

## Lessons Learned from Historic Plague Epidemics: The Relevance of an Ancient Disease in Modern Times

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### Abstract

Plague has been without doubt one of the most important and devastating epidemic diseases of mankind. During the past decade, this disease has received much attention because of its potential use as an agent of biowarfare and bioterrorism. However, while it is easy to forget its importance in the 21<sup>st</sup> century and view the disease only as a historic curiosity, relegating it to the sidelines of infectious diseases, plague is clearly an important and re-emerging infectious disease. In today's world, it is easy to focus on its potential use as a bioweapon, however, one must also consider that there is still much to learn about the pathogenicity and enzoonotic transmission cycles connected to the natural occurrence of this disease. Plague is still an important, naturally occurring disease as it was 1,000 years ago. This review highlights some of the important aspects of the disease throughout history with a discussion of the current situation of naturally occurring plague in the 21<sup>st</sup> century.

**Keywords:** Plague; *Yersinia pestis*; Plague control; Public Health; Plague surveillance

### Introduction

Throughout history, few infectious diseases have consistently captured the attention and imagination of mankind; however, three diseases, namely tuberculosis, smallpox, and plague, have occupied human minds for thousands of years. Plague, an ancient disease caused by the bacterium *Yersinia pestis*, has been the cause of several epidemics and three known pandemics, claiming the lives of millions of people [1]. The first pandemic occurred in antiquity at the times of the Roman emperor Justinian (“Justinian plague”) and is believed to have originated in Egypt around AD 532; the second pandemic, also known as the Great Medieval Plague (“Black Death”) likely originated in China around 1334 and quickly spread throughout the then known world to Europe [1-5]. The third pandemic probably originated around 1855 in the Chinese province of Yunnan and spread globally. Some experts believe that this third pandemic is still slowly progressing at the present time [1-5]. We will discuss this issue in greater detail at a later point in this review. Foci of plague have been described on all continents, except Australia and Antarctica [1]. Four categories of plague have been described: enzoonotic, epizoonotic, endemic, and epidemic; yet other authors have classified the disease as human plague, domestic rodent plague, and wild-rodent plague [2-4]. While the terms enzootic and epizootic refer to disease occurrence in non-human, commonly animal populations, the terms endemic and epidemic specifically refer to disease occurrence in human populations. The terms enzootic and endemic refer to diseases that are maintained typically at a low level in a population without causing major increases in prevalence, i.e. causing outbreaks. The terms epizootic and epidemic refer to the appearance of new cases within a population during a specific time period; the number of cases at that point exceed the expected baseline prevalence of the disease. Plague is generally regarded as an enzoonotic, vector-borne disease, primarily infecting rodents, most notoriously the black rat. However, other rodent species, including field mice, marmots, gerbils, and ground squirrels, have also been described a frequent reservoirs. In some literature, wild-rodent plague has also been referred to as sylvatic plague; however, this term is considered less accurate by some experts, since the wild-rodent plague is found in the steppe and plain, but not in the forest [2]. While wild-rodent plague exists in its natural foci and independent of human activities, domestic-rodent plague is intimately associated with rodents living among humans. The latter form

of this infection is known to ultimately have resulted in epidemics and pandemics [4]. In most of the surveyed endemic regions worldwide, incl. the United States, specific rodent species have been identified that acquire the infection via flea bites; however, virtually all mammals are considered susceptible to become infected with *Yersinia pestis*, the causative agent of plague [5]. In most instances, humans become infected via flea bites and the rat flea, *Xenopsylla cheopis*, has been described as the classic vector for disease transmission. Additionally, other fleas such as *Xenopsylla orientalis* and *Oropsylla montanus*, have been shown to be effective vectors for the transmission of plague [5-7]. However, it is worth recognizing that the divide between domestic-rodent and wild-rodent plague has historically been an arbitrary line of division, considering that many rodents are now found living in the wild as well domestic and suburban environments. Humans become accidentally infected when handling infected animals or after being bitten by a flea that has previously fed on infected rodents [3-5]. At the time of writing this review, this infamous disease is internationally recognized as a re-emerging disease [6], its causative organism *Y. pestis* classified as a select agent in the United States, and recognized as a potential agent of biowarfare and bioterrorism [8-10]. Immediately after the attack on the U.S. World Trade Center in New York on September 11, 2001, much attention was given to plague as a disease related to biowarfare and bioterrorism; however, during the past 2 decades plague has silently re-emerged as a natural disease in many parts of the world and unrelated to human activities. Despite major advances in diagnosis, treatment, and prevention, it has not been possible to eradicate this disease. In this review, we will provide a summary of previous, historic plague pandemics, followed by a discussion of lessons that may have been learned from these events, as those could apply

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to today's efforts in diagnosis, treatment, and foremost prevention of this re-emerging disease. In this respect we will also discuss the needs for maintaining diagnostic capabilities as well as active surveillance programs.

## Microbiology and Clinical Disease Spectrum

For the completeness of this review, here we will briefly describe the basic microbiology of *Y. pestis* and general aspects of the clinical disease spectrum, as some of this information is important for the understanding of the various plague epidemics.

