

## Plague: Antique and Medieval Emerging Infectious Disease

Massimo Giangaspero DVM\*

Faculty of Veterinary Medicine, University of Teramo, Italy

\*Corresponding author: Giangaspero M, Faculty of Veterinary Medicine, University of Teramo, Strada Provinciale 18, 64020 Piano d'Accio, Teramo, Italy, E-mail: giangasp@gmail.com

Received date: July 4, 2016; Accepted date: July 6, 2016; Published date: July 11, 2016

Copyright: © 2016 Giangaspero M. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Abstract

Plague is a well-known disease caused by *Yersinia pestis*, with the potential to cause significant morbidity and mortality in humans and major public health impacts. Many animal species are sensible to the disease and some play important epidemiological role in sylvatic and domestic cycles. Since ancient pandemics, the disease never disappeared and nowadays continues to represent a threat to humans and animals. Recent reports of antibiotic resistance and potential use in bioterrorism recall adequate awareness by human medicine and veterinary professionals.

**Keywords:** Plague; *Yersinia pestis*

### Plague

Many names such as peste, black death, bubonic plague, or pestilential fever, have been used to indicate plague, sculpted in the collective memory as one of the major threats for the human kind. This is easily due to the detailed historical records of the plague pandemic occurred during 1346~1400. *La Moria Grandissima* (the black death) of the XIVth century killed an estimated of at least 1/4 - 1/3 of the European population [1-3], and it was possibly related to the fall of the feudal system. In just a few years, the entire Europe was devastated by the pandemic.



**Figure 1:** “Come fu una moria in molti luoghi emozionò migliaia di persone” – “As mortality occurred in many places this induced emotion in thousands of people” Text in Italian language (red characters) referring to the medieval plague pandemic.

At least from 50 to 75 million people died, reducing dramatically the European population during the century, initially with about 20 million deaths over the course of a single decade in the 1300s. Unambiguous sentences, transmitted after 700 years to actual days, depicted the tragedy as “Such was the multitude of corpses that huge trenches were excavated in the churchyards in which the new arrivals were place by the hundreds” or “As mortality occurred in many places

this induced emotion in thousands of people” (Figure 1). Outbreaks continued sporadically in Europe for 300 years. In 1665, during the Great Plague of London, about 100,000 died out of the 500,000 inhabitants. It would take four to five hundred years for parts of Europe to regain previous population levels.

Multiple factors contributed to the rapid spread of the Black Death, primarily climatic and social aspects. Around the year 800, Europe entered a period of global warming defined as the “Little Optimum”. Average temperatures increased by over one degree Celsius. Such favorable climate influenced positively the agricultural productivity. Warm weather turned even marginal farmland to productive use. England and Poland became wine-growing countries. As agricultural productivity increased, living standards rose. Subsequently, also populations increased. Between the years 1000 and 1250, the population of Europe tripled. The continent contained at least 75 million people. In this context, trade flourished and late medieval commercial axes have been developed considerably. In the year 1000, trade between Italy and other northern European countries was very limited. By 1280 a merchant could easily travel across European land and maritime routes. From the ports of the sea powers of the time, Venice and Genoa, vessels travelled to East. The Europeans had wider opportunities for buying goods imported via the Silk Road trade route, sailing through the Bosphorus, and reaching the Crimean Peninsula in southern Russia, thus to have access to caravans bringing goods from the Orient. At East, in 1279, the vast Mongol Empire have been consolidated from China, most of Russia, Central Asia, Iran and Iraq, and similarly, like occurring at west, an efficient communications network was ensured, supporting movements of commercial caravans and armies across vast distances. The development of the global trading economy, allowed plague to overcome the vast distances and small populations that had previously provided a firewall to its global spread.

Early in the XIVth century, the weather changed dramatically. Known as the “Little Ice Age”, this change created hardship conditions including scarcity of food resources throughout Europe and Asia. Subsequent to crop failures associated with the dramatic weather changes of the early 1300s, high numbers of deaths have been reported during the Great Famine. A half million people in England, and 10-15% of the population of Flanders and Germany died of starvation.

