# Ecological impact on pandemic risk in the 21st century

G Woo*

*correspondence to Dr. Gordon Woo, RMS, Minster Building, 21 Mincing Lane, London EC3R 7AG, UK. Email: Gordon.Woo@rms.com.

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**Abstract**

The ecological context of the COVID-19 pandemic is the environmental harm caused by human encroachment on wildlife habitats, deforestation and intensive animal farming. New pathogens tend to emerge where a dense population has been changing its interface with the natural world. Beyond COVID-19, the World Health Organisation (WHO) has warned of 'The Big One', a pandemic with a substantially higher case fatality rate. Already, in the first two decades of the 21st century, there were five near-miss pandemics which gave warning of such a heightened pandemic threat. Each had roots in progressive ecological change. These were SARS (2003), H5N1 (2004), MERS (2012), H7N9 (2013) and Ebola (2014), A counterfactual risk analysis of these near-miss pandemics provides insight into the likelihood of 'The Big One', and the ecological impact on pandemic risk in the 21st century.

Keywords: pandemic, ecology, COVID-19, counterfactual, risk

## 1. Introduction

Over the past century, about two new viruses per year have spilled over from their natural hosts into humans (Dobson et al., 2020). Analysis of emerging infectious diseases (EID) between 1940 and 2004 (Jones et al., 2008) shows that the number of EID has increased significantly over time, after allowing for reporting bias. This emergence is driven by socio-economic, environmental and ecological factors. These increase close links between humans and wildlife disease reservoirs and accelerate the potential for global disease spread. In the period from 1940 to 2004, the majority of EID events were caused by pathogens having an animal source, and about 70% of these zoonoses were caused by pathogens with a wildlife origin. Zoonotic EIDs represent an increasing and very significant threat to public health. One such dangerous threat, which inspired the 2011 disaster movie 'Contagion' was the Nipah virus, which originated in 1998 with fruit bats in Malaysia, which contaminated mangoes eaten by pigs, which transmitted the Nipah virus to pig farmers. Forest had been slashed and burned to create pig farms.

The Contagion movie raised public risk awareness of global pandemics, which had not attained a disaster level since the 1918-1919 great influenza pandemic, which killed tens of millions of people. The Nipah virus causes encephalitis, and is highly lethal. Public perception of pandemic risk might have been biased towards complacency by being anchored to the mild 2009 Mexican flu pandemic, which had a case fatality rate lower than seasonal flu. At the time, the UK government was criticised for buying an excessive amount of the anti-viral medication Tamiflu.

Quite apart from the 1998 Nipah virus outbreak in Malaysia, which had a case fatality rate of 40%, there were five near-miss pandemic catastrophes with double digit case fatality rates in the first two decades of the 21st century. These were SARS coronavirus (2003); H5N1 avian influenza (2004); MERS coronavirus (2012); H7N9 avian influenza (2013) and Ebola filovirus (2014). The associated case fatality rates of 10%, 60%, 30%, 30% and 40%, were substantially higher than for COVID-19. For UK, the COVID-19 case fatality rate is about 3%. Because of a substantial degree of under-reporting of mild and asymptomatic cases, as well as lack of testing of confirmed cases, the COVID-19 infection fatality rate is estimated to be in the range 0.5% to 1% (WHO, 2020).

Outcome and anchoring cognitive biases tend to diminish the concern and attention given by decision-makers to events which failed to impact on their own domain of responsibility. However, these five near-misses were important tangible EID evidence of progressive ecological change. In order to understand the linkage between ecological harm and pandemic risk, the underlying causal drivers are reviewed next.

## 2. Ecological environmental change

Just as climate change impacts on extreme weather hazards, such as windstorms and floods, so ecological change impacts on pandemic hazards, such as influenza and coronaviruses. Encroachment of human settlements on wildlife areas, deforestation, and intensive animal farming degrade the ecological environment and facilitate the emergence of new human infectious diseases, originating from zoonotic pathogens. As with the climate environment, harm to the ecological environment needs to be constantly monitored and assessed because of the risk implications. Gibb et al. (2020) have shown that mammal species which harbour more pathogens are more likely to occur in human-managed ecosystems. Animals that increase in number as a result of human land use are not only more likely to be pathogen hosts, but also are more likely to harbour a greater number of pathogen species, including a number of pathogens that can infect humans.

Global changes in the mode and intensity of land use are creating expanding interfaces between people, livestock and wildlife reservoirs of zoonotic disease. When habitats are modified by humans, the survivor species, including rodents, bats and birds, appear to have the highest number of diseases. Civitello et al. (2015) suggest that human-induced declines in biological diversity may generally increase the abundance of zoonotic and vector-borne parasites, and consequently increase human disease risk. Biodiversity conservation may be a promising strategy to minimise pest outbreaks and mitigate these consequences. Large-scale land use change, such as deforestation and land conversion for agriculture, can alter the relationships between pathogen and host, and increase human contact rates with wildlife and pathogens, so increasing the likelihood of cross-species transmission.

Local climate change, disruption of important ecosystems, deforestation and urbanisation are drivers of a wide range of infectious diseases, including dengue fever, yellow fever and malaria. Brazil is an ecologically crucial illustration of how environmental changes can have a huge impact on the emergence of infectious diseases (Nava et al., 2017). A prime example of the impact of deforestation on the emergence of infectious disease is the bat-borne Ebola outbreak which emerged in December 2013 in a region of Guinea, bordering Sierra Leone and Liberia, which had witnessed extreme deforestation in recent decades.

