The Black Death: A Historical Overview of Zoonotic Plague

35

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ABSTRACT

This comprehensive review explores the socioeconomic effects, types, outbreaks, historical background, and transmission of the Yersinia pestis which caused the zoonotic plague. One of the deadliest pandemics in human history, the Black Death, is reviewed, with special attention to how it affected the Europe in the fourteenth century. The three known forms of plague—pneumonic, septicemic, and bubonic—are described in depth, emphasizing the various ways in which they spread and the symptoms that go along with them. Significant plague outbreaks throughout history are also discussed in the study, including the Justinian Plague to the 19th-century revival, and some recent cases. The study focuses particular emphasis on the spread of Y. pestis over the world today, the role fleas play in its transmission, and prior incidents of the plague being used as a biological weapon. The discussion of socio-economic repercussions serves to shed light on the plague's significant social effects, including labor shortages, economic downturns, and the scapegoating of communities like the Jewish community. Moreover, historical and modern contexts are discussed which includes the response to plague outbreaks and the mechanisms used to manage them, such as isolation and quarantine. The document additionally examines the medical side, discussing further about the signs, symptoms, and medications for each kind of plague, including antibiotics like gentamycin and streptomycin. It also explains the precautions to be taken, highlighting the significance of isolation and quarantine in halting the disease's spread. The review finishes with an emphasis on vaccination initiatives, recognizing the lack of a completely effective vaccine but focusing on previous and ongoing efforts for the development of live-attenuated vaccines. In conclusion, this review offers an in-depth examination of the zoonotic plague, covering its historical causes, dynamics of transmission, socioeconomic effects, and current initiatives for treatment and prevention of this renowned infectious disease.

Key words: Zoonotic plague, Yersinia pestis, Black Death, transmission, bubonic plague, pneumonic plague, septicemic plague, outbreaks, socio-economic consequences, quarantine, antibiotics, vaccination.

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1. INTRODUCTION

The plague, often known as the Black Death, was recorded as one of the worst pandemics (Green 2015). It refers to a contagious sickness caused by the bacteria *Yersinia (Y.) pestisa*, a gram-negative bacterium belonging to the Enterobacteriaceae family (Bhagat et al. 2023). Body fluids of living plague patients, dead bodies of diseased people and animal carcasses, and body fluids of infected dead bodies were discovered to be potential sources of infection. It was found that pneumonic plague can be spread by intense handling of the dead bodies of infected humans and animals, primarily by inhalation of respiratory droplets, and that bubonic plague can be transmitted through being in contact with the blood of a corpse or carcass's body fluids (Jullien 2021). The symptoms of the plague depend upon how the patient got exposed to the plague bacterium (Halabi 2020). Many plague complications occur quickly and are dangerous to life, which include tissue death and limb loss from gangrene, inflammation of the brain lining (meningitis), organ failure, and respiratory distress (Kasper et al. 20l5, Chung et al. 2020, Glatter and Finkelman 2021)

The bacteria *Y. pestis* is the cause of many large-scale economic and social destructions, unrivaled by many other infectious microbial diseases or military wars over the previous 2000 years (Callinicos 2023). It is widely assumed that three global pandemics of plague have occurred, indicating that these have resulted in 200 million deaths (Perry and Fetherston 1997).

Three types of plague reported are bubonic, septicemic, and pneumonic plague, among which only one spread while others do not. Coughing, sneezing, and close touch have been assumed to cause the spread of pneumonic plague (Ansari et al. 2020).

A wide range of negative consequences of the Black Death has been reported (Yimer et al. 2019). Sometimes, the trade was affected, conflicts were delayed, and many workers perished, which caused personal pain and economic issues for families. Additionally, it affected landowners who hired workers as tenant farmers. The landowners who have been able to maintain their tenants due to the scarcity of exertions did so via paying wages or cash rents rather than exertion offerings, which was advantageous for the tenants who have been alive. As Jews have been blamed for the spread of the Black Death and numerous Jews were killed in crowds or massacred with the aid of being put on fire, anti-Semitism remarkably accelerated all through Europe (Gupta et al. 2020; Hanna-Wakim et al. 2023).

