Plagues that decimated civilisations: pandemics as past, current and future threats to humanity

Fig. 1. Detail of 'The Triumph of Death' by Pieter Bruegel the Elder, c. 1562 (Museo del Prado, Madrid). This painting is thought to have been inspired by outbreaks of plague.

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Plagues that decimated civilisations

1. ***Introduction.*** Since larger animals evolved, infectious diseases have been an integral part of life on planet Earth as microbes adapted to colonize and infect these new hosts. While *Homo sapiens* evolved approximately 300,000 years ago, the transition from a hunter-gather lifestyle to agriculture which started 10,000 years ago caused a major shift in how infectious diseases emerged and spread. By living in permanent settlements and being surrounded by animals, the opportunities of microbes to jump from animal hosts to humans increased significantly.

In books and articles that describe infectious diseases, you will often encounter the terms endemic, epidemic and pandemic infections. Infections are endemic when they are present in a region practically continuously. For example, malaria can be considered to be endemic in practically all of sub-Saharan Africa. When infections spread in a relatively small geographic area, like a single town or region, we consider this an epidemic. Recently, many countries in Europe have seen epidemics of measles as vaccination rates against this potentially lethal childhood disease fall. When infectious diseases spread globally and cause significant number of deaths in a relatively short period of time, we speak of a pandemic. The first pandemic described by historic sources is arguably The Plague of Athens (around 430 BC) and since then dozens of pandemics have caused untold sickness and deaths. Pandemics can be extremely disruptive events that change the course of history. Indeed, while I write this, the world is in the grip of the COVID-19 pandemic, which is significantly impacting the global economy, has changed how we work and interact with friends and family, and will influence political agendas for many years to come.

2. ***Pandemics are caused by bacteria and viruses.*** Pandemics can be caused by both bacteria and viruses. Historically, some of the most important pathogens causing pandemics are the influenza virus (causing flu), the orthopoxvirus *Variola major* (the cause of smallpox) and the bacterium *Yersinia pestis*, which causes the disease plague (Fig. 2). Of these pathogens, the influenza virus is still a major threat to public health. Smallpox, however, has been eradicated due to an extensive vaccination campaign in the second half of the 20th century, while *Y. pestis* has only caused localised epidemics in the last 150 years. However, new pathogens continue to emerge, as illustrated by the Human Immunodeficiency Virus (HIV) in the 20th century, which causes the disease AIDS (Acquired Immune Deficiency Syndrome) and has claimed the lives of 30 million people. Most recently the disease COVID-19, with the coronavirus SARS-CoV-2 as the causative agent, has caused the deaths of more than 2.5 million people at the time of writing (Spring 2021).

3. ***Most pathogens causing pandemics have jumped from animals to humans.*** Almost all pathogens that cause pandemics are *zoonotic*, which means that they originated in an animal and subsequently jumped to humans. An important exception was smallpox which had humans as its only host, and thus could be entirely eradicated through vaccination, as it had no alternative animal host in which it could continue to propagate. This milestone in humanity's fight against infectious diseases was achieved in 1980.

Perhaps the clearest illustration of the role of animal reservoirs in pandemics is provided by *Y. pestis*. This bacterium causes the disease plague (black death), which is fatal to 30% to 100% of infected humans, when untreated. In the environment, *Y. pestis* spreads between rodent populations, like marmots, through fleas that feed on the blood of infected animals; in this case, the fleas act as vectors of transmission, moving the bacterium from one animal to the next.

Remarkably, many of these natural hosts of *Y. pestis* have no or very mild illness upon infection. *Y. pestis* can infect humans when fleas carrying the bacterium move on to animals that are in closer contact with humans, like rats. The transmission of *Y. pestis* from its natural ecosystem in marmots that populate the steppes of Central Asia via rats to humans caused the Black Death (1346 – 1353), the most fatal pandemic in the history of humankind, resulting in the deaths of one-third to half of the population of Europe. While localised outbreaks of plague still occur, primarily in sub-Saharan Africa, central Asia and the South West of the United States of America, the disease is now treatable through the use of antibiotics.

