**Infectious disease in an era of global change**

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**Abstract**

**The twenty-first century has witnessed a wave of severe infectious disease outbreaks, not least the COVID19 pandemic that has had a devastating impact on lives and livelihoods across the globe. The 2003 SARS-CoV outbreak, the 2009 swine flu pandemic, the 2012 MERS-CoV outbreak, the 2013-2016 Ebola epidemic in West Africa, and the 2015 Zika epidemic all resulted in substantial morbidity and mortality while spreading across borders to infect multiple countries. At the same time, the last few decades have ushered in an unprecedented era of technological, demographic and climatic change: airline flights have doubled since 2000, since 2007, more people live in urban areas than rural areas, population numbers continue to climb, and climate change presents an escalating threat to society. In this Review, we consider the extent to which these recent global changes have elevated the risk of infectious disease outbreaks, even as improved sanitation and access to healthcare have generated considerable progress worldwide.**

**[H1] Introduction**

In pre-modern times, colonization, slavery and war led to the global spread of infectious diseases with devastating consequences (Fig. 1a). Human diseases such as tuberculosis, polio, smallpox and diphtheria circulated widely, and before the advent of vaccines these diseases caused substantial morbidity and mortality. At the same time, animal diseases such as rinderpest spread along trade routes and with travelling armies, with devastating impacts on livestock and dependent human populations[1](https://paperpile.com/c/Gdvn6U/HaxSx). Yet, in the last two decades, medical advances, access to healthcare, and improved sanitation have reduced the overall mortality and morbidity linked to infectious diseases, particularly for lower respiratory tract infections and diarrheal disease (Fig. 1d). The swift development of the SARS-CoV-2 vaccine speaks to the efficacy of modern science in rapidly countering threats from emerging pathogens. Nevertheless, infectious disease burden remains substantial in countries with lower and lower-middle incomes, while mortality and morbidity from neglected tropical diseases, HIV, tuberculosis, and malaria remain high. Moreover, deaths from emerging and re-emerging infections, in comparison to seasonal and endemic infections, have persisted over the twenty-first century (Fig. 1c). This points to a possible new era of infectious disease, defined by outbreaks of emerging, re-emerging and endemic pathogens that spread quickly, aided by global connectivity and shifted ranges due to climate change (Fig. 1d).

Here, we review how recent anthropogenic climatic, demographic and technological changes have altered the landscape of infectious disease risk in the past two decades. In terms of climate change, we consider both the influence of recent warming as well as projected future changes. For demographic change, we include trends such as urbanization (Fig. 1b), population growth, land-use change, migration, ageing, and changing birth rates. For technological changes we primarily consider advances that enable cheaper, faster global travel and trade (Fig. 1b), as well as improved healthcare. We do not explicitly address economic change, however, economic changes, including economic development, are crucial drivers of these three factors: climate, demography and technology. We also do not explicitly discuss natural drivers of pathogen evolution or biological processes unless they interact with human-driven global change.

New infections chart a pathway beginning with emergence, followed by local-scale transmission, movement beyond borders and possible global-scale spread. Global changes may differentially affect the risk of emergence, the dynamics of disease within a local population, the global spread of diseases between populations. We provide an overview of each step, first considering features of recent global change that have altered the risks of spillover of viral, fungal, bacterial and apicomplexan (malaria) infections into human populations, then detailing how spread within human populations, driven by the seasonal dynamics of transmission, may be impacted by global change, of relevance to both emergent and established pathogens. Finally, we consider changes to the drivers of global spread, focusing in particular on travel, migration, and animal and plant trade.

**[H1] Pathogen emergence into human populations**

Recent decades have seen repeated pathogen emergence from wild or domestic animal reservoirs into human populations, from HIV-1 and HIV-2, to the 1918 influenza virus, to MERS-CoV, to SARS-CoV-2[2–4](https://paperpile.com/c/Gdvn6U/CaSrw+GiahF+UqF3k). For a novel pathogen to become a threat to human populations, first, contact between humans and the animal reservoir must occur; the pathogen must either have, or evolve (Box 1) the capacity for human to human transmission[5](https://paperpile.com/c/Gdvn6U/XIDpJ); and finally, this human to human transmission must enable expansion of the pathogen’s geographic range beyond the zone of spillover. Recent global changes have affected each of these steps.

Patterns of contact between human and wildlife reservoirs have increased as human populations move into previously unoccupied regions. Population growth and agricultural expansion, coupled with increasing wealth and larger property sizes, are a driving factor of these interactions and the resulting habitat destruction. This may occur alongside behaviors that increase potential for spillover, such as consumption of wild meat[6](https://paperpile.com/c/Gdvn6U/YdKZA), or intensifying contact between wild and domestic animal hosts. For example, Nipah virus has been identified in several bat populations, particularly flying foxes, but in 1999 caused a severe outbreak in Malaysia, primarily amongst pig farmers[7](https://paperpile.com/c/Gdvn6U/ifkEG). It is hypothesized that the spillover of Nipah virus from bats to pigs was driven by three factors related to global change: pig farms expanding into bat habitat, intensification of pig farming leading to a high density of hosts, and international trade leading to the spread of the infection among other pig populations in Malaysia and Singapore[8](https://paperpile.com/c/Gdvn6U/s7Z4s). Expanding agriculture and its intensification may create conditions that favour pathogen circulation within domestic animal (or plant) reservoirs via high density farming practices[9](https://paperpile.com/c/Gdvn6U/n0W8c). Beyond creating opportunities for emergence of problematic livestock pathogens, this could also increase opportunities for evolution of novel variants of risk to humans in domestic animal reservoirs. This may occur alongside increasing risk to workers interacting with animal populations[10](https://paperpile.com/c/Gdvn6U/J6WT1), as a result of work practices. Global increase in the demand for and resulting intensification of meat production will importantly drive these processes, and associated use of antibiotics in domestic animals has potential to select for resistant strains of bacteria with potential to affect human health[11](https://paperpile.com/c/Gdvn6U/Lqpsh).

