

Viral emergence and pandemic preparedness in a One Health framework

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Abstract

The risk of viral pathogen transmission between humans and animals (spillover events) and subsequent spread has been increasing due to human impacts on the planet, which lead to changes in the interactions between humans, animals, ecosystems and their pathogens. Key factors (drivers) that increase the risk of disease emergence include climate change, urbanization, land-use changes and global travel, all of which can alter human-animal-environment interactions and increase the likelihood of zoonotic spillovers and vector-borne diseases. Incorporating data on these drivers (such as ecological shifts and patterns of animal movement) into disease surveillance systems can help identify hot spots for disease emergence, which could in theory enable earlier detection of outbreaks and, in turn, increase the effectiveness of intervention strategies. A One Health approach, emphasizing the interconnectedness of human, animal and environmental health, is advocated for addressing these complex challenges. Although conceptually clear and widely endorsed, implementation of One Health approaches towards primary prevention of spillovers is extremely challenging. Here, we summarize current knowledge on disease emergence and its drivers, and discuss how this knowledge could be used towards primary prevention and for the development of risk-targeted One Health early warning surveillance. We consider integrating innovative tools for diagnostics, surveillance and virus characterization, and propose an outlook towards more integrated prevention, early warning and control of emerging infections at the human-animal interface.

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Introduction

In recent decades, the world has experienced multiple epidemics of novel emerging or re-emerging infectious diseases. The most notable example was the COVID-19 pandemic, which started in 2019 and was caused by the global spread of SARS-CoV-2. In 2022, another public health emergency of international concern (PHEIC) was declared with the global spread of clade Ilb Mpox virus¹. After decades of sporadic cases of Mpox in East, West and Central Africa, with more recent substantial undetected circulation in Nigeria, by 2022 an Mpox outbreak had rapidly spread within Europe, the Americas and, subsequently, globally. Subsequently, a second PHEIC was declared in 2024 when clade Ib Mpox virus was first detected in the East of the Democratic Republic of Congo, which then started spreading across continental borders². Another re-emerging virus is Oropouche virus, which is currently causing an epidemic in Central and South America, and overlaps with the largest dengue epidemic ever in the same region³.

Since the global COVID-19 pandemic, an unprecedented epidemic of highly pathogenic H5Nx clade 2.3.3.4 avian influenza has been ongoing in domestic and wild birds and mammals. Viruses belonging to this clade have spread from Southeast Asia to Europe since 2014, leading to the largest highly pathogenic avian influenza (HPAI) epidemic ever recorded in Europe during 2016–2017. By the end of 2021, the virus had expanded into North America, and reached regions as remote as Antarctica in 2022 and 2023 (refs. 4,5). This epidemic led to mortality estimates of more than 300×10^9 dead wild and domestic birds. Moreover, infections have been reported in at least 70 mammal species, such as wild and domestic carnivores, sea mammals and, most recently, millions of dairy cows in the United States^{4,6}. The number of human infections with the H5N1 clade 2.3.4.4.b avian influenza virus remained limited, with generally mild symptoms. However, since 2024 the number of reported human infections in the United States alone has increased to 70. Scientists worldwide have expressed their concerns on the possible pandemic risk of the circulating H5Nx influenza viruses⁷⁻⁹.

'One Health' is a concept that has been around for several decades but was updated in 2021 by the One Health High-Level Expert Panel (OHHLEP) into a definition that emphasizes that the health of humans. animals (including wildlife) and ecosystems is tightly linked 10. This view is particularly clear in the domain of emerging infectious diseases, where there is consensus that changes in the interactions between humans and animals and our shared ecosystems affect the exchange of microorganisms and viruses within and between species, potentially resulting in the emergence of new infectious diseases or changes in the epidemiology of known diseases¹¹. As the ecology of infectious diseases is complex, their dynamics can be affected by multiple factors, called drivers. Drivers are defined as underlying factors or mechanisms that influence interactions between pathogens, hosts and the environment, and that therefore contribute to the emergence or spread of infectious diseases^{12,13}. As such, research and surveillance of emerging infectious diseases should also take into account these interactions between humans, animals and the environment, and aim for an integrated approach to study and detect the emergence of novel pathogens.

Current literature on emerging infectious diseases, as well as outbreak preparedness plans, focuses mostly on the response to human disease outbreaks, after spillovers of viruses circulating in animals have led to an outbreak. A key question and the main focus of this Review is whether there is potential for early warning and even primary prevention of spillover events, by understanding the process of disease emergence at a fundamental level. This information could then be used to improve our capacity to predict risk of spillovers, and target

surveillance at the human-animal interface to detect outbreaks as early as possible. Although conceptually intuitive, this goal is not easy to achieve. Focusing on the entire system requires the involvement of multiple disciplines and sectors, shared goals (that might differ in different regions) and a long-term vision, all aspects that can be hampered by competing societal, economic and political interests¹⁴. Nonetheless, the continued threat of epidemics resulting from spillover events does call for more fundamental and long-term thinking about the potential for threat reduction. Therefore, we review current scientific literature on viral emergence and its drivers, with a focus on how this knowledge could be included to predict the risk of spillovers, and the design of risk-targeted improved early warning and surveillance systems. We further expand on the implementation of a One Health approach and integrating innovative tools for diagnostics, surveillance and virus characterization. We also provide an outlook towards a proactive approach for primary prevention, early warning and control of emerging infections at the human-animal interface.

Change as a driver for emergence

In this section, we describe which of the main drivers should be considered for potential inclusion in the design of risk-targeted prediction and early warning systems. We specifically focus on drivers for spillover and drivers for amplification and spread. When considering spillover risk, a central theme is the impact of the human presence on the planet through three major and interconnected drivers: climate change and climate change adaptation; land-use changes (including agriculture and urbanization); and changes in human and animal movements (travel, trade and migration).

Climate change

Climate change refers to long-term shifts in weather patterns (such as increasing temperatures and changes in precipitation) that can lead to droughts, heat waves, polarice melt and increases in extreme weather events (Fig. 1). These events in turn trigger increased numbers of wildfires, flooding events and sea-level rise¹⁵. A systematic review of the scientific literature assessed these climatic hazards for effects on infectious diseases and found that out of 375 infectious diseases covered by the review, 218 had at some point had been aggravated by one of the climate hazards and 60 had diminished in some way¹⁵. The different climate hazards do not occur in isolation but are part of a complex system that results in direct and indirect health effects, in a context of other drivers of human and animal disease¹⁶. For instance, extreme weather events and increased temperatures can affect water and soil quality, which increases the risk of food-borne and waterborne diseases (such as cholera and other non-cholera *Vibrio* infections) in humans¹⁴. Moreover, abrupt displacements of humans and animals caused by extreme weather events and other climate disasters can facilitate the introduction of infectious diseases into new geographic areas 15,17,18. More insidious changes in species abundances and migration patterns could also follow from gradual changes in climatic conditions¹⁹. Examples of species that have shown clear shifts in latitude, depth or altitude as a response to changes in climate are marine fish²⁰ and wild birds¹⁹. Changing ecology can affect contact patterns between and among humans and animals, which increases opportunities for viral host jumps in some areas but also decreases them in others¹⁷.