More than half of Earth's habitable land has been altered to meet the needs of an increasing population (Ostfeld and Keesing, 2020). One of the underlying anthropomorphic factors which drives both climate and ecological change is the growth in the global human population. Since 1989, the world's population has increased by 50%, and has more than doubled since the influenza pandemic of 1968, the most deadly pandemic of the past hundred years until COVID-19. From a pandemic hazard perspective, each person is a potential mixing vessel for virus reassortment, (which is the process by which viruses swap gene segments), a host for a notable virus variant as happened in England with SARS-CoV-2, as well as a link in a chain of community transmission. The reproduction number depends on the virus attack rate and the number of contacts of an infected person. The latter factor rises with population density (Li et al., 2018)

The rapid urban growth in China has seen the population of Wuhan increase fivefold since 1989. An outbreak of infectious disease in a city with a population of two million is much easier to control than if the population is ten million or more. Human population density is a common significant independent predictor of emerging infectious disease events. Disease emergence is a product of anthropogenic and demographic changes, and represents a hidden externality of economic development (Jones et al., 2008). One such grand economic plan is the Belt and Road Initiative in China. The southern branch passes through Yunnan province, which is the gateway to Myanmar and India.

## 2.1 Bats harbouring coronaviruses in Yunnan

Yunnan province in southwest China is one of the most biodiverse regions of the world, but this has come under threat over several decades from industrialisation and urbanisation (Qiu et al., 2018). In Yunnan province, the population increased from 19 million to 46 million in the period from 1958 to 2010. This population growth accelerated biodiversity loss, which has put pressure on the development and effective management of nature reserves in Yunnan (Qiu et al., 2018). The Belt and Road Initiative as well as the Yunnan provincial regional development strategy are bringing even greater pressure on regional biodiversity conservation.

With its attractive landscapes and ethnic diversity, Yunnan is the top Chinese province for tourism. Yunnan is noted for its natural scenery and is China's most biologically diverse province, with the largest range of wild animals in China, and most of the plants used in Chinese medicine. Inevitably, the rapid economic development and urbanisation in Yunnan, with increasing tourism and circulation between urban and rural areas, has led to human encroachment into remote areas where there are large bat colonies.

In 2018, a serological study of 218 residents in four villages located 1 to 6 km from caves in Yunnan found that six people (2.7%) had antibodies for coronaviruses (Wang et al., 2018). This indicates a chance of direct exposure to bat secretion, and subsequent infection, without intermediate hosts (Wang et al., 2018). For five years, virological surveillance was undertaken for one particular bat cave just 60 km from Kunming, the capital of Yunnan. This surveillance revealed the abundant diversity of SARS-like coronaviruses infecting multiple species of bats in this cave (Hu et al., 2017). Although few bats have been sold in the Kunming wildlife markets, hunters have been selling bats directly to restaurants. Without serological surveillance, it is not known how many people in and around Kunming have been infected by bat coronaviruses.

Farther from Kunming, a 2019 study of 227 bats from Mengla County, Yunnan, also revealed evidence of a SARS-like coronavirus (Zhou et al., 2020). Whatever level the risk had reached in 2019 of a bat-borne pandemic coronavirus emerging from Yunnan, it has increased significantly over the past several decades. In 1994, there were half a million foreign tourists in Yunnan; by 2019, there were 7 million. A high speed rail link connecting Kunming with Wuhan cut the journey time by twenty hours. This only started operation in January 2017, eroding the ecologically desirable provincial isolation of the bat caves of Yunnan, and elevating the risk of human transport of bat-borne coronaviruses to Wuhan, and beyond.

## 2.2 Ecological pressure of animal farming in China

COVID-19 has focused attention on China as a source of pandemic hazard. For intrinsic reasons of both human and physical geography, China is one of the largest contributors to pandemic hazard. China has dual seasonal patterns for influenza, which explains why China is often the origin of influenza outbreaks. Whereas northern China has a regular winter pattern, in southern China, influenza is prevalent all year round, with a clear peak in the summer, and a less pronounced peak in the winter (Shu et al., 2010). Both the 1957 and 1968 influenza pandemics originated in southern China, which has a unique ecological system, with many bodies of water and a high population density. Furthermore, one wave of the 1918 pandemic may also have emerged from southern China (Wan, 2012).

Pandemic hazard in China has been elevated since the 1980s as a result of national economic reforms, which have had a transformational impact on agriculture. The Maoist era was marked by episodic famine resulting from the failure of collective farming. Following the end of the era in 1976,

this system was reformed, and this led to a systemic increase in national food production. As of 1981, 90% of the Chinese population were living in extreme poverty. With little state money to invest in mechanising livestock production in the late 1970s, wildlife farming was encouraged as a practical means of economic development for rural communities. Farmers were encouraged to collect animals, and breed them for home consumption, and sale in wet markets. A diverse range of wild animals were farmed, including civet cats and bats.