The nature of human populations that are exposed to potential spillover is also changing. For example, the elimination of smallpox led to the cessation of smallpox vaccination, which may have enabled the expansion of monkeypox[12](https://paperpile.com/c/Gdvn6U/EiAUT). More generally, globally aging populations may provide an immune landscape that is more at risk of spillover, as aging immune landscapes are less capable of containing infectious agents[13](https://paperpile.com/c/Gdvn6U/blW5K). The intersection between declining function of immunity at later ages[14](https://paperpile.com/c/Gdvn6U/V7KBd) and globally aging populations may increase the probability of pathogen emergence, but this remains conjectural and an important area for research. The changing global context may allow existing human pathogens to both evolve novel characteristics and expand in scope. Selection for drug resistance now occurs worldwide, and antibiotic resistance has and will evolve repeatedly[15](https://paperpile.com/c/Gdvn6U/FCCok). As with antibiotic resistance, rapid global spread is commonplace for antimalarial resistance following evolution[16](https://paperpile.com/c/Gdvn6U/gttD8).

Climate change may play a role in the risk from pathogen spillover. Changing environmental conditions can alter species range and density, leading to novel interactions between species, and elevate the risk of zoonotic emergence[17](https://paperpile.com/c/Gdvn6U/Rhv27). A series of compounded environmental factors including a long period of drought followed by extreme precipitation **[Au: can you specify which environmental factors?]** is hypothesized to have driven an upsurge in rodent populations causing the emergence of pulmonary hantavirus in 1993[18](https://paperpile.com/c/Gdvn6U/D6vpA). Similarly, evidence suggests that populations of the black flying fox in Australia, a key reservoir of Hendra virus, have moved 100km southward in the last 100 years due to climatic changes. This shifting range likely caused Hendra virus to spill over into southern horse populations and these horses subsequently infected humans[19,20](https://paperpile.com/c/Gdvn6U/H8TVg+QRAcC). Patterns of change are likely taking place in other bat populations globally though remain understudied - a clear cause for concern given the crucial role bat populations play as a reservoir host for several high fatality pathogens[21](https://paperpile.com/c/Gdvn6U/iJVts).

Rapid rates of urbanization in low- and middle-income countries, and the increase in populations residing in crowded, low quality dwellings, have created new opportunities for the emergence of infectious diseases (Fig. 2). Urbanization has promoted the emergence and spread of arboviral diseases such as dengue, Zika, and chikungunya, which are transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes that are well adapted to urban areas[22–24](https://paperpile.com/c/Gdvn6U/9vzdv+870hq+K5dXx). Population density appears correlated with *Ae. aegypti* preference for human odor and hence the evolution of human-biting -- the transmission pathway for arboviral disease[24](https://paperpile.com/c/Gdvn6U/K5dXx). However the role of urbanization in vector-borne disease spread is complex: the preference of the *Anopheles* spp. vector for rural environments may have led to a decline in malaria prevalence in urbanizing regions[25](https://paperpile.com/c/Gdvn6U/M5Oau). Nevertheless, dense and highly connected urban areas are potential hot spots for the rapid spread of diseases such as COVID-19 and severe acute respiratory syndrome (SARS), and cities can serve as a catalyst for rapid local and global transmission.

**[H1] Local-scale disease dynamics**

Emerging, re-emerging and endemic pathogens in human populations may exhibit distinct dynamic patterns of spread at the local scale. These patterns will be governed by demographic factors, including the effects of human behavior on transmission (for example, school terms drive transmission of many childhood infections[26](https://paperpile.com/c/Gdvn6U/Hka4S), gender specific travel patterns may result in higher burdens of chikungunya in women in Bangladesh[27](https://paperpile.com/c/Gdvn6U/zWQMm)) and immunity (which, for immunizing infections like measles and rotavirus is in turn shaped by replenishment of susceptible individuals via births[28,29](https://paperpile.com/c/Gdvn6U/rEO09+WMUn7), and depletion by vaccination where vaccines are available[30](https://paperpile.com/c/Gdvn6U/Q5vO8)). Transmission may also be affected by climatic variables acting spatially or over the course of the year in line with seasonal fluctuations[31,32](https://paperpile.com/c/Gdvn6U/O8TBe+3WpyG). Recent global changes have affected each of these drivers of local scale dynamics.

As school attendance not only modulates transmission of childhood infections[26](https://paperpile.com/c/Gdvn6U/Hka4S), but also shapes human mobility[33](https://paperpile.com/c/Gdvn6U/ZfQzN), dramatic increases in rates of school attendance globally thus have the potential to substantially alter the dynamics of many infections. That this has yet to be documented is perhaps in part because this change has happened alongside expansion in access to vaccines that protect children against many of the relevant infections; as well as global declines in birth rates which also facilitate control efforts by diminishing the size of the susceptible pool[34](https://paperpile.com/c/Gdvn6U/ojEBg). If the burden of disease is age-specific, the intersection between immunity and shifting demography may be particularly marked: declining birth rates translate into a smaller pool of susceptibles and thus infected individuals, reducing the overall rate at which susceptible individuals become infected, and thus increasing the average age of infection or disease, reported for dengue in Thailand[35](https://paperpile.com/c/Gdvn6U/lcHVI), and rubella in Costa Rica[36](https://paperpile.com/c/Gdvn6U/wcwo1) as these countries went through the demographic transition. Conversely, aging populations may increase transmission, for example, longer shedding has been suggested with age for SARS-CoV-2[37](https://paperpile.com/c/Gdvn6U/Zhhtw).

Demographic changes to population size and density via urbanization may also affect dynamics. Influenza, for example, tends to exhibit more persistent outbreaks in more populous, denser urban regions[38](https://paperpile.com/c/Gdvn6U/fYK5q) (Fig. 2). A similar pattern was reported in the early SARS-CoV-2 pandemic[39](https://paperpile.com/c/Gdvn6U/L5dvk). If demographic change has importantly altered the context of infectious diseases in recent years, arguably an even larger effect is caused by changes in the occurrence of immunomodulatory infections, which, in turn, may affect other infections. For example, the emergence of HIV has amplified the burden of tuberculosis[40](https://paperpile.com/c/Gdvn6U/SwMsH). Mass drug administration efforts have reduced helminth prevalence, which will have knock-on effects on the burden of other infections such as malaria which may be increased in individuals experiencing a heavy worm burden**[Au: what is the relationship here?]**[41](https://paperpile.com/c/Gdvn6U/0NjAu); both will also intersect with the efficacy of vaccination programs[42](https://paperpile.com/c/Gdvn6U/C3bpH).

