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WHERE WILL FUTURE ZOONOTIC DISEASES COME FROM?

Briefing: Wildlife, origins of COVID-19, and preventing future pandemics

The widespread chaos caused by the COVID-19 pandemic and the virus's almost certain links with a wildlife reservoir (likely bats) [1] have re-focused global attention on the role of wild animals in spreading human disease. Over 70% of all emerging infectious diseases (EIDs) come from animals (i.e. zoonotic origin) [2], of which the vast majority originate in wildlife (e.g. Ebola, Severe Acute Respiratory Syndrome [SARS], Nipah virus) [3]. Given the increasing incidence of wildlife-associated outbreaks and their devastating impacts on public health and economies, mitigating these risks is a global priority [3,4]. This, however, necessitates an in-depth understanding of the high-risk zoonotic pathogens, the global distribution of potential wildlife reservoirs and the primary hotspots for future disease emergence [5].

How are zoonotic diseases transmitted to humans?

Zoonotic pathogens from wildlife include viruses, bacteria, helminths, protozoa, fungi and arthropods. Most pathogens require at least one reservoir host to survive and persist for long periods, although many have developed elaborate adaptions to live in and move between multiple reservoirs and intermediate hosts. In some instances, these pathogens might infect their animal hosts, but often the hosts are asymptomatic (i.e. showing no symptoms of infection). Irrespective of the reservoir, pathogen transmission must occur for a human infection to spread. Transmission of zoonotic pathogens to humans can arise through direct or indirect contact with a wildlife host, through various vehicles (e.g. contaminated food, water or air), or via a range vectors (e.g. mosquitos, ticks, fleas and flies) that carry the disease from one host to another (Fig. 1). Examples of important vector-borne diseases that have wildlife reservoirs include dengue fever, West Nile Virus and yellow fever.

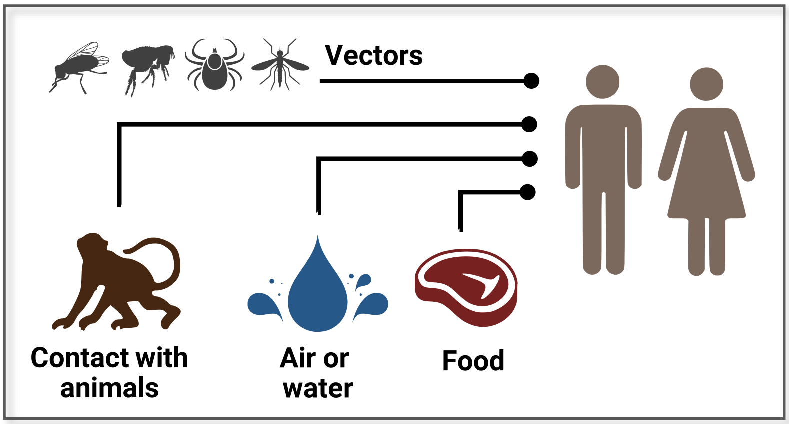


Figure 1 | Main routes of zoonotic disease transmission to humans

Important terms

Emerging infectious disease (EID): a newly recognised, clinically distinct infectious disease, or a known infectious disease that is increasing in incidence or geographic range

Epidemic: A large outbreak of disease that takes place over a short time period

Hotspot: a region where infectious diseases are likely to increase in incidence or geographic range, or one that is likely to generate novel disease events

Land-use change: changes to the structure of ecosystems due to human activities, which lead to perturbation of biotic systems

Outbreak: a group of epidemiologically connected disease cases that exceed historical incidence

Pandemic: an epidemic that has spread to multiple countries or continents

Pathogen: a biological agent capable of causing disease

Spillover: transmission of a pathogen or parasite from one species to another

Vector: an organism that can pass an infectious agent to another organism

Zoonosis or zoonotic disease (plural, zoonoses): a disease or infection that is naturally transmitted from animals to humans

Zoonotic host: any species that carries one or more zoonotic diseases, either as natural reservoirs or hosts

Zoonotic reservoir: an animal in which a pathogen persists for long time periods

Which pathogen types pose the greatest zoonotic disease risk?