*Yersinia pestis*, is a nonmotile, gram-negative, non-spore-forming bacillus that displays a typical bipolar staining pattern when using Wright, Giemsa, or Wayson stains [11]. The organism belongs to the family of *Enterobacteriaceae*. Patient blood, sputum, and aspirates from buboes are considered to be suitable specimens for submission to laboratories for the identification of the organism. *Y. pestis* grows well on blood agar and MacConkey agar, preferably at 25°C to 28°C, and typically requires 48 h of incubation for observable growth to occur. *Y. pestis* is catalase positive, oxidase negative, the organism ferments glucose, but is a lactose non-fermenter, in addition to being urease, citrate, and indole negative [10,12]. Since the organism is nowadays considered a "tier-1 select agent" in the United States [11], routine clinical microbiology laboratories in the U.S. should notify their local public health laboratory upon recognition of a bacterial isolate suspicious of being *Y. pestis*, and then refer the isolate for further confirmatory identification [11]. Based on biochemical profiles, three biovars have been defined for *Y. pestis*: Antigua, Orientalis, and Medievalis [13-15]. The biovar Antigua is present only in regions of Africa and the biovar Medievalis only in Asia; however, biovar Orientalis strains are widespread around the globe and are believed to be the cause of the 3<sup>rd</sup> and present pandemic. Based on DNA-DNA-hybridization studies, 16S ribosomal DNA sequence analysis, and the complete genome sequence analysis of *Y. pestis* biovars Medievalis and Orientalis, as well as *Y. pseudotuberculosis*, it is now widely accepted that *Y. pestis* diverged from the enteric pathogen *Y. pseudotuberculosis* within the last 20,000 years [16-21]. In the course of transition from an enteropathogenic organism to a systemic pathogen transmitted by a flea-vector, various *Y. pestis* genes were acquired, rearranged, or inactivated [22].

Disease in humans presents in one of three distinct clinical primary forms: bubonic plague, pneumonic plague, septicemic plague [8-10,23,24]. In most cases, human infection presents as primary bubonic plague, as a result of being bitten by infected fleas. Direct contamination of skin lesions with infective material is another route by which the organism can be acquired with subsequent spread via the lymphatic system [3]. Bubonic plague is characterized by a prominent regional lymphadenopathy, in addition to severe malaise, fever, and headache. This form of plague can be successfully treated with antibiotics; however, if untreated, the bacteria will disseminate from the lymph nodes into the bloodstream, spleen, and/or bone marrow, ultimately causing secondary septicemic plague. In up to 50% of untreated patients this complication of the disease rapidly progresses to an overwhelming bacteremia, resulting in death due to septic shock within less than 6 days of the onset of symptoms. Primary septicemic plague is less common and occurs in up to 25% of all cases of human plague. This form of plague presents in the absence of the typical primary lymphadenopathy, when the bacteria transmitted by the flea bite bypass the lymphatic system and nodes and directly invade the bloodstream, leading to a rapidly progressive severe sepsis with high mortality rates [10]. Primary pneumonic plague, the third form of the disease, follows the inhalation of aerosolized droplets containing *Y. pestis* [10]. It is the most fulminant

form of the disease, associated with almost 100% mortality, irrespective of antimicrobial therapy provided to the patient. The incubation period is shorter than in the other forms of the disease, usually 1 to 2 days, and is associated with a sudden onset characterized by chills, fever, headache, generalized body pains, weakness, and chest discomfort [9,10,23,24]. For the majority of all human plague cases, human-to-human transmission is very rare; it only occurs in the pneumonic form of the disease, and specifically when there is close-contact inhalation of aerosolized droplets between the infected person with copious sputum production and the unprotected household/family member or healthcare worker [11,25,26]. More detailed descriptions of the various forms of plague presentation in humans are beyond the scope of this review and the authors refer the interested reader to appropriate other medical literature [9-11,23-25].

## A Review of Plague History

Infectious diseases, from local disease outbreaks to pandemics, have been shown to be strongly associated with the course of human evolution from earliest times. Many of these diseases have been a major influence on the development of human societies and cultures [27,28]. Among these diseases are smallpox, tuberculosis, leprosy, and plague; while the cumulative mortality due to smallpox was likely the highest among selected infectious diseases historically, none of these diseases impacted both ancient and modern world societies over the past 1,500 years as plague has done [28]. Despite its high mortality rate (ca. 30%), smallpox is thought to have been more continuously present in human societies, affecting primarily children and adolescents due to their naïve immune status, with those surviving the first infection, however, being immune for the remainder of their life. On the other hand, plague occurred in form of three major epidemics/pandemics, killing large numbers of populations in a short period of time [29]. Here we provide an overview on plague throughout the past two millennia based on some of the most pertinent literature and reviews available at the present time. We recognize, however, that the interpretation of historical texts may be limited by the absence of the historical text itself, the lack of precise medical terminology of the modern world, and problems related simply to translation of ancient texts. Nonetheless, this brief review of history is important to understand societies' response to plague outbreaks in modern times. In the subsequent paragraphs, we will show that despite the advances in scientific knowledge and understanding of this disease together with the advancements in diagnosis and treatment, society's perception and response to re-emerging plague today is not that dissimilar from the response in past and historic times.

Some of the earliest texts describing bubonic plague-like symptoms date back to 1000 BC, although very few physicians of those times might not have stayed around to witness the infection in their surroundings [30,31]. One of the first formal depictions of plague is probably given in the Bible (First Book of Samuel) describing in great detail an epidemic disease among the Philistines [31]. Other outbreaks and epidemics of plague in the ancient world are found in the accounts of various Greek historians and physicians; Thucydides recorded an epidemic of plague to have occurred in 430 BC at the time of the Peloponnesian War [32]. In the First century AD, Rufus of Ephesus, a Greek physician, described plague-like outbreaks in Libya, Syria, and Egypt [33]. Throughout many ancient texts, however, plague has been described using different names, often leading to misinterpretations of either the disease described or the translation of the word itself [30,31]. Therefore, modern historians recently questioned whether these accounts of authors in antiquity were truly descriptions of plague, considering the fact that many other diseases such as smallpox, typhus, and tuberculosis, were widely

prevalent during these times. While these accounts provide some evidence that plague and other, plague-like infectious diseases were the cause of local epidemics throughout antiquity, little is known about the approach to treatment or interventions to prevent further spread of the disease. However, some evidence supports the notion that physicians such as Galen (AD 126-199) may have fled their respective cities once plague began to infect the citizens.