Measures taken in response to climate change can also have impacts on infectious diseases. Urban and rural landscapes are being transformed to deal with increasing temperatures, changing precipitation patterns and subsequent consequences. For example, several

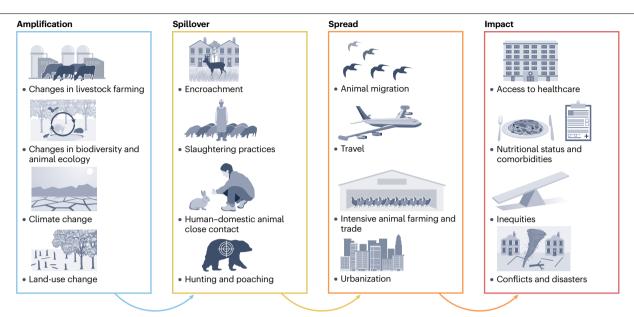


Fig. 1| **Viral emergence and its key drivers.** Four key steps towards high-impact epidemics and pandemics: amplification, spillover, spread and impact. Changes in the environment, including wildlife habitats, affect reservoir demography and behaviour, leading to changes in pathogen circulation. These changes also affect the human–animal interface, increasing the chance of spillover events. Due to our

increasingly connected world, with national and international transport of humans, animals, products and associated viruses, any emerging pathogen has an increased chance of rapid international spread. Changes in human and animal comorbidities, as well as policy changes and disasters, affect the implementation of preventive and response measures, and might increase the impact on human health.

countries are adopting strategies to improve water resource management (during times of drought as well as flooding) by wetland restoration and development of water buffers²¹. Changes in agricultural practices are also necessary, for example, by changing water and soil management and replacing crops to adapt to increasing periods of drought, or salinizing soil and groundwater. In cities, common strategies are the implementation of 'green and blue infrastructures', which include urban parks, green roofs and water buffer areas, to achieve cities with increased water storage capacity, better capacity to deal with peak precipitation, and reduced surface and air temperatures²²⁻²⁴. However, research on possible adverse effects of such climate adaptive measures on human health is very scarce, especially in the area of infectious diseases²⁵. Some work has been done on the effects of urban greening on rat-borne pathogens, where the researchers showed that urban greenness is associated with higher abundances of rats^{26,27}, as well as associated rat-borne zoonotic pathogens²⁸. Another example is the increased malaria incidence that was found near dams, particularly smaller dams, in sub-Saharan Africa. This is likely due to the standing water that is a suitable breeding ground for Anopheles mosquitoes, the primary vectors of malaria parasites²⁹. Urban design could also have a large effect on mosquito proliferation and associated mosquito-borne pathogens24.

Vector-borne diseases are the category of diseases that seem to be the most climate-sensitive; for instance, owing to the effect of temperature on habitat suitability for reservoir hosts and vectors. In addition, temperature can affect vector spread, increase biting rates, and also increase pathogen replication in the vector required for transmission³⁰. Importantly, although the global burden of vector-borne diseases is expected to increase under climate change scenarios, such increases might not always occur at a more local scale. Temperatures could also

surpass the thermal optimum of local habitats with animal hosts, vectors or associated pathogens. This optimum can be different for each vector and associated pathogen. For example, the disease burden of vector-borne diseases in Africa could shift from *Anopheles*-transmitted malaria to arboviruses spread by *Aedes* mosquitoes, with large local differences, due to the direct effects of increasing temperatures³¹.

Factors impacting land use

In addition to climate change, land-use change ranks high as a driver for disease emergence, through several possible trajectories that could overlap.

Changes in agriculture. Around 71% of the Earth's surface is classified as habitable land, without ice or desert, of which almost half is currently in use for agriculture 32 . Around 42 million km² more land is used now than 1,000 years ago, when only 4% of habitable land was used for agricultural purposes 33 . The increase in agricultural land is in line with the increase in the world human population and the associated demand for crops, meat, milk and eggs and associated increase in livestock. Combining grazing land and cropland used for livestock production, 80% of agricultural land is currently in use for livestock production (United Nations Food and Agricultural Organization (FAO) 33,34). In 2022, there were an estimated 1.55×10^9 cattle $(0.94 \times 10^9$ in 1961), 28.3 $\times 10^9$ poultry $(4.3 \times 10^9$ in 1961) and 0.98×10^9 pigs $(0.41 \times 10^9$ in 1961) worldwide. A 2023 study estimated the global protein mass of mammals and found that the majority (94%) of total biomass consists of domesticated animals (mainly livestock) and humans 35 .

High numbers of farmed animals have led to increasing average farm sizes, increased human–domestic animal–wildlife interfaces and general land-use changes, which all increase the risk of zoonotic disease

emergence and spread36,37. For example, increasing farm sizes and overall numbers of domestic poultry increase the chances of novel HPAI viruses, as introductions of low-pathogenic viruses by live birds can be followed by their evolution into HPAI viruses in domestic poultry³⁸. Also, large-scale fur farms with mink or foxes can pose considerable risks when avian influenza viruses are introduced via wild birds, owing to the possibility of generating additional animal reservoirs and ongoing (or increased) evolution of viruses that could become better adapted to mammals^{39,40}. The ongoing increase in agricultural land is associated with deforestation, estimated at 6.4-8.8 Mha per year⁴¹, which has been shown to be a driver of disease emergence on its own^{42,43}. Of specific interest for pathogen spillover is the commercial farming of wildlife. A 2023 review showed that at least 487 wildlife species are farmed globally⁴⁴, resulting in greatly increased circulation of and spillover opportunities for wildlife pathogens. For example, commercially farmed masked palm civets (Paguma larvata) were likely the source of SARS-CoV that led to the early 2000s human outbreak of SARS in Southeast Asia45.

The large numbers of live animals, animal products and food that are traded on the national and international scales can also facilitate rapid spread of existing and novel pathogens. Examples of international spread of infectious diseases partly facilitated by domestic and wild animal trade include swine influenza⁴⁶, African swine fever⁴⁷, Mpox¹, avian influenza⁴⁸ and rabies⁴⁹. Of specific importance are live animal and wildlife markets, as exemplified both by the detection of the novel SARS-CoV-2 at the Huanan Seafood Wholesale Market in Wuhan, China, and the role of live animal markets in the spread and spillover of avian influenza viruses 48,50. At live animal markets, local circumstances can facilitate disease transmission between animals as well as between animals and humans, owing to limited hygienic conditions and large numbers, densities and varieties of animal species in close contact with humans^{51,52}. International trade and consumption of wild meat is also a risk factor for spillover and spread of zoonotic pathogens. A literature review published in 2022 identified more than 90 spillover events resulting from wild meat consumption, including Ebola virus (EBOV), hepatitis E and brucellosis⁵³, Moreover, disease outbreaks in one industry can lead to cascading effects in others. For example, a large African swine fever outbreak in China during 2018–2019 led to the culling of ~150 million pigs, which resulted in a decrease of ~11.5 million metric tons of available pork in 2019. This event might have led to a shift in protein consumption, including wild meat, possibly driving the spillover and spread of SARS-CoV-2 (refs. 54,55).

Urbanization. Urbanization changes local land use and can lead to increased local temperature, increased pollution, and changes in biodiversity and human–animal–environmental interfaces^{56,57} (Fig. 1). Generally, urban expansion is associated with decreased biodiversity⁵⁸, but some native and invasive animal species can adapt to urban environments and their population can increase in cities. The increased presence of these animal reservoirs also changes usuch as rodent-borne protozoans, *Bartonella* spp. and *Leptospira* spp. ^{28,59}, and zoonotic pathogens such as rabies virus and *Leishmania* parasites in urban foxes⁶⁰. Also, reverse zoonotic events are more likely, possibly leading to new animal reservoirs where ongoing pathogen adaptation and evolution occurs, as shown in urban deer infected by SARS-CoV-2 (ref. 61). Overall, as shown in an extensive data analysis of host–pathogen associations, known wildlife hosts of human-shared pathogens and parasites are

found more often in urban ecosystems compared with nearby undisturbed habitats⁶². In addition, urbanization can also affect the local climate, which can result in urban areas experiencing higher temperatures than their surrounding rural areas, a phenomenon called the 'urban heat island effect'. These higher very local temperatures affect mosquitoes, vector-borne pathogens and waterborne pathogens. Additionally, warmer winters and increased food availability in urban settings can increase the replication success of some animal hosts, such as rats⁵⁷.