Likely permanently impaired by the poverty of their nutrition, people become much more susceptible to diseases. In Central Asia, Tartar herdsmen were forced out of their traditional pastureland by the climate change in a desperate search for new grazing land. They found themselves on the northern steppe, exposed to the endemic marmot population with its plague carrying bacteria. From the herdsmen, the plague would have rapidly spread among different populations through major commercial routes. It is supposed that the black death pandemic originated in Kyrgyzstan, in the area of Lake Issyk Kul, which was a trading center along the route to China. Furthermore, among multiple factors, hygiene and war played a relevant role. General poor hygiene was likewise a contributing factor to the spread of plague. Few centuries have been as violent as the XIVth. In the decades before the plague, many conflicts occurred. Larger armies, concentrations of dirty men, attracted larger populations of rats and fleas.

In 1266, the Genoese arrived in southern Russia, and, under a grant from the Mongols, developed a settlement on the Crimean Peninsula: Caffa (the actual Feodosiya), a strategically located commercial port. In 1343, following a dispute between locals and the Italians, the Mongols decided to lay siege to the city. By 1346, the plague first appeared on the western shore of the Caspian Sea. Within a year the disease arrived at the Crimean Peninsula. The Tartar army was severely affected by the rapid spread of the disease. While soldiers were decimating by plague arrived from East, their commander, Gani Bek, elaborated a last plan to resolve the siege. Cadavers of soldiers killed by plague were catapulted over city walls, to spread the infection to the Genoese and reduce their resistance. The effect of the induced epidemic was not sufficiently rapid against sieged peoples. Thus, by the spring of 1347, the exhausted and decimated Tartar army was forced to abandon the military campaign. Genoese were finally free to sail from the harbor of Caffa and to return to Italy, bringing the pestilence with them, and starting the most lethal catastrophe in recorded history. Long term devastating effect were visible shortly after not only in Caffa but also in the rest of Europe. In early summer of 1347, after leaving the Crimea, the plague bearing Genoese ship arrived in the harbour of Byzantium. By the fall of that year there were reports that the city was becoming emptier and emptier as the number of graves increased. Some contemporary estimates suggest that 90 per cent of the city population perished. From Byzantium, twelve Genoese galleys reached the port of Messina, on the coast of Sicily, in October 1347. As accurately described by a local Franciscan Friar, Michele da Piazza, people began to fall ill. The friar described: "a sort of boil...the size of a lentil, erupted on the arm, then the victims violently coughed up blood, and after three days of incessant vomiting for which there was no remedy, they died. And with them died everyone who had talked to them, but also anyone who touched their belongings". Plague entered in the record of the European history, constantly progressing along the trade routes. Once reached Pisa, another sea power of the time, the disease spread to Florence after only two months. In the summer of 1348, the plague crossed the English Channel from Calais. By the following year, half of the English population had perished. From 1348 to 1349, the plague spread eastward across France, Germany and Switzerland. From June to December 1350, the plague reached Sweden and Norway.

But before the black death, the first described plague pandemic, and even more serious than the medieval plague, occurred between the years 540 and 590 AD. The so called "Justinian's pandemic", originated from Egypt or Ethiopia, caused an estimated 100 million deaths (50-60% of the population), with 10,000 deaths per day, and the possible relation with the fall of the Roman Empire [2,3]. Such high

levels of reported mortality were primarily due to the almost complete lack of control or preventive measures. Only after the occurrence of the medieval plague pandemic, Venetians reacted introducing the quarantine (name derived from the Italian word for forty), a process that implied ships stay in a restricted area of nearby islands for forty days as a means of clearing their crew for arrival. Following the major epidemics occurred in ancient and medieval times, a third most recent pandemic, the "modern plague", which began in China in the late 1800s, spread worldwide and caused an estimated 12 million fatalities by 1930 [4,5].