Ultimately, plague gave rise to three well-documented major pandemics. The first pandemic, the “*Plague of Justinian*”, named after the Roman emperor of that time period, spread around the Mediterranean Sea during the 6<sup>th</sup> century AD. It originated most likely in the city of Pelusium, Egypt, around the year 450 AD, after its arrival from Ethiopia [15,32]. The disease eventually spread throughout the “known world” – North Africa, the Middle East and Mediterranean basin, eventually reaching Turkey, Constantinople, and Greece in 541/542 AD [1,34]. Around 543 AD the disease had reached Italy, and shortly thereafter it spread to France and even parts of Germany in 545/546 AD. A detailed account of the plague outbreaks that occurred between 556 AD and 622 AD in Constantinople can be found in the book “*De Bello Persico*” by Procopius of Caesarea [15,33]. The “*Justinian plague*” was actually comprised of approximately 11 consecutive shorter epidemic periods, which occurred in 8 to 12 year cycles [35]. The mortality rates during these epidemics (1<sup>st</sup> plague pandemic) were 15% to 40%, ultimately causing an approximate total loss of 50%-60% of the population in the affected regions of Europe, the Mediterranean basin, North Africa, the Middle East, and Central to Southern Asia [15,35,36]. From today’s viewpoint, however, it seems reasonable that the cumulative depopulation during this first plague pandemic was not solely due to plague (*sensu strictu*), since other epidemics (e.g. smallpox, tuberculosis) occurred during the same time period. Historians attribute various political, economic, and religious consequences in part to this first pandemic; among those consequences are the weakening of the Roman and specifically the Byzantine Empire [35,36].

During the 600 years following the time of the “*Justinian Plague*”, Europe escaped most epidemic diseases, likely due to its significantly diminished population and infrastructure. However, the paucity of historic recordings of that time period may not allow modern historians to ascertain an accurate reflection of epidemic diseases during this period. By the mid-14<sup>th</sup> century, Europe had seen a significant population increase coupled with a significant expansion of its trade routes to and from Southeast Asia and Africa. Between the years 1330 to 1346, originating most likely in the steppes of central Asia, plague outbreaks were recorded; ultimately, the disease was spreading westward along the Silk Road and other major trade routes [15,31,32]. The arrival of plague in the port cities of Venice, Genoa, and Sicily in 1347 is considered by many historians the beginning of the Second Plague Pandemic. Plague spread slowly from village to village by infected rats and humans; faster spread occurred along trade routes between countries via merchant ships [37]. Like the first pandemic, the second pandemic was comprised of various shorter epidemic periods, which continued late into the 17<sup>th</sup> century, and affected again the entire “known world” [15,33]. The first epidemic lasted from AD 1347 to AD 1351 and subsequently became known as the “Black Death”. During these years an estimated 17-28 million Europeans died, representing an approximate 30% to 40% loss of Europe’s population [15]. Subsequent epidemics had mortality rates of 10-15% and occurred in 2 to 5 year cycles. In most instances, the recurrent outbreaks and epidemics likely originated from residual plague foci; however, in other cases a complete reintroduction of plague may have occurred [38]. In continental Europe, trade and travel along three major corridors are believed to

have facilitated the expansion of plague during the 16<sup>th</sup> to 18<sup>th</sup> century: i. 1<sup>st</sup> route connecting Low Countries with the Rhineland; ii. 2<sup>nd</sup> route parallel to the Weser and Elbe rivers linking Bohemia to Northwestern Germany; iii. 3<sup>rd</sup> route along the coastal regions of the North Sea and Baltic Sea [38]. Much like the reactions of society and physicians in antiquity, many physicians of Medieval Europe probably fled their towns once plague had arrived; but others upheld the highest values of their profession and continued to care for the sick [31]. Scholars in the 16<sup>th</sup> and 17<sup>th</sup> centuries published numerous accounts regarding the plague and other related febrile illnesses, however, few contributed to true scientific medical understanding of this disease, and the true cause of the illness remained unknown. One of the first complete theories of plague was published by Girolamo Fracastoro (1478-1553) [39]. In his book called “*De Contagione et Contagiosis Morbis*” he suggested the role of infective agents (“*seminaria contagionis*”) as a cause of plague. From today’s perspective, however, one must understand that Fracastoro did not describe these agents as microorganisms (in today’s scientific understanding), but rather as minute particles with “material and spiritual properties”. Therefore, his theory cannot be regarded as a major improvement in the understanding of infectious diseases, when compared to the other prevailing theories of that time, which followed earlier proposals by Hippocrates and Galen, who believed in the miasmatic corruption of the air as the cause of disease. While there was still a lack of understanding of the microbiology and epidemiology of plague, it is important to recognize the fact that numerous behavioral guidelines and devices were established during the times of the second pandemic, often to aid in the “treatment of plague victims” and protect physicians, rather than establishing a true cure (Figure 1). From



**Figure 1:** The *Plague Doctor* (German woodcut, around 1650). The image appears in: “*Thomas Bartholin; Historiarum anatomicarum...Hafniae, 1654-1661*”. The person depicted in the image is wearing a hat, goggles, and a long gown, in addition to a mask shaped in the form of a bird beak. Historic descriptions indicate that the gown was apparently made from heavy fabric or leather and was usually waxed. The beak may contained piquant substances, which were believed to purify the air and protect from the disease. The rod, worn in the person’s left hand was likely used to keep patients at a distance.

This image is provided by courtesy and of the National Library of Medicine reprinted with the permission.

today's perspective, it appears that the second plague pandemic greatly influenced economic, societal, religious, political, and medical beliefs in various European countries. As described by some authors, the advent of hospital construction, public health regulations, regulatory health boards, and to some extent medical research, are just a few examples of such new developments believed to have their origin in Europe's experience with plague during the centuries of the second pandemic [15,33]. As we will show in subsequent paragraphs, some of the basic concepts of this time, e.g. regulations and thoughts on interventions to limit spread of disease, have prevailed as far forward as far as into policies and regulations during the 20<sup>th</sup> and 21<sup>st</sup> centuries.