Approximately 55% of people worldwide live in cities, and this proportion is expected to increase to about 68% by 2050 (ref. 63) leading to substantial local increases in human densities ^{64,65}. The rise in global population, including the urban population, is expected to mainly take place in low and middle-income countries (LMICs), potentially in the context of weak and unstable governance, which will increase poverty, inequality and the further expansion of slums⁶⁶. A clear example of an emerging infectious disease in such an urban context was the 2014-2015 EBOV outbreak in West Africa, where the usual pattern of small-scale localized (Fig. 1) outbreaks in remote areas suddenly shifted to explosive spread involving urban communities in three of the poorest countries of the world⁶⁷. Phylodynamic analysis confirmed that urban areas were pivotal to the spread of the virus, by showing that the population size and higher chances of EBOV introduction are significantly associated with virus dispersal. This outbreak put the world on alert owing to concerns for further international spread^{68,69}. Within urban environments, the risk of infectious diseases can vary notably, often reflecting health inequities driven by underlying social, economic and political factors⁷⁰. The COVID-19 pandemic showed the influence of the socio-economic status of countries, as well as individuals, on the disease burden and impact. The age-specific infection fatality rate was estimated to be twice as high in LMICs compared with high-income countries⁷¹. Also within countries, poverty exacerbated the health consequences of the pandemic^{72,73}.

On the other hand, the prevalence of some infectious diseases is lower in urban areas than in rural areas. Often, the reasons described are improvements in sanitation and access to public health programmes. Example pathogens include those that spread via the faecal–oral route, such as hepatitis A virus 74 . Also, air and water pollution can actually hinder vector proliferation, such as sand flies and *Anopheles* spp. that transmit malaria parasites 75,76 .

Travel, migration and trade

Land-use change is a key driver for disease emergence; however, population growth, urbanization, and migration and travel are important drivers for the spread of infectious diseases⁷⁷ (Fig. 1). Migration and travel result in increased human connectivity and contact rates within and between countries. Large shifts have occurred in both the scale and geographic patterns of human presence and movement in the past decades. The United Nations World Tourism Organization estimates that the number of tourist arrivals increased 56-fold in the period 1950-2018. The contribution of this change to the infectious disease landscape was evident in 2020, when the SARS-CoV-2 outbreak detected in Wuhan rapidly spread across China with the high-speed railway system, and internationally through direct flights from Wuhan to major airports across the globe⁷⁸. The opportunity provided by this widespread seeding undoubtedly played a role in the further adaptation of SARS-CoV-2 to transmission in humans, as was observed over time⁷⁹. In addition, patterns in movements of displaced people can change rapidly over time, following natural disasters or political instability.

Movements of displaced people often result in large shifts in population and contact patterns, and large refugee camps are also known hot spots for infectious disease outbreaks due to high densities of people, influxes of people from different regions, unhygienic circumstances and high chances of malnourishment or other comorbidities that can increase susceptibility for severe disease 80 .

Driver-based spillover risk prediction

Early detection of outbreaks is key to their containment and control, particularly in the case of infectious diseases that have the capacity to transmit among humans or animals. One example in humans was the containment of the SARS outbreak, which was detected in Hong Kong. The first human patient was detected in November 2002, and on 5 July 2003 the World Health Organization (WHO) declared the global SARS outbreak to be contained⁸¹. Successful containment was due to the rapid implementation of public health interventions in Hong Kong and across the world, including rapid diagnostics development and roll out, case finding and contact quarantine, screening of travellers, social distancing, use of personal protective equipment and travel restrictions⁸². There was an important viral factor: SARS transmission between humans was occurring mostly after people became symptomatic and the viral tropism preference for lower respiratory tissue limited its transmissibility. For outbreaks in domestic animals, early detection is also crucial as a large range of control measures (such as culling and stand-stills) are often imposed to restrict all animal movements around an outbreak83.

Clearly, once a fully human-to-human transmissible pathogen emerges, control of an outbreak becomes incrementally more difficult. The trait of efficient human-to-human transmission, however, is often not fully known with many spillover pathogens, and the window of opportunity for control therefore lies at the earliest possible moment of detection, as has been advocated in pandemic preparedness plans⁸⁴. Yet early (Fig. 2) detection of the needle in the haystack of an early spillover is extremely challenging. A key question is whether mining of the information on drivers for disease dynamics could be incorporated into developing risk-targeted surveillance strategies (Fig. 2). The first question is which drivers to include in such an approach. Literature on hot spots for disease emergence is available, but typically not at the level of granularity needed for risk-targeted surveillance. Studies focusing on single diseases illustrate how complex such approaches can become. It remains to be seen whether risk predictions based on driver data at a more aggregated level will become accurate enough for practical application⁸⁵. For instance, a recent study in seven countries in the Balkan region found remarkable differences in the prevalence of four mosquito-borne diseases, even at this relatively small geographic scale^{86,87}. A study in Australia found that incursion pathways of two species of exotic mosquitoes were fundamentally different, further emphasizing the need for careful validation of any prediction model88.

Given the complexity of disease emergence pathways, a driver-based approach would need to be focused on specific modes of transmission. For example, vector-borne disease outbreaks, zoonotic disease outbreaks related to wildlife versus farm animals, and food-borne and waterborne disease outbreaks all have different drivers, although overlap likely exists.

Vector-borne diseases

For vector-borne diseases, studies have been conducted that attempt to predict environmental suitability for specific vector species through

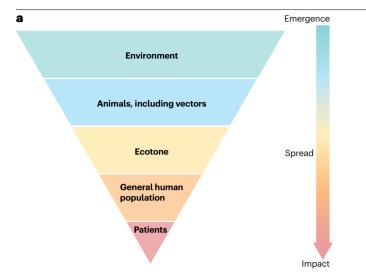
ecological niche modelling and other statistical and modelling approaches (Fig. 2). Such studies can be done either by focusing only on suitability for vector presence, or by combining that information with data on the risk of introduction or spread of specific pathogens⁸⁹. Globally, the impact of many arboviruses is directly related to urbanization and the expanding range of *Aedes* mosquitoes (particularly *Aedes aegypti* and *Aedes albopictus*). Thus, it has been proposed to include global suitability maps and risk predictions in urban planning and the targeting of virus surveillance, disease surveillance and public health measures⁹⁰. Similarly, the risk of tick-borne disease occurrence and geographic expansion has been assessed, showing that forestation and temperature, as well as the presence of the yellow necked mouse (*Apodemus flavicollis*), influence the occurrence of tick-borne encephalitis in humans, linking back to land-use change and climate change drivers⁹¹.

Not only do these studies aim to guide risk-targeted surveillance and early warning detection but they also can be used to inform interventions and risk communication campaigns⁸⁵. Once established, models can be used for longer term forecasting of potential future risks, using climate change scenarios^{89,92}. Validation of models is important and can only be done if high-quality surveillance data are available, which can also be used to explore and identify possible drivers for occurrence and spread, as has been explored with studies on Oropouche virus in the Americas⁹³, tick-borne encephalitis virus in Europe^{91,94} and several infectious diseases in Africa⁹⁵.

