of many diseases [55,56] by influencing current and future pathogen [57], host [58,59], and vector [60] distributions [61-63]. Additionally, climate, in conjunction with anthropogenic disturbances, also affects host species diversity [64] and is another critical driver of zoonotic disease spillover risk worldwide. Host species diversity affects disease risk because high pathogen diversity provides a larger genetic pool of novel pathogen lineages with the potential to spill over into human populations [65]. Thus, disease spillover has been hypothesized to be more common in relatively undisturbed areas of the world with high biodiversity [8,66]. However, the preponderance of empirical evidence indicates that disease spillover risk is generally elevated in areas with high levels of anthropogenic disturbance and thus relatively low levels of biodiversity [5,6,36,67-72].

The enhanced risk of disease spillover in disturbed areas may be driven by two mechanisms acting independently or in concert. First, anthropogenic disturbance can increase spillover by increasing the spatial overlap between wildlife and humans, as humans invade natural habitats or wild

species invade anthropogenic habitats [73,74]. Second, human disturbance can affect disease risk by negatively influencing biodiversity—a response termed the "dilution effect," which occurs because diversity in many systems increases the proportion of hosts with low pathogen competence, thus "diluting" the risk of infection across the entire host community [75,76]. Although not universal [77,78], recent meta-analyses have revealed broad evidence of the dilution effect in many host-pathogen systems [79,80] and at multiple spatial scales [81]. Critically, both species richness and composition are likely to play roles in disease spillover dynamics [36]. For example, anthropogenic disturbance can lead to the biotic homogenization of natural communities in which many highly specialized species are replaced by several widespread generalists [82,83], because generalist species are relatively less sensitive to disturbance and tend to be "r-selected" (i.e., their populations are governed by their reproductive ability) [73,84]. Additionally, rapid reproduction favors the epidemic spread of disease, because a constant supply of susceptible individuals hinders adequate herd immunity in these populations [85]. Importantly, as described above, generalist species that are more likely to invade anthropogenic habitats may also be more competent hosts for pathogens [86], particularly zoonotic pathogens [36,72,87].

At finer spatial scales (i.e., at the individual host level), host switching, as with any invasion process, is facilitated by propagule pressure [88,89], and the disease spillover risk increases as interspecific contacts increase. In such situations, ample opportunities exist for spillover infections that originate in the reservoir host (off-the-shelf) or that successfully adapt to humans and thus undergo a true host-switch (i.e., tailor-made) [90]. Consequently, commercial farms housing many animals in restricted spaces can be major sources of novel pathogens [91]. For example, the 2009 "swine flu" epidemic was caused by a novel influenza virus (H1N1) that was a product of reassortment among three viruses (H3N2, H1N2, and Eurasian avian-like swine viruses) circulating in domestic pigs [14]. As large-scale commercial animal operations increase globally, these "melting pots" are likely to continue to be major sources of novel pathogens [92]. High spillover risk also exists at live-animal markets (often referred to as "wet markets"), which sell wild and/or domestic animals [93,94]. The recent SARS epidemics associated with novel coronaviruses (SARS-CoV-1 in 2002–2003 and SARS-CoV-2 in 2019–2021) have been suspected to be associated with such markets in China at the beginning of the outbreaks [93,95,96]. However, solid evidence of the specific sources remains elusive [97]. Although SARS-CoV-2 itself does not appear to be a recombinant of any currently known sarbecoviruses [98], coronaviruses generally do show high recombination rates [99], and such viral recombination can increase the risk of emergence of novel zoonotic pathogens. Consequently, the real risk associated with live-animal markets might be that they provide opportunities for viruses, particularly generalist viruses, from different animals to meet and recombine, thus enhancing the risk of emergence of novel viruses.

Future countermeasures

Most emerging and novel zoonoses are due to stochastic host switching (or spillover) events that are inherently unpredictable. Therefore, numerous challenges exist in understanding the emergence and control of diseases of animal origin (Box 1). Preventing spillover into human populations will primarily depend on establishing the association between eco-epidemiological contexts and transmission mechanisms. We argue that the prevention of future pandemics must be based on a holistic approach comprising the following countermeasures:

(1) ***Establish eco-epidemiological contexts:*** Spillover events are inherently stochastic and unpredictable, given the complex eco-epidemiological contexts in which diseases are transmitted via multiple mechanisms and are

BOX 1 | Major challenges relating to the emergence and control of diseases of animal origin.

