NARRATIVE REVIEW

Pandemics of the past: A narrative review

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Abstract

Infectious diseases resulting in epidemics and pandemics have moulded human history and continue to do so even today. Cholera, plague, human immunodeficiency virus (HIV), and influenza have been some of the most brutal killers. The advancement of medical science has helped us win the war against several of these deadly agents. However, despite all our efforts, new agents continue to emerge. Studying the pandemics of the past helps us respond better to those affecting the globe today. In this narrative review, we present the greatest pandemics of the past, and discuss how the lessons from history may aid us in preparing for the future.

Keywords: Pandemic, Spanish flu, Black death, World Health Organization, CDC.

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Introduction

Over time, infectious diseases have been humanity's constant companion. Plagues and epidemics have ravaged mankind, often changing the course of history. Pandemics have impacted human civilization, with lasting implications on both the sanctity of human life and the need for economic survival. The fact that pandemics still occur despite advancements in medical science is testimony to the fact that the war with constantly mutating microorganisms is far from over.

In the course of this article, the authors give an overview of pandemics from a historical perspective and discuss the challenges that need to be overcome. Table-1 summarises the greatest pandemics impacting the human race.

Definition of a pandemic

The word pandemic comes from the Greek word pandemos ("of all the people"), which itself is derived from pan- ("all, every") and demos ("people"). Epidemic, the precursor of pandemic, is defined as 'an increase, often sudden, in the number of cases of a disease above what is normally expected in that population in that area'.[1] Center for Disease Control and Prevention (CDC) defines a pandemic as 'an epidemic that has spread over several countries or continents, usually affecting a large number of people'.[2]

There is scepticism about the classical definition of a pandemic as it does not include disease severity, virology or population immunity.[3] Seasonal epidemics occur annually in the temperate southern and northern hemispheres and cross international boundaries and affect a large number of people; however, these seasonal outbreaks cannot be considered as pandemics.[3] Definition of pandemics when based solely on disease transmission across several countries can indicate two very different scenarios: emergency and non-emergency disease outbreaks.[4] It has therefore been suggested that redefining pandemics as 'severe and rapidly spreading infectious disease outbreaks' would probably result in more timely and effective emergency responses and pandemic preparedness.[5]

The Influenza Pandemics

The influenza A virus has two critical antigens on the glycoprotein envelope: the hemagglutinin and the neuraminidase designated as H and N respectively. Genetic mutation results in a change in the structure of H and N; this occurs frequently with the influenza A virus. Minor changes are known as antigenic drifts and major changes are known as antigenic shifts.[6]

As many as 9 pandemics of influenza A have affected the human race starting from the late 19th century. However, of these, three have been particularly severe — the Russian flu or Asiatic flu of 1889, the Spanish flu of 1918 and the Asian flu of 1957.[7]

The Spanish flu of 1918 is perhaps the worst pandemic known to mankind. It is said to have affected 500 million people (close to one-fourth of the population at that time) and led to the death of an estimated 17-50 million people. The case fatality rate (CFR) was more than 2.5% which is ten times that of other influenza pandemics. The pandemic followed the First World War. However, it killed more people than the Great War and lasted until

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Table-1: A summary of notable pandemics in the human history.

Name	Infection causing agent and subtype	Dates	Possible region of origin	Reported deaths	Case fatality rate
Plague of Justinian	Yersinia Pestis	541-42	Unclear	25-100 million	Unknown
The Black Death	Yersinia Pestis	1347-50	Asia	75-200 million	Unknown
The First Cholera Pandemic	Vibrio cholerae	1817-24	India	1-2 million	Unknown
The Second Cholera Pandemic	Vibrio cholerae	1826-37	India	Unknown	Unknown
The Third Cholera Pandemic	Vibrio cholerae	1846-60	India	1-2 million	Unknown
Russian Flu or Asiatic Flu	Influenza A (Subtype unclear)	1889-90	Russia	1 million	0.1-0.28%
The Third Plague Pandemic	Yersinia Pestis	1894-1959	China	15 million	Unknown
Spanish Flu	Influenza A (subtype H1N1)	1918-20	Unclear	17-50 million	>2.5%
Asian Flu	Influenza A (subtype H2N2)	1957-58	China	1-4 million	<0.2%
HIV/AIDS Pandemic	HIV	1960-Present	Africa	32 million	100%
The Seventh Cholera Pandemic	Vibrio cholerae	1961-Present	Indonesia	155 thousand	Unknown
Hong-Kong Flu	Influenza A (H3N2)	1968-69	Hong-Kong/China	1-4 million	<0.2%