Ultimately, the invention of the microscope by Anton van Leeuwenhoek in 1674 provided the basis to develop a better understanding of infectious diseases. It was not until Robert Koch's discovery of *Bacillus anthracis* as the causative agent of anthrax in the year 1876 that put the widespread theory of miasmatic cause of disease finally to rest [38]. However, an additional 20 years had to pass after Koch's discovery, before the mystery of plague was finally resolved. The Third Plague Pandemic began most likely in 1855 in the Chinese province of Yunnan, and because of ongoing local wars in the affected area, plague spread quickly to the southern coast of China and eventually reached Hong Kong and Canton in 1894 [15,31,33]. From there it spread further to colonial British India, reached Bombay in 1898, and by steam ship the disease was ultimately disseminated to all other inhabited continents, except Australia; between 1894-1903, plague had entered 77 ports on 5 continents. At the time, plague reached Hong Kong in 1894, the French Colonial Ministry of Health at the Pasteur Institute in Saigon dispatched Alexandre Yersin to Hong Kong with the task to investigate the outbreak; at the same time; the Japanese government dispatched a commission including the bacteriologist Shibasaburo Kitasato with a similar task. Both scientists arrived in Hong Kong in June 1894 [15,33]. For the first time in history, public health officials chose a scientific approach to achieve a better understanding of disease outbreaks, applying laboratory based methods to investigate the epidemiology, methods of spread, and the disease and its causative agent. Kitasato was first to describe and publish on the causative organism of plague in the *Lancet*, only a few days before Yersin published his findings in the *Annales de l'Institute Pasteur* [40,41]. Although Kitasato was initially credited with the discovery, Yersin's description of the plague bacillus was found to be ultimately more accurate than Kitasato's analyses [15,33,42]. In the decades following the discovery of the plague bacillus, a lengthy dispute arose regarding the question of who should be credited with the discovery. Since its discovery, the microorganism causing plague has undergone numerous nomenclature changes: until 1900 it was named *Bacterium pestis*; until 1923 *Bacillus pestis*; after 1923 it was named *Pasteurella pestis*, named after Yersin's mentor, Louis Pasteur. Finally, in 1970, its name was changed to *Yersinia pestis*, therefore giving Yersin the definitive credit for the discovery of the organism [15,33,42,43].

Although Yersin had early on in his research suggested a connection between rats and plague, it was not until 1897 during the epidemic in India, that Paul-Louis Simond and Masanori Ogata independently of each other discovered the role of fleas in the transmission of plague [15,33,42]. Although a complete account of all historic events of these pandemics and the third pandemic in particular is beyond the scope of this review, a few additional historic highlights of these early years of plague research should not be left unnoticed. In 1895, Alexandre Yersin together with Albert Calmette and Amédée Borrel developed the first form of immunization against plague. These three scientists introduced an inactivated plague vaccine by applying heat treatment to virulent

plague bacilli; they tested their vaccine on rabbits [30]. However, the most widely used plague vaccine at this time was introduced by Waldemar Haffkine in 1896/1897 during a large outbreak of plague in Bombay (today's Mumbai), India [33,44-47]. Based on his successful development of a cholera vaccine, the Indian Government requested that Haffkine be deployed to Bombay to develop a plague vaccine [44]. There he developed a vaccine by culturing plague bacilli in nutrient broth with the addition of an abundant amount of fat (obtained from milk), followed by heat inactivation at a temperature of 70°C [45]. Haffkine demonstrated the effectiveness of his vaccine first on rabbits, followed by inoculation of human "volunteers" during a plague outbreak in a prison facility in Bombay [33,44]. Despite these efforts in achieving a better scientific understanding and deploying effective countermeasures targeting treatment and prevention, plague continued to affect this region of the world; by 1903, in India alone approximately 1 million people died annually of plague. The combined death toll between the years 1898 to 1918 was 12.5 million [15]. By 1899, plague had reached San Francisco, U.S., by steamships carrying infected rats, and by 1900 the infection had established itself among the city's population. During the following years, cases of plague occurred in ports along the Pacific and Gulf coast regions in the U.S. Globally, the disease spread in the form of regional epidemics through all continents, except Australia and Antarctica.

Other noteworthy advances in understanding and combating plague include Ricardo Jorge's 1927 discovery of the role of wild living rodents as reservoirs for the endemic form of plague [48] and Henri Mollaret's work describing the "burrow-rodent-burrow" cycle in the transmission of *Y. pestis* [49]. Concluding this review of plague history, it must be recognized that most scholars support the theory that the third pandemic is still ongoing at the present time. Between the years 1967 to 1993, the World Health Organization (WHO) recorded an average of 1666 cases of human plague worldwide per year. Between 1991 and 1999, there was a nine-year outbreak of plague in Mahajanga, Madagascar [4,8,15,50,51]. Since its first introduction into South America (Paraguay 1899), numerous foci have been recorded over time in all countries in Central and South America [52]. While the prevalence had decreased by the 1960s, 154 cases of plague were reported during the past 10 years, and four countries are now considered as being endemic foci of plague: Bolivia, Brazil, Ecuador, and Peru [52]. More recently, plague has been recognized as a re-emerging infectious disease in 2002 and 2003, as the number of cases grew in Malawi, Mozambique, and India [6,17]. Other reports indicate its re-emergence in various countries, predominantly in sub-Saharan Africa, including Uganda, Zambia, and the Democratic Republic of the Congo [53-58]. In the United States, most human cases are reported in New Mexico, Arizona, Colorado, California, and Texas [48,59]. In 2010, two cases of human plague were reported from Oregon, a state that had been "plague-free" since 1995 [60]. At the time of writing this manuscript, cases of plague in ground squirrels have been reported in Wrightwood, California. As a result of these cases, the Table Mountain Campgrounds in the Angeles National Forest near Wrightwood were closed to the public as of July 24<sup>th</sup> 2013 (Figures 2a and 2b). With the understanding that the 2<sup>nd</sup> plague pandemic comprised of numerous epidemics during the course of 200 years and considering the above referenced cases and outbreaks of plague during the most recent decades, it seems intuitive to accept the fact that the "third pandemic" has not yet ended, but rather consists of a "continuum of smaller epidemics and regional foci of recurrent disease". As we will show in the subsequent section, it might further be intuitive to consider that the complexity of enzootic and epizootic cycles are closely linked to the occurrence of outbreaks. Nowadays, such (recurrent) outbreaks



**Figure 2a:** Table Mountain Campgrounds in the Angeles National Forest near Wrightwood, CA, (closed to the public as of July 24<sup>th</sup> 2013)

Figure 2a depicts a Plague Warning sign at the Table Mountain Campground in the Angeles National Forest Thursday, July 25, 2013. Closure signs were posted at three other campgrounds: Broken Blade, Twisted Arrow and Pima Loops of the Table Mountain Campgrounds in the Angeles National Forest near Wrightwood due to plague found in a ground squirrel. All these sites were officially closed at 1:00 p.m. Wednesday, July 24, 2013 for duration of at least 7 days. (Photo by Walt Mancini/SGVN; reprinted with permission).



