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Search And Survey

Major Pandemics in the History of Mankind

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Abstract

Pandemics of gigantic proportions have afflicted humanity since antiquity. Various types of viruses, bacteria and other deadly pathogens have decimated populations across the globe over millennia. Bubonic plague is one such scourge that terrified millions of people once-upon-a-time. Many of the pandemics have died away over time, but some still persist. Cholera is one such pandemic that's still smouldering. The current COVID-19 pandemic is still omnipresent and still creating havoc in many parts of the globe. Hence, it's far from over and far from becoming "history", which is why it hasn't been dealt with here. Nevertheless, it has taught us to be ever vigilant and always be on our vanguard in case another catastrophic pandemic strikes. It's not a question of "if", it's a question of "when". It may come tomorrow, it may come next decade, or the next century. Only time will tell.

INTRODUCTION

The term "pandemic" is derived from the Greek words *pan* (all) and *demos* (people). In the context of pathogens, it essentially means the spread of an infectious disease across the globe that affects everyone, everywhere, and sparing none.

Infectious diseases have a greater chance of spreading among populations as a result of the transition from hunter-gatherer to agrarian societies [1]. The spread of infectious zoonotic diseases across the world has increased hand-in-hand with the growth in international trade and commerce, expansion of cities, a steady rise in air travel, burgeoning populations, among others. This has a tremendous impact on the environment, along with disruption of fragile ecosystems, that catalyzes the occurrence of explosive disease outbreaks, large-scale epidemics, and even pandemics, such as the currently ongoing COVID-19 pandemic [2].

Emerging and re-emerging infectious diseases first manifest in a cluster of people and gradually spread to new geographical locations [3]. The mechanism of transmission of novel infectious pathogens have mainly been from animals to humans through an intermediate host. This mode is known as zoonotic transmission and holds true for all pathogens throughout history [4]. More interactions with animals through hunting, animal husbandry, trade of animal-based food, establishment of wet markets, or slaughter of exotic animals for meat, has significantly increased the likelihood of pathogens spreading between species [5].

There are 5 different stages involved in the transmission of pathogens across species [4].

- The pathogen only infects animals naturally
- Evolution of pathogens can make it easier to transmit to humans, albeit not for a long time

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- Secondary transmission of the pathogen between humans occurs only for a few cycles of replication
- Prolonged periods of secondary human-to-human transmission can occur without any animal hosts, despite the fact that the disease persists in animals
- The disease is contracted only by humans

It is hypothesized that changes in land use and climate have a significant impact on the spread of pathogens from wildlife to people [6]. The ever-expanding habitats of several common zoonotic disease vectors, including *Aedes albopictus* mosquitoes and ticks, along with climate change, have a dramatic impact on the transmission of pathogens, such as dengue, chikungunya, zika, Japanese encephalitis, West Nile viruses, and *Borrelia burgdorferi* [7]. Explosive epidemics frequently occur when vector-borne pathogens emerge in areas where they are not endemic. Increased human population has an impact on both land use and the distribution of disease-carrying vectors [8]. Furthermore, cholera outbreaks in areas affected by natural disasters like earthquakes and floods are also being increasingly reported in recent times.

The major pandemics that have afflicted humanity since antiquity are discussed below and summarized in Table 1.

Table 1: Major pandemics in human history

Pandemic	Year	Pathogen	Death Toll
Plaque of Justinian	541-543	*Yersinia pestis*	100 million
Black Death	1347-1351	*Yersinia pestis*	200 million
Third plague	1855-1960	*Yersinia pestis*	15 million
Cholera pandemics	1st: 1817-1824 2nd: 1827-1835 3rd: 1839-1856 4th: 1863-1875 5th: 1881-1886 6th: 1899-1923 7th: 1961-ongoing	*Vibrio cholerae*	1st: 0.7 million 2nd: 0.8 million 3rd: 1.7 million 4th: 1.2 million 5th: 0.5 million 6th: 2.4 million 7th: 5.2 million (till 2023)
Russian flu	1889-1893	Influenza virus (H3N8)	1 million
Spanish flu	1918-1919	Influenza virus (H1N1)	50 million
Asian flu	1957-1959	Influenza virus (H2N2)	1-2 million
Hong Kong flu	1968-1970	Influenza virus (H3N2)	0.5-2 million
Swine flu	2009-2010	Influenza virus (H1N1)	0.1-0.2 million