Zoonotic spillover hot spots

Similar efforts have tried to identify hot spots for zoonotic spillovers, with many studies focusing on bats (Fig. 2). Bats are hypothesized to serve as important reservoirs for zoonotic viruses 96,97, partly owing to the large species diversity of the taxonomic order Chiroptera, combined with their abundance and global distribution 98. One way to predict spillover risks is to model animal host distribution, as has been done for vampire bat roosts and rabies virus introductions into livestock in Latin America⁹⁹. These hotspot analyses can also shed light on the underlying landscape, including climatic and anthropogenic factors that affect host abundance, although they typically cannot explain underlying causes or mechanisms 99,100. When data are available, possible drivers of pathogen emergence and spread can be connected to actual pathogen data to confirm possible correlations, which could provide additional information in terms of possible risk areas. For example, one study combined the presence and richness of bat species with coronavirus co-evolution patterns and showed that hot spots that are predicted in this manner are different from those that only took species richness into consideration¹⁰¹. Examples of known factors that increase coronavirus infections in several bat species are habitat fragmentation, livestock density, deforestation and mining¹⁰²⁻¹⁰⁴. However, in most studies, human-animal contact rates or at least human density, and thus the true risk of spillover, are not taken into account. As an example of how human density can be considered, one study on the risk of SARS-like coronavirus spillover in China showed that locations of horseshoe bat populations overlap with locations with risk factors for coronavirus presence in bats, as well as human population density¹⁰³.

A key gap in the current scientific literature is the lack of actual spillover data, especially connected to risk and hotspot analyses. Although the risk of spillover of SARS-like viruses has been extensively discussed, actual quantitative information on spillover events is very rare 100,102,103,105,106. One study, again on SARS-like virus spillover,



Zoonotic transmission		Vector-borne transmission		
Driver	Method	Driver	Method	
Habitat loss (e.g. deforestation), livestock-wildlife interactions, wild meat consumption	Satellite imagery, tracking, eDNA, observations, wild meat seizures	Climate change, vector habitat data, vector community change	Weather monitoring, satellite imagery, nuisance reporting, vector monitoring	
Live animal and products trade, animal migration, intensive livestock farming	Trade data, wildlife population data, tracking, farm and livestock density	Urbanization, travel, used tyres and bamboo trade, animal host migration	Satellite imagery, travel and trade trends, bird population trends and tracking	

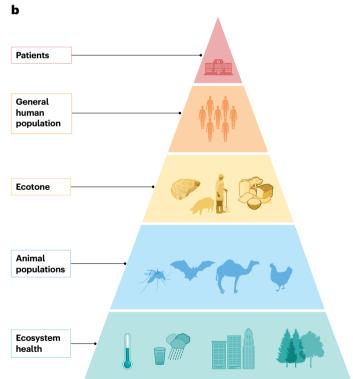


Fig. 2 | **One Health surveillance to monitor drivers and disease. a**, One Health surveillance of drivers. Surveillance of drivers should focus on the monitoring of drivers that facilitate spillover and spread of zoonotic pathogens, before the development of large human epidemics or pandemics. Examples of drivers and methods for monitoring them are provided for two transmission modes: vector-borne and zoonotic spillover and spread. **b**, One Health disease

Surveillance	Methods	Key outcomes
Healthcare data anomalies Undiagnosed patient follow-up Hospitalized patients with animal contact	Hospital records Patient metagenomics	 Early warning (Disease X detection) Human health impact Human disease prevalence Input risk assessment
Population health (symptoms) Comorbidity prevalence Pathogen circulation Import (travel)	Syndromic surveillance Pathogen and antibody screening (e.g. wastewater, bloodbank) Traveller monitoring	Human health impact Human disease prevalence Early warning (detection) Input risk assessment
Food and feed quality Human and animal risk population health Hotspot monitoring	Targeted pathogen and antibody monitoring Metagenomics	Early warning (disease X detection) Spillover detection Input targeted surveillance and risk assessment
Domestic animal and wildlife health Vector diversity and infections Microbiome and virome	Syndromic surveillance including mortality Pathogen and antibody screening Vector collection, eDNA, citizen science Next-generation sequencing	Risk mapping Animal outbreak detection and impact Input targeted surveillance and risk assessment
Climate Water, soil, air quality and pollution Biodiversity Plant health	Satellite, sensors, citizen science Census, eDNA, bioacoustics Environmental pathogen monitoring	Risk mapping Input targeted surveillance and risk assessment

surveillance. Surveillance of the human–animal–environment interface for integrated zoonotic disease monitoring requires targeted surveillance of risk populations, risk regions and risk interfaces. For each of the targeted populations or interfaces, (a combination of) different methods may be most suitable. eDNA, environmental DNA.

attempted to quantify spillover by including data from the literature on human-bat contacts, SARS-like seroprevalence in humans with bat contact and antibody waning, generating one of very few risk maps that takes into account actual evidence of virus exposure¹⁰⁶. Most likely, however, true risk prediction requires more granular information,

geared towards local practices and incorporating laboratory data on virus infections and exposure, with contact rate information, animal host modelling and environmental drivers, to further refine and validate zoonotic virus surveillance that targets possible hot spots for spillover.

One Health surveillance

Routine surveillance systems for human and animal diseases are typically not designed with a focus on spillover detection. Therefore, risk targeting requires working with other approaches that can be integrated into risk prediction modelling and that will need to be validated for use in routine surveillance.

Tools for ecosystem and pathogen surveillance

In order to better model and map possible spillover hot spots and design interventions, detailed longitudinal data are required on climate, land use, human and animal population structures and movements, as well as prevalence of pathogens and exposures (Figs. 2 and 3). However, traditional field data collection is often time-consuming, laborious and expensive. Therefore, most innovations focus on novel and scalable sampling and identification methods that reduce the amount of manpower involved. One example is the use of earth observation data (such as the use of satellites for remote sensing) to monitor changes in land use, plant phenology and climate, with continuous spatial and temporal coverage107. In addition, satellite data can be used to monitor bird migration and could potentially be used to estimate wildlife population sizes, specifically of the larger mammal and bird species 108. Oher innovations have focused on automated and/or high-throughput detection methods of animals or plants, such as the use of automated mosquito trapping and classification, and the use of bioacoustics for bird identification¹⁰⁹⁻¹¹¹. In addition, initiatives to implement digital health surveillance are increasing 112. A well-known first example was Google Flu trends, which used Google search queries to monitor influenza outbreaks¹¹³. Also, data mining from social media has been used to study and monitor diseases¹¹⁴. Moreover, the rapid development of artificial intelligence and machine learning is expected to vastly advance the opportunities for digital surveillance, on the levels of data collection (for example, biodata via smart watches), data mining (for example, multilanguage online text mining and classification) and real-time risk assessments 115,116.