The climate plays a key role in driving the local-scale seasonal dynamics of many infectious diseases, which may thus be altered by global change in climatic conditions[43,44](https://paperpile.com/c/Gdvn6U/kgTnF+ETIK0). Considering these impacts requires recognizing that interactions with climate vary by pathogen type. For directly-transmitted infections, the role of climate is revealed by marked latitudinal gradients in epidemic timing[32](https://paperpile.com/c/Gdvn6U/3WpyG)[45](https://paperpile.com/c/Gdvn6U/0EY89). Several respiratory pathogens, including influenza virus, are more highly seasonal in temperate climates and exhibit greater year-round persistence in tropical locations[32,46](https://paperpile.com/c/Gdvn6U/ZReqR+3WpyG). Climate change is expected to lead to an expansion of these tropical patterns with possible implications for pathogen evolution[47](https://paperpile.com/c/Gdvn6U/dEobS)[43](https://paperpile.com/c/Gdvn6U/kgTnF). At the individual level, susceptibility to respiratory viral infections may be impacted by exposure to local air pollution: a concern for rapidly urbanizing locations where urban air pollution may disproportionately affect low-income communities and communities of color[48,49](https://paperpile.com/c/Gdvn6U/6u6mW+wY0Qq). At the same time, globally, a move to an urban location may bring benefits in terms of increased access to healthcare (Fig. 2).

For some bacterial and fungal diseases, climatic changes may affect the pathogen’s environmental reservoir. Coccidioidomycosis (Valley fever), caused by inhalation of *Coccidioides* spp. fungal spores, is expected to worsen with climate change as the region with optimal conditions for fungal spore production expands[50](https://paperpile.com/c/Gdvn6U/sYbKU). Climate change may also have played a role in the emergence of the drug-resistant fungal pathogen Candida auris. C. auris emerged in several continents at the same time and has been shown to have elevated thermotolerance when compared to other closely related fungal species, perhaps evolved in response to global warming [51,52](https://paperpile.com/c/Gdvn6U/XYin+qRqa). This elevated thermotolerance may have allowed the pathogen to jump from its environmental habitat into an intermediary avian host, given the higher body temperatures of avian fauna, before infecting humans [52](https://paperpile.com/c/Gdvn6U/qRqa).

Demographic change and technological changes may alter a host’s interaction with the environmental reservoir. Cholera, caused by bacterial pathogen *Vibrio* *cholera*, persists in the environment, particularly aquatic settings. Changes to environmental conditions including elevated sea temperatures, lead to increased reproduction of the pathogen and local epidemics[53](https://paperpile.com/c/Gdvn6U/8fbCo), with clear links to longer term climate phenomena such as El Nino **[G] [Au: I have highlighted suggestions for glossary terms throughout your manuscript. Please provide succinct, one-sentence definitions for these specialist terms at the end of the manuscript.]**[54](https://paperpile.com/c/Gdvn6U/phFpz). However, improved sanitation lowers the risk of *V.* *cholera* exposure and has led to a decline of the disease in many locations[53](https://paperpile.com/c/Gdvn6U/8fbCo). **[Au: Candida auris emergence has also been suggested to be linked to climate change (**[**https://journals.asm.org/doi/10.1128/mBio.01397-19**](https://journals.asm.org/doi/10.1128/mBio.01397-19)**); might be interesting to include this too (here or above in the spillover section).]**

For vector transmitted diseases, biological traits of both the vector and pathogen may be sensitive to climate. Many transmission-related life cycle traits of the mosquito (biting rate, adult lifespan, population size and distribution) and pathogen (extrinsic incubation rate) are temperature sensitive, and oviposition patterns depend on water availability[55](https://paperpile.com/c/Gdvn6U/dT8Lp). Consequently, the geographical range for dengue, malaria, and other vector-borne diseases[56](https://paperpile.com/c/Gdvn6U/T9G9c)[57,58](https://paperpile.com/c/Gdvn6U/8HEfN+pTsTR),[56](https://paperpile.com/c/Gdvn6U/T9G9c) are affected by the local climate, and substantial effort is underway to understand how these ranges may alter with climate change[59–61](https://paperpile.com/c/Gdvn6U/KNcP6+bWMkD+Xv0mL). For certain vector-borne diseases such as Zika, climate change may lead to an expanded range[62](https://paperpile.com/c/Gdvn6U/Yx87I). However, for others such as malaria, climate change may shift the spatial range of the infection to higher latitudes[63](https://paperpile.com/c/Gdvn6U/Mm07X). As ever, the footprint of human interventions may loom larger than these changes in local conditions[25](https://paperpile.com/c/Gdvn6U/M5Oau).

At the local scale, one of the strongest footprints detectable on the dynamics of many endemic infections in recent years is declines in incidence associated with access to vaccinations[64](https://paperpile.com/c/Gdvn6U/G6yzH). However, the introduction of a vaccine does not imply immediate elimination. As vaccination coverage increases, measles outbreaks, for instance, follow a pathway towards elimination defined by declines in mean incidence but high variability in outbreak size[34](https://paperpile.com/c/Gdvn6U/ojEBg). Imperfect vaccine coverage may allow population susceptibility to increase such that substantial outbreaks can occur if the disease is re-introduced, for example, the 2018 measles outbreak in Madagascar which led to over 100,000 cases[65](https://paperpile.com/c/Gdvn6U/tvVOd). Improved surveillance of the landscape of population immunity, via serological surveys, could help determine gaps in vaccination coverage[66](https://paperpile.com/c/Gdvn6U/bpgZY).

**[H1] Global spread**

As local conditions alter demographically, or as a result of climate change potentially expanding the range of locations suitable to a particular pathogen or vector, increased global connectivity will enable pathogens to reach these new environments more rapidly (Fig 4). Here we review the impact of global change on three forms of global connectivity: international travel, human migration and local-scale mobility, and the international trade of animals, animal-products and plants, while considering the impact on infectious disease risk. Technological change over the last two decades has dramatically lowered the cost of international travel while demographic change has led to heightened demand for inexpensive flights (Fig. 1b). Demographic and climatic drivers have altered patterns of local mobility and regional migration while rising demand and technological change have elevated the trade of plants and animals. At the same time, an increasingly urban population is better connected than ever before to global travel networks (Fig. 4). These changes to global connectivity will present unique risk factors for infectious disease spread, enabling pathogens to travel further and faster than ever before.