Significant plague outbreaks have occurred throughout history, with the most infamous in the 14th century (DeWitte 2015; Gómez 2022). World Health Organization (WHO) has received reports of 100-200 deaths and 1000-5000 human cases of plague annually for the last 20 years. Several features of the Black Death shock are critical to understanding its impact. Jedwab et al. (2019) reported that 40% of Europe's population was killed by plague between 1347 and 1352. It was the greatest solitary demographic catastrophe in European history as 50% to 60% of England, France, Italy, and Spain's population was lost in two years.

The plague has an extended history of being used as a biological weapon (Mussap 2019). Historical reports from ancient China and medieval Europe describe the Xiongnu/Huns, Mongols, Turks, and other groups contaminating enemy water supplies with infectious animal carcasses such as cows or horses and human remains. General Huo Qubing of the Han Dynasty was said to have perished from similar contamination while fighting the Xiongnu. Plague victims were also said to have been catapulted into

besieged cities (Schama 2000). The plague primarily affected people in a few African countries, but cases are documented in Asia and America annually (Barbieri et al. 2020). Madagascar and Congo are most affected. In the United States, plague is more common in rural areas of western states. If you deal with animals where plague is present, you are at a higher risk (Park et al. 2020; Glatter and Finkelman 2021). A sub-unit vaccination effective against bubonic and pneumonic plague has also been developed (Richard et al. 2015).

2. TRANSMISSION

Fleas transmit *Y. pestis,* but the other two species *Y. enterocolitica* and *Y. pseudotuberculosis* are considered dangerous for humans and are transmitted through faeces and cause mild intestinal symptoms (Hordofa 2022). It is thought that *Y. pestis* is a mutant of *Y. pseudotuberculosis,* first seen between 1500 to 2000 years ago (Achtman et al. 1999; Achtman et al. 2004). The fleas are believed to be the primary cause of the Black Death. Infected fleas' esophagus becomes obstructed, and they attack rats and humans, transferring the causative agent into the bite wound. Human-to-human transmission is less observed (Mordechai et al. 2019).

Transmission among rats and flies has been associated with epidemics in urban areas. Sick rats (for example, delivered by ships) enter a new city in this typical urban plague scenario and spread the disease to house rats in the area and their fleas, which served as a source of human plague. At times, individuals develop a pneumonic plague, passed from person to person by sneezing, coughing, and respiratory droplets (Mwengee et al. 2006, Vallès et al. 2020). The majority of the time, rodents carry the plague by consuming infected fleas, but it can also spread through contact with sick people or animals. Plague is also transmitted by inhalation of infectious respiratory droplets. As a zoonosis, it primarily affects rodents and has complicated zoonotic/epizootic cycles, as depicted in Fig. 1. When it infects people, it can lead to sporadic instances, outbreaks, or even sizable epidemics (Vallès 2020).