Nowadays, although of great historical importance, plague is still of concern in some parts of the world, as demonstrated by a serious outbreak occurred in India in 1994. The current geographic distribution of plague indicates the disease as enzootic in rodents on every populated continent except Europe or Austral Asia. Averages of 2,000 cases of human plague are reported each year worldwide. From 1,000 to 5,000 human cases and 100 to 200 deaths are reported annually to the World Health Organization (WHO) [6], and many additional cases are probably not diagnosed. Most outbreaks occur in Asia and Africa (76% of the cases and 81% of the deaths were reported from Africa over the past decade). Sporadic cases and outbreaks can be seen in any endemic region. Plague may reoccur after a long period when the disease seems to disappear; recent outbreaks followed quiescent periods of 30 to 80 years. Plague is therefore categorized as a reemerging infectious disease. According to WHO [7], seven countries have been affected by plague virtually every year during the last 45 years: Democratic Republic of the Congo, Madagascar, Myanmar, Viet Nam, Brazil, Peru and USA. During January 2008 to January 2013, the number of human plague cases reported in Madagascar ranged from 312 to 648 per year [8]. In other countries, information on media is not so uncommon. For example, in Kyrgyzstan, on the 27th of August 2013, health officials feared an outbreak of bubonic plague in central Asia after a 15-year-old boy died from the disease and three more were admitted to hospital [9]. The teenage reportedly died from bubonic plague after eating an infected barbecued marmot. In China, on the 23th of July 2014, China Central Television reported the death of a 38-year-old man due to bubonic plague after feeding his dog a marmot [10]. The victim had found a dead marmot. He developed a fever the same day. Authorities have sealed off an entire Chinese city, placing 151 people in quarantine. The 30,000 people living in Yumen in the northwestern province of Gansu were not being allowed to leave, and police placed roadblocks on its perimeter.

Plague is considered closely related to humans, rats and fleas. However, and it is easily conceivable, also nonhuman primates are highly susceptible to plague and exhibit symptoms similar to those seen in humans [3]. In reality, many more animal species are susceptible to the causative agent *Yersinia pseudotuberculosis* subsp. *pestis*, generally named *Yersinia pestis*, clearly indicating the importance of the disease also in veterinary medicine. Among wild animals, about 200 species of rodents are susceptible, and play an important epidemiological role. Difference occurs among rodents as source of plague infection in different geographical regions. In the USA, California ground squirrel (*Spermophilus beecheyi*) and Rock squirrel (*Otospermophilus variegatus*) are very important epizootic hosts and their fleas are commonly associated with transmission to humans [4]. Central Asian marmots (*Marmota* spp), part of the squirrel family, carry plague and transmit the disease to human through the bite of the tarbagan flea (*Ceratophyllus silantievi*), or through consumption of meat. Close contact can expose to pneumonic plague. Giving that the Asian marmot territory is equivalent to 7 times

France, it is evident the potential importance for the actual plague epidemiology. Furthermore, consensus is that the medieval plague originated amongst marmots living along the steppe in Central Asia (Kazakhstan, Gobi Desert and northern Himalaya). Other species of rodents, as the pikas (*Ochotonidae*) are important reservoir in central Asia, whereas gerbils play a role in India and Africa. Hares (*Lepus* spp), some mustelids like the endangered species of the black-footed ferret (*Mustela nigripes*), and wild carnivores like the mountain lion (*Puma concolor*) and bobcat (*Lynx rufus*) are highly susceptible, developing rapidly septicemic lethal forms. The infection is also clinically observable in wild ruminants as the pronghorn (*Antilocapra americana*), the mule deer (*Odocoileus hemionus*) and the black-tailed deer (*Odocoileus hemionus columbianus*). Marsupials like the South American opossums, white eared opossum (*Didelphis paraguayensis paraguayensis*) and grey short tailed opossum (*Monodelphis domestica*), or the kangaroos and wallabies are highly susceptible too. While, at present Australia is free of plague, mortality among Australian marsupials occurred during the third pandemic, in coincidence with outbreaks among the human population, as reported by newspapers of the early years of the XXth century (Figure 2) [11].