**Figure 2b:** Plague countermeasures at Table Mountain Campgrounds in the Angeles National Forest near Wrightwood, CA. Figure 2b depicts crews from the County of Los Angeles Agriculture Weights and Measures were spraying Delta Dust to kill the fleas from squirrels and chipmunks around the entrance of burrows and at the base of trees containing squirrel nests in the same area. (Photo by Walt Mancini/SGVN; reprinted with permission).

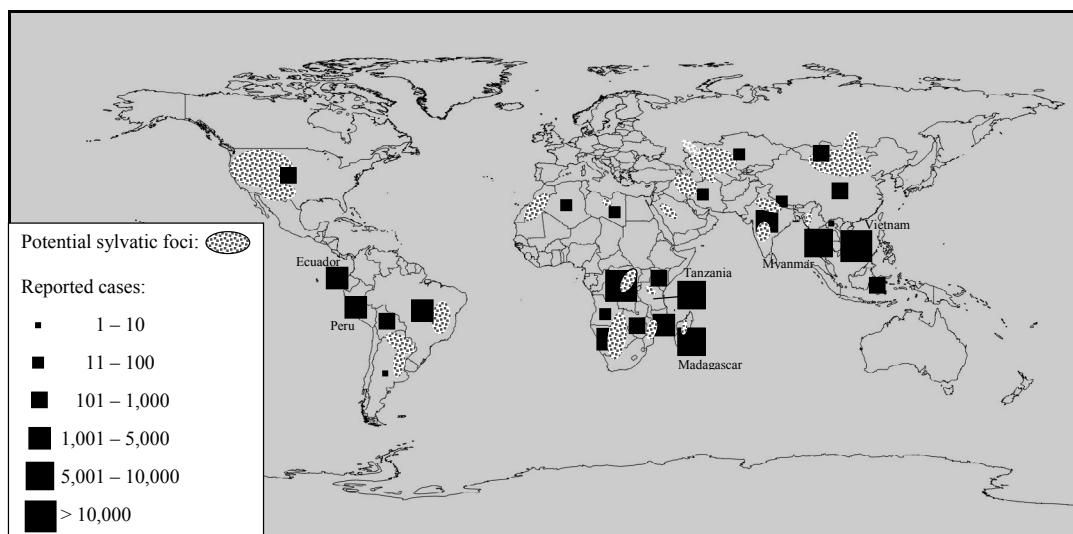
are then quickly recognized, specifically when active disease surveillance programs exist in areas of endemicity. Within the following sections of this review, we will describe various components that may contribute to the occurrences of human plague in the modern world. We will furthermore illustrate that many of these factors may have already been identified as contributing circumstances in historic plague outbreaks and epidemics, and that ecologic and sociological factors, together with microbial evolutionary factors play a critical role in the re-emergence of plague and perhaps other infectious diseases.

### Plague in the 20<sup>th</sup> and 21<sup>st</sup> Centuries: Public Health Implications and Possibilities for Future Research and Development

From the time of plague discovery to the mid-20<sup>th</sup> century, the

landscape of infectious diseases changed significantly, worldwide. The discovery of antimicrobial agents such as penicillin and streptomycin in the 1930s and 1940s provided for the first time in history the means to treat bacterial infections. Together with a new understanding of the epidemiology of many infectious diseases and zoonoses, the world gained greater confidence that eradication of infectious diseases from the earth was possible. In 1963, Adrian Cockburn, a distinguished epidemiologist at The Johns Hopkins University and advisor to the World Health Organization (WHO) stated in his renowned monograph ‘*The Evolution and Eradication of Infectious Diseases*’ that “eradication of infectious disease as a concept in public health has advanced only within the last two decades, yet it is replacing control as an objective” [61]. Just one year following the eradication of smallpox, the WHO envisioned at the World Health Assembly, convened at Alma-Ata (today’s Almaty, Kazakhstan) in 1978, the virtual absence of serious infectious diseases by the end of the century, as stated in the “Health for all by the year 2000” document [62,63]. Several factors contributed to such ostentatious confidence, among which were declining morbidity and mortality rates from infectious diseases in the industrialized Western World since the beginning of the 20<sup>th</sup> century and particularly after the two world wars. At the same time, these European and other developed countries saw a significant social uplift with remarkable improvements in living standards, particularly housing, diet, and education; furthermore improvements in infrastructure (e.g. sewers, water treatment plants) provided a solid foundation for better public health systems. Together, these improvements in treatment of infectious diseases and public health infrastructure contributed to the decline of the feared maladies of the past: plague, cholera, typhoid, and tuberculosis. Inspired by the results of public health improvements and scientific discoveries, the U.S. Surgeon General William Stewart stated publically in 1969 that “the time has come to close the book on infectious diseases” [64].