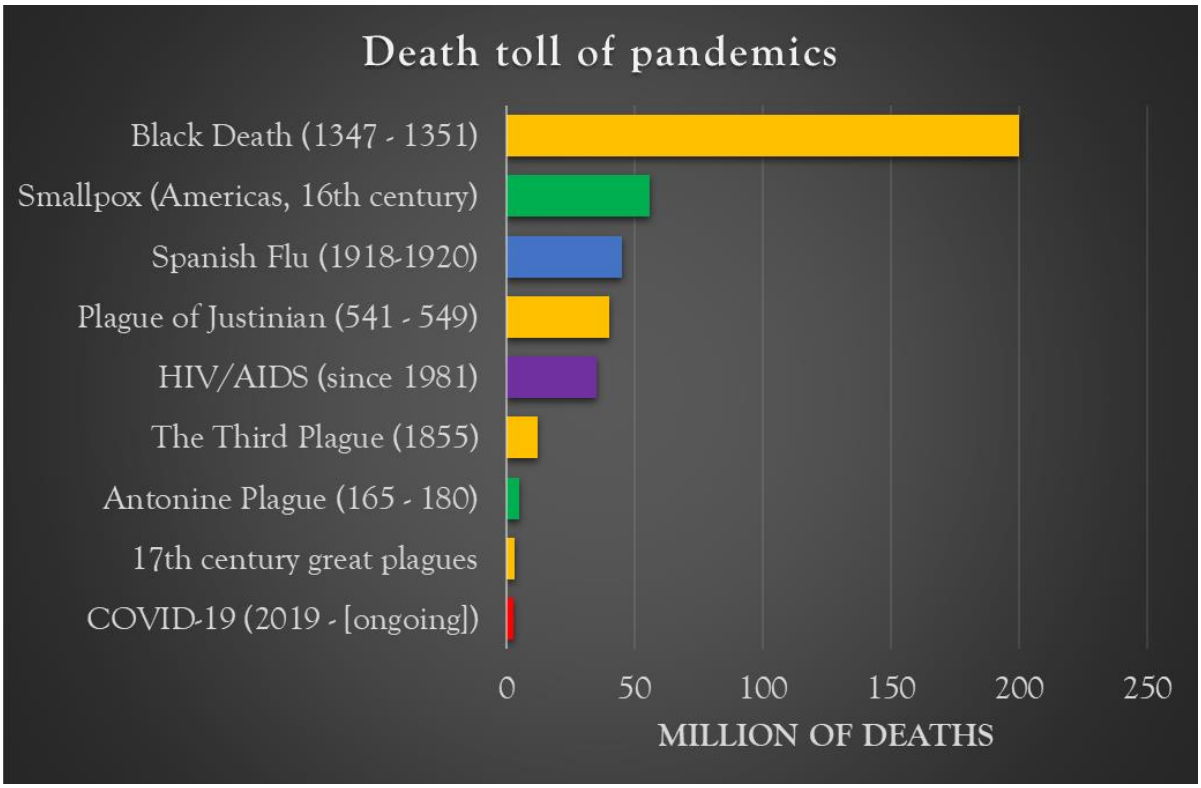

Fig. 2. Death toll of the most lethal pandemics in human history. Bars are colour coded according to the disease (yellow: plague, green: smallpox, blue: influenza, purple: HIV/AIDS, red: COVID-19). Death tolls of pandemics are estimates which a significant degree of uncertainty. There is some controversy on the exact nature of the agents that caused some of the historic pandemics. Note that three of these most lethal pandemics, Spanish Flu, AIDs and COVID-19, have occurred in the last 100 years.

4. ***The impact of the Black Death on medieval European society.*** The Black Death rocked the foundations of European medieval society. Death was everywhere, as evidenced by the writings of Agnolo di Tura del Grasso who describes the Black Death in graphic detail (Box 1).