I. Structure and dynamics of disease systems: For all systems, the following must be better understood:

1. The combined roles of various drivers of global change (e.g., climate, land use, global transport, and socio-economic factors) on zoonotic risks, particularly in landscapes undergoing rapid climatic (e.g., high elevation areas) and/or habitat (e.g., peri-urban areas) modifications.
2. The relative pandemic potential of endemic pathogens (i.e., emergence driven by local land-use and/or socio-economic factors) vs. exotic pathogens (i.e., emergence driven by alterations in global transport and/or altered distribution due to climate change).
3. How the interaction between host and pathogen diversity affects disease risk across ecological systems and spatial scales. For example, do macroecological differences in host and/or pathogen diversity across ecosystems affect infection risk in similar ways to human-mediated alterations in biodiversity within ecosystems?
4. How do the population size and density of hosts and pathogens influence the emergence of new host-pathogen combinations, and what are the relative effects of human population density vs. altered host community structure in anthropogenic habitats?

II. Surveillance and control: For all zoonotic systems, the following must be developed:

1. Effective surveillance efforts directed at both at-risk human populations and high-risk animal populations
2. Reliable techniques to identify "competent" vs. "non-competent" hosts of zoonotic pathogens in a community, and better frameworks to characterize how community competence varies with human-mediated changes to the environment
3. Optimal measures to minimize zoonotic disease emergence (e.g., ban of wildlife sale and improved sanitation in live-animal markets) and spread (e.g., contact tracing and improved border control), respecting socio-cultural norms and economic needs at the local and global scales

modulated by various drivers. In this case, clarifying the eco-epidemiological contexts in which these stochastic events are most likely to occur is a key scientific countermeasure. As indicated above, the development of a pandemic episode is highly associated with a sequential probability of pathogen-human encounter, infection, and transmission. These probabilities are essentially determined by several factors that modulate human exposure to novel pathogens. Among these factors, agricultural intensification dramatically increases disease emergence risk in human populations through the increased use of chemicals (e.g., antibiotics, pesticides, and fertilizer), changes in land use (e.g., conversion of forest to agricultural or pastural lands), and increased contact between humans and domestic animals. Indeed, agricultural drivers have been estimated to be associated with approximately 25% of all diseases and 50% of zoonotic diseases that have emerged in human populations [3]. Understanding the complex and interacting effects of such eco-epidemiological drivers in affecting disease spillover risk is important, and modern modeling approaches can provide robust predictive risk assessment frameworks [100,101]. Additionally, recent advances in model-inference frameworks are expected to substantially contribute to contextualizing disease dynamics in diverse eco-epidemiological settings and to provide powerful assessment tools to identify regions with high disease spillover risk [102,103].

(2) ***Scale up surveillance at human-animal interface:*** Scaling up active surveillance at human-domestic animal interface, with a focus on high-risk human populations (e.g., veterinarians, farm workers, and workers in dairy or meat processing plants), is critical to rapidly identify spillover events. With respect to wildlife, the selection of species and locations for surveillance may be more challenging. Kress et al. [104] have argued that, with the advent of modern genomic tools, only a small fraction of the resources allocated to suppressing COVID-19 would be needed to identify every zoonotic pathogen hosted by birds and mammals. However, surveillance efforts are likely to need to be focused in terms of both the species surveyed and the geographic regions targeted. We propose that species could be targeted according to underlying ecological traits that affect their potential to harbor zoonotic pathogens. For example, in wild mammals, three variables are significantly associated with a species harboring at least one zoonotic pathogen, as explained above: the phylogenetic proximity to humans, the spatial overlap between the species distribution and human populations, and the diversity of non-human pathogens that the species harbors (Fig 3A). This framework should enable the identification of species that have a high likelihood of harboring zoonotic or potentially zoonotic pathogens but are poorly surveilled. Unfortunately, a critical weakness in the above approach is that the number of host species with good data on pathogen diversity remains limited. This limitation could be addressed through modeling approaches using phylogenetic data to predict zoonotic pathogen risk in poorly surveyed species, on the basis of data from well surveyed species (for example, ref. [36]). Alternatively, wildlife surveillance programs could also focus on specific eco-geographic areas according to the risk of transmission of pathogens between wild animals and humans. One way to effectively target geographic areas for surveillance is to prioritize them according to both the diversity of hosts known to harbor zoonotic pathogens and human density. Thus, for mammals, poorly surveyed areas in eastern and southeastern Asia would have higher priority than poorly surveyed areas in Australia (Fig 3B). Additionally, this framework could also help inform which taxa should be prioritized in different geographic regions (Fig 3C-F). For example, this framework indicates a need to prioritize the surveillance of bats across much of India and China. Critically, as in previous studies [5,36], our framework emphasizes the need to focus surveillance on global regions undergoing rapid land-use change. In many cases, these regions are also the most socio-economic challenged and therefore the most vulnerable to the effects of outbreaks [8]. Recently, researchers have advocated for a "pandemic interception" platform to proactively address pandemic risks, consisting of global genomics-based bio-surveillance programs [104], such as the Earth BioGenome Project, the Global Virome Project, BIOSCAN, and the PREDICT project [105,106]. Critically, the interaction of these international programs with regional programs focusing on biodiversity and ecological change (e.g., Mexico's Commission for Biodiversity) can help develop a global surveillance synergy well poised to address the urgent need for proactive measures, in light of the pandemic risks in the Anthropocene.