December 1920. The pandemic was caused by the H1N1 strain of influenza A. A large number of deaths in this pandemic were caused by secondary bacterial infections.[8]

The 'Russian flu' or the 'Asiatic flu' started in 1889 and killed close to a million people worldwide. This was the earliest flu pandemic recorded in human history. The CFR were estimated to range from 0.1-0.28%.[9] The antigenic characteristics of the influenza strain have been a subject of debate.[7]

One of the most recent influenza pandemics to affect mankind was the Swine flu pandemic of 2009. It was caused by the H1N1 strain of influenza A. The index case was reported from Vercruz, Mexico.[10] The pandemic affected 1.6 million people worldwide and estimated deaths range from 151,700 - 575,400 worldwide.[11] Though initial reports of high mortality from Mexico led to an overestimation of the CFR,[12] the final CFR was estimated to be close to 0.04% which was much lower than the other great influenza pandemics of the past.[13]

The Cholera Pandemics

Cholera is an acute, diarrhoeal illness caused by intestinal infection with the bacterium Vibrio cholerae commonly spread by ingestion of contaminated food or water. The spectrum ranges from mild to severe, with a classical clinical presentation of profuse watery diarrhoea, sometimes described as "rice-water stools".[14]

Although there is a distinct possibility that cholera was recognised by ancient Greek physicians, Hippocrates (5th-4th century BCE) and Galen (2nd-3rd century CE), Gaspar Correa, a Portuguese historian, gave one of the first detailed accounts of the clinical aspects of an epidemic of "moryxy" in India in 1543.[15]

Seven cholera pandemics have occurred in the past 200 years, with the first pandemic originating in India in 1817. Additionally, there have been several documented outbreaks in recent times, such as the 1991-1994 outbreak in South America and, more recently, the 2016-20 Yemen cholera outbreak.[16]

The first pandemic occurred near Calcutta, starting in 1817 through 1824, and dispersed from India to Southeast Asia, the Middle East, Europe, and Eastern Africa through trade routes. The second pandemic lasted from 1826 to 1837 and particularly affected North America and Europe. The spread was due to the result of advancements in transportation and global trade, and increased human migration.[17]

The third pandemic erupted in 1846, lasting 14 years, and extended to North Africa reaching as far as South America. The fourth pandemic lasted from 1863 to 1875 and spread from India to Naples and Spain. The fifth pandemic was from 1881-1896 and started in India and spread to Europe, Asia, and South America. The sixth pandemic started in India and lasted from 1899-1923.[17]

The seventh pandemic originated in 1961 in Indonesia and is marked by the emergence of a new strain, nicknamed El Tor, which perhaps still persists in developing countries.[18]

The Plague

Plague is a deadly disease that continues to be relevant today, with re-emergence (about 2000 cases a year) reported in parts of Africa, Asia and the Americas.[19] The causal agent is Yersinia pestis, an enzootic gram-negative bacterium, famously harboured by the black rat.[20] The infection is acquired through the bite of infected vector fleas, but can also be transmitted via bodily fluids or respiratory droplets. The incubation period is 1-7 days, after which a flu-like illness develops.[21,22] There are three major forms of plague; bubonic (the most common,

characterised by lymph node swellings known as "bubos"), primary or secondary pneumonic (rarest form, but most virulent), and septicaemic. If untreated, the CFR is 50-60%. The mainstay of treatment is supportive care and antibiotics, although multidrug resistant strains are evolving.[23] A vaccine for long-term prevention is under development for individuals with high risk of exposure and as a deterrent for bioterrorism.[24,25]