***[H2] International travel***

The late 20th and early 21st century has been marked by technological developments enabling ever swifter movement of people and pathogens over large distances - from trains to planes, and an expanding international airline network (Fig. 4). The total number of airline passengers has doubled from just under 2 billion in the year 2000 to over 4 billion in 2019 (Fig. 1b). This rampant increase in global connectivity brings about new risks from emerging pathogens [see Box 2]. Yet, many endemic pathogens also circulate via transit routes: seasonal influenza circulation in the US can be predicted by flight patterns[67,68](https://paperpile.com/c/Gdvn6U/ZkkdZ+xK6bJ), with evidence that flight bans following 9/11 caused a delayed outbreak, and a prolonged influenza season within the US as measured by a 60% increase in time to transnational spread**[Au: Why was it prolonged? I can see why it would be delayed.]**[68](https://paperpile.com/c/Gdvn6U/xK6bJ). Similarly, rapid global air travel is expected to have played a key role in the global spread of SARS-CoV-2. Genetic analyses demonstrate multiple introductions of SARS-CoV-2, driven by air travel, in the Middle East[69](https://paperpile.com/c/Gdvn6U/9xW9e), Northern California[70](https://paperpile.com/c/Gdvn6U/pKAZC) and Brazil[71](https://paperpile.com/c/Gdvn6U/BOHPT). **[Au: Has there been any work on the speed of international spread of SARS-CoV-2 vs SARS-CoV? With much higher international travel numbers in 2019/2020 than 2003, one would expect more rapid spread. Obviously there are also other differences (R0, asymptomatic spread etc) but increased connectivity must have made a difference. Besides that, the spread of SARS-CoV-2 EU1 by tourists from Spain is a particularly well-documented example of the role of international travel (https://pubmed.ncbi.nlm.nih.gov/34098568/).]**

International travel can lead to the global spread of vector-borne diseases via the introduction of new vectors into regions with suitable environmental conditions or the introduction of new pathogens into native and invasive vector populations. Historically, vectors have been introduced via trade routes: ships are thought to have been key to the global dispersal of *Ae. aegypti* and *Ae. albopictus* which then established in locations with appropriate environmental conditions[72,73](https://paperpile.com/c/Gdvn6U/vKN2i+H4fxo)*. Anopheles gambiae,* the primary vector of malaria in Africa,was introduced into Brazil in the 1930s **[Au: when did this happen?]** and established in a region with a similar climate to native Kenya[74](https://paperpile.com/c/Gdvn6U/7sGeg). Although malaria was already endemic to Brazil at the time, *A. gambiae* proved a much more effective vector, leading to a severe outbreak and a costly (but successful) eradication campaign[73](https://paperpile.com/c/Gdvn6U/H4fxo). There has been relatively little documented evidence of the introduction of new vectors via air travel. This is likely due to the low probability of vectors surviving the flight, and disembarking in a suitable region, in sufficient numbers to establish and drive an epidemic[75](https://paperpile.com/c/Gdvn6U/Zvt8P). However, cases of ‘airport malaria’, that is, malaria transmitted within international airports, even outside of endemic regions, are rare but becoming more common[76](https://paperpile.com/c/Gdvn6U/pEHMp).

A more feasible scenario is that air-travel can bring an infected human host into contact with a native or invasive vector population that then establishes local transmission. Climate change has driven a shift in the range of several key vectors which may make this introduction more likely. The range of the biting midge *Culicoides imicola*, a vector of Bluetongue virus (BTV) which causes disease in ruminants, has expanded over the last few decades from sub-Saharan Africa and the Middle East into Europe, bringing a wave of Bluetongue epidemics[77](https://paperpile.com/c/Gdvn6U/jQWE9). Following this expansion, BTV then spread outside the range of *C. imicola* into native *Culicoides* spp. populations in more northerly regions of Europe. In terms of air travel, the 2015 Zika virus epidemic in the Americas may provide a recent example of a pathogen spreading into a susceptible vector population, likely facilitated by high connectivity[78](https://paperpile.com/c/Gdvn6U/WBqds). Zika virus is expected to have been introduced to Brazil from French Polynesia and vectored by *Aedes* spp., though the volume of air travel during this time period makes it almost impossible to conclusively determine the origin[78](https://paperpile.com/c/Gdvn6U/WBqds). Similarly, it is hard to pinpoint the pathway via which West Nile virus was introduced in the U.S. in the 1990s, however transport by either shipping (transporting vectors) or aircraft (transporting a human host) is likely[79](https://paperpile.com/c/Gdvn6U/6GOEE). After introduction, West Nile virus spread in the native *Culex* spp. mosquito population. More broadly, climate change complicates the picture in terms of possible future introductions. As the range of locations with environmental suitability for certain vector species changes, successful introductions of pathogens into these vector populations may become more likely[80](https://paperpile.com/c/Gdvn6U/5eZMf). At the same time, changes to population structure e.g. via urbanization, may alter the suitability of an environment for vector reproduction (Fig. 2).

***[H2] Migration and local mobility***

Human migration is an intrinsic component of population dynamics driven by socio-economic, political, and environmental factors, and one that has undergone considerable upheaval in the modern era. It is estimated that globally the number of international migrants, those who intentionally relocate to a country other than their birth country, is almost 272 million representing 3.5% of the world’s population. By contrast, temporary migration, often considered ‘seasonal migration’ is largely driven by economic patterns including agricultural seasons that require short periods of intense labor. The rate of migration continues to increase due to both social, economic, political, and environmental drivers in origin countries, as well as economic opportunities, physical safety, and security in destination countries. Future projections for migration are unclear, with the UN projecting stable rates post-2050[81](https://paperpile.com/c/Gdvn6U/hV02L). However, climate change will likely provide an escalating push factor, with sea-level rise and extreme weather events leading to forced migration from exposed regions[82](https://paperpile.com/c/Gdvn6U/I1AaQ).

Given the movement of people between countries, there remain introduction risks of infectious diseases, including those common and uncommon in the country of migration[83](https://paperpile.com/c/Gdvn6U/wP9Jc). It is possible for a infectious disease common in the source country, such as latent tuberculosis, malaria, viral hepatitis, and infection with intestinal parasites, to be imported via this mechanism[84–86](https://paperpile.com/c/Gdvn6U/7bErt+9yqVu+YsqMQ). For example, in many destination countries, a large proportion of cases of tuberculosis are observed in the foreign-born population. However, the ultimate impact of these introduction events will largely depend on the population-level susceptibility and environmental suitability for sustained transmission in the destination country. More importantly, migrant groups often have more limited access to healthcare, treatment, and resources, particularly those displaced who are often provided with limited options to safely seek care and treatment[87](https://paperpile.com/c/Gdvn6U/YmW9j). Minimizing the impact of these possible disease threats depends on providing appropriate healthcare to these high risk groups that takes into account the multifaceted social, political, and economic components[88](https://paperpile.com/c/Gdvn6U/oEn5U).