At least 170 zoonotic pathogens from wildlife species can cause human disease (i.e. medium to high certainty of causing infection). Approximately 41% of these are vector-borne and 59% are non-vector borne (Fig. 2a). Most wildlife zoonoses that infect humans are caused by viruses (42%) and bacteria (29%), with comparatively fewer caused by helminths, protozoa and fungi (Fig. 2b). In particular, viral pathogens pose major threats to public health and global security, due to their high mutation rates and extraordinary capacity to adapt to new hosts, including humans [6]. Indeed, viral zoonoses have caused most human epidemics and pandemics in recent history (Table 1).

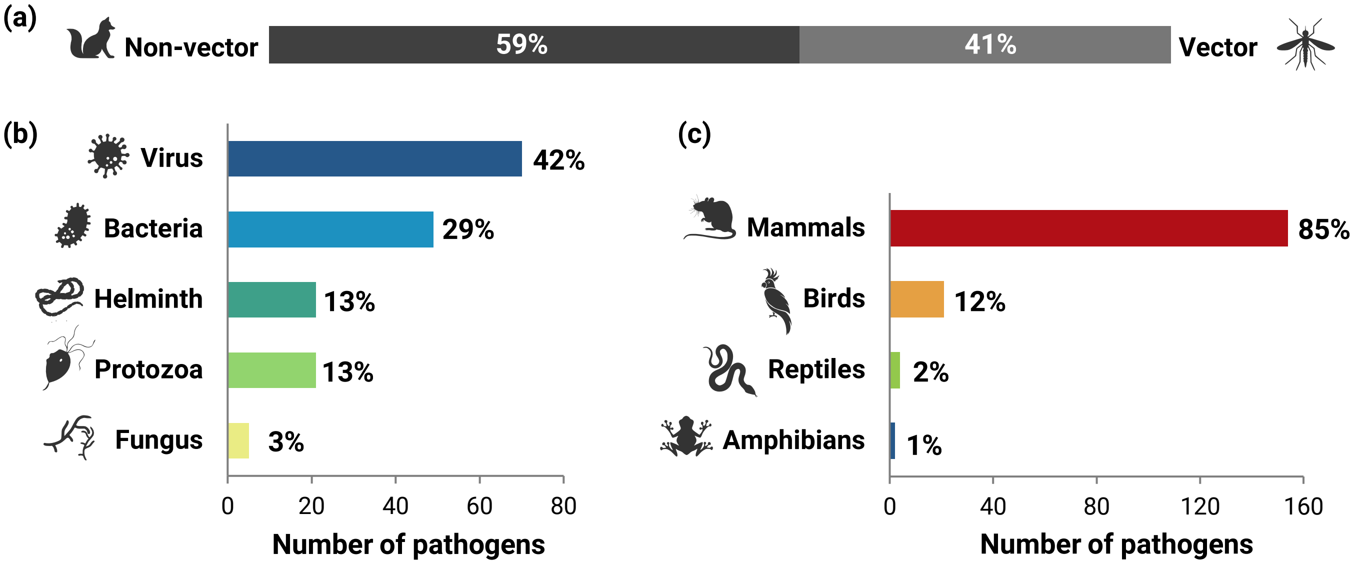


Figure 2 | Proportions of wildlife zoonotic pathogens by (**a**) routes of transmission, (**b**) pathogen types, and (**c**) primary wildlife reservoir groups. Data derived from the Global Infectious Disease and Epidemiology Network, GIDEON, database [7]. Only pathogens with medium to high certainty of causing human disease are included [5].

Table 1 | Recent human epidemics / pandemics caused by viral zoonoses, including animal hosts, outbreak details and case fatality rates. Data from the Global Infectious Disease and Epidemiology Network, GIDEON, database [7].

Disease	**SARS**	**MERS**	**COVID-19**	**Nipah virus**	**Ebola**	**Marburg**
Pathogen type	Virus – RNA (**Coronaviridae**)	Virus – RNA (**Coronaviridae**)	Virus – RNA (**Coronaviridae**)	Virus – RNA (**Paramyxoviridae**)	Virus – RNA (**Filoviridae**)	Virus – RNA (**Filoviridae**)
First outbreak	2002: South China	2012: Saudi Arabia	2019: Wuhan, China	1998: Malaysia	1976: Democratic Rep. of Congo	1967: Marburg, Germany
Most likely reservoir host	Horseshoe bats (*Rhinolophus sinicus*)	Bats (*Taphozous*, *Rhinopoma* spp.)	Bats (suspected)	Pteropid fruit bats	Pteropid fruit bats	Pteropid, insectivorous bats
Likely intermediate host	Palm civet (*Paguma larvata*)	Camel (*Camelus dromedarius*)	Unknown	Pigs	Primates. Possibly antelope, rodents, shrews.	Grivet monkey (*Chlorocebus aethiops*)
No. of Outbreaks	8 (ca. 8,446 outbreak cases)	5 (ca. 8,446 outbreak cases)	245 (>20,000,000 outbreak cases)	20 (ca. 665 outbreak cases)	39 (ca. 35,251 outbreak cases)	10 (ca. 551 outbreak cases)
Fatality rate	10.9%	36%	2-5%	32%	25-90%	24-88%