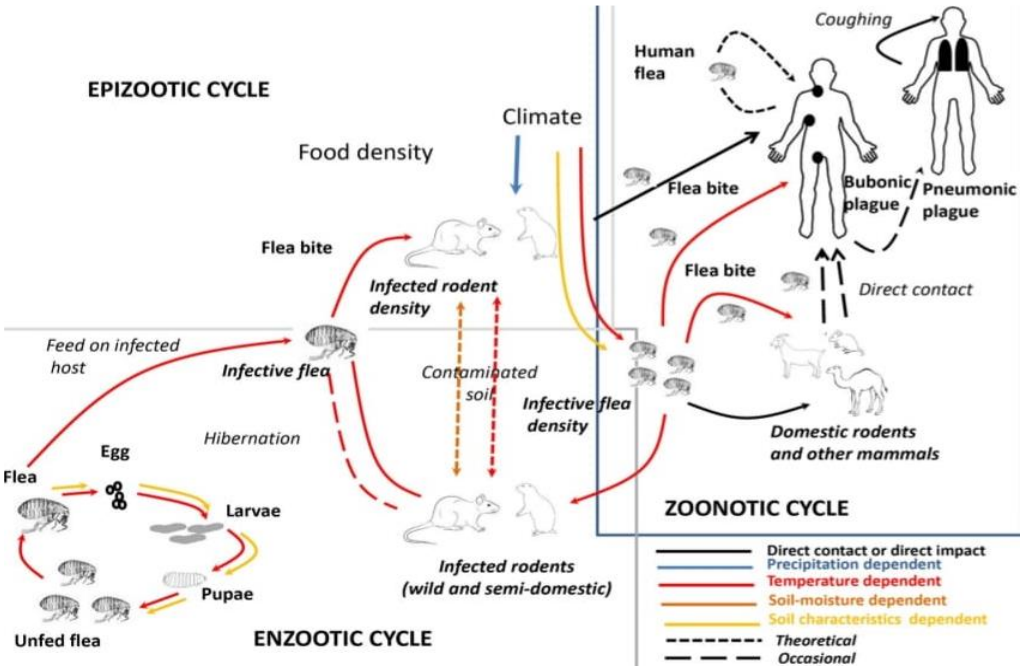

Fig. 1: Epizootic/enzootic cycle of *Y. pestis* (Vallès et al. 2020).

3. TYPES OF PLAGUE

3.1. BUBONIC PLAGUE (BLACK DEATH)

The Black Death, also called the bubonic plague, is one of the deadliest pandemics in recorded human history, which killed almost more than 25 million people or about a third of Europe's population during the fourteenth century, which draws immediate analogies to the recent coronavirus "modern plague" (Zietz and Dunkelberg 2004).

The major carriers of the bubonic plague are infected fleas from small animals. It can also happen if the person comes into contact with the carcass of an animal that had a plague. Animals affected by bubonic plague, such as rabbits, hares, and many cat species, often die (CDC, 2019).

When a flea bite causes bubonic plague, the bacteria enter the skin and move to the lymph node through the lymphatic system, where they cause the enlargement of the lymph node (Sebbane et al. 2006).

The symptoms include fever, headaches, nausea, and enlargement of the lymph nodes in the area closest to the region from where the bacteria gained entry into the skin. Another sign is acral necrosis, which is a darkening of the skin. Sometimes, the enlarged lymph nodes called "buboes" may burst open (Aberth 2016). The bubonic plague can be treated with a variety of antibiotics (Uddin et al. 2021). These include tetracyclines (particularly doxycycline), fluoroquinolone ciprofloxacin, and aminoglycosides like streptomycin and gentamycin (Nelson et al. 2020).

Many rodents died during the plague outbreaks, leaving fleas to seek alternative blood supplies (Anstead 2020). People and animals living where plague-affected rats have recently died are in danger of getting the disease through flea bites. Cats and dogs may introduce the infected fleas into the home (Kugeler et al. 2015).

3.2. PNEUMONIC PLAGUE

The bacterium *Y. pestis* causes pneumonic plague, a severe lung infection. Some major symptoms include fever, headache, difficulty breathing, chest pain, coughing, *etc*. The signs usually appear within seven days following exposure (Dennis et al.1999).

Pneumonic plague can be caused by inhaling infected droplets or by the untreated bubonic or septicemic plague that has progressed to the lungs (Theriot et al. 2023). Pneumonia can result in respiratory failure and shock (Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Vector-Borne Diseases (DVBD). In most cases, the disease begins with the patient having the bubonic form of the disease, which then spreads from the lymphatic system into the respiratory system (Armstrong 2022).

The disease progresses quickly unless discovered and treated quickly enough, often within a few hours. The death can occur in one to six days. In untreated instances, mortality is about 100% (Hoffman 1980; Ryan 2004).

3.3. SEPTICEMIC PLAGUE

Septicemic plague happens when *Y. pestis* enters the bloodstream and multiples (Zhou and Guo 2020). Fever, chills, abdominal pain, weakness, shock, and bleeding beneath the skin or other organs are caused by septicemic plague. Disseminated intravascular coagulation (DIC), necrosis of small blood

vessels, and purpura are also caused by septicemic plague. Sometimes, fingers, toes, and nose can have gangrene, giving rise to the name "black death" (Purba et al. 2019).
Person-to-person transmission of septicemic plague is rare, but it can become so if the disease progresses to the pneumonic stage or is associated with buboes (Sherman, 2009).

4. OUTBREAKS AND IMPACT

4.1. FIRST OUTBREAK

The Justinian plague happened between AD 542 and AD 750. The plague was entitled after Byzantine Emperor Justinian I (r. 527-565), who got the disease and regained health in 542, at the height of the pandemic that killed nearly a fifth of the imperial capital's inhabitants, according to his court historian Procopius (Arrizabalaga and Larraz-Andía 2010; Stathakopoulos 2018).
At the height of the pandemic, some new-age researchers believe that the plague killed more or less 5,000 people every day in Constantinople. According to one theory, the original epidemic killed up to 40% of the city's residents and killed up to a quarter of the Eastern Mediterranean's human population (Mango 1990; Mordechai et al. 2019).