The subsequent emergence of SARS in 2003, and now SARS-CoV-2 in 2019 are a consequence of the establishment and boom in the Chinese wildlife economy. By 2003, when SARS infected people via civet cats, there were 660 civet farms, with a total of about 40,000 civets (Patou et al., 2009). As of 2020, there were several thousand wildlife breeding operations in each province, especially in the less economically developed provinces in northeast and southern China (Alberts, 2020). As of 2016, the Chinese wildlife trade was valued at $77 billion, and employed 14 million people (Kukreti, 2020). Authorisation of this lucrative wildlife trade has advanced the Chinese government's aim of eradicating rural poverty. As of 2012, there were 100 million impoverished rural residents. According to China's National Bureau of Statistics, this fell to 16.6 million by the end of 2018.

The two SARS coronaviruses became major international public health threats, but they are far from the only deadly pathogens to have emerged in China since the post-Mao agricultural reforms. Private ownership was encouraged by the Chinese government in the 1980s, so ducks and geese were commonly kept in rice-growing areas of southeast China (Hugo, 1995). In 1996, the highly pathogenic H5N1 virus was isolated from a domestic goose during an outbreak with 40% mortality on a goose farm in Guangdong province (Webster et al., 2002).

In the 1980s, the Chinese government promoted duck-fish integration as a popular model of integrated fish farming. One of three provinces with the most popular duck-fish integration in the 1980s and 1990s was Zhejiang. By 2010, as many as 80% of farmers had started within the previous decade (Miao, 2010). However, this rapid expansion of duck farming prosperity in southeast China came with a hidden human healthcare cost. On 31 March 2013, Chinese authorities reported the identification of a novel avian H7N9 virus causing severe disease to people. Most of the cases of human infection had recent exposure to live poultry markets, or potentially contaminated environments. Significantly, phylogenetic analysis of the gene segments of the H7N9 virus indicated that the H7 gene segment was most closely related to the HA gene from H7N3 viruses isolated from ducks in Zhejiang province.

Both the H5N1 and H7N9 avian influenza viruses had very high human case fatality rates (60% and 30%) and had pandemic potential. With some additional mutations, they might have transmitted much more easily from person to person. H5N1 influenza viruses are endemic in China and are continuing to evolve in Asia; multiple genotypes of H5N1 have the potential to be pathogenic in mammals (Chen et al., 2004). Southern China has a complex agricultural system, as well as being an important wintering area for migratory birds. Another highly pathogenic avian influenza virus, H5N8, which has not had human infections, was first detected in poultry in eastern China in 2010, but may well have been introduced by migratory birds (Zhou et al., 2016).

In Guangdong province, chicken production doubled from 1990 to 1995. Pork production increased threefold from 1980 to 1995 (Wan, 2012). The surge in domestic, animal and bird populations increased the likelihood of virus spread through contacts between these populations. According to Nunez and Ross (2019), with the huge expansion in farming, China now has about two-thirds of the world's duck population, and 95% of the domesticated goose population.

China is the world's largest pork producer and consumer, and accounts for half of the world's total pig producers. By 2016, the number of pigs slaughtered per year had risen to 715 million (Sanders, 2018). Pigs are susceptible to avian, swine and human influenza viruses, and are mixing vessels for

the generation of influenza viruses with pandemic potential. China has the most complex ecosystem of swine influenza viruses. There are classical swine (CS); North American triple-reassortant (TR); and Eurasian avian-like (EA) lineages (Sun et al., 2020). This complexity reflects the global trade of live pigs, which facilitates the international movement of viruses from one continent to another. The 2009 influenza pandemic originated in Mexico. This is not so surprising given that in the decades leading up to the pandemic, there had been a large increase in the live pig trade in Mexico, with pigs being imported from North America.

Diligent surveillance is essential for early warning and preparedness in advance of a pandemic. A Eurasian avian-like (EA) H1N1 virus which bears 2009 pandemic and triple-reassortant (TR) internal genes has been predominant in pig populations in China since 2016. Serological surveillance from 2011 to 2018 indicates that 10.4% of pig workers were positive for this virus. This degree of infectivity greatly enhances the opportunity for virus adaptation in humans, and raises fears of the pandemic potential of this virus (Sun et al., 2020).

Whilst China is the most important source of pandemic threats, there is a sizeable risk from neighbouring countries in southeast Asia. Half of poultry production there is from intensive medium to large scale commercial farms. The other half are raised in backyards of small farmers, who keep less than a hundred chickens, geese, ducks or turkeys. Southeast Asia's poultry production expanded over a decade from 5.9 million tons to 9.2 million tons in 2018, and is projected to reach 12.5 million tons by 2028, an annual projected growth rate of 3%. In contrast with commercial poultry farms, small backyard poultry farms are characterised by high poultry density, the presence of different poultry types, and frequent contacts between domestic poultry and wild birds. With primitive biosecurity, these conditions facilitate the reassortment of viruses, as has been observed for example in West Java (Karo-Karo et al., 2019).

### 2.4 Mutation of pandemic viruses

A dangerous adverse mutation of the pandemic virus is a major downward step in a pandemic crisis, requiring crisis managers to have a good scientific understanding of virus mutation, and knowledge of how past pandemic viruses have mutated. Significant adverse mutation is not unusual: four out of the past five influenza pandemics appear to have mutated in the generation of second waves.

RNA viruses are the most common class of pathogens generating new human diseases. Notable 21st century RNA viruses include influenza, Ebola, MERS, SARS and SARS-CoV-2. RNA viruses have high mutation rates. Through random mutation and subsequent selection, RNA viruses may evolve into a form better adapted for human to human transmission.