Within-country population mobility can also play a key role in disease spread, however, it is typically difficult to track these movements. Aggregated cell phone data is a valuable tool for tracing patterns of local mobility and predicting future outbreaks[89](https://paperpile.com/c/Gdvn6U/9yhZq) . In recent work, mobility data has been shown to be predictive of inequities in COVID19 burden in the US[90](https://paperpile.com/c/Gdvn6U/4zZk)

**This has been extensively used for SARS-CoV-2, maybe also use this as an example. There are plenty of references, eg** [**https://www.nature.com/articles/s41586-020-2923-3**](https://www.nature.com/articles/s41586-020-2923-3)**,** [**https://www.nature.com/articles/s41467-021-21358-2**](https://www.nature.com/articles/s41467-021-21358-2)**,** [**https://www.medrxiv.org/content/10.1101/2021.01.05.21249196v1**](https://www.medrxiv.org/content/10.1101/2021.01.05.21249196v1)**]**. Similarly, population mobility was found to predict the spread of the 2011 dengue epidemic in Pakistan[91](https://paperpile.com/c/Gdvn6U/BR0uJ), while local travel following the Eid holidays was found to predict the spread of the chikungunya outbreak in 2017 in Bangladesh[92](https://paperpile.com/c/Gdvn6U/33QyZ). As the trend of urbanization continues, mobility to and from dense, urban centers, that is, megacities, will likely play a future role in local spread of infections[92](https://paperpile.com/c/Gdvn6U/33QyZ). Better tracking of within-country population mobility, using novel data streams, may present an opportunity for forecasting future outbreaks[93](https://paperpile.com/c/Gdvn6U/GaMnH).

**[H1] Intensification of animal and plant trade**

International trade has expanded rapidly in the modern era and has been matched by a global proliferation of infectious diseases affecting not only humans, but also animals and plants[94,95](https://paperpile.com/c/Gdvn6U/rkP2T+31nIo). Trade drives this pattern by facilitating the translocation of hosts and pathogens across the geographic and ecological boundaries that constrain their spread. The economic and environmental threats posed by trade-driven infectious diseases of plants and animals are increasingly recognized, and calls for more stringent containment measures have intensified in recent years[96,97](https://paperpile.com/c/Gdvn6U/lK8PK+czUgR).

*[H2] Plant trade*

Deliberate transport of plant products has existed since the emergence of trade. Increases in the speed of transport during modern times have allowed for more live plant tissue, and as a result more viable pathogen propagules **[G]** , to be transported over long distances. Combined with the intensification of trade at the global scale, this pattern has driven a rise in long distance transmission and disease emergence[98,99](https://paperpile.com/c/Gdvn6U/xOSU8+gB2nq). Trade drives the emergence of novel plant diseases by creating novel interactions between hosts and pathogens[100](https://paperpile.com/c/Gdvn6U/tfuSw). One pathway through which this can occur is the introduction of novel pathogens to native plants. For example, *Xylella fastidiosa*, a generalist bacteria vectored by xylem-feeding insects, was introduced into Europe in 2013 from the United States, likely as a result of trade. In Italy, *X. fastidiosa* is causing an ongoing epidemic of ‘olive quick decline syndrome’ resulting in severe losses of an economically and culturally important crop[101,102](https://paperpile.com/c/Gdvn6U/eTDNQ+0WNSN). Trade can also drive the emergence of plant disease by introducing novel hosts to native pathogens. Eucalyptus rust, a disease caused by the fungal pathogen *Puccinia psidii*, emerged when the pathogen transmitted from its native South American hosts in the Myrtle family (*Myrtaceae*) to non-native *Eucalyptus* trees (which also belong to the Myrtle family) being grown on plantations[103](https://paperpile.com/c/Gdvn6U/YDCVo). The disease now threatens to ‘spill back’ into naive endemic *Eucalyptus* populations in Australia.

*[H2] Animal and animal-product trade*

Animal trade has contributed to multiple outbreaks and emergence events globally which have had major consequences on the agricultural sector as a whole and poses substantial risk for animal and public health. Large numbers of livestock are traded annually between countries and may facilitate the spread of pathogens. Rift Valley fever for example, is a zoonotic vector borne viral disease causing abortion and high neonatal mortality in domestic ruminants. The disease is widespread on the African continent and has recently been detected in Saudi Arabia and Yemen. Live cattle movement between East Africa and the Arabian peninsula or from the Union of Comoros to Madagascar are thought to have contributed to the introduction of the Rift Valley fever virus and caused outbreaks in these countries in 2000 and 2008 respectively[104](https://paperpile.com/c/Gdvn6U/FbvWw).

Additionally, the trade of animal-derived products such as meat may enable the movement of pathogens over large distances and between continents. For instance, African swine fever is a highly contagious viral disease affecting several members of the suidae family, including domestic pigs and wild boars. Infection by African swine fever virus (ASFV) may result in up to 100% morbidity and mortality in affected pig herds and substantial economic losses for producers. In 2007, the accidental introduction of the ASFV to Georgia led to the first outbreak of ASF in Europe since the early 1990’s[105](https://paperpile.com/c/Gdvn6U/aKpPg). The virus which used to primarily occur in sub saharan Africa was allegedly introduced to the caucasian peninsula through meat products contaminated with viruses closely related to the ones found in Madagascar, Mozambique or Zambia[106](https://paperpile.com/c/Gdvn6U/FX8Oq). Despite efforts to contain the virus, the disease has spread to more than 20 countries in Europe and Asia[107,108](https://paperpile.com/c/Gdvn6U/1vxMJ+hsHU6).