4.2. SECOND OUTBREAK (1347-1351)

The other wave, the Black Death in Europe, happened between 1347 and 1351 and spread from Asia to Europe (Koulesser 2020). It had high mortality rates (estimated 25-50%). It wiped away an estimated one to two-thirds of Europe's population. Venetian authorities kept The ships isolated for 30 days at the seaport in 1347 to guarantee they were not exposed. The quarantine period was extended up to 40 days, and the term quarantine was also derived from 40, which means quarantine in Italian (Perry and Fetherston 1997). This epidemic should have started in Central Africa and expanded over the Mediterranean basin (Perry and Fetherston 1997). In Europe, 25 million deaths were caused by the plague, which lasted hundreds of years, leading to the Great Plague of London in 166 (Dennis 1994).
Because plague is predominantly a zoonotic disease of rodents, it has been widely considered that when the Black Death arrived in Europe from Asia, the bacteria developed in European wildlife and urban rodent reservoirs (Slavin 2021). The sickness would have spread from these reservoirs to humans until the bacterium vanished from Europe in the early nineteenth century (Keeling and Gilligan 2000).

4.3. THIRD OUTBREAK

Between 1899 to 1947, there were 1692 cases of plague reported in Europe, with 457 deaths. In the Beed District of Maharashtra and Surat in Gujarat, other plague outbreaks occurred in India between August and October 1994, one bubonic and the other pneumonic, respectively (Das and Deobhankar 2022). In the five impacted Indian states and the Union Territory of Delhi, 693 suspected cases and 56 deaths were observed. These instances originated in Maharashtra (488), Gujarat (77), Karnataka (46), Uttar Pradesh (10), Madhya Pradesh (4), and New Delhi (68). There have been no reports of cases being transferred to other nations, as per data from the Centers for Disease Control and Prevention (CDC 1994).
Based on available materials, the 1993 earthquake became the main factor, which led to the loss of food grains in many residences. Due to the destabilization of both domestic and wild rat populations, where

the plague was widespread, the disease could travel from wild rats to house rats and eventually to people (Evans et al. 2018).

4.4. CURRENT INCIDENCE OF PLAGUE

According to World Health Organization (WHO) statistics, plague is still a public health threat, particularly in numerous countries like Africa, Asia, and South America. Fig. 2 shows the global distribution of Plague. The plague, cholera, and yellow fever are internationally quarantinable infections (World Health Organization 1994).

These primarily included cases of the bubonic form of plague (84%), septicemic plague (13%), and pneumonic plague (2%) (koirala 2006). There is a risk of human plague wherever there are coexisting human populations and plague natural foci. As a result, plague epidemics frequently occur across Africa, Asia, and North and South America. However, more recently, the most endemic countries were the Democratic Republic of the Congo, Madagascar, and Peru (WHO 2017). The plague-causing *Y. pestis* is endemic in Madagascar, specifically in the central highlands (Pandey et al. 2023). Although there have not been any prior reports of plague in northern Madagascar, a pneumonic plague outbreak happened there in 2011. Within 27 days, 17 suspected, 2 probable, and 3 confirmed human occurrences were found, and all 20 untreated people died. Using molecular typing, it was possible to identify 4 clustered regularly interspaced short palindromic repeat patterns and the 1. ORI3-k unmarried-nucleotide polymorphism genotype that is rare for Madagascar in *Y. pestis* was isolated from 2 survivors and five Rattus samples. The case-fatality rate for this outbreak was 100% for those who went untreated (Richard et al. 2015).