The first influenza pandemic in the modern scientific era of molecular virology was that of 2009, which originated in Mexico. In the 2009 H1N1 influenza pandemic, the average number of mutations increased slightly from April to November. Some mutations occurring in receptor binding sites first appeared after the first wave ended, and as the pandemic spread, the number of such mutations increased around the world. The higher virulence associated with mutations in receptor binding sites is a driver of a second wave of infection (Mummert et al., 2013).

The preceding 1968-1969 H3N2 influenza pandemic, which emerged from Hong Kong in July 1968, came in two waves. The second was a larger outbreak with a higher reproduction number $R_0$ of 1.21 – 3.58, compared with 1.06 – 2.06 for the first. This increase in transmissibility may be associated with a drift in the viral neuraminidase which originated from the 1957 H2N2 pandemic (Jackson et al., 2009). In UK, there were 80,000 deaths overall from the pandemic.

Whenever a second wave of viral infection is worse than the first, and there are no obvious seasonal or lockdown effects, this is prima facie evidence for a viral mutation. This can only be confirmed

through virological studies, such as have been routinely performed in medical and public health laboratories around the world over the past few decades.

This was not possible for the Russian pandemic at the end of the 19th century. This spread across Europe in three waves: 1889-1890; 1890-1891; 1891-1892. In England and Wales, the first wave peaked in January 1890, and the influenza death rate was 157 per million. From staff absenteeism, about a quarter of London's population was infected (Parsons, 1893). By contrast, the influenza death rate in 1891 was 571 per million, even though the epidemic that year coincided with the spring. The third wave coincided with the winter, and the influenza death rate was 534 per million (Honigsbaum, 2011). About one-third of London's population were immobilized in the second and third waves (Smith, 1995). The higher lethality of the second wave suggests that some mutation of the virus occurred in the year following the arrival of the pandemic from Russia.

A few decades later, there were three main waves of the great H1N1 1918-1919 influenza pandemic. The first in the spring of 1918 was fairly mild, caused comparatively few deaths, and mainly affected military personnel. A UK epidemiologist observed the similarity between the peak in mortality observed in London in 1890 and the initial wave of influenza in the spring of 1918. On this basis, he predicted a more severe second wave (Arnold, 2018). Most fatalities did indeed occur in the second wave. Virological distinction of the individual waves is not possible because the only samples are from second wave patients. Thus the possibility that the first wave was caused by a different virus from the second wave is not resolved (Taubenberger and Morens, 2006). However, from a Bayesian inference perspective, the likelihood that the second wave of the pandemic had a Chinese origin is amplified by the high historical prior probability that, out of all candidate regions of origin, China was the likely source (Woo, 2015).

COVID-19 is the worst global pandemic since the great 1918-1919 pandemic. In December 2020, evidence accrued in southeast England of a significant variant, B.1.1.7, which has an increased reproduction number between 0.4 and 0.7 relative to the original strain of SARS-CoV-2 (Volz et al., 2020). One of the mutations (N501Y) is located within the receptor binding domain. Rather than emerging through the gradual accumulation of mutations, the much more transmissible variant might have originated haphazardly in a single chronically ill patient, with reduced immune-competence.(ECDC, 2020; Choi et al., 2020). This is the kind of more transmissible dangerous random variant which might have emerged with SARS back in 2003, and motivates a counterfactual perspective on pandemic risk.

**3. Counterfactual analysis of pandemic risk: 2000-2019**

Absolute poverty in east Asian developing countries decreased from one-third in 1970 to one-fifth in 1980, to one-tenth in 1990 (Johansen F., 1993). Meat demand increases with growth of income in developing countries. The associated progressive rise in meat consumption has had a detrimental impact on the ecological environment.

Allowing for a time lag of several decades between ecological harm and zoonotic pathogen emergence, most relevant for future pandemic risk assessment is the experience of the past two decades, which bears the imprint of ecological harm in near-miss pandemics. As has been done with many other insured perils, both natural and man-made, pandemic catastrophe risk in the first two decades of the 21st century from 2000 to 2019 can be assessed within the conceptual framework of counterfactual risk analysis (Woo, 2016). There is a substantial degree of randomness in the emergence and mutation of pathogens. Global experience of infectious diseases in the past two decades is only one out of numerous possibilities. This intrinsically stochastic process can be analysed by considering alternative realisations of history (Woo et al., 2017).

Prior to COVID-19, the world was fortunate that there had not been a global pandemic catastrophe in the 21st century. Lessons might have been learned from a series of near-miss events in 2003 (SARS), 2004 (H5N1), 2012 (MERS), 2013 (H7N9) and 2014 (Ebola). Each of these five infectious diseases had a double-digit case fatality rate, and posed an extremely serious public health threat. No other emerging infectious diseases, in particular other influenza strains, posed such an extreme threat.

The executive director for the WHO emergencies program, Mike Ryan, gave a public warning at the end of 2020 of 'The Big One' (Gander, 2020). He pointed out that the case fatality rate of COVID-19 was reasonably low in comparison to other emerging diseases, such as the five infectious diseases listed above. COVID-19 was a wake-up call for such a more deadly pandemic outcome.