Similarly, in recent decades there has been an expansion in infections of *Vibrio parahaemolyticus* - a bacterial pathogen found in shellfish and the leading cause of seafood-related illness globally. The pathogen is endemic to regions of the U.S. Pacific Northwest but has recently spread to other parts of the U.S., Europe and South America[109,110](https://paperpile.com/c/Gdvn6U/qcPN8+t90qS). The concerning increase in *V. parahaemolyticus* infection is expected to have several drivers connected to global change. Declines in sea ice have increased ship traffic through the Bering strait, with cargo ships possibly transporting *V. parahaemolyticus* in ballast water. At the same time, warming sea temperatures may have increased the global environmental suitability for *V. parahaemolyticus* in the marine environment[109](https://paperpile.com/c/Gdvn6U/qcPN8). Finally, dispersal of the pathogen may have occurred via increasing global trade in shellfish, with evidence suggesting possible dispersal via Manila clams introduced into Spain from Canada[110](https://paperpile.com/c/Gdvn6U/t90qS). This combination of possible drivers speaks to the complexity of understanding infectious disease risk in an era of global change, and the necessity of exploring concurrent changes.

Transboundary spread of diseases through legal and illegal trade of live animals may also have important consequences on biodiversity on a global scale. For example, the amphibian trade contributed to the expansion of novel strains of the fungal pathogen genus *Batrachochytrium* into naive hosts, devastating wild amphibian populations globally[111](https://paperpile.com/c/Gdvn6U/z26ez). Conversely, infectious diseases also hamper trade, resulting in indirect economic losses in affected populations. Foot and Mouth Disease virus is a major reason for trade restrictions on livestock. While endemic in certain countries in Asia and Africa, FMDV causes outbreaks in naïve populations resulting in large economic losses[112](https://paperpile.com/c/Gdvn6U/vID3l). While trade is a major driver of pathogen spread, food animal production has transformed in recent history into large-scale intensified systems with high density, genetically homogenous populations, ideal for pathogen emergence and maintenance[113](https://paperpile.com/c/Gdvn6U/HSEQH). Critically, animal production systems often serve as the interface between wild and human populations, and multiple viral spillover events have occurred at this nexus. Nipah virus spilled over from fruit bats to the domestic pig population multiple times before subsequently infecting humans[114](https://paperpile.com/c/Gdvn6U/LABvy). Pandemic variants of human influenza A virus are often the result of reassortment **[G]** between human and avian viruses, with both domestic poultry and wild birds posited to play a role[115](https://paperpile.com/c/Gdvn6U/sMCOv)[116,117](https://paperpile.com/c/Gdvn6U/pkayp+TMjU6). A non-viral example is the spillover of antimicrobial resistant pathogens from livestock into humans: intensive antibiotic usage in industrialized and smallholder livestock production systems to promote growth and prevent infections has been linked to the emergence of antibiotic resistance in humans[118](https://paperpile.com/c/Gdvn6U/IdmOJ). Tackling emergence and disease spread in animal systems will require rethinking both food animal production and global trade of animals.

**[H1] A new era of infectious disease…**

In recent decades, declines in mortality and morbidity, particularly childhood mortality have been one of the great triumphs of public health. Greater access to care, such as therapeutics (including antibiotics), improved sanitation and the development of vaccines[119](https://paperpile.com/c/Gdvn6U/nveSd) have been core drivers of this progress. Even as medical advances in the twenty-first century have spurred advances in population health, inequalities in access to these advances remain widespread between and within countries[120](https://paperpile.com/c/Gdvn6U/j8NcD). Reducing inequities in access to health care and improving surveillance and monitoring for infectious diseases in low-and-middle income countries, and in underserved populations within countries, should be a priority in tackling pathogen emergence and spread.

While life expectancy continues to increase, and life-years lost to infectious diseases decline, the new threat of infectious disease will likely come from emerging and re-emerging infections. Climatic change, rapid urbanization and changing land use patterns will elevate the risk of disease emergence in the coming decades. Climate change, in particular, may alter the range of global pathogens, allowing infections, particularly vector-borne infections, to expand into new locations. A continued uptick in global travel, trade and mobility, will transport pathogens rapidly, following emergence. Yet there are counterpoints to this trend: the rapid growth of connectivity observed in the early twenty-first century may stabilize and structural changes wrought during the COVID19 pandemic may persist[121](https://paperpile.com/c/Gdvn6U/1En1R). Increased investment in outbreak response, such as the recent formation of a WHO Center for Pandemic and Epidemic Intelligence, could help mitigate the threat from future emerging infections. In addition, efforts to develop universal vaccines, that is, vaccines that engender immunity against all strains of influenza viruses or coronaviruses, could provide a monumental leap forward in tackling present and future infections[122](https://paperpile.com/c/Gdvn6U/tyCma).

A changing world requires changing science to evaluate future risks from infectious disease. Future work needs to explicitly address concurrent changes: how shifting patterns of demographic, climatic and technological factors may collectively affect the risk of pathogen **[Au: I’d suggest to say pathogen. Yes, viruses likely are the biggest threat but this also applies to bacteria, parasites etc]** emergence, alterations to dynamics, and global spread. More forward-looking research, to contend with possible future outcomes, is required in addition to the retroactive analyses that typically dominate the literature. Increasing attention needs to be paid to pathogens currently circulating in both wild and domestic animal populations, especially in cases where agriculture is expanding into native species’ habitats and conversely, invasive species are moving into populous regions due to climate change. As the battle against certain long-term endemic infections is won, institutional structures built to address these old enemies can be co-opted and adapted for emerging threats. At the same time, new technologies, including advances in data collection and surveillance, need to be harnessed. There is much recent innovation around surveillance, with development of techniques for extracting epidemiological information by reinterpreting information available from classic tools such as PCR with simple cross-sectional designs[123](https://paperpile.com/c/Gdvn6U/z9aTh); or to leverage multiplex serology **[G]** approaches to identify anomalies that might suggest pathogen emergence; and there is increasing interest in integrating multiple surveillance platforms (from genomic to case data) to better understand**[Au: understand?]** pathogen spread. Finally, future research needs to align with a global view of disease risk. In an increasingly connected world, the risk from infectious disease is globally shared. The COVID19 pandemic, including the rapid global circulation of evolved strains, highlights the need for a collaborative, worldwide framework for infectious disease research and control.