Box 1

The mortality began in Siena in May (1348). It was a cruel and horrible thing (…) the victims died almost immediately. They would swell beneath their armpits and in their groins, and fall over dead while talking. (…) And none could be found to bury the dead for money or friendship (…) And in many places in Siena great pits were dug and piled deep with the multitude of dead. And they died by the hundreds both day and night, and all were thrown in those ditches and covered over with earth. And as soon as those ditches were filled more were dug.

And I, Agnolo di Tura, buried my five children with my own hands. (…) There was no one who wept for any death, for all awaited death. And so many died that all believed that it was the end of the world.

"The Plague in Siena: An Italian Chronicle" by Agnolo di Tura del Grasso

('quaranta' in Italian) days, which led to the term quarantine, which is still a powerful intervention to stop the spread of infectious diseases.

The impact of the Black Death on European society in the late Middle Ages was profound. For many decades after the Black Death years, art reflected this exceptionally grim experience (Fig. 1). Population levels only reached pre-Black Death levels in the early 15th century and the Black Death completely upended the social fabric of medieval European society. Prior to the Black Death, most of Europe was divided into small city-states and fiefdoms, with its population mostly working under slave-like conditions to yield profits for the governing classes. The Black Death changed this dynamic as surviving labourers were in a much stronger position to request changes to how they were treated. Due to a shortage of skilled labour, craftsmen could amass a significant fortune by travelling across the continent to cities in which their products would be sold at the highest prices. The Black Death thus contributed to the shift from a European society dominated by fiefdoms and city-states, to the emergence of nation states which recognised that basic social services (e.g. the establishment of orphanages and support for education) were essential for the long-term future of the nation.

The Catholic Church was a dominant force in medieval European society but it had no explanation, or solution, to the mass mortality caused by the Black Death. The widespread disillusionment with the Church led to the emergence of new religious groups, including the Flagellants, who walked across towns and cities, while lashing themselves with whips in an act of penance. Perhaps more worryingly for the Church, it was also widely felt that priests and bishops profited financially from the horrors of the pandemic, sowing the seeds for the major changes in Christianity during the Reformation in the 16th century.

5. ***Smallpox decimated indigenous populations in the Americas and Oceania***. Pandemics have also significantly shaped the power balance of our planet. When Europeans started exploring the world, they not only brought their weapons, but also introduced microbial pathogens, including those that cause diseases like smallpox, measles and tuberculosis, to