Among domestic animals, rabbits are highly susceptible, rapidly succumbing to septicemic forms. Goats with plague develop clinical illness. Camels are also susceptible. There have been human outbreaks of plague attributable to ingestion of *Y. pestis* infected camel meat, insufficiently cooked or uncooked camel liver in several Middle Eastern countries, food safety problems similar to those due to infected guinea pig or marmot flesh consumption. Sheep and pigs are sensible to the infection as demonstrated by sero conversion but do not develop clinical symptoms [12]. Among pet animals, primarily domestic cats are highly susceptible to plague. Cats become often infected by hunting rodents, and subsequently represent a risk of transmission of the infection to humans (Figure 3). Various studies demonstrated cats-human's transmission by various routes related with bites or scratches, inhalation, handle or care of sick animals, accounting up to about the 20 % of elucidated cases [4,13]. Domestic dogs are also susceptible to infection by *Y. pestis*, although they are relatively resistant to clinical disease.

Various international and national norms take into account plague. Plague is a disease that the health authorities are empowered to apprehend, detain, medically examine or conditionally release a suspect having this illness. Plague in humans is a reportable disease; all cases of suspected plague should be reported immediately to local and state health authorities. In many states of USA, plague in animals is also reportable. As required by the international health regulations, all cases should be reported to the WHO. In the European Union, according to the Decision No 2000/96/EC of the European Parliament and of the Council as amended [14], along with cholera, malaria and viral haemorrhagic fevers, plague is a communicable disease, included in the list of serious imported diseases to be covered by epidemiological surveillance in the Community network pursuant to Decision No 2119/98/EC [15]. However, despite the interest to develop combined sanitary-veterinary preventive strategies in accordance to the one health principle, *Y. pestis* is not considered by the World Organisation for Animal Health (Office International des Epizooties: OIE).

The recent identification of naturally occurring multiple-drug-resistant strains of *Y. pestis* in Madagascar represents a serious issue for the prevention and the control of a species that was considered uniformly susceptible to agents that are active against gram-negative

bacteria. In particular, one clinical isolate showed high-level resistance to all of the antimicrobial agents recommended for treatment and prophylaxis of plague and another strain was resistant to a smaller array of drugs [16,17]. Fortunately, both patients, from whom strains have been isolated, recovered after treatment with trimethoprim-sulfamethoxazole. Nevertheless, the demonstration that horizontal high-frequency conjugative transfer of plasmids containing drug resistance from coinhabiting bacteria to *Y. pestis* can occur in the flea midgut, and may be the source of antibiotic-resistant *Y. pestis* strains isolated from plague patients in Madagascar [17,18], underlines the risk of the spread of resistance in *Y. pestis* species.