(3) ***Reduce spillover frequency:*** The current approach to combat zoonotic pandemics is reactive, focusing on successful host switching events (i.e., pathogens that have already emerged in the human population). However, successful host switching events represent only a small proportion of the preceding unsuccessful host switching opportunities. Thus, a more proactive approach to preventing future pandemics would be to decrease host switching opportunities by shifting focus toward interrupting animal-human spillover and subsequent transmission chains. The successful interruption of such transmission chains critically depends on decreasing the contact rates between humans and zoonotic reservoirs, on the basis of a better understanding of disease ecology and pathogen transmission dynamics. For example, to decrease the risk of spillover of pathogens transmitted by direct contact or aerosol transmission, focus must be placed on high-risk locations where close contact between humans and potentially infected animal tissue or live animals is common (e.g., locations where hunted wildlife are trafficked or traded, live animal markets, or high-intensity commercial livestock farms) [74,92,107]. Alternatively, in the case of orally transmitted diseases,

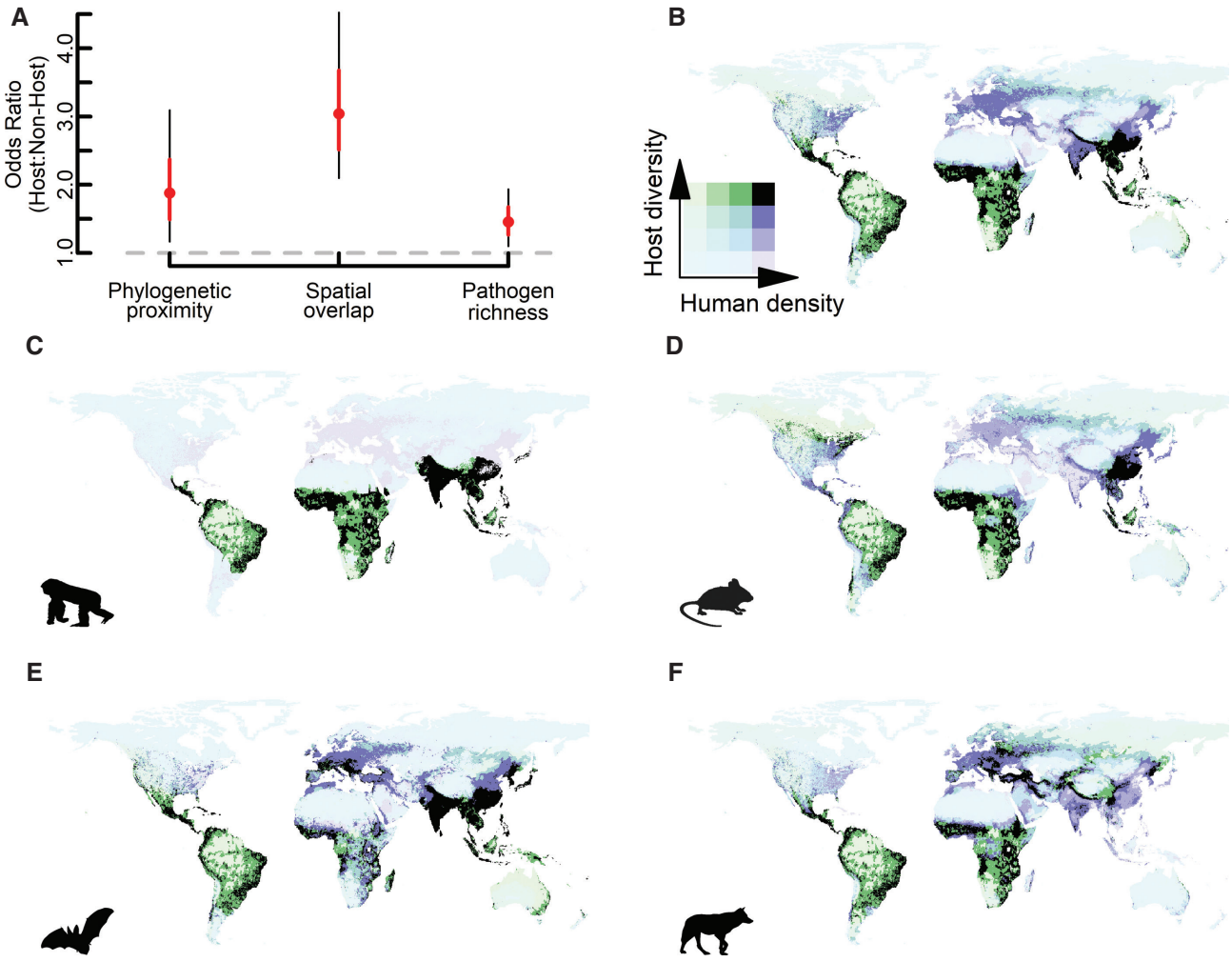

FIGURE 3 | A framework to prioritize species and geographical areas for zoonotic disease surveillance.
(a) The likelihood of a wildlife species being a zoonotic host (as measured by the binomial odds ratio) significantly depends on various species characteristics, including the phylogenetic distance between the animal species and humans (Phylogeny), risk of spatial overlap between the host species and humans (Spatial) and the richness of the pathogen community hosted by the species (Patho. Rich.). Analyses restricted to mammalian species only and error bars are 67% (red lines) and 95% (black lines) quantiles obtained from non-parametric bootstrap or Bayesian regression analyses (see Supplementary Online Methods for details). (b) Zoonotic disease emergence risk depends on the diversity of hosts that harbor zoonotic pathogens and the density of humans in the area. The map shows the joint distribution of zoonotic mammalian host diversity and human population density. Areas with high diversity of zoonotic hosts and high human density (black areas) need to be prioritized over those with only high zoonotic host diversity (light green areas) or high human density (light blue areas), which in turn need to be prioritized over areas with low zoonotic host diversity and human density (light cyan areas). Priority areas for surveillance also depend on the specific mammalian orders considered. Maps are shown for four major orders that have high numbers of zoonotic hosts: (c) Non-human primates; (d) Rodentia; (e) Chiroptera; (f) Carnivora. See Supplemental Material for details.