However, at the beginning of the 21<sup>st</sup> century, epidemics of infectious diseases continue to pose a threat to human societies. In many instances today’s outbreaks and epidemics of infectious diseases are often accompanied by civil war or natural disasters; however, other factors like concentration of people in refugee camps, tourism, climate change, emergence of new pathogens, and ecologic changes have been identified as contributing to the emergence of infectious diseases and epidemics [64-68]. While several diseases, such as HIV/AIDS or severe acute respiratory syndrome (SARS) come readily to mind, in most countries/societies in today’s world, plague has been relegated to the sidelines of infectious diseases. As we described in the previous paragraph on plague history, this disease is still prevalent in several parts of the world and one might be inclined to describe the continuation of its presence as the “ongoing third plague pandemic”. Between the 1950s and now, plague outbreaks have been reported on three continents (Figure 3): namely Asia, Africa, and the Americas. Specifically, a continuous annual occurrence of plague cases has been reported in five countries: Madagascar, Tanzania, Vietnam, China, and the USA [4,69]. Plague outbreaks occurring in a rather sporadic fashion have been reported from the following countries: Democratic Republic of Congo, Namibia, Zimbabwe, Mozambique, Malawi, Uganda, Botswana, Zambia, Kenya, Algeria, Ecuador, Brazil, Peru, Bolivia, India, Indonesia, Laos, Myanmar, Mongolia, and Kazakhstan (Table 1) at the present time, the highest prevalence of plague is seen in Africa [4,69]. In these next paragraphs, we will describe several factors associated with these recent outbreaks of plague, and furthermore we will describe risk factors that should be considered when attempting to prevent larger outbreaks, epidemics, and further spread of the disease.



**Figure 3: Worldwide distribution of human and sylvatic plague reported by country, 1954 - 2009**

(Data for this map are compiled from WHO and CDC sources, and references 4, 56, 69, and 163)

The map depicts reported (cumulative) cases of plague in humans, worldwide, during 1954 – 2009 (data derived from WHO). Plague outbreaks and epidemics occurred in Africa, Asia, and South America; the majority of cases were reported from Africa. Given the timeframe for plague surveillance reflected in this map, most recent cases and/or outbreaks are not included in this map; a current list of countries with reported human cases of plague includes Madagascar, Tanzania, Democratic Republic of Congo, Namibia, Zimbabwe, Mozambique, Malawi, Uganda, Botswana, Zambia, Kenya, Algeria, India, Vietnam, China, Mongolia, Kazakhstan, Kyrgyzstan, Indonesia, Laos, Myanmar, Ecuador, Brazil, Peru, Bolivia, and the USA. While there is great variation of reported cases between various countries, it is likely that for many countries in Asia and Africa the total number of cases could be much higher. For example, countries with established surveillance programs (e.g. China, India, and Vietnam) reported larger number of cases, however, there is virtually no reported cases in countries that are in close proximity (Thailand or Bangladesh). The geographic proximity and similar climates and topography of these countries would suggest the possibility of plague occurrence, yet in the absence of surveillance programs, no cases have been reported to the WHO.

Region / Country	1954 – 1970	1971 – 1986	1987 - 2009	
Africa	Algeria	-	15	
	Angola	-	76	
	Botswana	-	173	
	DRC <sup>^</sup>	404	189	13,589
	Kenya	129	398	44
	Libya	-	54	5
	Madagascar	308	630	16,718
	Malawi	30	-	835
	Mozambique	-	124	2,387
	Namibia	92	102	2,189
	Uganda	22	493	1,188
	Tanzania	534	1,829	6,384
Zambia	-	-	1,628	
Zimbabwe	62	62	417	
Asia	China	-	78	574
	India	3,983	-	900
	Indonesia	971	-	106
	Kazakhstan	-	-	24
	Laos	-	-	10
	Mongolia	-	3	118
	Myanmar	1,641	3,138	774
Vietnam	21,447	10,601	3,425	
Americas	Bolivia	525	341	41
	Brazil	1,608	1,912	173
	Ecuador	2,018	128	14
	Peru	1,879	700	1,577
	USA <sup>*</sup>	50	240	174

**Abbreviations:** <sup>^</sup>DRC, Democratic Republic of the Congo; <sup>\*</sup>USA, United States of America

**Table 1:** Plague cases by country 1954-2009 (based on data reported to WHO). Data for confirmed and suspected plague cases were compiled from WHO and CDC sources [4, 56, 69, and 160]

### Some Specific Examples of Plague Occurrences in the 20<sup>th</sup> and 21<sup>st</sup> Century:

Keeping in mind that this review is concerned with contributing factors to a potentially reemergence of plague, a particularly interesting outbreak of plague in modern times occurred in September 1994 in the city of Surat, in the State of Gujarat in Western India. Despite the relatively small toll (700 cases of bubonic and/or pneumonic plague with 56 deaths [70,71]), this outbreak caused widespread panic. During the third week of September 1994, news reports of cases of suspected pneumonic plague in the city of Surat, India, occurred; this news spread so quickly and with such a devastating effect that it resulted in a mass exodus of more than 500,000 people from the city of Surat. People leaving for other major cities in the region, likely contributed to subsequent further transmission of the disease and secondary, smaller outbreaks. The Indian government instituted massive relief and control measures, including the search for new cases, expedited hospital admission of all cases with the slightest suspicion of pneumonic plague, antimicrobial treatment of all suspect cases, massive spraying with insecticides, and closing down of public infrastructures such as food vendors, restaurants, and public gatherings [72]. Within a few weeks of the announcement of the outbreak, many countries suspended air traffic and cargo movement from and to India, despite the fact that the WHO had advised countries to the contrary [72,73]. Many other “countermeasures”, e.g. fumigation efforts, quarantine, restrictions on air and sea travel and trade, were implemented, based on recommendations by health authorities in various countries [72,74-76]. The total economic loss due to the collapse of trade and tourism was estimated to be \$ 1.8 billion [77]. From today’s perspective and considering the overall small number of cases combined with the significant impact on public life and economy during that time, the

control efforts taken in 1994 seem overly reactionary and perhaps to some degree hastily implemented.