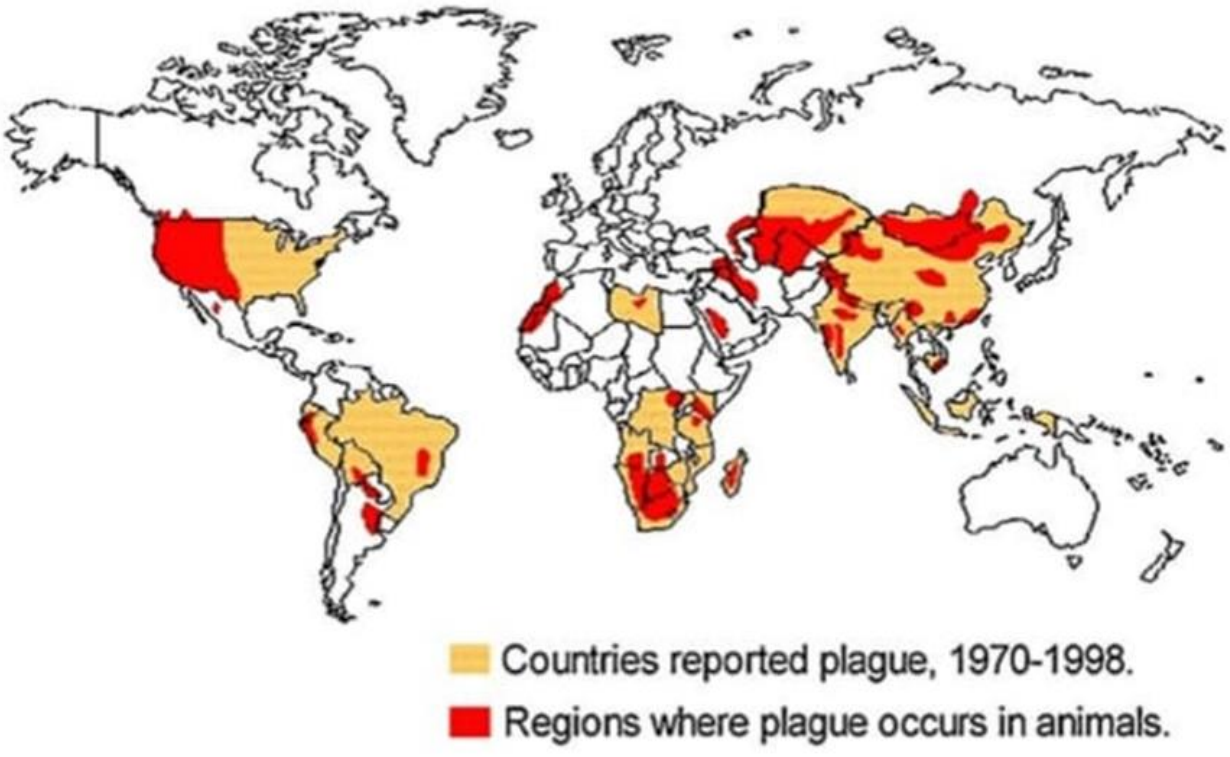

Fig. 2: Global distribution of plague, 1970 to 1998 (Centers for Disease Control and Prevention).

5. SOCIAL AND ECONOMIC CONSEQUENCES

Justinian's Plague of 421-540 AD, which is thought to have killed 25–50 million people in Europe and the Mediterranean, and the Black Death Pandemic of 1347–52 AD, which killed up to 50 million people in those same regions, as well as untold numbers in the Middle East, Central Asia and some areas of China, were two of the three pandemics in human history (Wuk 2020). It killed roughly half of the people in Europe and the Mediterranean (estimates range from 35 to 60%). Black death was a pure population and economic shock to society. As a result, it is not surprising that the Black Death is widely regarded as having had the most significant economic impact (Alfani et al. 2023). The loss of skilled and unskilled laborers was the most visible and immediate result of the first wave of the Black Death. In the arts, productivity usually decreased, artistic traditions were streamlined, and much more attention was devoted to phenomena such as the danse macabre and the memento mori tradition (Armstrong 2022). When the plague struck England in 1348, the immediate result was a 20% reduction in real income over the ensuing years for both professional and unskilled workers (Horrell et al. 2020). The estimated constant per capita GDP decreased by 6% between 1348 to 1349. Similarly, in Spain, where the Black Death occurred in 1348, real income decreased by 9% in 1350 and anticipated per capita GDP fell by 3.3% (Hatcher and Dunn 2011; Jedwab et al. 2019).