PLAGUES

There have been three plagues throughout history, namely, the plague of Justinian, Black Death, and the third plaque [9]. Plague is caused by the bacterium, *Yersinia pestis*, which is carried by fleas. This bacterium is named after the Swiss scientist Alexandre Yersin who isolated it in 1894 from plague patients and dead rats in Hong Kong [10].

There are three forms of plague, namely, bubonic, septicemic, and pneumonic, depending on the way the infection spreads [11]. The most typical form, caused by the bite of infected fleas, is bubonic plague. The flu-like symptoms, such as fever, chills, headache, body aches, weakness, vomiting, and nausea are among the clinical manifestations, which are followed by painfully swollen lymph nodes. The bubonic form has a 50-90% chance of being fatal. Septicemic plague consists of a developing bloodstream infection without lymphadenopathy. Patients with septicemic plague have a higher mortality rate

than patients with the bubonic form. When the bacteria infect the lungs, either directly through infectious respiratory droplets or indirectly as a complication of bubonic plague, pneumonic plague develops. When left untreated, this form has a fulminating onset and is quickly fatal.

Plague of Justinian

Egypt was the starting point for the Justinian plague, which spread to the rest of the Eastern Roman dominion and its neighbors. A hundred million people are thought to have perished in the Roman Empire between 541 and 543, with Constantinople (modern-day Instanbul) as the plague's epicenter. The Justinian plague was easier to spread along the Roman Empire's trade and military routes thanks to its highly developed organizational structure. In contrast, barbarian societies outside Rome were unaffected by the plague. The Byzantine Empire may have weakened and eventually fallen due to the high mortality rate brought on by the disease. Following this initial pandemic, plague outbreaks continued sporadically approximately every decade for over 200 years, after which they abruptly stopped for unknown reasons.

Black Death

Black Death (Figure 1) was spread through the medieval Silk Road's land and sea trade routes from East Asia through Central Asia and into Europe [9]. In Europe, the Black Death, which killed 200 million people and affected 30% of the continent's population, persisted until the early 19th century. It was succeeded by subsequent waves, including the plagues of Milan (1630), London (1665-1666), and Marseille (1720-1722). It has been speculated that the bacteria may have survived in mice and rats in Europe and reemerged from time-to-time, afflicting humans [12]. Then, all of a sudden, the plague vanished. It has been suggested that the sudden disappearance of the bacteria from Europe may have been caused by the elimination of regional rodent reservoirs [13].

There was no effective cure for plague at the time. During the Black Death, the idea of public health strategies for disease control emerged. These included quarantining and isolating infected patients [14]. Armed guards established a sanitary cordon along transit routes and at city entrances. In camps and eventually permanent plague hospitals (lazarettos), healthy and infected people were segregated. Ships arriving from areas afflicted by plague were prohibited from entering port cities. Ships suspected of carrying people suffering from plague were placed in quarantine. The crew and passengers were segregated in lazarettos, and the ships were thoroughly fumigated and held for 40 days. Medieval Europe was decimated by the Black Death, which also had a significant impact on its socioeconomic development, literature, culture, art, religion, and politics [15].