In the case of the coronaviruses SARS and MERS, there might have been a virus variant making the virus more transmissible between people. In the case of the flu virus H5N1, a reassortment of human and avian flu viruses might have produced a readily transmissible pandemic flu virus. In the fourth case, apart from the reassortment risk, gain-of-function research on the novel influenza virus H7N9 might have led to a potential accidental laboratory release. In the fifth case, the prolonged exponential spread of Ebola in Liberia might have triggered civil disorder resulting in perfect storm conditions for the failure of contact tracing and the loss of regional control of the pandemic.

A counterfactual risk analysis is presented. The analysis of pandemic potential for each of the five near-miss events is described in the sections below. The results of this analysis are summarised in the following table, which lists the estimated range of chance, together with the underlying downward counterfactual, which is a reimagined history with a worse outcome (Woo, 2016).

Table 1: Downward pandemic counterfactuals prior to SARS-CoV-2

| EMERGING CONTAGION | CASE FATALITY RATE | DOWNWARD COUNTERFACTUAL | RANGE OF CHANCE |
|---|---|---|---|
| 2003: SARS | 1 in 10 | More transmissible mutation | 1% to 5% |
| 2004: H5N1 | 6 in10 | More transmissible mutation | 1% to 5% |
| 2012: MERS | 3 in 10 | More transmissible mutation | 1% to 5% |
| 2013: H7N9 | 3 in 10 | Gain-of-function research | 1% to 2% |
| 2014: Ebola | 4 in 10 | Civil disorder triggered by epidemic | 1% to 3% |

In the second column of this table, the case fatality rate is also listed for each emerging contagion. COVID-19 has demonstrated that the emergence of any transmissible pandemic virus with a case fatality rate in excess of 1 in 100 would have the potential to cause a lockdown crisis. No pandemic since 1918, (i.e. 1957, 1968 and 2009), has had a case fatality rate as high as 1%.

It has been said of COVID-19 that the world has been lucky that the case fatality rate has not been higher than 5%. The table above shows that the world has indeed been fortunate that there has not been such a 'Big One' pandemic catastrophe in the previous two decades. A stochastic simulation of pandemic risk in this twenty-year period would yield an aggregate chance of a 'Big One' pandemic in the range of 5% and 20%. Normalising to a 20-year time window, this corresponds to a return period of between 100 and 400 years for a 'Big One' pandemic catastrophe. This is sufficiently high as to galvanise government pandemic preparedness and insurance Probable Maximum Loss assessment. The sizeable variability in the return period reflects the fundamental risk ambiguity associated with outcome sensitivity to individual and collective human behaviour, as well as the inherent randomness in virus mutations, as exemplified by the emergent more transmissible variants of COVID-19.

To explain the counterfactual analysis, details of the five near-miss events of the 21st century are provided in the following sections.

### 3.1 SARS: 2003

In 2003, the SARS coronavirus was one of a large number of similar viruses originating from a reservoir found in Chinese horseshoe bats. Some of these SARS-like coronaviruses would have been more severe. After the SARS epidemic ended in July 2003, a second event occurred in late 2003 and early 2004, resulting in the re-emergence of four cases in China. Fortunately, the new virus had a much lower affinity for binding to the human receptor ACE2. Counterfactually, the variant might have had a higher affinity for human transmission, perhaps like B.1.1.7 originating in Kent in the second wave of SARS-CoV-2. The N501Y replacement on the spike protein increased ACE2 binding (Volz et al., 2020).

It is widely accepted that many viruses have existed in their natural reservoirs for a very long time. The spillover to humans and other animals is largely due to human activities (Cui et al., 2019). In the twenty years of major Chinese agriculture reform and wildlife farming prior to the emergence of SARS in 2003, a transmissible SARS-like coronavirus might well have emerged. The fact that this did not happen, despite coronavirus infection amongst inhabitants near bat caves, indicates that the chance of such a spillover is quite small. Accordingly, the likelihood of the downward counterfactual of the 2003-2004 variant having a higher affinity for human transmission is also small, and might be conservatively estimated at 1:20. The lack of any documented evidence of widespread coronavirus infection in the twentieth century experience of modern China suggests a lower bound of 1:100.

### 3.2 H5N1: 2004

In 2004, there was a major H5N1 influenza epidemic in Asian bird populations. Human infections with this virus were identified early in Vietnam in January 2004. A study of ten patients in Vietnam, in which eight died (Tan et al., 2004), provided a grim early warning of the high lethality of H5N1 influenza. In all these cases, infection was acquired from infected poultry. Indeed, most cases of human infection due to avian influenza viruses have resulted from close contact with infected poultry.

In addition to bird-to-human, and environment-to-human transmission of the H5N1 avian virus, some limited amount of human-to-human transmission was observed in some household clusters. However, human-to-human transmission might become much more widespread through reassortment, which is the process by which influenza viruses swap gene segments. This genetic exchange is possible due to the segmented nature of the viral genome, and occurs when two differing influenza viruses co-infect a cell. Reassortment between two very different strains is associated with marked genotypic changes which are described as genetic shift.

Ferguson et al. (2004) warned that the reassortment of avian and human influenza viruses in people who were coinfected could trigger a potentially devastating pandemic. Reassortment has been an important mechanism for influenza viruses to evolve. The influenza pandemics of 1957, 1968 and 2009 were the result of reassortment events. Insight into the chance of reassortment is provided by the following mathematical analysis of Ferguson et al. (2004). A typical influenza season lasts for about twelve weeks. Assuming that about 10% of the population are infected with human influenza, and that there is a short time window in early infection of one day where co-infection is possible, then 0.12% of the population are susceptible to coinfection with an avian strain at any time.