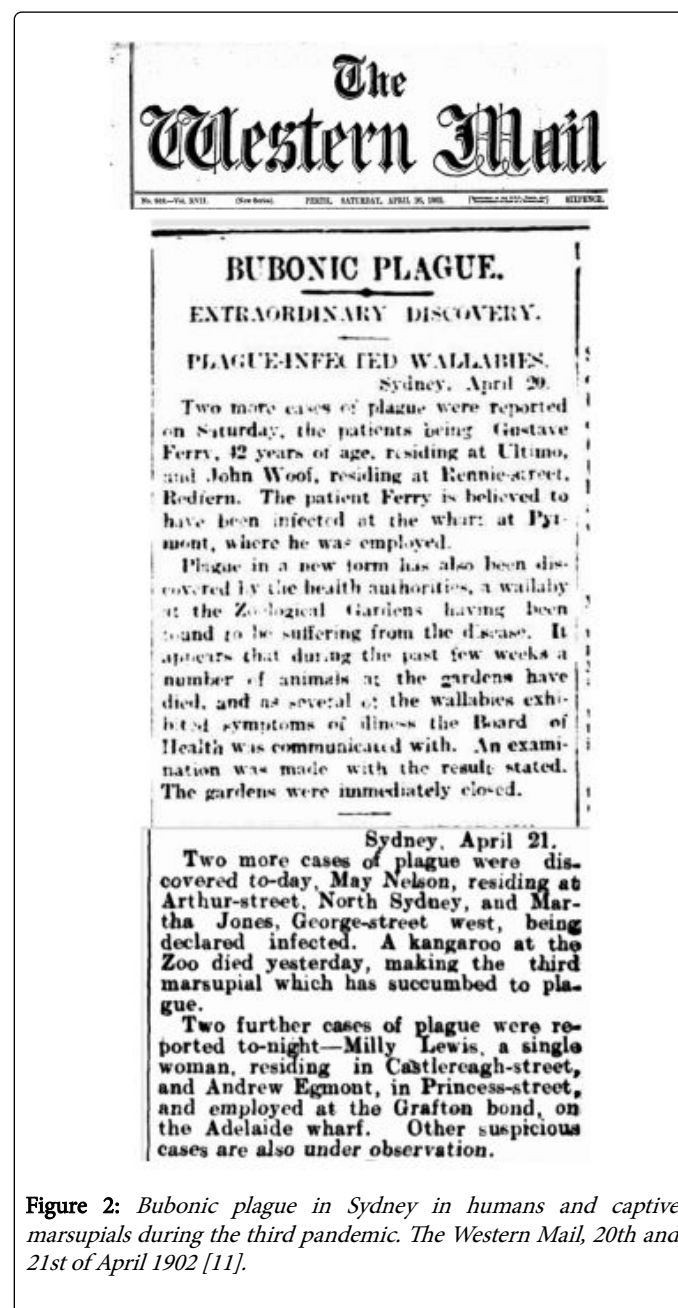


Figure 2: Bubonic plague in Sydney in humans and captive marsupials during the third pandemic. The Western Mail, 20th and 21st of April 1902 [11].

Vaccination was recommended until 1999 only for laboratory and field personnel working with *Y. pestis*. A formaldehyde inactivated human plague vaccine was licensed in USA [19], inducing immune-

response through a primary series of 3 doses of vaccine IM, with a third dose administered 6 months after the first dose. The efficacy of accelerate schedule, with 3 doses administered at least 1 week apart, has not been determined. In addition, about 7% of individuals did not produce antibody [19]. Currently, vaccines based on virulence factors of *Y. pestis*, F1 antigen and V antigen, are under experimental development [20]. Similarly, experimental live attenuated vaccines have been developed using the reference strain CO92 [21]. Promising results have been obtained through the deletion of the *yopH* gene for the attenuation of virulence in both bubonic and pneumonic plague models, providing a high degree of protection from parental and respiratory challenge with unmodified *Y. pestis* CO92.



**Figure 3:** Domestic cat hunting rodents: a risk factor in plague endemic areas.

A further concern of primary importance with plague is the potential use as a biological weapon. With its ability to spread via aerosol transmission and high mortality rates, plague has been classified as a Category A Critical Biological Agent by the Centers for Disease Control and Prevention (CDC) [22]. It has been estimated that the use of 50 kg agent as aerosol on a city of 5 million will rapidly induce 150,000 pneumonic cases, with 80,000 to 100,000 hospitalizations, 36,000 deaths, and subsequent 500,000 secondary cases, with a total mortality up to 100,000 [23]. This estimation was made considering the use of antibiotic sensitive strains, but, according to current knowledge, it cannot be excluded that a biological attack with *Y. pestis* might employ a natural or engineered antimicrobial-resistant strain [24], with obvious more severe impacts.

In conclusion, plague is neither a solely historical disease, since number of human cases and outbreaks are regularly reported from various countries, nor a disease of exclusive human medical domain, giving the amplitude of clinical and epidemiological aspects related to animals. Especially taking into accounts problematics linked to antibiotic resistance and bioterrorism, and that it is virtually impossible to eradicate plague from wildlife populations, knowledge and awareness on the disease (clinical signs, transmission, risk that animals pose for plague, precautions to be taken when visiting plague endemic areas) should be improved and disseminated to health services and veterinarians, and to the general public, as a very important element for plague prevention and control.