Figure 1: Pictorial representation of the Black Death

Third Plague

A significant bubonic plague pandemic that started in Yunnan, China, in 1855 was the third plague pandemic [16]. All inhabited continents were affected by this bubonic plague outbreak, which resulted in the deaths of over 15 million people worldwide [17]. The pandemic was regarded as active by the World Health Organization (WHO) until 1960, when the number of fatalities decreased to 200 per year globally [18]. Every year since, there have been fewer plague deaths. The casualty patterns suggest that the waves of this pandemic in the late 19th and early 20th centuries may have originated from two different sources. The first was primarily bubonic and was spread throughout the world by ocean-going trade,

which also carried rats, infected people, and flea-infested cargo. The second, more dangerous strain was largely confined to Asia. It had a pneumonic character and was transmitted from person to person very fast.

CHOLERA

Cholera is caused *Vibrio cholerae*, a Gram-negative, coma-shaped bacterium (Figure 2). Based on their major lipopolysaccharide O antigens, *V. cholerae* strains are divided into approximately 206 serogroups, of which serogroups O1 (comprising of two biotypes known as classical and El Tor) and O139 are responsible for cholera epidemics [19]. Cholera is an acute and frequently fatal disease of the gastrointestinal tract. The cholera toxin, after colonizing the gut, causes a rapid and massive loss of body fluids that results in hypovolemic shock, dehydration, and death. The cardinal feature of cholera is an explosive diarrhea with "rice-water stool". *V. cholerae* flourishes in water and humans become infected when they use contaminated water for drinking or cooking purposes. The bacterium is usually eliminated with feces in 1-2 weeks, and the symptoms are usually mild or completely absent.

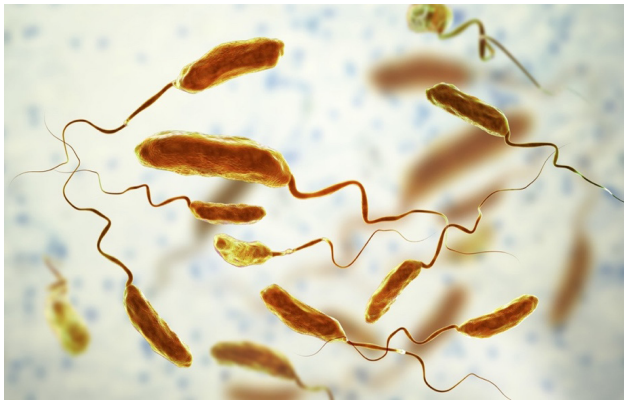

Figure 2: *Vibrio cholerae* - The etiologic agent of cholera

The Seven Cholera Pandemics

Cholera was confined to Asia, up until 1817, when the first pandemic spread from India to several other parts of the globe [20]. This pandemic started during a time when globalization was intensifying due to advancements in transportation technology. In fact, the development of steamers and railroads significantly reduced travel time as well as an increase in trade. At the time, methods for preventing illness were almost same as those used to combat the Black Death [14]. People who were infected were kept apart in lazarettos. Ships that arrived from cholera-endemic areas were prohibited from entering ports. Travelers were placed in quarantine if they had contact with infected people or if they originated from an area where cholera was spreading.

Then, between the 19th and 20th centuries, there were five more significant cholera pandemics that started in India and spread to other continents [20]. The O1 classical biotype of *V. cholerae* is thought to be the culprit behind the second and sixth pandemics, as well as possibly the others [21,22]. The British Isles were affected by the second cholera pandemic. In order to identify the exact location of the cholera outbreak in the West End of London, John Snow (Figure 3) in 1854, used epidemiological techniques for the very first time. He explained the outbreak's timeline and its geographic distribution in the city. He realized the public water pumps in those locations were the source of the contaminated water in which *V. cholerae* thrived. The removal of the pump handles in the urban areas where the outbreak occurred was his next effective prevention strategy [23].