Which wildlife species pose the greatest zoonotic disease risk?

Mammalian wildlife species harbour by far the greatest number of zoonotic pathogens (ca. 85% of all infectious wildlife pathogens), followed by birds (12%), reptiles (2%) and amphibians (1%; Fig. 2c). Nonetheless, there is considerable variation across terrestrial wildlife orders in terms of the number and diversity of pathogens that are capable of infecting humans. Among mammals, rodents are the most common reservoirs, followed by carnivores, primates, bats and even-toed ungulates (Fig. 3). Species in other mammalian orders (Lagomorpha, Eulipotyphla, Cingulata, Didelphimorphia, Pilosa) also share zoonotic pathogens with humans, but these appear to be in lower proportions. Among birds, Passeriformes are associated with the highest number of zoonotic pathogens.

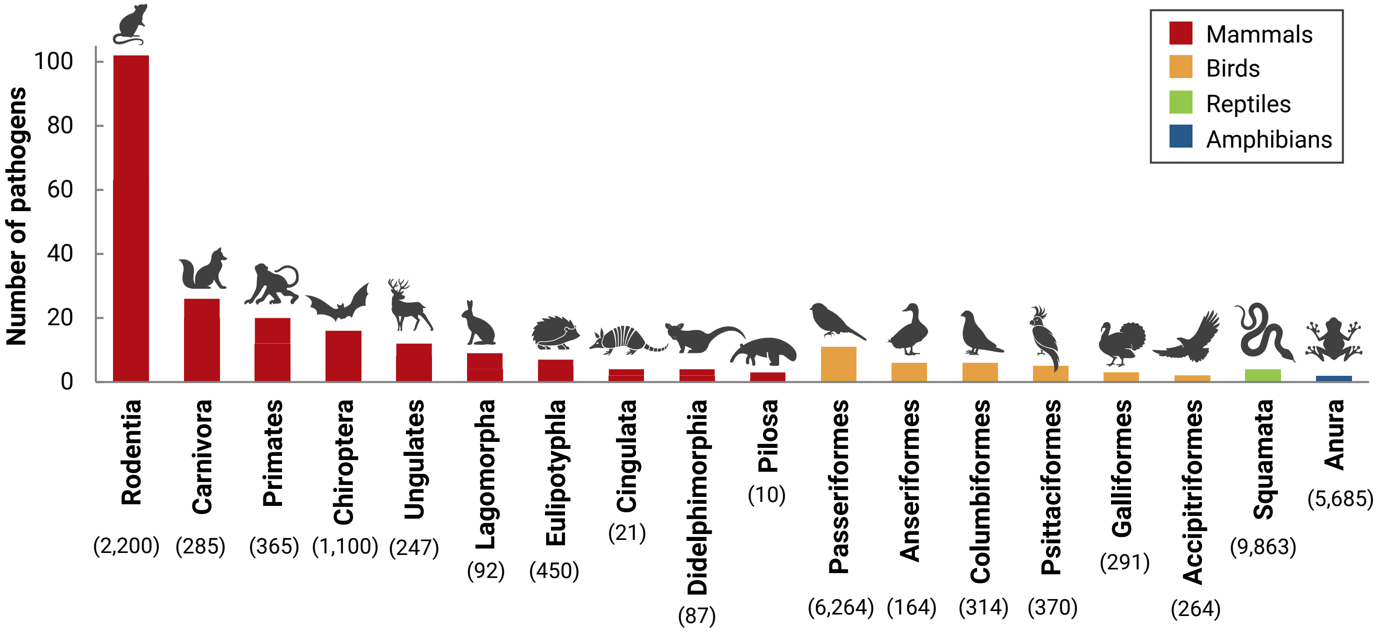


Figure 3 | Number of zoonotic pathogens in different terrestrial wildlife orders that can cause human disease. The numbers given in parentheses below the labels refer to the estimated number of extant species existing in each order. Data derived from the Global Infectious Disease and Epidemiology Network, GIDEON, database [7]. Only pathogens with medium to high certainty of infecting humans are included [5].