When a person is infected with both avian and human influenza viruses, reassortment is not inevitable, but happens with some small probability q. If there are N cases of avian influenza, the probability of a reassortment not having occurred is $(1- 0.0012*q)^N$. The number of H5N1 cases of

infection escalated from 4 in 2003 to 46 in 2004 and 98 in 2005, most of which were in Vietnam. With an aggregate of about three hundred cases of avian H5N1 influenza by spring 2007, the reassortment probability would have been about 3.5%, if q is taken to be 0.1. This is consistent with the occurrence of five influenza pandemics in the 140 years from 1880 to 2020. Allowing for reassortment of avian and influenza viruses to occur through other animals, e.g. pigs which can be infected by both, the probability of reassortment might be as high as 5%.

Apart from reassortment, influenza viruses can evolve through the introduction of random errors into the genome. Influenza viruses replicate with extremely low fidelity, which is the ability to avoid or correct errors. This limits pandemic predictability. High mutation rates increase the rate at which an influenza virus will adapt to a new host, acquire a new route of transmission, or escape from host immune surveillance (Visher et al., 2016). Accounting for the rapid evolution of the influenza virus, the minimum chance of a more transmissible mutation of H5N1 is estimated to be 1%.

### 3.3 MERS: 2012

Middle East Respiratory Syndrome coronavirus (MERS-CoV) causes an acute and severe respiratory illness with a high mortality rate of about 35%. It was first identified in Saudi Arabia in 2012, and dromedary camels have been identified as the primary source of infection. But bats have been proposed to harbour the progenitor viruses of MERS-CoV. The majority of reported cases have been associated with outbreaks in the Middle East. Since the 1960s, the urban population in Saudi Arabia has risen from about 20% to 85%, and the camel population has increased an order of magnitude from 80,000 to 800,000. Serological evidence suggests that dromedary camels have harboured MERS for more than 35 years (El-Kafrawy et al., 2019).

Outside the Middle East, from May to July 2015, there were 186 confirmed cases with 38 deaths in South Korea. These were mainly associated with health care institutions. The index case was a 68-year-old man who had returned from Bahrain, UAE, and Qatar. The outbreak in South Korea was marked by the rapid emergence and spread of a mutant MERS which had a reduced affinity to the human CD26 receptor (Kim et al., 2016). Unlike SARS, MERS does not use ACE2 as its entry receptor. The adaptation of MERS may have been driven by host immunological pressure. Considering that the case fatality rate of 20% is lower than the overall mortality rate of all MERS cases, the spread of the mutation with reduced affinity is potentially associated with milder consequences.

The MERS evolution seems to have driven the virus down a pathway that predominantly results in a significant cost in viral fitness. However, it has been thought that human adaptation of the human coronavirus might be achieved through sequential mutations that enhance receptor affinity. This motivates the downward counterfactual whereby MERS mutated to enhance receptor affinity.

The role of the superspreader was particularly important for the spread of MERS in South Korea. 83.2% of MERS patients were associated with five superspreading events (Park et al., 2018). According to a pessimistic MERS scenario (Breban et al., 2013), if another index patient had eight or more secondary infections, there would be 5% chance that the reproduction number would exceed unity and that MERS would have pandemic potential. A conservative lower bound of 1% is estimated, if there had been only a few secondary infections. The reproduction number would, with 99% likelihood, have remained below the epidemic threshold, with such a small change in secondary infections.

### 3.4 H7N9: 2013

Human infections associated with avian H7N9 influenza were first reported in China in March 2013. Most cases had severe respiratory illness, and many had connections with live bird markets. Some human infections with H7N9 were reported outside of mainland China, Hong Kong or Macao. But all these cases had travelled to China before falling ill. By the end of 2013, there had been 144 cases of which 46 died. Given that migratory birds were implicated in H7N9 transmission, they might be vectors for regional spread. CDC rated H7N9 as having the greatest potential to cause a pandemic, as well as potentially posing the greatest public health threat, if it were to achieve sustained human-to-human transmission.

The majority of human H7N9 cases featured a hemagglutinin mutation previously associated with a switch in receptor specificity from avian-type to human-type, as documented for the 1957 (H2N2) and 1968 (H3N2) pandemic viruses (De Vries et al., 2017). This raised fears that the H7N9 was adapting to humans. But fortunately, the mutation was insufficient to switch the receptor specificity of H7N9. Accordingly, this has not led to sustained human transmission, thus the CDC concerns over H7N9 were not realised.

But soon after the emergence of H7N9, Fouchier, Kawaoka et al. (2013) suggested laboratory experiments that would explore the transmissibility gain-of-function of the H7N9 virus associated with a series of mutations. In July 2013, Kawaoka reported that laboratory studies using ferrets indicated that one of the H7N9 strains could transmit through respiratory droplets. Gain-of-function research was also undertaken by De Vries et al. (2017) to determine if the H7 hemagglutinin was capable of acquiring human-type receptor specificity. They discovered that three amino acid mutations could switch specificity, resembling that of the 2009 pandemic influenza virus. These authors were not allowed to assess if these mutations would lead to efficient transmission in the ferret model. However, the pause in research has been temporary. In 2017, the National Institutes of Health lifted a 3-year moratorium on funding gain-of function research.