The most likely reason why this outbreak created such a disproportionate fear could be based on the fact that mentioning the word Plague itself evoked cultural memories of the Black Death that killed a quarter of Europe's population in the 14<sup>th</sup> century. The ultimate response chosen to respond to the outbreak in India can simply be described as a "fire-fighting" approach, meaning that governmental and international efforts were designed to be not only expeditious but also wide-ranging in order to achieve an instant control of the outbreak, ongoing disease monitoring, and treatment of all confirmed and suspected cases. Even at present times, such approach is frequently favored by most authorities and countries, and teams are brought in to kill arthropod vectors and rodent reservoirs using insecticides and other poisonous substances; confirmed human cases are typically quarantined and treated with broad spectrum antimicrobials, while antimicrobial chemoprophylaxis is given to potentially exposed but asymptomatic individuals. In the absence of robust surveillance programs for specific infectious diseases like plague, this "fire-fighting" approach is considered by experts a logical and reasonable response to an infectious disease outbreak. However, other experts have argued against the use of this "fire-fighting approach", considering it to be ineffective, as the disease incidence may already be declining naturally at the time of countermeasure implementation. A proposed alternate approach would be focused on informed, pre-emptive decisions about plague management and favor preventative measures before outbreaks occur. While such an approach would certainly be more sustainable and cost-effective [1], it would most certainly require a well-designed and maintained disease (in this case: plague) surveillance program. Such programs exist in the U.S.A. and in Russia and many countries formerly belonging to the USSR [78].

A discussion on plague in the 20<sup>th</sup> and 21<sup>st</sup> century would not be complete without mentioning its use in biowarfare and bioterrorism. Problems related to sudden occurrences of (small) plague outbreaks relate to the possibility of deliberate release of the organism during armed conflicts or in form of terrorism. In the months and years following the terrorist attacks on the World Trade Center (WTC) in New York City, concerns regarding the use of various biological agents, including *Y. pestis*, as agents of bioterrorism were raised, and appropriate preparedness and response programs were developed. For an in-depth review of this topic, we will refer the interested reader to other publications [9,12,25,79-81]. Briefly, it is well known that plague has been used as a bioweapon since the 14<sup>th</sup> century; the perhaps most successful programs on a large scale was reportedly developed during World War II by the Japanese, and during the "cold war" by the former Soviet Union [9,25,80]. Considering the global distribution of plague in nature, mass production and dissemination of *Y. pestis* in aerosolized form may be relatively easy to achieve, even in limited resource settings, therefore making the organism a highly probable candidate as a bioweapon. Release of *Y. pestis* in aerosolized form would typically result in larger numbers of people with pneumonic plague; however, the initial symptoms of fever, dyspnea, and cough could be easily confused with other respiratory tract infections, therefore requiring a high index of suspicion by the treating physician [80,82]. A comprehensive report published by the World Health Organization in 1970 determined that in the event of an aerosolized biological attack, plague bacilli would only remain infectious for one additional hour after the release [83]. Additional studies and reviews, however, have highlighted that despite an aerosolized dispersal, *Y. pestis* would unlikely last long enough in the environment to cause continued infection to further merit

environmental decontamination as part of the response to the attack [25,84]. Furthermore, most experts agree that pneumonic plague is not easily transmissible between affected individuals based on the existing epidemiologic evidence from past outbreaks and epidemics [25,85,86]. The last case of person-to-person spread of pneumonic plague in the United States was reported in 1924 [87], and despite its devastatingly high mortality rate, pneumonic plague continues to have a low transmission rate [26]. Based on several consensus statements and reviews by expert groups have been published during the past 15 years [80-82], it is reasonable to conclude that plague outbreaks in places other than those known to have enzootic disease occurrence, and in patients who did not report any travel to plague enzootic areas or rodent exposure prior becoming ill, an act of bioterrorism should be considered. While such guidance statement clearly considers the possibility of enzootic, naturally-occurring plague, since the events of 9/11/2001, plague reemerged in the public eye almost exclusively as an agent of bioterrorism. During the past 15 years, tremendous resources were assigned to national bioterrorism preparedness and biodefense programs. Some people asserted that such bioterrorism preparedness efforts diverted resources from other important public health needs, while others stated that the development of bioterrorism response programs leverage public health programs through improved infrastructure, planning, and exercises, thus improving one's ability to counter emerging and re-emerging infectious diseases. The authors of a comprehensive review published in 2005 on this very topic, concluded that the programs developed in the spirit of bioterrorism preparedness could in fact be used to improve the public health infrastructure in general, and specifically in its response capability to emerging and re-emerging infectious diseases [88]. It is apparent that in today's times various public health agencies worldwide are the key stakeholders in developing responses to emerging infectious disease threats. These agencies organize their response to challenges posed by emerging infectious diseases traditionally in a pyramidal, program-specific manner. During the past 15 years, however, the growing demands of responding to a potential event of bioterrorism as well as naturally occurring outbreaks may require the development of different approaches. Within the following paragraphs, we will discuss some of the emerging concepts and analyze factors in the context of a possible emergence of plague outbreaks. We will specifically address factors pertaining to human activity (population dynamics, trade, socio-economic factors), and natural determinants (ecological, environmental, and climate factors). These determinants act rarely as single factors, and the complexity of interaction was highlighted in the 2003 Institute of Medicine (IOM) Report, "Microbial Threats to Health – Emergence, Detection, and Response" and others [67,89].

### Human Activity Factors Associated with Infectious Disease Outbreaks

In recent years, the classic approach to modeling epidemics was revised in order to incorporate elements of demography, including mortality, fecundity, and migration, of both hosts and vector populations. While the classical model assumes that populations during epidemics remain constant, the experiences with more recent pandemics demonstrated host and vector population changes, as well as transient or even permanent migration and diffusion of hosts [90-92]. As described by Lloyd-Smith et al., the emergence of epidemics due to zoonotic diseases (resulting from cross-species spillover) depend on the prevalence of the infection in the animal reservoir, the rate at which human hosts have contact with the diseased animal reservoir, and lastly the probability that humans become infected upon contact with diseased animals [92]. If one accepts that these three components must be fulfilled prior to the

occurrence of sustained disease transmission and epidemics, then it seems intuitive that all three components will inevitably be influenced by natural, agricultural, and manmade conditions. The majority of changes to disease reservoir populations affecting the emergence of outbreaks are frequently related to human activities, rather than results of random events in nature. The following paragraphs will describe various human activities that may influence the possibility for infectious disease epidemics, and plague in particular, to occur.