Rodents (order Rodentia)

Among mammals, rodents are the most abundant and species-rich order and harbour the greatest number of zoonoses. Approximately 10.7% of all rodent species are hosts (244/2,220 species) [8], carrying at least 102 unique pathogens capable of infecting humans (Fig. 3) and including a wide range of viruses, bacteria, helminths and protozoa (Fig. 4). The high zoonotic reservoir potential of rodents, especially rats and mice, is likely due to their fast-life history profiles, early sexual maturity and high reproductive rates [9].

Carnivores (order Carnivora):

About 49% (139/285) of carnivore species – the greatest proportion of any mammalian order – are zoonotic hosts [8]. Wild carnivores harbour at least 26 unique zoonotic pathogens that can cause human disease (Fig. 3), most of which are zoonotic helminths (Fig. 4).

Primates (order Primates):

Approximately 21% (77/365 species) of non-human primate species are zoonotic hosts [8]. Primate species carry at least 20 zoonotic pathogens capable of infecting humans (Fig. 3), most of which are viruses (Fig. 4). The close phylogenetic relatedness and spatial overlap between human and non-human primates likely contributes to the high risk of pathogen spillover [8].

Bats (order Chiroptera):

Bats are the second most species-rich mammalian order and ca. 9.8% (108/1,110 species) are zoonotic hosts [8]. Bats carry at least 16 unique zoonotic pathogens capable of infecting humans (Fig. 3), with viruses being of greatest concern (Fig. 4). Indeed, most recent viral epidemics appear to have bats in common as reservoir hosts (Table 1), suggesting a unique role of these mammals as sources of human pathogens.

Even-toed ungulates (order Artiodactyla):

Approximately 32% of wild ungulates (excluding domesticated species) are zoonotic hosts [8], carrying at least 12 unique pathogens capable of causing human disease (Fig. 3). Ungulate reservoirs of zoonotic disease are of concern due to high human contact rates through hunting, as well as the close relatedness and contact between wild and domesticated species (livestock) [8].

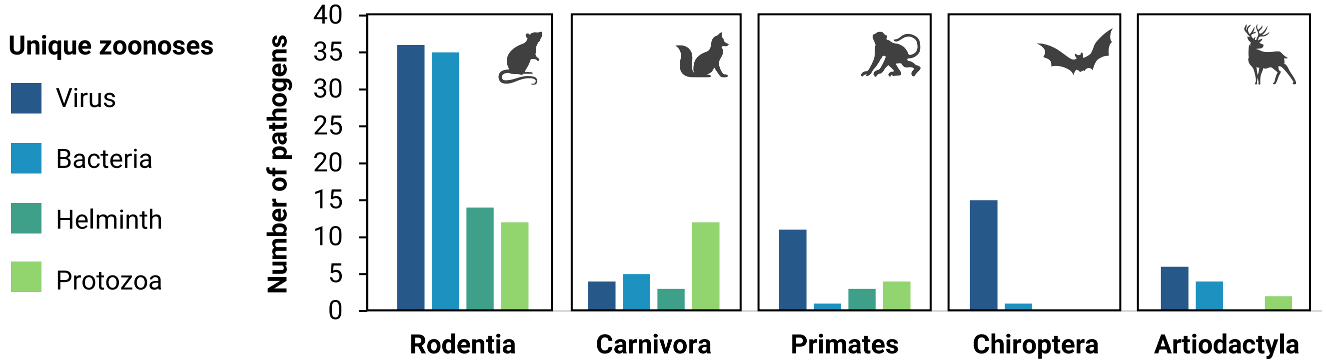


Figure 4 | Number of unique zoonoses caused by different pathogen types in the five mammalian orders that carry the highest number of infectious agents for humans: rodents (order Rodentia), carnivores (order Carnivora), non-human primates (order Primates), bats (order Chiroptera) and ungulates (order Artiodactyla, excluding domesticated species). Data derived from the Global Infectious Disease and Epidemiology Network, GIDEON, database [7]. Only pathogens with medium to high certainty of causing human disease are included [5].