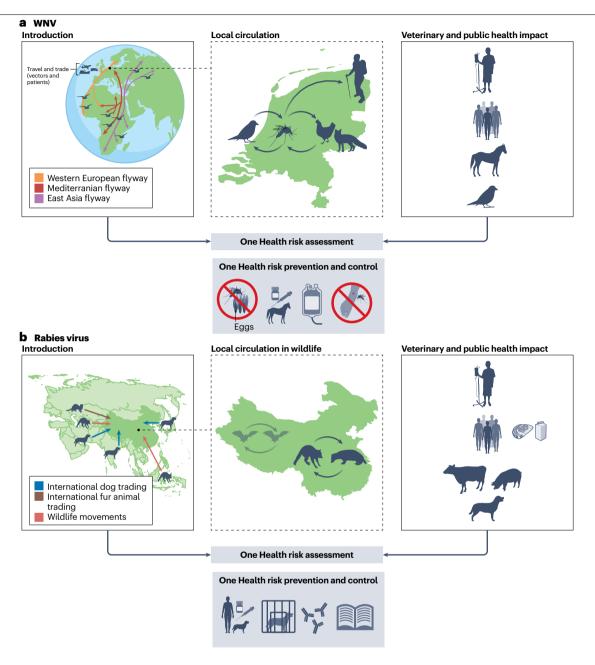
High-quality data on pathogen characteristics, presence and exposures are key for development of prediction models (Figs. 2 and 3). Usually, individual animal and human samples are used to test for pathogen presence, although this approach often comes with notable challenges including the need for ethical permission, large sample sizes (with associated costs), and inconvenience and welfare concerns in the case of invasive sampling. Implementing sampling of the environment can circumvent many of these disadvantages. For example, coronaviruses in bats have been studied by only testing faecal pallets that were found under their roosting sites¹¹⁷. Moreover, bird-borne infectious agents, such as avian influenza virus and Usutu virus, can also be monitored using environmental surfaces, eggs (for antibodies) or feathers (for RNA)^{118–120}. In addition, some environmental samples represent multiple humans or animals, such as sewage or air samples¹²¹. Currently, multiple countries use wastewater to monitor different variants of SARS-CoV-2, as well as other pathogens and antimicrobial resistance 122-124. Moreover, in-depth studies of the human virome have been described using wastewater, which could also be extended to the animal host virome and microbiome studies¹²⁵. Particularly promising is the use of environmental DNA (eDNA) approaches to assess biodiversity and the presence of possible reservoir animals or vectors, which can also be combined with data on microbial composition. However, the sensitivity of environmental samples could be lower than those using traditional, invasive sample types. For example, in hospital studies where air samplers are placed in rooms of patients infected with respiratory syncytial virus, only a low proportion of the air samples are positive 126,127 . In addition, the inability to link samples to individual humans or animals affects the possibility to understand viral dynamics 128,129 .

Although viral metagenomics is widely implemented, numerous challenges remain in the execution, analysis and interpretation of the data (Box 1). First, obtaining the true composition of viral communities in a sample is challenging; for example, owing to low concentrations of viruses present in some matrices and biases introduced in preprocessing, sequencing and bioinformatic analysis steps 123,130 . In addition, the analysis and interpretation of metagenomic data are not easy, as only the minority of generated sequence data can be annotated to species level, resulting in a large proportion of 'viral dark matter'. Therefore, although metagenomic sequencing has gained in popularity, studies that allow extrapolation of findings for risk mapping are scarce 131 . Looking forward, the continuing expansion of metagenomic datasets combined with artificial intelligence approaches could have an important role in the analysis of metagenomic data and associated possible phenotype and zoonotic risk prediction 132,133 .

Another issue with pathogen detection in environmental and animal reservoirs is that it is difficult to incorporate data from such catch-all methods in risk assessments. For instance, most viruses that are detected in animal hosts through metagenomics are not able to overcome the biological barriers to infect a human host (for example, physical barriers such as skin or mucus, the human immune system or other factors prohibiting receptor binding or cell entry)¹³⁴. In addition, viruses should be able to replicate and spread between humans before there is a true risk of outbreaks or even a pandemic. In order to assess the zoonotic potential of viruses found in animal hosts, follow-up laboratory assays can be performed to assess traits associated with human cell entry and replication¹³⁵ (Box 1). Examples are laboratory infections using human cell lines or cell models (for example, organoids) to assess and quantify infection potential and replication, or immune assays to assess pre-existing immunity against the novel virus¹³⁵. However, performing such extensive follow-up analyses for each novel virus is laborious, time-consuming and expensive. In addition, whether the risks associated with such types of studies outweigh the potential benefits has been debated. The probability of animal to human spillovers is largely determined by human-animal contact rates (frequency of contact between human and animals) and human exposure rates (intensity and duration of contact leading to virus exposure opportunities)¹³⁶.

All of society approaches

Citizen science is also increasingly used to generate data on vector and animal host abundance, water quality, air pollution and many more direct and indirect risk factors for human health¹³⁷. Participation of volunteers can vary from systematic monitoring by competent citizen scientists to 'mass participation' (easy participation by anyone, anywhere), which is often easier and without obligation¹³⁸. One example is Mosquito Alert, an initiative to engage citizens in monitoring mosquito species, bites and breeding sites, involving schools and interested citizens in Europe using the Mosquito Alert app¹³⁹. Similar programmes that use citizen reporting to monitor vectors and wildlife are implemented in other regions^{140,141}. Most initiatives are based on submission of observations or photographs, but citizens can also be involved in actual sample collections; for example, by submitting mosquito specimens or by collecting lake water samples to monitor biodiversity^{142,143}. A very successful example of the involvement of volunteers in disease



monitoring in animals is the collaboration between volunteer ornithologists and bird ringers, who collect samples for the purpose of avian influenza virus or West Nile virus (WNV) monitoring^{144,145}.

Smartphones are also used to support medical, veterinary and public health practice¹⁴⁶. For example, smartphone-based systems can read out point-of-care tests, based on measuring colour intensity or fluorescent signals and smartphone-based microscopy. Such techniques have proven useful, particularly in remote areas without laboratory infrastructure¹⁴⁷. In addition, participatory disease surveillance is increasingly being investigated as a suitable alternative to, or in addition to, traditional surveillance systems. Often, citizens are involved via digital platforms, reporting disease symptoms that can be used to complement traditional healthcare surveillance data¹⁴⁸. Well-known examples of participatory disease surveillance are systems

to monitor influenza-like symptoms, such as those included in the European Influenzanet consortium¹⁴⁹. Also, self-sampling using swabs or dried blood spots is increasingly used to supplement traditional surveillance systems and infectious disease research^{150,151}.

Risk-targeted surveillance to hot spots

To achieve true early warning, risk assessment and prevention of emerging zoonotic pathogens, virus monitoring of animals in risk locations can be performed to detect novel viruses before significant disease is noted (Fig. 3). Guided by outcomes of hotspot prediction studies, surveillance can target populations of farmed animals; a possible effective target for research and surveillance, as high numbers of animals are often kept in high density, which can potentially lead to extensive virus amplification, and their close proximity and contact with humans

Fig. 3 | Examples of regional One Health surveillance: WNV and rabies virus. a, West Nile virus (WNV) surveillance in the Netherlands, combining human, animal and ecosystem surveillance to feed into risk assessments and target One Health interventions 145,183-186. The introduction of WNV can be tracked by monitoring infected humans (travellers), animals (wild birds along flyways) and vectors. Imported infections must be distinguished from local infections and surveillance of the spread of WNV can be performed by testing mosquitoes, resident birds and symptomatic dead-end hosts (horses and humans). Detailed travel and vaccination history is essential. Sentinel animals, such as chickens but also wild boar, rodents or dogs, can be used to further detect WNV circulation in a sensitive and timely manner. The public and veterinary health impact can be assessed by screening symptomatic patients (human and animal) and population surveys. All components of the surveillance system feed into a risk assessment framework for evidence-based control measures to protect humans, animals and the environment. These include mosquito control measures (for example, removal of breeding sites, larvicides and adult mosquito control), vaccination of domestic horses and zoo animals, blood donor screening and mosquito

bite prevention (for example, bed nets, repellants and protective clothing).

b. One Health rabies virus surveillance to monitor rabies at the humananimal interface in China, to feed into risk assessments and target One Health interventions 187,188 . The introduction of rabies virus can be tracked by monitoring infected wildlife, fur animal trade, and domestic and stray dogs. Monitoring local wildlife shows endemic presence and geographical distribution in wildlife populations, including bats and other mammals. Rabies virus infections cause mortality in humans, livestock and domestic dogs, which might also impact human livelihoods. Rabies is almost always fatal unless treated with postexposure prophylaxis. Dogs are the most common reservoir and dog bites are responsible for most infections in humans and livestock. The consumption of milk and meat from a rabies-infected animal is strongly discouraged, although the risk of infection is extremely low. All components of the surveillance system feed into a risk assessment framework for evidence-based control measures to protect humans, animals and the environment. These include the human risk group, dog and wildlife vaccinations, stray dog control, quarantine of exposed or imported companion animals or livestock, rabies post-exposure prophylaxis in the case of human risk contacts with infected animals, and education campaigns for healthcare workers and the community, including dog owners.