Li et al. (2014) reported several cases of co-infection with H7N9 and seasonal H1N1 influenza virus. These cases, along with a co-infection with H7N9 and H3N2, raise concern over reassortment risk. However, unlike H5N1, there are hardly any cases of H7N9 outside China, so a genetic shift associated with a reassortment may not necessarily be significant globally. Allowing for minor reassortment risk, the minimum chance of a significant transmissible mutation of H7N9 is estimated to be 1%.

To complement this base risk, there is a contribution from accidental or malicious laboratory mishaps in gain-of-function research on H7N9 (Klotz, 2019). Breaches of protocol in high-security laboratories have happened. Vials of smallpox have been left lying around in a National Institutes of Health storeroom; CDC unwittingly sent out samples of influenza virus contaminated with H5N1. At the Chinese National Institute of Virology in Beijing, which was investigating SARS, a laboratory researcher travelled by train, and infected her mother, who died (Parry, 2004). Lipsitch (2015) has estimated a small chance of 0.2% per laboratory per year for laboratory-acquired infections during gain-of-function research. This additional modest contribution might be estimated at up to a maximum of 1%. Potential mutations of an accidentally released virus might increase the minimum base risk. Overall then, the annual chance of an infectious disease disaster associated with H7N9 is estimated to be low at between 1% and 2%.

### 3.5 Ebola: 2014

The Ebola filovirus disease, formerly known as Ebola haemorrhagic fever, is a severe illness, with a case fatality rate of 40%. The virus is spread through blood or bodily fluids, and the reproduction number can exceed 1, resulting in an epidemic. In 2014, the worst outbreak struck the West African

neighbouring countries of Sierra Leone, Liberia and Guinea. The index case was a Guinea boy, who lived in a village in a forest, and played in a tree infected with fruit bats.

WHO has described the combination of military conflict and civilian distress as a perfect storm that could lead to a rapid worsening of an infectious disease outbreak. Since January 2015 there has been a prolonged military conflict in Kivu province of D.R. Congo. The Kivu Ebola epidemic started in August 2018. By May 2019, a thousand had died. Numerous deliberate attacks on health facilities and health workers slowed the control of the Ebola epidemic. The WHO director-general declared in September 2019 that the outbreak of Ebola was a symptom, the root cause being political instability.

The perfect storm of civil conflict and Ebola outbreak might also have happened in West Africa in 2014. The region has a tragic history of political instability. The first Liberian Civil War was an internal conflict which lasted from 1989 to 1997. The second Liberian civil war, instigated by a rebel group backed by neighbouring Guinea, began in 1999, and lasted for four years until August 2003. The two Liberian civil wars led to the deaths of hundreds of thousands of Liberians and the displacement of millions. The Sierra Leone Civil War broke out in March 1991, with the involvement of Liberian forces, and lasted until January 2002.

The political situation in 2014 was still unstable. Ten years after the signing of a peace accord, President Ellen Johnson's Liberian government was slow in implementing reforms. There was still no accountability for the war crimes committed during the two Liberian Civil Wars. In September 2014, Liberian minister, Lewis Brown, warned that the slowness of the international aid response might cause Liberia to slip back to civil war, along with neighbouring Sierra Leone, if the Ebola epidemic was allowed to spread (Aljazeera, 2014).

In October 2014, with Ebola spreading exponentially, Liberia requisitioned as many as 80,000 body bags. Had a massive death toll materialised, it might have triggered large scale civil disorder, and resulted in a runaway pandemic. Fortunately, foreign assistance arrived just in time to pay for vital measures such as contact tracing and field hospitals, and so limit the number of deaths in Liberia to 5,000. Counterfactually, there was a tail epidemiological probability that a tipping point in Liberian fatalities might have been reached, resulting in the pandemic spread of Ebola. From historical experience of civil conflict, this tail probability is estimated at about 2%, with a range from 1% to 3%.

## 4. Stabilising pandemic risk in the 21st century

With all natural hazards, risk assessment starts with risk awareness, and risk mitigation starts with risk avoidance. It is now established that the evolutionary lineage giving rise to SARS-CoV-2 has been circulating in bats for decades (Boni et al., 2020). It would clearly be desirable to identify dangerous viruses before they emerge, but the diversity and dynamics of recombination among lineages in the bat reservoir makes this task very challenging. As with any dangerous peril, avoidance is the best strategy. But over the past half century, there has been progressive encroachment into bat cave regions, and deforestation for commercial exploitation. Continued rural economic development driven by the goal of raising GDP will sustain the emerging pathogen threat associated with bats.

Whatever the bat population, at least the wildlife trade can be regulated. After SARS in 2003, there was a temporary ban on Chinese wildlife markets, but this was lifted three months after the outbreak. This ban was reinstated with SARS-CoV-2, and over 100,000 farming operations were shut down by the end of February 2020. However, the pressure of rural poverty will inevitably drive subsistence farmers to continue breeding for Chinese medicine and the fur trade, as well as for local food supply. And even with fewer wildlife markets, the increasing pig and fowl populations in southeast Asia, sometimes mixing with wild birds, exacerbate the risk of the reassortment of pandemic viruses.