attention should be focused on populations at high risk of exposure to these pathogens, such as local communities that consume bush meat [108-111]. Finally, integrated vector management (e.g., WHO's Global Vector Control Response 2017–2030) remains a key strategy to disrupt the transmission, and thus combat the ever-increasing burden, of vector borne diseases [112-114].

(4) ***Decrease epidemic potential:*** For newly emerging infectious diseases, identification of the pathogen and transmission routes remain critical for effective epidemic control. Although the identification of the animal source of a pathogen is critical to prevent future spillover events, it often is a highly challenging undertaking [115]. For example, more than 40 years after the discovery of the Ebola virus, the actual natural reservoir remains unknown, although strong evidence supports the involvement of bats [116]. For the SARS outbreak in 2002–2003, researchers took several months to identify the pathogen but did not identify the potential source for more than a decade [117]. For the COVID-19 pandemic, in 2019–2020, scientists took only several weeks to identify the pathogen, and have identified horseshoe bats as a potential source of the ancestral virus; other intermediate host(s) are suspected but remain unconfirmed [97]. In many cases, the potential source of novel pathogens has been identified through spatial associations. For example, live animal markets selling

domesticated species have been identified as sources of numerous pathogens in humans (e.g., swine-origin influenza A viruses) [118]. However, the risks of novel zoonoses are particularly high in live animal markets that sell wildlife, because these markets bring humans and wild animals into proximity, often under conditions of poor hygiene [106,119]. In the case of the recent SARS-CoV-2 outbreak, the Chinese Center for Disease Control and Prevention detected SARS-CoV-2 RNA in 33 of 585 environmental samples from the Huanan Seafood Market in Wuhan. Moreover, 93.9% (31/33) of the positive samples were from the western end of the market, where booths selling wildlife were concentrated [120]. However, the exact role of wildlife in maintaining or amplifying the virus in the Huanan Seafood Market remains unclear; for example, the market environment might have amplified the pathogen after it had already entered the human population [121]. Given the real risks of novel zoonoses entering human populations through live animal markets selling wild animals, governments worldwide must decrease the nutritional dependency of local populations on meat procured from wild animals and ban the trade of wildlife species [122]. The regulation of live animal markets must also be improved to decrease the risks of zoonotic disease transmission by segregating live animals of different species from one another and from humans, improving slaughter techniques to meet international standards of ethics and safety, and improving sanitation and hygiene [107,123]. However, until these biosecurity measures are in place, improved surveillance of potentially high-risk locations, such as live animal markets, will be critical [122].