increases spillover chances. For example, although wild birds are the main reservoir for avian influenza viruses, most human avian influenza virus infections have been linked to direct contact with poultry, or more recently with infected dairy cattle⁴. Also, farmed animals can function as an intermediate host for viruses with a natural wildlife host, where a virus can further evolve and replicate before spilling over to humans¹⁵². This pathway is seen for many emerging coronaviruses, which often have bats as natural reservoirs. Notable examples are HCoV-OC43, MERS-CoV, SARS-CoV and SARS-CoV-2, with cattle, dromedary camels, palmed civet cats and an unknown animal species acting as an intermediate host, respectively¹⁵³. Ideally, risk-targeted surveillance would require the incorporation of catch-all tools into routine surveillance, rather than the development of separate surveillance systems. For instance, programmes that monitor the health of free-range farm animals could be interesting to access for broad-range testing for other pathogens.

As an alternative, humans in contact with animals can be monitored for novel and existing zoonotic viruses, rather than animals¹⁵⁴. This approach would mean moving from prediction to early warning; yet by targeting the next stage in zoonotic disease emergence, the success rate of actually detecting and identifying a zoonotic pathogen is much higher. A combination of regular serological and virological monitoring of people in frequent contact with bats, or working on live animal markets or farms, can be a valuable tool to assess and quantify the risk of spillover events (Box 1). The use of generic detection methods (such as antibody arrays and metagenomic sequencing) can be used to guide the selection of viruses that should be subjected to further study¹⁵⁴. Importantly, pathogens usually need numerous additional adaptations to move from cross-species transmission to sustained transmission between novel hosts, such as humans. Therefore, most novel viruses that are detected at the human-animal interface do not pose an immediate risk for human outbreaks¹⁵⁵.

One example of a risk population approach is the surveillance of patients presenting with a fever with a history of animal exposure in eastern China. This strategy resulted in the detection of a new *Henipavirus*, Langya henipavirus (LayV). Thirty-five patients with acute LayV were detected and subsequent animal screenings identified shrews as a possible reservoir¹⁵⁶. In this case, the patients with animal contact serve as sentinels: a specific cohort (for example, in a geographic area or population subgroup) that can be monitored to

estimate infectious disease trends in a larger population ¹⁵⁷. A sentinel system can also consist of a selection of healthcare sites that report specific syndromes or pathogens, or strategically placed or selected animals that are monitored regularly. In general, sentinel surveillance is more cost-efficient than population-wide approaches owing to its targeted approach and can generate high-quality data, especially when combined with training and feedback to the sentinel sites and sample providers. Thus, sentinel surveillance can also help correct for gaps in regular surveillance data. Possible selection bias and limited coverage are potential disadvantages of sentinel surveillance systems, as well as the need for committed study sites and continuous support.

To further identify pathways for zoonotic disease spillover, in-depth knowledge of local contexts and cultural habits has been extremely valuable in studying the ecology of novel and existing viruses, and the design of surveillance and risk-targeted interventions. In the case of the emergence of MERS-CoV, knowledge on camel handling and local habits around camel products (such as consumption of raw milk and urine) proved to be indispensable in the understanding of transmission pathways and subsequent control measures¹⁵⁸. The current Mpox outbreaks show that in-depth knowledge of the population at risk and associated risk behaviours, and determinants thereof, are essential in the understanding of disease transmission, as well as when designing appropriate prevention and control measures¹⁵⁹. During the EBOV outbreak in West Africa between 2014 and 2016, social scientists and anthropologists were also successfully involved in outbreak control, and their inclusion led to better knowledge of local practices, improved community engagement and, ultimately, better disease control¹⁶⁰. This success calls for the further inclusion of social sciences in One Health surveillance and research.

Conversely, human infectious disease can also spill-back into animals, which could result in subsequent spread and establishment of an animal reservoir. The circulation of a human pathogenic virus in another host can lead to parallel evolution and accumulation of mutations, which could give rise to new variants with altered properties¹⁶¹. Moreover, animal reservoirs affect the efficacy of human-focused control measures and the chance of viral eradication. However, spill-back events are rarely systematically monitored, even though they could have severe economic and human health consequences¹⁶²⁻¹⁶⁴. One example was the SARS-CoV-2 outbreaks in mink, resulting in mink-adapted viruses that might be less well recognized by the human

Box 1 | The role of genetic monitoring and molecular techniques

Currently, polymerase chain reaction methods are most commonly used to detect genetic material of microorganisms in different matrices of humans, animals and the environment. In addition, next-generation sequencing methods are increasingly implemented. Whole genomes can now be generated with high throughout and at fairly low costs and high speed. The unprecedented number of SARS-CoV-2 sequences produced and shared during the COVID-19 pandemic shows the clear need for and use of whole-genome sequencing for public health surveillance and control¹⁸⁹. Whole-genome sequencing has been used to study the origins of SARS-CoV-2 (ref. 190), to monitor national and international spread of SARS-CoV-2 variants¹⁹¹, to determine introduction and transmission routes in outbreaks (for example, in healthcare facilities¹⁹² and on mink farms¹⁹³) and to distinguish between chronic infections and reinfections¹⁹⁴. Whole-genome sequencing analysis is carried out using phylogenetics, which aims to study the evolutionary history and relationships of pathogen sequences. With more complex phylodynamic and phylogeographic approaches, one can further understand the transmission dynamics of epidemics, by combining evolutionary biology with epidemiology. For example, phylodynamic analyses of the spread of West Nile virus (WNV) in Europe have shown that high coverage of wetlands, intensity of agricultural activities and migratory bird flyways were associated with the WNV spread direction 195. The combination of incidence data, epidemic dynamics models and phylodynamics produces more reliable estimates of transmission rates than epidemiological data alone 196,197. Moreover, specific mutations can be monitored that could affect virus traits, such as antiviral susceptibility 198, vaccine efficacy^{199,200} and mammalian adaptation²⁰¹. These data can be used for public health risk assessments and control measures.

In addition to the targeted sequencing of one pathogen, unbiased metagenomic sequencing can be used to characterize all genomic material (DNA and RNA) in a sample. Furthermore, clinical and environmental samples can be processed with procedures that enrich for bacteria, parasites or viruses, or specific families. The metagenomics research field involves studying and profiling genetic material abundance in diverse matrices and environments, and is rapidly growing. As such, the number of novel viruses that are being discovered and described is increasing²⁰². Considering that most emerging human viruses stem from an animal reservoir, a baseline understanding of the diversity of viruses that can be found in animals is important for preparedness. Although pooled

samples (per species or per location) are certainly of value for virus discovery, analysing viromes and microbiomes of individual animals is necessary for further understanding of virus dynamics and spread in animal reservoirs, including co-infections²⁰³.