Where are the global hotspots for wildlife zoonoses?

In general, zoonotic disease 'hotspots' are expected to align with global patterns of biodiversity and host species richness [3, 4, 8, 10], although this relationship is complex and context-specific [11]. Indeed, most zoonoses with wildlife origins have emerged in human populations inhabiting biodiverse regions (as measured by wildlife species richness) [3], which largely correspond with the tropics (Fig. 5a). Zoonotic risks are especially elevated in tropical forested areas and those experiencing anthropogenic land-use changes and agricultural expansion [4]. Similarly, the hotspots for vector-borne diseases are mostly concentrated in lower-latitude developing countries [3] (Fig. 5b).

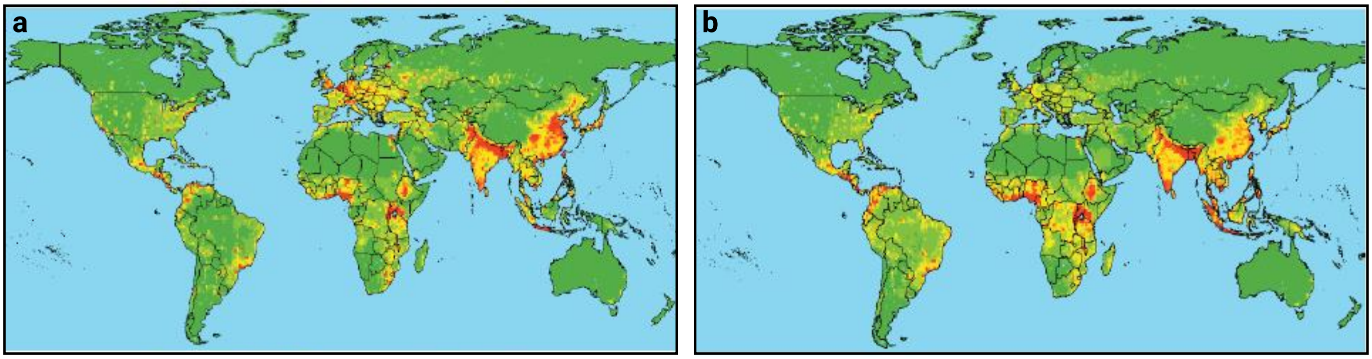


Figure 5 | Global distribution of relative risk for emerging infectious diseases caused by: (**a**) zoonotic pathogens from wildlife, and (**b**) vector-borne pathogens. Maps are from Jones et al. [3].

The relationship between zoonotic risks, biodiversity and host species distribution are particularly evident for primates, bats and ungulates. Primate diversity and zoonotic host richness are greatest in the global equatorial zone, with the highest risk of primate-associated outbreaks and novel zoonoses predicted for African rainforests, the Neotropics and Southeast Asia [3, 6] (Fig. 6). Hotspots for zoonotic bat hosts include Central and South America, as well as Southeast Asia, which generally coincides with global bat diversity patterns [3, 6]. A notable departure relates to Africa, with has similar bat species richness to Southeast Asia, but fewer identified zoonotic bat hosts, which might suggest that Africa is understudied in this regard [3]. Wild ungulates cover a broader spatial extent than primates and bats; however, the highest host species overlap and emerging zoonotic disease risk for ungulates occurs in East and Southern Africa [3] (Fig. 6).

Although overall mammal diversity is lower in the northern latitudes, the zoonotic disease hotspots in Europe and temperate areas of North America (Fig. 5) may be partially attributable to the high diversity of rodent and small-bodied insectivore hosts (shrews and hedgehogs), along with their predators (i.e. carnivores) [8, 9]. It is also worth noting that the predictors of wildlife zoonoses differ somewhat from those associated with non-wildlife hosts (i.e. domesticated species), with the latter more likely to be linked with human population growth and densities, and with no identifiable links with biodiversity [3].