Genetic and genomic analyses have demonstrated highly efficient in surveillance, and the identification of origins and routes for the spread of pathogens [110,124,125]. Surveillance of known pathogens is easily performed with PCR tests (to detect ongoing infections) or antibody-based tests (to test for past infections) in the human population. Because viruses and bacteria have small genomes, complete genomic studies of many samples can be performed at high speed and low cost with NGS techniques [110,126]. This capability has provided unprecedented access to detailed information on the origin, migratory routes, and critical mutations, all of which are crucial for understanding the changes in pathogen transmission efficiency [110]. Genomic data can also be effectively leveraged to develop improved diagnostics (e.g., PCR-based assays) and control measures (e.g., vaccines) [127]. Genomics has provided an unparalleled ability to identify the causative agents of past pandemics through emerging ancient DNA approaches [128], as well as to effectively track disease outbreaks, better understand transmission chains and elucidate population dynamics, as seen in the COVID-19 pandemic [129].

(5) ***Improve future preventive measures:*** Effective intersectoral collaboration and mutual benefits of joint actions of international communities with respect to the Sustainable Development Goals can be leveraged for effective preparedness and response to epidemics. A particularly urgent need exists for global governments to recognize the value of biodiversity protection in pandemic prevention [130]. Consideration of environmental determinants, climate changes and related risks to human health, and ecosystem integrity and relevant management systems will be critical. In proactively addressing future emergencies, a critical need exists to understand that human health is inextricably associated with animal health, as well as ecosystem structure and function (e.g., OneHealth). Thus, cross-sector collaboration must be strengthened, particularly as it relates to emergency preparedness and response, including the harmonized translation of policy guidance (WHO, OIE, and FAO) into action. Specific programs such as the Global Virome Project and BIOSCAN (described above) are examples of such collaborations. International collaboration is also highly important for source tracing [131]. For example, in the 2002–2003 SARS epidemic, civets were initially suspected as the source; however, continual international collaborations determined that the source of SARS-CoV was most likely to be bats [117]. COVID-19 is a disease currently straining international political relationships and economic development, and international and multi-disciplinary collaborative teams are urgently needed to mitigate the pandemic's effects, such as the team mobilized by the WHO to identify the source of SARS-CoV-2 [121]. The unprecedented rapid response to SARS-CoV-2 has demonstrated that international collaborations have facilitated the two pillars of disease management: non-pharmaceutical interventions and vaccine development. Non-pharmaceutical interventions, such as case isolation, contact tracing, travel restrictions, and cancellation of mass gatherings, were crucial in the early response to the rapid diffusion of the pandemic [132-136]. These measures have collectively decreased the transmission, and the time required for vaccine development and for designing general intervention frameworks [137] and prototypical pathogen approaches [138] to pandemic preparedness. Indeed, as the risk of zoonotic disease emergence increases globally, an urgent need remains for strategies to prevent future zoonotic pandemics. Such strategies will require an interdisciplinary research agenda, as well as robust intra- and international collaboration at the interface of science, policy and society.

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CONFLICTS OF INTEREST

The authors declare they have no actual or potential competing interests.

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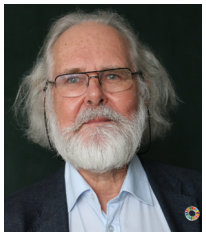
Guha Dharmarajan (https://krea.edu.in/sias/guha-dharmarajan/) is a faculty member of the School of Interwoven Arts and Sciences, Krea University. His research uses both empirical field-based methods and theoretical modeling to elucidate disease dynamics in natural populations. Specifically, he is interested in understanding how human-mediated environmental perturbations – global climate change, habitat modification and environmental pollution – alter disease dynamics in human and wildlife populations, and in turn how these altered disease dynamics affect ecosystem health through their impacts on eco-evolutionary processes at the level of the individual, population and community.



Nils Chr. Stenseth (www.mn.uio.no/cees/stenseth) is an evolutionary biologist and ecologist who has worked on a broad spectrum of ecological systems including terrestrial, freshwater, and marine systems. For the past two decades, he has worked on zoonotic diseases, particularly the plague (*Yersinia pestis*), both historic and current, by using a broad spectrum of techniques (statistical modeling and aDNA). Most recently, he has worked on COVID-19. He is a lead author of the 6th IPCC report (part 2).