Unknown viruses are often classified based on their similarity to known viruses, as the human health risk is considered higher if a new virus belongs to a virus family that also contains known human pathogens. However, all viruses that have been characterized to date likely only make up a minor fraction of the estimated total number of viruses on earth²⁰⁴. Thus, the number of newly identified viruses and possibly also virus families will increase immensely in the coming years. Moreover, the lack of closely related reference virus genomes makes assessment of the phenotype and possible zoonotic potential of novel viruses challenging, when based on genomic information alone²⁰⁴. Even viruses belonging to a known virus family that also includes known human viruses do not necessarily have a risk of spillover to humans. Only for some known viruses can some indications of phenotype or zoonotic risks be derived from the sequence, based on the presence of specific mutations^{200,205}. Also, in silico epitope prediction can sometimes predict B cell epitopes based on sequence data²⁰⁶ as well as possible resistance markers and host binding motifs^{207,208}. However, all such inferences need to be validated with experimental data. When there are indications for a novel virus with zoonotic potential, targeted monitoring in at-risk animal and human populations can supplement in silico and in vitro analyses. Serological and molecular screenings can be executed to understand the prevalence in the possible animal reservoirs^{209,210}. In addition, people in close contact with the possible animal reservoir can serve as sentinels for early detection of spillover events²¹¹.

To be able to make full use of genomic data, the collection and sharing of metadata is paramount for correct interpretation and analysis of the large amount of data that are generated. Metadata, or contextual data, can be subdivided into laboratory (for example, sample type and cycle threshold value), clinical (for example, symptoms), epidemiological (for example, date, place and outbreak type) and methodology (for example, sequencing platform and analysis) information. Although multiple metadata standards exist, these are often not aligned with each other, they require minimal datasets and, even then, poorly described sequence data are submitted²¹². In practice, collecting and sharing metadata can be hampered by practical, ethical and privacy concerns²¹³.

immune system ^{40,165}. Therefore, monitoring of spill-back events is crucial, so control measures can be implemented in a timely manner. This monitoring is particularly important for animals that are in close contact with humans, as well as farmed animals that are kept in large numbers and in close proximity to each other, facilitating large-scale animal-to-animal transmission.

Implications for preparedness: early warning and prevention

One Health surveillance and spillover prevention

One Health surveillance encompasses monitoring activities at the human-animal-environmental interface. A risk-based approach is warranted, based on data collected on local drivers of disease emergence

and spread. National or international monitoring schemes that include such a risk-based approach are very limited ^{166,167}, although some schemes were developed with specific risk populations, locations or timing in mind. Examples are the increased frequency of avian influenza monitoring in free-range poultry as compared with poultry that are kept indoors in the Netherlands ¹⁶⁸, and the targeted surveillance of patients with fever following animal contact in China that led to the detection of LayV ¹⁵⁶. However, with the current body of evidence available, the implementation of such risk-based One Health monitoring schemes seems possible. Collaboration to share challenges, opportunities and best practices will be important when setting up these schemes. This effort will require transforming traditional disease surveillance, by working across silos and

including cost-efficient innovative data streams and agnostic pathogen detection methods.

By setting up multidisciplinary teams, with diversity of knowledge, networks and backgrounds, stronger research teams can be built, with shared improved understanding of viruses at the human-animal interface. This strategy is in agreement with the new One Health definition that was developed by the OHHLEP in 2021, which states: "The approach mobilizes multiple sectors, disciplines and communities at varying levels of society to work together to foster well-being and tackle threats to health and ecosystems. It addresses the collective need for clean water, energy and air, safe and nutritious food, promoting action on climate change, and contributing to sustainable development" 169,170. Indeed, several instruments for international agenda setting, collaboration, and financing pandemic preparedness and response have been set up that include mention of the One Health approach, such as the World Bank Pandemic Fund and the WHO Pandemic Agreement¹⁷¹. However, international concerns have been raised regarding the lack of attention and strategic approach to reduce the risk of spillover events from humans to animals¹⁶³. The currently developed instruments seem to remain anthropogenic in nature, with human health protection as a main goal. Moreover, implementing truly multidisciplinary programmes, policies and research that benefit human, animal and environmental health equally remains a challenge. Including opportunities for critical reflection in One Health approaches is important, in order to assess common goals and objectives, values, impact and collaborations (One Health has been called a silo on its own)¹⁷².

Currently, most funding and efforts are aimed at surveillance and control after a pathogen is already circulating in humans. Oftentimes, medical countermeasures such as vaccines and medication are developed and implemented, sometimes combined with exposure reduction measures such as the use of personal protective equipment, mosquito bed nets and improved biosecurity on farms. When combined with improved One Health surveillance, early warning and risk assessment, these measures can be implemented in an earlier stage of the outbreak, reducing socio-economic and health impacts. Beyond disease outbreaks, reducing the frequency and intensity of interspecies contacts at different ecotones (transitional areas between different ecosystems) would also reduce the number of spillover events. Particularly in predicted hotspot locations, the frequency and intensity of interspecies contacts can be reduced; for example, by personal hygiene measures, use of personal protective equipment, biosecurity approaches, and smart city and landscape design. In addition, interventions can target underlying ecological drivers and risk factors, an approach known as primary prevention (Box 2). Ultimately, true primary prevention should target known drivers of disease emergence, such as deforestation, carbon emission (causing global warming), wildlife trade and large-scale landscape transformations for agriculture. However, intervening at the level of drivers is a long-term challenging process, with many interests and actors involved, and is not likely to generate risk reduction in the short term.

Barriers

Human behaviour is key in infectious disease prevention and control; the uptake of preventive measures is shaped and determined by underlying determinants of behaviour. It has proven extremely difficult to accomplish good levels of adherence to infectious disease preventive measures, especially in the absence of disease. For example, although horse vaccination is an effective and well-known intervention to prevent Hendra virus infections in horses as well as humans (Box 2),

the estimated vaccine uptake in the risk areas of Australia is only around $12\%^{173}$. In addition, an analysis of questionnaires distributed amongst horse owners that live close to previous Hendra cases indicated that the majority of horse owners did not implement preventive measures, such as coverage of food containers or water, or keeping horses off pasture when flying foxes are active. Reasons for the limited uptake of preventative measures were practicalities (for example, costs and daily routines), risk perception and lack of appropriate guidance from the local veterinarian 174 .

Studies of the barriers to and facilitators of the uptake of mitigation measures can help better implement and communicate such measures and improve adherence. Individual variables influence the practical implementation and adoption of mitigation measures, as well as organizational and systemic factors. In the case of the fur farming bans introduced in some countries following SARS-CoV-2 outbreaks (Box 2), political priorities in other countries have favoured economic interests and cultural traditions of mink and fox farming and fur wearing over public health and animal welfare. Similarly, the implementation of One Health surveillance and preventive measures to prevent spillovers between humans and animals is not only a technical challenge but is also largely dependent on local political will, funding and existing infrastructure. Especially in LMICs, where many predicted hot spots for emerging viruses are located, primary prevention and extensive One Health surveillance are generally not a key priority.

Costs of integrated surveillance and prevention

A key question is whether investing in improved One Health surveillance is worth the cost. Spillovers that result in a pandemic are extremely costly. The COVID-19 pandemic had a massive impact, with an estimated 4.4% decrease in the global economy. The total economic losses of the pandemic were estimated at nearly US \$14 trillion (2020–2024)¹⁷⁵. Estimations for the costs of future pandemics range from US 30.1×10^9 to US \$500 × 10⁹ per year 176,177. However, increased preparedness and One Health surveillance also comes with associated costs. For example, a combination of measures that would reduce the worldwide wild meat trade, deforestation and spillovers from livestock, combined with improved monitoring, was estimated at US $22 \times 10^9 - 31 \times 10^9$. This combination of measures was aimed at significantly decreasing disease emergence at the human-animal interface. On the other hand, reduced deforestation could generate US \$4 × 10⁹ per year in societal benefits from reduced greenhouse gas emissions, as well as reduced regional warming and biodiversity loss 178-180. Also, pre-pandemic studies modelled that globally coordinated adaptation strategies for pandemic prevention can significantly and cost-effectively reduce the economic and human health burdens of novel outbreaks¹⁸¹.