**Fig. 1**

**Human connectivity and infectious disease outbreaks in pre-modern and modern times**

**A.** Examples of epidemic periods associated with different eras of human transportation (land, maritime, and air travel) are shown. Overland trade networks and war campaigns are thought to have contributed to multiple epidemics in the Mediterranean in late classical antiquity (green) beginning with the Antonine plague, which reportedly claimed the life of Roman Emperor Lucius Verus[124–127](https://paperpile.com/c/Gdvn6U/1ShsA+asclJ+KFO4U+P7G3P). Maritime transportation (red, gray) leading to European contact with the Americas and the subsequent Atlantic slave trade resulted in the importation of *Plasmodium falciparum* malaria and novel viral pathogens[128](https://paperpile.com/c/Gdvn6U/5dLyc). In modern times, air travel (purple) resulted in the importation of SARS-CoV to 27 countries before transmission was halted[129](https://paperpile.com/c/Gdvn6U/aCyUl). **B.** In recent years, increases in air travel, trade, and urbanization at global (left) and regional (right) scales have accelerated, indicating ever more frequent transport of people and goods between growing urban areas (source: World Bank, https://data.worldbank.org/). **C**. Log deaths from major epidemics in the twenty-first century (source: World Health Organization, https://www.who.int/) **[Au: What is the source for C?]** . **D**. Disability-adjusted life years lost from infectious diseases (source: Our World in Data, https://ourworldindata.org/).

**Fig. 2**

**Impacts of urbanization on infectious disease. [Au: Please add a descriptive legend.]**

**Fig. 3**

**Climatic, technological and demographic change effects on disease emergence, dynamics and spread. [Au: Please add a descriptive legend.]**

**Fig. 4**

**Mapping changes to travel and climate**

**A.** The global international air travel network expanded substantially from 1933 to 2020 (from Worldpop.org) **[Au: What is the source of this data?]** . **B.** Average monthly maximum temperature (tmax) in 1970-2000 **[Au: I don’t understand this. Is the average temperature of 2000 shown or of the whole range? Same for 2100.]** ) and difference between 2070-2100 and 1970-2000 averages (data from WorldClim, <https://www.worldclim.org>, Shared Socioeconomic Pathway 3 (SSP3) **[Au: What does SSP3 mean?]** ). **C.** Population projections under SSP3 in 2010 and relative change (population in 2100)/(population in 2010).

**Box 1: Global change and evolution of hosts and pathogens**

Mutations constantly arise in the genomes of all species, from viruses to elephants. Some genetic changes may have no observable effects on fitness (and thus will be selectively neutral), but can be used to track pathogen spread, for example, to trace the impacts of global connectivity on an outbreak[70](https://paperpile.com/c/Gdvn6U/pKAZC). Some genetic changes will affect disease phenotypes, potentially increasing the transmissibility, virulence or immune escape of a pathogen lineage[130](https://paperpile.com/c/Gdvn6U/WrT3r). The degree to which such mutations increase in frequency or spread geographically will depend on the degree to which they increase fitness, as well as pathogen population dynamics, which may be modulated by the global change context. Increases in the density and geographic distribution of susceptible hosts (whether it be people, crops or livestock) may provide greater opportunity for novel variants to emerge[9](https://paperpile.com/c/Gdvn6U/n0W8c) simply by amplifying pathogen populations and thus circulating mutations. While understanding the nuance of cross-scale selection, that is, how the selective context of the individual host translates into the selective context at the scale of populations, remains a challenging frontier[131](https://paperpile.com/c/Gdvn6U/qpcMo), it is likely that aging populations, or presence of immunosuppressive pathogens might further modulate selection pressures Indeed, it has been suggested that the emergence of more transmissible, or less immune- vulnerable variants of SARS-CoV-2 was enabled in part by selection processes occurring during chronic infections in immunosuppressed individuals [132](https://paperpile.com/c/Gdvn6U/jtEh)**[Au: This is really interesting. Do you think the observation of chronic SARS-CoV-2 infection in immunosuppressed patients leading to the rise of mutations that resemble the more transmissible and/or more immune invasive variants is relevant here (**[**https://www.nature.com/articles/s41586-021-03291-y**](https://www.nature.com/articles/s41586-021-03291-y) **and others)?]** . Greater global connectivity leads to more frequent exchange of this genetic material between populations of the same or different species, potentially leading to the erosion of evolved or engineered host resistance and increased rates of pathogen evolution[133](https://paperpile.com/c/Gdvn6U/LGWK) **[Au: Please insert superscript reference.]** ). Associated spillover followed by spillback can create scenarios that facilitate amplification and potentially selection of problematic pathogen variants[134](https://paperpile.com/c/Gdvn6U/SIA6F), an issue highlighted by recent documentation of human to mink to human transmission of SARS-CoV-2[135](https://paperpile.com/c/Gdvn6U/uoLb2). Likewise, increased rates of pathogen importation provide increased opportunities for pathogen populations to evolve the ability to utilize novel vectors (as has been observed in the Americas for malaria[128](https://paperpile.com/c/Gdvn6U/5dLyc)). Increased population connectivity can also enable pathogens and their vectors to shift to novel host species, from infected mosquitos traveling on boats or in planes to agricultural pathogens being inadvertently relocated. Hosts that have not previously been exposed to such pathogens, and thus have no co-evolved defenses, yet are phylogenetically and/or genetically similar to the original host often are most at risk[136,137](https://paperpile.com/c/Gdvn6U/WCawM+mosAJ), a fact that makes homogenization of crops[138](https://paperpile.com/c/Gdvn6U/4dgjs) or livestock a concern. Novel pathogen introductions can have large scale population and ecosystem impacts, of which one famous example is the extirpation of the American Chestnut tree by chestnut blight **[Au: or more recently white-nose syndrome in bats]**[139](https://paperpile.com/c/Gdvn6U/iq7cE). Changes in selection pressure resulting from changes in health care strategies (for example, introduction of vaccination) may have the potential to select for different pathogen characteristics, and could potentially drive the evolution of virulence in pathogens[140,141](https://paperpile.com/c/Gdvn6U/TMIA6+vWHwP).

**Box 2: Will there be another pandemic like COVID19?**

COVID19 has had an unprecedented impact on both human lives and our society, and we will likely be dealing with consequences for decades to come. As we reckon with these consequences, one concern is that a suite of global changes has elevated the risk from emerging pathogens, such that pandemics similar to COVID19 could be a more frequent occurrence. However, there are biological features of SARS-CoV-2 that have made the pathogen distinctly difficult to control, primarily the virus's ability to spread asymptomatically, and pre-symptomatically. Many pathogens do not exhibit these features, which may be a cause for cautious optimism going forward.