A termination of wars and an abrupt decline in exchange instantly started. The deaths of many labourers had a large and disastrous impact on the quantity of land, which became below cultivation, resulting in a large decline in the area under cultivation. Many landlords have been ruined because of this mess. Because of a body of workers scarcity, they have been obliged to substitute pay or cash rents in place of help and employment offerings to maintain their tenants. In general, wages for artisans and peasants were also increased. These revolutions provided a new fluidity to society's formerly strict stratification. The instant effects of the 1349 outbreak seem to have been lived for a quick period in England, and the economic downturn that reached a low within the mid-15th century can also probably be attributed to the pandemic recurrence of the plague (Hanna-Wakim et al. 2023).

The richest 10 percent of the population experienced a 15–20% decline in overall wealth due to the outbreak. Since the richest 10% did not regain control of typical wealth until the second half of the 17th century, this fall in inequality persisted for a very long time (Alfani et al. 2023).

People evacuated to different areas of the arena, abandoned their friends and family, and fled their towns. Work ceased, and funeral rituals either became ceremonial or disappeared altogether. Some humans had the self-belief that God's vengeance was falling on them, so they confronted the disorder with prayer. Some felt they should follow the adage, "Eat, drink, and be merry, for tomorrow you can die." Faith in faith began reducing after the plague, as a result of the deaths of so many clergy, in addition to the failure of prayer to save you from the occurrence of disorder and deaths (Bollet et al. 2004).

It also had religious impacts on society along with social and economic effects. The scapegoating of Jews was a well-studied initial effect of the pandemic. Pogroms, expulsions, and violence against Jews have become more common since the 12th century. The Black Death, on the other hand, resulted in the most heinous persecution in medieval European history. There were at least 363 cities in Europe with Jewish communities on the eve of the Black Death. During the Black Death pandemic, half of these Jewish communities were either slaughtered or evicted. Jews were accused of spreading the illness, and municipalities took advantage of the chaos and shock of the plague to expropriate populations who had long faced antisemitic animosity (Jedwab et al. 2019).

6. RESPONSE AND MEASURES

6.1. ISOLATION AND QUARANTINE

The pillars of preventive and control measures include surveillance, environmental management, and personal protective measures. A mandatory method of separating people, animals, and objects that may have been exposed to a dangerous illness is called quarantine (from the Italian "quaranta," which signifies 40). Since the fourteenth century, quarantine has been the central part of a complete plan of action for controlling the spread of disease. It includes isolation, sanitary cordons, health certificates, fumigation, disinfection, and control of populations considered to be the source of the infection (Matovinovic 1969.

When the plague first arrived in Sicily from the eastern Mediterranean, it was carried by sailors, rats, and goods. It swiftly moved throughout Italy and wiped out the populations of significant city-states like Florence, Venice, and Genoa. The disease then spread from Italian ports to French and Spanish ports. The disease spread over the Alps from northern Italy to Austria and central Europe. The epidemic had subsided but not stopped by the end of the fourteenth century for the next 350 years as many cities saw pneumonic and septicemic plague outbreaks. The presence or establishment of robust healthcare systems, defined by collaboration between governmental, non-governmental, and academic partners as well as long-term commitments, is necessary for plague management. The plague, Ebola, and other possible threats that might (re-)emerge in nations with few resources and deficient healthcare systems are all examples of this (Tognotti 2013).

7. PREVENTION AND MEDICAL TREATMENT OF PLAGUE

The chances of infecting close contacts is very low for a patient with bubonic plague but do not have secondary and septicemic plague. *Y Pestis* transmitted to individuals by mean of coughing and respiratory droplets from the patients with primary and secondary plague. The patient has a high fever and increased heartbeat with the beginning of pneumonic plague, but there is no coughing or expectorating blood in sputum. This time frame is not contagious (Kool 2005). Sputum that a patient has expectorated is extremely infectious. However, Nishiura et al. (2006) stated that the transmissibility of pneumonic plague via this pathway is not strong. Because pneumonic plague is efficiently prevented through covering mouth using a face mask, prevention is relatively simple (Wang et al. 2011). A person suspected of suffering septicemic plague, bubonic plague, or pneumonic plague should be isolated (Wang et al. 2011).