## References

1. World Health Organization (2014) Plague. Fact sheet N°267.

- Perry RD, Fetherston JD (1997) *Yersinia pestis*--etiologic agent of plague. Clin Microbiol Rev 10: 35-66.
- Gasper P, Watson R (2001) Plague and yersiniosis. In Williams ES, Barker IK eds., Infectious diseases of wild mammals. Ames, Iowa State University, 313-329.
- Gage KL (1998) Plague. In Collier L, Balows A and Sussman M eds., Topley and Wilson's Microbiology and Microbial Infections, 9th edition, New York, Oxford University Press, Inc., 885-906.
- Achtman M, Zurth K, Morelli G, Torrea G, Guiyoule A, et al. (1999) *Yersinia pestis*, the cause of plague, is a recently emerged clone of *Yersinia pseudotuberculosis*. Proceedings of the National Academy of Sciences, 96: 14043-14048.
- World Health Organization (2010) Human plague: review of regional morbidity and mortality, 2004-2009. Weekly epidemiological record 85: 37-48.
- World Health Organization (2016) Plague around the world, 2010a €"2015. Wkly Epidemiol Rec 91: 89-93.
- Ratovonjato J, Rajerison M, Rahelinirina S, Boyer S (2014) *Yersinia pestis* in *Pulex irritans* fleas during plague outbreak, Madagascar. Emerg Infect Dis 20: 1414-1415.
- The Guardian (2013) Bubonic plague outbreak feared in central Asia.
- China Central Television (CCTV) (2014) Chinese man dies of bubonic plague after feeding his dog a marmot.
- Western Mail (1902) Bubonic plague. National library of Australia (Perth, WA: 1885 - 1954).
- Marshall JD, Harrison DN, Murr JA, Cavanaugh DC (1972) The role of domestic animals in the epidemiology of plague. 3. Experimental infection of swine. J Infect Dis 125: 556-559.
- Gage KL, Dennis DT, Orloski KA, Ettetad P, Brown TL, et al. (2000) Cases of cat-associated human plague in the Western US, 1977-1998. Clin Infect Dis 30: 893-900.
- European Union (2000) Commission Decision 2000/96/EC of 22 December 1999 on the communicable diseases to be progressively covered by the Community network under Decision No 2119/98/EC of the European Parliament and of the Council.
- Guglielmetti P, Coulombier D, Thinus G, Van Look F, Schreck S (2006) The early warning and response system for communicable diseases in the EU: an overview from 1999 to 2005. Euro Surveill 11: 215-220.
- Galimand M, Guiyoule A, Gerbaud G, Rasoamanana B, Chanteau S, et al. (1997) Multidrug resistance in *Yersinia pestis* mediated by a transferable plasmid. N Engl J Med 337: 677-680.
- Guiyoule A, Gerbaud G, Buchrieser C, Galimand M, Rahalison L, et al. (2001) Transferable plasmid-mediated resistance to streptomycin in a clinical isolate of *Yersinia pestis*. Emerg Infect Dis 7: 43-48.
- Hinnebusch BJ, Rosso ML, Schwan TG, Carniel E (2002) High-frequency conjugative transfer of antibiotic resistance genes to *Yersinia pestis* in the flea midgut. Mol Microbiol 46: 349-354.
- Centers for Disease Control (1982) Recommendation of the Immunization Practices Advisory Committee (ACIP). Plague vaccine. MMWR Morb Mortal Wkly, 1982. 31: 301-304.
- Center for Infectious Disease Research and Policy (2005) US, UK, Canada to jointly test plague vaccines 2005.
- Bubeck SS, Dube PH (2007) *Yersinia pestis* CO92 delta *yopH* is a potent live, attenuated plague vaccine. Clin Vaccine Immunol 14: 1235-1238.
- Schmaljohn C (2009) Vaccines for hantaviruses. Vaccine 27 Suppl 4: D61-64.
- World Health Organization (1970) Health aspects of chemical and biological weapons. 98-109.
- Galimand M, Carniel E, Courvalin P (2006) Resistance of *Yersinia pestis* to antimicrobial agents. Antimicrob Agents Chemother 50: 3233-3236.