The expansion of regional and global air travel, along with the increasing development of high speed railway networks, has resulted in a substantial degree of connectivity between human populations[73](https://paperpile.com/c/Gdvn6U/H4fxo). At the same time, land use change and climate change may have elevated the risk of pathogen emergence. In combination, these drivers imply an era where pathogens are more likely to emerge, and more likely to spread globally on emergence. Yet, while the last century has borne witness to several pandemics (Fig 1), SARS-CoV-2 is unrivalled in its rapid, global reach. A key question is why SARS-CoV-2 was so successful at spreading globally and whether this was due to recent increases in global connectivity as opposed to epidemiological and biological characteristics of the virus itself[142](https://paperpile.com/c/Gdvn6U/xAkzz).

A clear distinction between SARS-CoV-2 and other recently emerged pathogens, for example SARS-CoV and Ebola virus, is that an individual infected with SARS-CoV-2 may become infectious prior to developing symptoms[143](https://paperpile.com/c/Gdvn6U/E9WdC). This presents a unique challenge from a disease control perspective. A standard approach for limiting the onward spread of a new outbreak is to isolate infected individuals when they show symptoms. Case isolation proved successful in mitigating earlier SARS[144](https://paperpile.com/c/Gdvn6U/isTW6) and Ebola[145](https://paperpile.com/c/Gdvn6U/WWD2f) outbreaks. However, symptoms for SARS-CoV-2 likely occur after an individual is already infectious[143](https://paperpile.com/c/Gdvn6U/E9WdC). This possible presymptomatic spread limits the efficacy of case isolation interventions as by the time the infected individual is isolated they may have already spread the pathogen to others[146](https://paperpile.com/c/Gdvn6U/p0dMC). In the box figure, we plot the time to infectiousness (latent period) against time to symptom onset (incubation period) for four pathogens that have caused severe outbreaks in recent decades. When the latent period equals the incubation period (dashed line), symptoms occur at a similar time to infectiousness, for example, influenza. The shaded region to the right of this line indicates possible pre-symptomatic spread which may be uniquely difficult to control.

The 2-3 day delay between infectiousness and symptom onset provides ample time for long-distance spread of the disease, given current transport networks (see the box figure). Control policies, such as testing prior to travel, provide a more effective option in this context, yet developing and distributing a test takes time, during which the disease may spread rapidly. The good news is that this presymptomatic spread appears somewhat unique to SARS-CoV-2, at least compared to other acute infections such as influenza, SARS and Ebola (Fig. 4) **[Au: Besides presymptomatic spread, asymptomatic or paucisymptomatic spread might also a particular problem for SARS-CoV-2. With Ebola, for sure, symptoms are so severe that the disease is hard to miss and SARS also showed more severe disease and higher mortality than COVID-19, making case identification a bit easier.]** . In comparison, asymptomatic spread explains some of the difficulty in controlling Acquired immunodeficiency syndrome (AIDS), prior to anti-retroviral measures.

**Box 3: Big data for disease [Au: Please cite Box 3 in the main text.]**

Recent technological advances in collecting, sharing and processing of large datasets, from satellite images to genomes, represent a new opportunity to answer critical questions in global health. However, challenges remain including the uneven geographical distribution of available data as well as biases in representative sampling. We highlight three areas of future growth:

**Serological surveys**

These surveys detect the presence of antibodies in blood - recent advances in testing now enable the detection of exposure to multiple pathogens using a small sample of blood[147](https://paperpile.com/c/Gdvn6U/LJSPu). Serological surveys have garnered attention during the COVID19 pandemic as a means to track population exposure given under-reporting though test performance characteristics vary widely between epidemiological contexts as well as the choice of assays used **[Au: maybe add here though that sensitivity and specificity can be a problem; there have been egregious surveys claiming cases in Europe before the first cases were identified in China…]**[148](https://paperpile.com/c/Gdvn6U/wxcPm). Historically, serological surveys have been financially and logistically expensive to run, but declining costs are leading to increased availability of serological data.

**Genomic surveillance systems**

Genomic surveillance systemsare able to characterize and track the emergence of novel variants, for example, during the COVID19 pandemic. Undoubtedly these data have enabled the rapid development of diagnostics, vaccines, and, when combined with epidemiological information, are able to provide a more detailed picture of ongoing transmission dynamics. Efforts to develop national and international genomic surveillance networks are varied but with clear success stories[149,150](https://paperpile.com/c/Gdvn6U/fsLiR+HEord)and efforts, even in low resources settings[151](https://paperpile.com/c/Gdvn6U/HtlrJ). However, resource limitations including sequencing platforms, bioinformatic pipelines, and the regular collection of samples for processing, have limited the global expansion of sequencing.

**Artificial intelligence and machine learning**

These techniques are frequently proposed as tools for answering key public health questions, yet specific use-cases remain elusive[152](https://paperpile.com/c/Gdvn6U/xBUdP). Using these tools to predict viral emergence, for example, may prove difficult due to microbiological complexities and the cost of data collection[153](https://paperpile.com/c/Gdvn6U/h2jcM), yet could prove valuable for targeting sampling efforts[154](https://paperpile.com/c/Gdvn6U/56Q9p). In terms of uncovering population-level drivers, statistical approaches, including machine learning, can be used to leverage novel, and high volume, data streams. Yet, more classical, mechanistic models may provide a more robust framework for projecting future outcomes for the disease system under demographic, technological and climatic change. Future work should aim to improve the integration of machine learning approaches within the traditional mechanistic modelling frameworks, in order to rapidly and accurately assess prospective challenges.

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**Glossary**

**El Nino:** A correlated series of climate events associated with the warm phase of the El Nino Southern Oscillation cycle.

**Propagules:** A pathogen unit responsible for infection, such as a fungal spore or viral particle.

**Reassortment:** The mixing of genetic material of different pathogens within an infected cell.

**Multiplex serology:** The measurement of antibody responses to multiple pathogens simultaneously.

**ToC blurb**

Global change, including climate change, urbanization and global travel and trade, has affected the emergence and spread of infectious diseases. In the Review, Baker, Metcalf and colleagues examine how global change affects infectious diseases, highlighting examples ranging from COVID-19 to Zika. **[Au:OK? Please note that the limit for the blurb is ~40 words, so no details can be included.]**