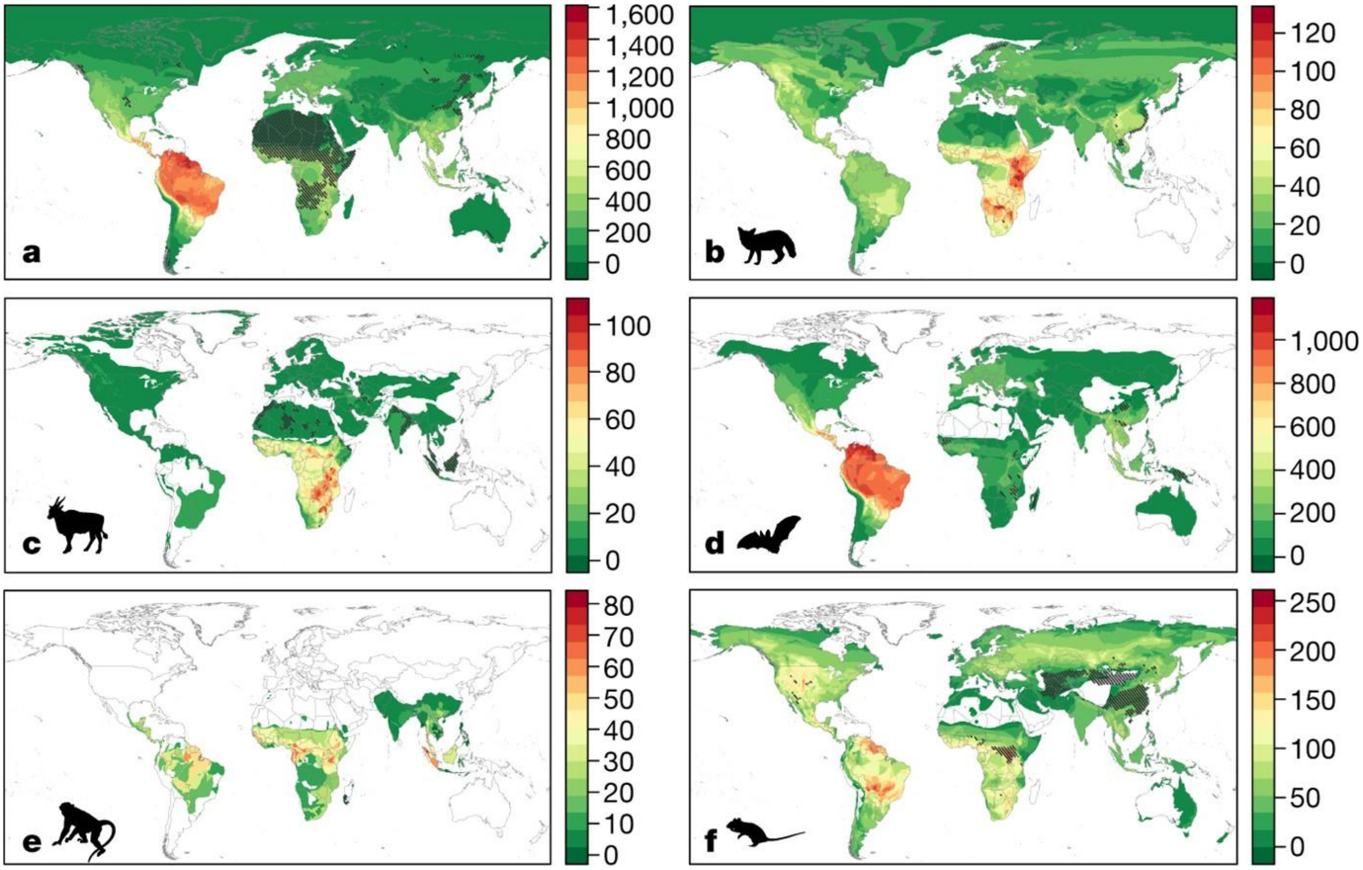
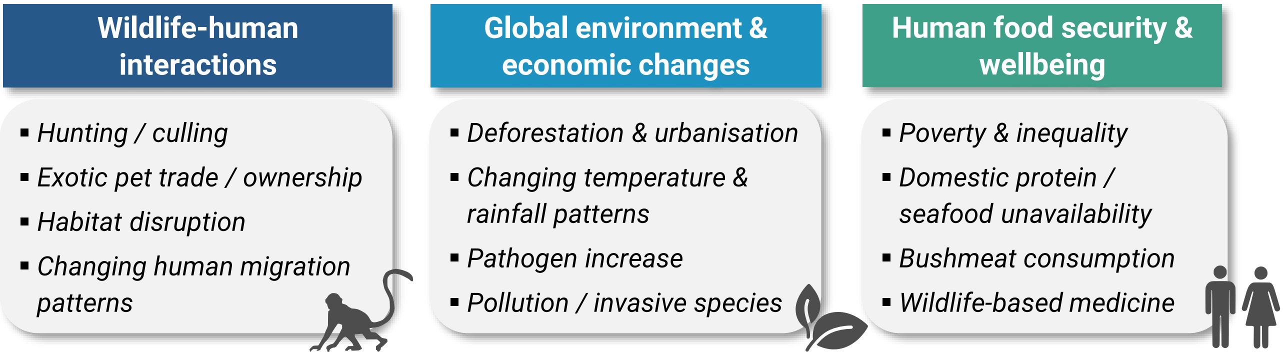