Aside from physical protection, the WHO Expert Committee on Plague (1970) (WHO 1970) suggested antibiotics for treating plague patients using tetracycline, streptomycin, and chloramphenicol. Historically, streptomycin has been the drug of choice for treating plague patients, especially the pneumonic type. Adults are advised to take a daily dose of 2g intramuscularly for up to 10 days. Since streptomycin is bacteriolytic, caution must be used to prevent the induction of endotoxic shock. Gentamycin is also used for treating plague patients, typically considered adequate to streptomycin. Gentamycin is widely accessible than streptomycin, and a study has shown that it may effectively cure human plague infections when given intramuscularly at a dose of 2.5 mg per kg every 12 hours (Mwengee et al. 2006). Three days after their temperature has returned to normal, patients are often switched to another antibiotic, usually tetracycline, due to the toxicity of streptomycin. Tetracycline is bacteriostatic; however, it works well to cure simple plague. Tetracyclines can also be taken orally, but they shouldn't be used by anybody pregnant, breastfeeding, or under the age of seven. The treatment of

choice for plague meningitis is chloramphenicol because of its capacity to enter tissue. For 10 days, 50 mg per kg per day can be given parenterally or orally. Although fluoroquinolones like ciprofloxacin, gatifloxacin, and moxifloxacin have been demonstrated to be effective in treating laboratory animals, sometimes this class of antibiotic has been used to treat human plague (Kuberski 2003). Ciprofloxacin is now included in CDC recommendations with a recommended dose of 400 mg given intravenously or 500 mg orally twice a day (Inglesby et al. 2000). Based on its effectiveness in African Green monkeys, the fluoroquinolone antibiotic levofloxacin was licensed by the US FDA in 2012 for the treatment or prevention of plague infections (Layton et al. 2011). Penicillin, cephalosporin, and macrolides are a few more antibiotics demonstrated ineffective in treating plague. It should be emphasized that late medication decreased antibiotic efficiency, especially with powerful antibiotics such as gentamycin and doxycycline (Mwengee et al. 2006). In rats, mice, and primates other than human models of pneumonic plague (less commonly), the effectiveness of aminoglycosides, tetracyclines, fluoroquinolones, β-lactams, rifamycin, chloramphenicol, sulfonamides, ketolides has been examined (Sebbane and Lemaître 2021) From one animal research to the next, the resulting level of protection against plague frequently differs.

For instance, based on data calculated with the *Y. pestis* strains, which were generally used in models of animals distinguished by the synthesis of a protein capsule (F1), a therapy based on doxycycline, ampicillin, or cefoperazone may be advised. However, mice who get infected with a strain lacking an F1 capsule respond poorly to treatment with either of these three antibiotics (Samokhodkina et al. 1994)

8. VACCINATION

Plague caused by *Y. pestis* is one of the most dangerous infectious diseases (Wang et al. 2013). There is currently no effective vaccination to protect from the plague, but several live-attenuated vaccines have been available. Live bacterial vaccinations offer protection and frequently include almost all natural antigens, lowering the risk of developing resistant diseases. However, live attenuated vaccines are also thought to be more reactogenic than other vaccination approaches, and they may raise safety concerns in some groups of the community (such as older people or immune-compromised). It also elicits only temporary immunity depending on the vaccination strategy (Sun and Singh 2019; Rosario-Acevedo et al. 2021). Recombinant *Y. pestis, Y. pseudotuberculosis,* and Salmonella strains have all been used as potential live vaccines (Branger et al. 2009; Branger et al. 2010).

9. CONCLUSION

Three types of plague have been reported, the bubonic plague (one of worst pandemics of human history), the pneumonic plague caused by the bacterium *Yersinia pestis* results in respiratory failure and shock, and Septicemic plague occurs when *Y. pestis* gains entry in the blood and starts multiplying. Over three types of plague (bubonic, septicemic and pneumonic plague), only pneumonic plague spread by coughing, sneezing, and close touch. In human history, Black Death appeared to be a significant loss by causing the death of about 5 million people and resulted in population and economic shock to society. Quarantine has served as the main part of a complete plan of action for controlling the spread of disease, including isolation, sanitary cordons, health certificates, fumigation, disinfection, and managing the populations of people considered to be the source of the infection. WHO suggests the antibiotics tetracycline, streptomycin and chloramphenicol for treating plague patients. Streptomycin has historically been the drug of choice to treat plague patients, especially pneumonic patients. Gentamycin, which is typically regarded as more effective than streptomycin, has also been used to treat plague

patients. Further, live bacterial vaccinations offer protection and frequently include almost all natural antigens, lowering the risk of developing resistant diseases.

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