With the International Monetary Fund forecasting a loss of tens of trillions of dollars from COVID-19, coordinated international measures must be taken to combat the future pandemic threat, which increases inexorably with ecological change. On 26 September 2020, the UK Prime Minister addressed the United Nations in New York and outlined a five point plan to protect humanity against another pandemic. Notably, this five-point plan does not cover pre-emptive action to tackle the root causes of emerging pathogens, which remains a politically contentious agenda:

- Global research into dangerous pathogens;
- Development of the manufacturing capacity of treatment and vaccines;
- Design of a global pandemic early warning system;
- Establishment of protocols for pandemic emergency response;
- Cancellation of tariffs on critical supplies such as protective equipment.

For ecological change, as with climate change, a framework is needed for capturing the dynamics of threat and counter-measures for risk assessment. Such a framework is provided by the Pressure-State-Response (PSR) model developed by OECD (2013) to structure work on environmental policies. This methodology emphasises causal relationships, and is suitable for application to analysing the public health consequences of the pressures which human activities exert on the environment. Ecological change linked with rising economic development in southeast Asia, exerts increasing pressure on the state of the environment. These changes have impacts on human health protection, to which a societal response is needed to stabilise pandemic risk so that a destructive pandemic catastrophe of the scale of COVID-19 does not have a high chance of occurring again in the 21st century.

Achievement of such a response requires major investment in pandemic preparedness: pathogen surveillance, diagnostic testing, effective contact tracing, and electronic systems for ensuring isolation and quarantine compliance. As shown in Taiwan, South Korea and Southeast Asian countries, such preparedness measures can avoid the need for economically crippling lockdowns. The demonstration that plug-and-play on demand vaccine technology can be both safe and effective provides encouraging evidence that a strong rapid response could be mounted against latter waves of a future pandemic.

### 4.1 Beyond the 1918-1919 influenza and COVID-19 pandemics

In the great 1918-1919 influenza pandemic, there were 230,000 UK deaths, most of which were in the second wave, associated with influenza virus mutation. Scaling this up to the 2020 UK population, this would be equivalent to about 400,000 deaths. Such a large number of UK deaths would only be attained in current times if a large number of people died in hospital without adequate access to ICU treatment. COVID-19 has demonstrated that exhaustion of ICU capacity is a red line for the UK government. When 500,000 deaths were forecast by epidemiologists, a national lockdown was immediately introduced on 23 March 2020. In a situation where ICU capacity is threatened, draconian social distancing measures, including national lockdown, would aim to flatten the epidemic curve, and avoid a critical shortage of ICU capacity. Extreme levels of mortality are mitigated at high national economic cost.

The 1918-1919 influenza pandemic had a similar basic reproduction number of between 2 and 4 to COVID-19 (He et al., 2020), as well as a broadly similar moderate UK case fatality rate of about 2.3%. WHO (2020) has warned that ‘The Big One’ would have a substantially higher case fatality rate than either the 1918-1919 influenza pandemic or COVID-19.

Given that the waves of COVID-19 have stretched NHS capacity to its limits, ‘The Big One’ would hardly be containable through lockdowns and other non-pharmaceutical interventions, and catastrophic levels of pandemic mortality might well result. WHO has called for improvements in

science, logistics, training and communication to meet this daunting future challenge of the 21st century.

Looking back in history before the 20th century, the ultimate 'Big One' was the bubonic plague which brought the Black Death in the 14th century. Prior to COVID-19, the Church of the Holy Sepulchre in Jerusalem was last closed in 1349. But with the global ecological changes of recent decades, the most relevant historical reference frame for 'Big One' risk analysis is not the experience of the past seven centuries, but rather the first two decades of the 21st century, during which there were as many as five near-miss 'Big One' events, each one of which had roots in progressive harmful ecological change.

One of these, the Ebola outbreak in 2014 began in a region subject to extreme deforestation, caused by mining and lumber operations, and had an alarmingly high case fatality rate of 40%. This raised the profile of pandemic risk for life insurers, and international risk mitigation initiatives were investigated. However, because this was just a near-miss event for countries outside West Africa, and not a significant loss, cognitive outcome bias discouraged substantial preparedness measures in most countries.

However, the COVID-19 catastrophe has alerted life insurers to the stark reality of an increasing pandemic threat in the 21st century, associated with ecological change. The counterfactual analysis presented above indicates a return period for 'The Big One' of between 100 and 400 years, which spans the standard return period of several hundred years for insurance Probable Maximum Loss. Crucially for governments and business organisations, in the absence of the important driver of global ecological change, the return period would be much longer.

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**London**

7th Floor · Holborn Gate · 326-330 High Holborn · London · WC1V 7PP
Tel: +44 (0) 20 7632 2100 · Fax: +44 (0) 20 7632 2111

**Edinburgh**

Level 2 ·Exchange Crescent · 7 Conference Square · Edinburgh ·EH3 8RA
Tel: +44 (0) 131 240 1300 · Fax +44 (0) 131 240 1311

**Oxford**

1st Floor · Park Central · 40/41 Park End Street · Oxford · OX1 1JD
Tel: +44 (0) 1865 268 200 · Fax: +44 (0) 1865 268 211

**Beijing**

6/F · Tower 2 · Prosper Centre ·5 Guanghua Road · Chaoyang District · Beijing · China 1000020
Tel: +86 (10) 8573 1000

**Hong Kong**

2202 Tower Two · Lippo Centre · 89 Queensway · Hong Kong
Tel: +11 (0) 852 2147 9418 · Fax: +11 (0) 852 2147 2497

**Singapore**

163 Tras Street · #07-05 Lian Huat Building · Singapore · 079024
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