Figure 6 | Global distribution of relative risk for discovering novel zoonotic viruses. (**a**) All wild mammals, (**b**) Carnivores (order Carnivora), (**c**) Even-toed ungulates (order Artiodactyla), (**d**) Bats (order Chiroptera), (**e**) Primates (order Primates), (**f**) Rodents (order Rodentia). Maps are from Olival et al. [6].

What factors amplify zoonotic disease risk?

In addition to the diversity of zoonotic pathogens and the distribution of their wildlife reservoirs, there are numerous compounding factors that can contribute to zoonotic disease emergence. Thus, zoonotic disease risk can be regarded as a function of both underlying zoonotic potential and those interacting factors that drive this zoonotic potential to be realised as human infection and disease [5]. In general, any opportunities that increase human exposure to wildlife groups with high zoonotic potential will amplify the risk of zoonotic disease in humans. High human contact with wildlife can be due to human behaviours and habits, such as the ownership and trade of wild animals for pets [12], or their use in traditional medicine products. The hunting and butchering of bushmeat (or 'wild meat') for food, which is common across the tropics and often linked with food and livelihood insecurity, is a major driver of zoonotic host contact – particularly in terms of bats, primates and ungulates [13, 14]. Moreover, key anthropogenic activities and land-use changes – including urbanisation, human encroachment, agricultural expansion and extractive industries (e.g. logging) – can expose humans to previously undistributed habitats with high levels of wildlife diversity and reservoir hosts [14, 15]. The propensity for zoonotic pathogens to cause disease may also be influenced by the susceptibility of the human population in a given area, which is often conferred by poverty or prosperity [16].



Wildlife-human interactions

- *Hunting / culling*
- *Exotic pet trade / ownership*
- *Habitat disruption*
- *Changing human migration patterns*

Global environment & economic changes

- *Deforestation & urbanisation*
- *Changing temperature & rainfall patterns*
- *Pathogen increase*
- *Pollution / invasive species*

Human food security & wellbeing

- *Poverty & inequality*
- *Domestic protein / seafood unavailability*
- *Bushmeat consumption*
- *Wildlife-based medicine*

Figure 7 | Human-nature interactions that amplify zoonotic disease risks

Concluding remarks

The frequency with which new zoonotic diseases are emerging, especially those from wildlife, underscores the pressing need to shift from a reactionary to a pre-emptive approach to reduce future human disease risks [8]. This calls for baseline data, including information on potential zoonotic wildlife hosts and how these are distributed globally in relation to human populations.

This synthesis highlights that a disproportionate number of wildlife-associated pathogens come from mammal species, with viruses and bacteria being of greatest concern for future zoonotic outbreaks. It is also reveals a significant risk of wildlife zoonotic and vector-borne diseases originating in lower latitude developing countries, where reporting effort is generally low. The global effort for zoonotic disease surveillance thus appears to be misallocated, with most monitoring and research occurring in the developed world (i.e. Europe, North America, Australia, parts of Asia) where novel zoonotic pathogens are less likely to originate [3]. A re-allocation of resources is consequently required for 'smart surveillance' of disease hotspots in lower latitudes (e.g. tropical Africa, Latin America, Asia) so that early case clusters of potential novel zoonotic diseases can be identified before their broadscale emergence [3]. Global focus should also be placed on mitigating activities that increase human exposure to zoonotic wildlife hosts, including risky human behaviours and anthropogenic land-use changes.

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