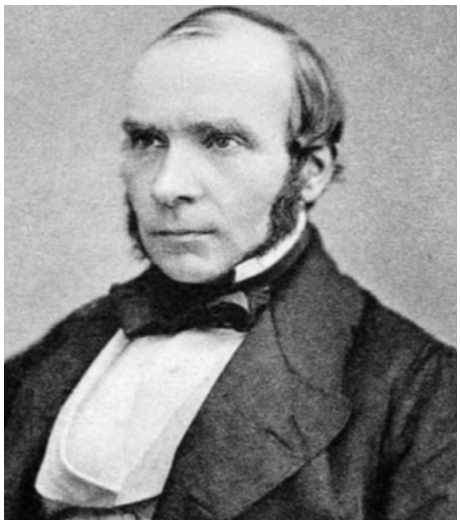

Figure 3: John Snow

Robert Koch (1884) [24], who also recognized the significance of using clean water to halt the transmission of the disease, isolated the bacterium during the fifth pandemic that severely affected Latin America. In 1959, the cholera toxin was identified by Sambhu Nath De in the erstwhile Calcutta [25]. In terms of geographic reach and

duration, the seventh cholera pandemic has been the most severe [26,27]. The El Tor biotype strain of *V. cholerae*, which picked up virulence genes from the environment, caused the seventh cholera pandemic [28]. It started in Indonesia in 1961 and spread throughout the world and became endemic. Major epidemics are occasionally brought on by it, including those that occurred in Zimbabwe (2008), Haiti (2010), Sierra Leone (2012), Mexico (2013), South Sudan and Ghana (2014), and Yemen (2016). Cholera epidemics have by-and-large subsided due to unfavorable environmental conditions that do not allow the vibrios to survive. However, the seventh cholera pandemic is still ongoing, albeit at a lower intensity than originally. It is estimated that approximately 12.5 million people have been killed in all the seven cholera pandemics put together. Since the seventh pandemic is still ongoing, the mortality data till 2023 i.e., at the time of writing has been given (Table 1). The numbers are based on a minimum of 100,000 annual deaths in each of the seven pandemics [29].

INFLUENZA

Influenza viruses are enveloped, negative-sense, single-stranded RNA viruses that belong to the family *Orthomyxoviridae* [30]. The influenza virus genome consists of eight RNA segments, having eight genes that encode 11 proteins. Some of the structural proteins include hemagglutinin (H), neuraminidase (N), two matrix proteins, a nucleoprotein, and the membrane proteins M1 and M2. The H and N proteins are involved in the infection process, as they are involved in viral attachment and detachment from the surface of the host cells [31]. Some of the non-structural (NS) proteins include NS1, NS2/nuclear export protein (NEP), and three RNA polymerases. These polymerases are involved in viral replication, but are prone to errors during replication and also lack proofreading ability. This results in variations that may progress slowly (antigenic drift) or abruptly (antigenic shift). This is the basis of viral evolution that leads to new strains of the virus, having different behavioral characteristics, such as transmissibility, incubation period, severity of disease, survival potential, among others.

Influenza viruses are of four types, namely, A, B, C, and D. While influenza A viruses are the only ones having a pandemic potential, influenza A and B viruses cause outbreaks in tropical areas and seasonal epidemics in temperate areas [32]. In fact, the influenza A virus is endemic to many species, including pigs, birds, and humans [33]. Thus, gene reassortments between human and animal influenza A viruses can happen, leading to the appearance of new virus subtypes that can be potentially harmful to humans [34].

In a typical influenza season, usually 3 to 5 million serious cases occur, with roughly 500,000 deaths globally [35]. Most common seasonal influenza cases are asymptomatic and symptomatic cases are usually mild with classical influenza symptoms that last for four to five days. These symptoms include fever, cough, chills, headache, muscle pain, weakness, sometimes affecting the upper respiratory tract also [36]. However, severe complications may occur in vulnerable individuals, including the elderly, infants, those with comorbidities, such as diabetes, hypertension, heart disease, and diseases of the lungs. Notably, pneumonia is one of the most serious complications.