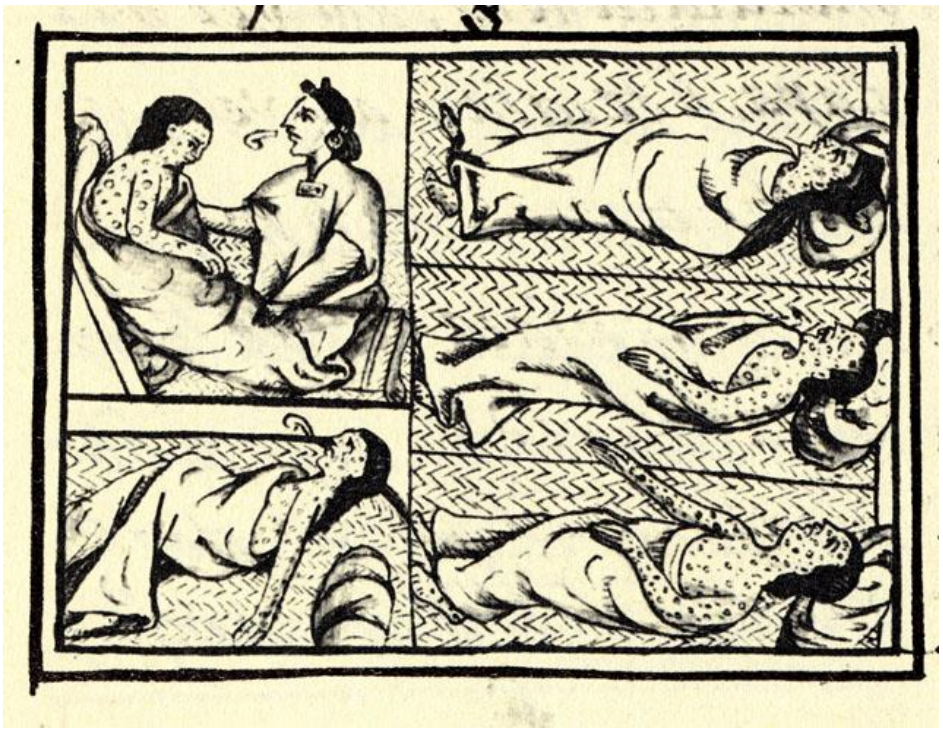

Fig. 3. An illustration from the 16th century Florentine Codex showing smallpox patients in Central America.

indigenous populations that had not encountered these before. European invaders would have almost certainly contracted these diseases, and survived, during their lives and thus had some degree of immunity. The introduction of new pathogens to the Americas and Oceania by Europeans had disastrous consequences and led to very high numbers of deaths due to infectious diseases after Europeans invaded new continents.

The Spanish army started their conquest of the Americas in the early 16th century, and first targeted the Aztec empire which had the city of Tenochtitlan (present day Mexico City) as its capital. Tenochtitlan was one of the largest cities on the planet at that time, having between 200,000 and 400,000 inhabitants. Smallpox is estimated to have killed approximately half of the population of the city, thereby fatally weakening the city, as there were not enough people left to work on the land and defend the city against the invading Spanish. The smallpox virus also nearly wiped out the North American Native American populations, and the Maya and Inca civilizations in South America. More than two centuries later, outbreaks of smallpox similarly decimated Aboriginal Australian populations almost from the moment the British first established a settlement in Australia in 1788.

6. ***The present and future of pandemics.*** While modern science has provided the developed world with a formidable armamentarium against pandemics, they still pose a significant risk to global public health. Since the start of the 21st century, we have witnessed the emergence of new infectious diseases, including SARS (2002, <1000 deaths), the 'swine flu' influenza pandemic (2009; 284,000 deaths) and Zika (2015, 1000 deaths). While these large epidemics should have warned humanity of the potential for new pathogens to emerge, most countries were completely unprepared for the rapid spread of the SARS-CoV-2 coronavirus. After SARS-CoV-2, the virus that causes the disease COVID-19, emerged in China in late 2019, it spread rapidly across the world, claiming more than 2.5 million lives by the time of writing (Spring 2021). While vaccines against COVID-19 have been developed and deployed at an incredible speed, without sacrificing safety or efficacy, the COVID-19 pandemic highlights that humanity cannot afford to be complacent regarding the risk of future pandemics.

We should perhaps also consider the steadily increasing number of infections caused by antibiotic-resistance bacteria to be a slow-moving pandemic, which will increasingly claim lives in the future. Some of the grimmest projections predict that by the year 2050 more than 10 million people may die of antibiotic-resistant infections every year. In addition, new viruses will continue to jump from their animal hosts to humans, leading to the emergence of new infectious diseases. Indeed, due to the increasing size of the human population on the planet, there is an increasing risk that humans will explore and settle in new environments, thereby coming into closer contact with animal reservoirs of pathogens that can potentially cause pandemics. In addition, climate change will lead to upheavals in many ecosystems, again leading to the displacement of humans and animals potentially leading to new host jumps.

Continued awareness of the risk of pandemics, and the risk of them spreading rapidly across the globe, will be essential to ensure global public health in the future. To mitigate the threat of future infections, the deployment of novel techniques to rapidly detect new infections on a global scale will be crucially important. In addition, the development of novel vaccine technologies and antimicrobial drugs will be important to ensure that future infections can

continue to be treated. Pandemics have made their mark on human history and there is no doubt that they will continue to do so in the future.

The Evidence Base, Further Reading and Teaching Aids

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