Despite such estimates, evidence for the economic benefits of a One Health approach is scarce, as well as cost–benefit analyses of current practices that could alter pandemic risk (such as wildlife trade, land-use changes and more) that take effects on biodiversity, health and climate into account. However, a recent literature review of cost–benefit analyses of a One Health approach to prevention found clear examples of positive cost–benefit ratios, but concluded that it is difficult to provide a global assessment, as these studies are highly dependent on social, cultural, economic, political and ecological contexts and need to be assessed in various settings¹⁴. Nevertheless, financing the necessary actions remains a challenge, especially in LMICs. As a possible step forward, the Independent Panel for Pandemic Preparedness and Response already advised to design and implement a burden-sharing formula, to share the costs of global pandemic

Box 2 | Examples of 'true prevention' — case studies of spillover prevention at the source

Preventing Henipavirus spillover from bats to humans

Hendra virus is a member of the genus Henipavirus of the family Paramyxoviridae, subfamily Orthoparamyxovirinae. Hendra virus was first discovered in 1994 and infects horses as well as humans (via infected horses) after spillover from Pteropus spp. of bats (flying foxes)214,215. A study in subtropical eastern Australia described a shift in lifestyle of flying foxes from nomadic, driven by availability of nectar from flowering trees, to year-round roosting in smaller groups closer to alternative food sources in urban gardens and agricultural areas. The changes were likely driven by the loss of winter foraging habitats²¹⁶. According to this study, an increase in spillover events was further driven by increased virus shedding following food shortages due to the periodic absence of winter flowering 216,217. Taking into account virus epidemiology and risk factors, one approach to limit or prevent spillover events in horses is to restrict their access to trees that are frequented by bats and to refrain from placing feed and water containers under trees, especially during the flowering and fruiting seasons. This intervention would also reduce the risk of infection of humans, as so far all patients were infected following contact with an infected horse²¹⁵. In addition, there is a licensed Hendra vaccine available for horses. In subtropical eastern Australia, the loss of winter foraging forest seems to be a major underlying driver of bat virus spillover events. Therefore, restoration of those habitats, providing sufficient nectar for flying foxes, is expected to reduce spillover events. This effect could also hold true in other regions and for other bat-borne viruses.

Banning fur farming

According to most estimates, approximately 100 million animals per year, mainly mink, foxes and raccoon dogs, are bred for fur²¹⁸. In recent years, multiple outbreaks with human-relevant viruses have been described in these animals, including SARS²¹⁹, SARS-CoV-2 (ref. 220) and highly pathogenic avian influenza (HPAI) H5N1 (ref. 221). Up to 50% of animal workers on SARS-CoV-2-infected mink farms were also infected with variants derived from their mink¹⁹³. Moreover, spill-back infections from humans can lead to adaptation to the animal reservoir, which is particularly relevant for avian influenza viruses, as adaptation to mammals increases the risks of subsequent human infections and human-to-human transmission³⁹. A 2024 study showed that a range of other zoonotic and novel viruses could be found in fur animals in China²²². Moreover, the open set-up of fur farms permits

regular contact with wildlife, increasing risks of spillover to and from wildlife around fur farms 37,222 . National and international organizations recommend increased surveillance of avian influenza virus and SARS-CoV-2, as well as the use of personal protective equipment for animal workers 223,224 . However, surveillance does not cover viruses other than SARS-CoV-2 and avian influenza virus, and the intensity differs per country. Due to the SARS-CoV-2 outbreak in mink that could not be controlled, the Netherlands banned fur farming in 2021-3 years earlier than originally planned. Also, some other European countries banned fur farming, for animal welfare as well as public health reasons. This ban completely eliminates the chance of novel and known virus outbreaks and adaptation in fur animals, as well as associated risks of spillover events to wildlife and humans.

Ecological countermeasures to control mosquitoes

Mosquito species Aedes aegypti and Aedes Albopictus are the main vectors for the mosquito-borne pathogens: dengue virus (DENV), chikungunya virus (CHIKV), zika virus and yellow fever virus (YFV). The effects of climate change, and worldwide increased travel and trade, are expected to result in an extended geographical range of A. aegypti and A. Albopictus, as well as associated viruses³⁰. For many Aedes-transmitted viruses, prevention and treatment options are limited — although novel vaccines against DENV and CHIKV have been developed recently, in addition to the long available YFV vaccine^{225,226}. Therefore, vector control has historically been the key control measure, which mainly includes breeding site removal and use of larvicides and insecticides, combined with avoidance of mosquito bites. However, prevention of mosquito breeding can also start at the level of urban planning. Examples are the installation of a constant water supply to reduce the need for water storage containers, improved solid waste management and designing houses that prevent adult mosquitoes from entering^{24,227}. Careful design of urban environments is especially relevant in the context of urban blueing and greening strategies. A notable example was the enormous mosquito nuisance in new plant-covered residential towers in Chengdu, China²²⁸. Moreover, adding mosquito predators to possible breeding sites such as rice fields or ponds has been attempted, although this approach was not always successful²²⁹. In addition, permanent water bodies that are linked to well-established ecosystems, including mosquito predators, reduce the number of Culex pipiens larvae and adult mosquitoes²³⁰.

preparedness activities and goods, acknowledging mutual dependency and responsibility¹⁸². In addition, the new WHO Pandemic Agreement specifically mentions that countries should provide "financial assistance and support for capacity-strengthening for those Parties that lack the means and resources to implement the provisions of the WHO Pandemic Agreement"¹⁷¹. The Pandemic Fund, established by the World Bank in 2022, could have an important role in this assistance, as it is set up to fund critical pandemic prevention, preparedness and response capacities of LMICs.

Conclusions

In the coming decades, the question is not whether new spillover events will occur, but when, where and how often. However, we can learn from

the past decades to prepare for improved and risk-targeted early warning detection of any emerging virus, thereby increasing chances for successful control of outbreaks. Innovative methods for data collection and surveillance can aid in understanding all components of the One Health triad that could affect spillover events and disease emergence. Moreover, many drivers are anthropogenic by nature, which also poses opportunities to adapt our current behaviours and their effects on the health of humans, animals and our environment, thus preventing novel pandemics. The complicated interplay of different drivers varies between regions, which makes local partnerships and tailored priority setting essential.

Primary prevention of zoonotic spillovers requires addressing the upstream drivers that facilitate pathogen transmission between

animals and humans. Risk-based One Health surveillance plays a critical part in this effort by furthering our understanding of spillover pathways and identifying where the spillover risk is highest. By integrating data across human, animal and environmental health sectors, this approach enables the detection of high-risk interfaces (such as wildlife trade routes, deforestation zones or areas of intensive livestock production) before transmission occurs. These insights enable the design of targeted interventions (such as habitat preservation, improved biosecurity or community engagement) that reduce contact between humans and potential animal reservoirs. In this way, surveillance is not merely reactive but becomes a foundational tool for guiding proactive, evidence-based prevention strategies that can stop pandemics before they start (Box 2).

Global One Health and pandemic preparedness are shared responsibilities requiring collaborative efforts. In the current political climate, with severe budget cuts and lack of support for the WHO and national and international funding mechanisms for infectious disease control, international aid and infectious disease research, these efforts might be increasingly difficult. However, the accelerating series of outbreaks reinforce the need to find and implement global strategies that enable us to co-habit with all other organisms on earth.

Published online: 03 October 2025

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

The authors declare no competing interests.

Additional information

Peer review information *Nature Reviews Microbiology* thanks Gregory Gray, who co-reviewed with Franciso Guerra; and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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