Russian Flu

The Russian flu pandemic occurred between 1889-1893 and was the first documented influenza pandemic [37]. On the basis of serologic and epidemiologic data, it has been suggested that the etiologic agent was the H3N8 strain of influenza virus. The virus transmitted very quickly and spread throughout the globe within 4 months [38]. The pandemic went on for three years and killed approximately 1 million people worldwide. The median reproduction number (Ro), which is an indicator of how fast the virus is transmitting, was estimated to be 2.1. The case fatality rate ranged between 0.1 to 0.28% and the median clinical attack rate was 60% [38].

Spanish Flu

The Spanish flu pandemic began soon after the end of World War 1 in 1918 and continued till 1919 and was caused by the H1N1 strain of the influenza virus, which was established based on laboratory studies [39]. The attack rate was 25-33% and the median Ro was estimated to be 2-3 [40]. This pandemic exhibited three waves, each nine months apart. The first wave occurred

between spring-summer of 1918 and exhibited high morbidity and mortality. The second wave occurred in summer-autumn of 1918, while the third occurred in the winter of 1918-1919. Both of these were killer waves that took millions of lives. In total, 500 million people became infected and at least 50 million died, which is absolutely staggering [41]. Most of the deaths, on average, occurred within 7-10 days after the onset of symptoms [42].

Typically, in case of influenza epidemics, the majority of deaths occur in the very young (<5 years) or the very old (>60 years). However, the mortality pattern of the Spanish Flu was peculiar, since it not only killed the young and old, but also healthy young adults in the age group 20-40 years [43]. It has been suggested that this uncommon mortality pattern was not only due to the virulence of the virus, but also due to host immunological factors that didn't allow the body to fight the infection. In this context, it was reported that a H3N8 strain of influenza virus was circulating in 1890-1900 and those born during this time lacked immunity against the antigenically different Spanish flu strain (H1N1). This is the most plausible explanation for the high mortality in the 20-40 years age group [44]. The most common symptoms exhibited by the Spanish Flu include severe bronchopneumonia, epithelial and vascular necrosis, hemorrhage, edema, and extensive lung tissue damage [45], often accompanied by secondary bacterial infection [46]. Acute Respiratory Distress Syndrome (ARDS) was also observed in 10-15% of cases [47].

Asian Flu

The Asian flu pandemic occurred between 1957-1959 and was caused by the H2N2 strain of influenza virus. This strain is derived from the Spanish flu strain with three additional avian influenza virus gene segments (H, N, and PB1 polymerase) incorporated by reassortment [48]. There were several waves over a span of three years [49]. While the morbidity was primarily confined to children, mortality occurred in the very young and very old. The case fatality rate was 0.13% [50]. This pandemic killed approximately 1-2 million people [51]. The Ro was calculated to be 1.65 [52]. The attack rate was highest in school-going children and young adults, while in the elderly it was much lower [53]. The primary cause of death, based on autopsy histopathological studies, was bronchial epithelial necrosis of rapid onset [54].

Hong Kong Flu

The Hong Kong flu pandemic occurred between 1968-1970 and was caused by the H3N2 strain of influenza virus, which evolved through genetic reassortment [48]. This H3N2 reassortant completely replaced the Asian flu strain (H2N2) which was is circulation since 1957. This pandemic killed approximately 0.5-2 million people globally [55]. The mean age of death was 62-65 years and the Ro value was calculated to be 1.8 [52]. This pandemic was relatively mild, as most of the population had pre-existing immunity against the H and N antigens. As a result, public health measures were not deployed during this pandemic.

Swine Flu

One of the most recent pandemics was Swine flu, which occurred between 2009 and 2010 and was caused by the H1N1 strain of influenza virus. H1N1 was a triple reassortant, consisting of genes from pigs (matrix, NS, and nucleoprotein), humans (polymerase basic 1 or PB1), and birds (polymerase acidic and PB2) and was transmitted from pigs to humans [56]. Swine flu was first detected in Mexico, followed by southern parts of the US, and subsequently across the globe [57]. With regard to symptomatology, approximately 10% of infected individuals were asymptomatic, while others exhibited a wide spectrum of symptoms - from mild respiratory problems to severe pneumonia, and sometimes, even ARDS [58]. The Ro value was calculated to be 1.46 [52]. The number of deaths was between 148,000 and 249,000 [59] and the case fatality rate was 0.5% [60]. The mean age of death was 37 years [61]. In contrast to the Hong Kong flu, in this pandemic public health measures, such as handwashing with soap and water, masking, self-isolation, respiratory etiquette, and quarantining were in place [62]. Notably, this was the first pandemic where vaccines and antivirals were deployed. The timeline of the above flu pandemics is presented in Figure 4.