Three major plague pandemics have occurred, each irretrievably reshaping civilization.[26] The first, the Justinian plague occurred in 542-546 AD, spreading from Africa to Egypt, the Mediterranean and up to Constantinople, causing nearly 100 million deaths. The social and commercial disruption marked the end of the Roman Empire. The second pandemic, the notorious "Black Death", occurred in 1347-1350, with outbreaks continuing for almost 500 years. It originated in Asia and spread to Europe and Russia, resulting in the loss of a quarter of the European population.[27] The concept of "quarantine" was implemented with travellers arriving in the port of Venice being isolated for 40 days.[28] In addition, doctors started using a special leather uniform in order to avoid direct contact with patients. The final pandemic began in China in 1894 and spread rapidly throughout the world carried by rats aboard steamships; related outbreaks continued until 1959, resulting in a final death toll of about 15 million, the majority in India.[29]

The HIV Pandemic

Among the infectious agents plaguing humans, human immunodeficiency virus (HIV) emerged as a global threat relatively recently in the late twentieth century. Acquired immunodeficiency syndrome (AIDS) was first recognised as a disease in the early 1980s when young homosexual men succumbed to atypical opportunistic infections and rare malignancies.[30,31] Fear spread rapidly across nations of what was termed the "gay plague". HIV-1, a retrovirus, was subsequently identified as the causative agent that preferentially infected CD4+ T lymphocytes.[31]

It is believed that HIV-1 started as a zoonosis from primates, but evolved to spread in humans through sexual activity and intravenous drug use, as well as vertical transmission from mother to child. Heterosexual spread of the virus was identified later and haemophiliacs were found to be at greater risk of infection.[31]

Unfortunately, the initial HIV epidemics of the 1980s were not self-limiting and could not be contained. Human behaviour and migration, together with the long, infectious and asymptomatic incubation period of the virus facilitated its spread.[32] AIDS-related illnesses spared no region of the world, and wreaked the most havoc among the world's poorest and underprivileged communities, with the highest prevalence rates recorded in sub-Saharan Africa.[33,34]

Advances in understanding the molecular biology of the HIV virus together with a concerted global effort has led lifesaving international surveillance, screening, preventative measures and antiretroviral treatment. However, this has not been without considerable challenges related to drug toxicities, non-compliance with regards to complex treatment regimens, drug resistance and variable access to treatment.[35,36]

The pandemic form of HIV-1 has infected almost 75 million people and 32 million have died from AIDS-related illnesses over the last four decades. Given its devastating consequences, there remains an unmet need to stop the transmission of this deadly virus, and the most important challenge is therefore to develop a safe and effective HIV vaccine. Constant efforts to change human behaviour and reduce the stigma surrounding AIDS remain crucial.[37]

Lessons to Learn

This review clearly shows the recurring nature and persistence of pandemics. Certain microorganisms are more successful than others in being causal agents. Influenza has the ability to mutate with relative frequency and will continue to be relevant. Cholera and plague rely on manmade situations. These agents can thrive after wars or natural disasters and are more likely in crowded living conditions and poor sanitation. With conflict zones and millions living in poverty, outbreaks will continue to occur, having profound social and economic consequences. The HIV virus shows us how a novel agent can change human behaviour. The discrimination against certain groups was driven by fear and ignorance among the population. It also showed us how, despite a slow government response, pressure from activists and the implementation of public health programmes pushed the testing and treatment forward, helping to control the pandemic and destigmatise the disease.

Returning to where we are today, a world in which the growing global connections and interactions function as a driving force behind pandemics. Passenger air traffic has nearly doubled in the past decade. Urbanisation in the developing world brings more and more rural residents into denser population centres. The population explosion, together with greater longevity is also relevant. These macro trends are having a profound impact on the spread of infectious disease throughout the world. The current coronavirus pandemic has brought new challenges. Social distancing and quarantine measures,

although novel for most of us, have been recorded throughout history to combat such invisible threats, since neither treatment nor vaccines were available. Prevention was the only strategy.

Conclusion

Pandemics reshape society in their wake. The world will be a different place after COVID-19, new lessons will have to be learnt, as otherwise we will continue to be poorly prepared for the outbreaks of the future.

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