THE WAY FORWARD

The foregoing discussion has clearly shown

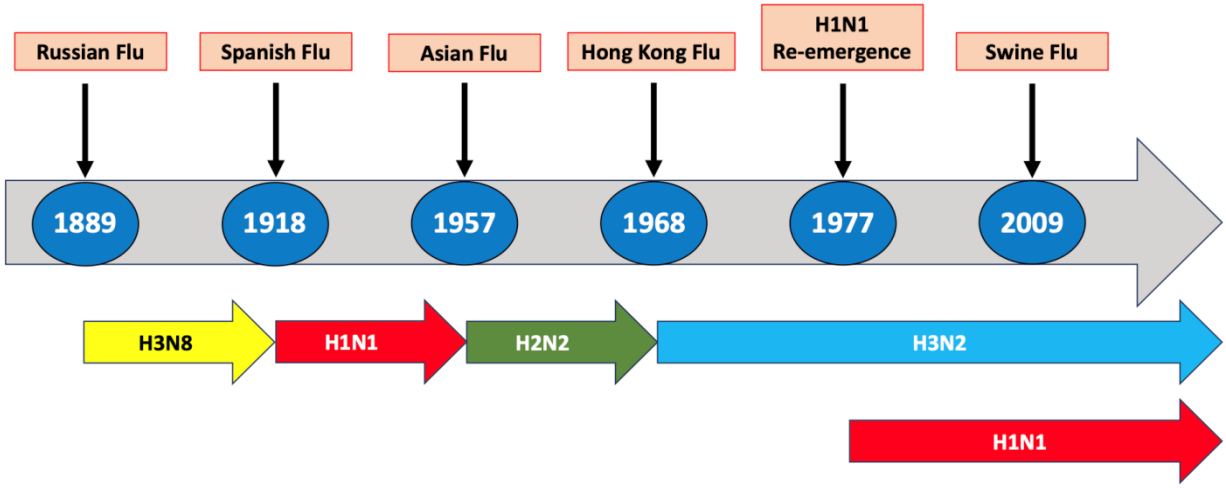

Figure 4: Timeline of the influenza pandemics

that pandemics can be catastrophic for humans worldwide. History has revealed this fact over-and-over again. The current COVID-19 pandemic is still ongoing and hence, not become history yet. That's why it hasn't been discussed in this article. But during the last three years, it has taught us much. It has taught us how a tiny microscopic pathogen can hold the world to ransom and bring about losses amounting to trillions of dollars per month, which had to be replenished just to keep the world economy afloat. Till date, it has killed nearly seven million people across the globe, making it the deadliest viral pandemic in over a century, second only to the Spanish flu of 1918-1919, which claimed over 50 million lives. Therefore, there is an urgent need to put stringent disease surveillance programs in place so that deadly pathogens can be detected early and prevented from wreaking havoc worldwide by transforming into pandemics. Monitoring the environment is also very important, as dangerous microbes can transmit at the animal-human interface, as well as spread from endemic to non-endemic areas. Additionally, vector control measures are required for halting the transmission of pathogens that drive vector-borne zoonotic diseases. It should be noted that WHO's Global Influenza Surveillance and Response System (GISRS) is an excellent example of a surveillance system that specifically focuses on influenza. Therefore, this is a time to end the present pandemic, but at the same time, prepare for the next one, which could be even more devastating!

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