### Population dynamics

Specifically, the increasing density of human populations, the rise of megacities exceeding 10 million inhabitants, and the spawning of teeming peri-urban slums without sanitary, educational, and other infrastructure have been identified as risk factors, contributing to the rise of infectious disease outbreaks and epidemics. Rapid population growth and uncontrolled rapid urban expansion are often linked to escalating poverty and widening social inequalities [64,93], these issues are significant challenges for many of today's megacities in Southeast Asia and South America (e.g. Manila, Jakarta, Rio de Janeiro, and Mexico City). However, the problem in itself is not novel, as it has been described as a key element for disease outbreaks during the 18<sup>th</sup> and 19<sup>th</sup> centuries [94]. A specific example is that of plague in Sydney, Australia, in the year 1900, when the city underwent a rapid population growth. It was then, that an outbreak of bubonic plague was linked to the high density of people in areas of extremely poor sanitation. With rapid expansion of the city, basements of homes and properties became informal solid waste storage sites, sewer systems were either nonexistent or poorly managed, and many businesses operated with little regard for sanitation and proper waste management [94]. Although government regulations and provisions existed for the general control of urban construction and proper sanitation, such regulations were poorly reinforced. As a result of such mismanagement of public health infrastructure, the arrival of plague in the year 1900 caused a widespread panic in the city. Many similar factors can also be found as contributing elements of the re-emergence of plague in Madagascar [50,51]. The importance of socioeconomic factors has also been reported for the more recent plague occurrences in the United States, where natural plague foci in rodents cover the entire western third of the country. One study describes socioeconomic factors associated with temporal changes in the distribution of human plague in the State of New Mexico [95]. While in past decades (1980s) plague cases were described in people of lower socioeconomic status and those living in poor housing conditions, a repeat analysis during the 2000s, plague cases were more often seen in people living in affluent areas such as Santa Fe and Albuquerque. Among contributing factors, many of which may remain unknown at this point, the authors identified development of newer housing and migration of people into areas that are suitable plague habitats as a key factor, therefore bringing humans closer to the natural sylvatic cycle of plague.

### Human activities: deforestation and agriculture

Deforestation, increasing density of monotypic domestic animal and crop plant populations and the crowding together of wildlife are additional contributing risk factors for the occurrence of newly emerging and re-emerging infectious diseases. Deforestation in the case of plague outbreaks in Madagascar had ultimately two consequences: the first relates to the possibility of enhanced contact opportunities of humans with sylvatic plague in the forests of the High Plateau; the second relates to the change in landscapes favoring the development of rodent populations as plague reservoirs [96,97]. In the case of

Madagascar, rodent surveillance initiated in the 1990s demonstrated a replacement of *Rattus rattus* by *Rattus norvegicus* in some regions of the island [97]. The construction of modern houses and sewage networks in urban areas was believed to have resulted in the change of rodent populations, most likely resulting in humans having lesser contact with rodents and rat fleas, therefore accounting for a decrease of plague in coastal urban dwellings. However, plague reemerged and now persists predominantly in rural areas of Madagascar with predominantly agricultural activities. As described in the above referenced analyses, deforestation of the High Plateau and transformation of the landscapes into agricultural areas, subsequent human expansion into these rural areas, coupled with poverty, and cultural practices neglecting a scientific medical rational toward the disease, have all been contributing factors for the persistence of recurrent plague outbreaks in central Madagascar. Similar processes have also been described for plague foci in China [98]. Some authors have proposed that changes in ecosystems not only lead to the development of new disease reservoirs and potential new vectors, but perhaps result in shifts in the genetic structure of the microorganisms themselves due to adaptation to new hosts and vectors [97]. The discussion of these complex interactions between pathogens, vectors, and rodent host populations are beyond the scope of this review and the authors refer the interested reader to the corresponding referenced literature on this topic [3,4,92,97,98].

### Commerce and travel

As we described in the historic review of plague above, travel and trade had a significant role in the transmission and spread of plague during past pandemics, including the Black Death of Europe in the 14<sup>th</sup> century. For as long as goods and spices were shipped throughout the New and Old World, pathogens have likewise traveled into new lands. And today, with worldwide increasing population densities, travel and trade are just as likely to be a key factor in the spread of infectious diseases as they were centuries ago [64,67]. The key difference between trade then and now is speed, where goods and supplies are crossing barriers in days where previously months were required. In today's world, a tradeoff has arisen between the demands of commercialism/consumerism and the interests of public health. While rapid spread/transmission of bubonic plague via air travel remains to be an unlikely event, spread of plague by infected rats via nautical and land trade routes continues to be viewed as a major problem for public health agencies, worldwide. In an effort to limit the spread of disease via nautical trade and travel, the WHO implemented several interventions aimed at curtailing the spread and introduction of vectors and animal hosts. Ship sanitation certificates, mooring line rat guards, and periodic deck sweeps are all recommended procedures by the WHO [99]. Unfortunately, experts attested that these measures as a whole may be ineffective throughout the developing world, even when applied with the best intentions. Procedures and protocols are frequently overlooked because of inefficiency and corruption of those people charged with their reinforcement [100]. While there is ample evidence from historic accounts that highlights the role of nautical trade in the spread of plague and countermeasures to combat such spread (e.g. quarantine) during the medieval times, the rapid spread of the disease during the 3<sup>rd</sup> pandemic (less than 5 years from its beginning in China), and its rapid arrival on all continents is furthermore an attestation of the major role of sea traffic by steamboats with respect to the speed of the diffusion of the disease. Although there is no published evidence or examples for plague-infected rats being spread via nautical trade routes at the present time, on a worldwide scale, the importance of human and rodent movements in the context of trade was clearly demonstrated by



the spread and mode of diffusion during the second and third plague pandemics [101]. Comparing the speed of diffusion and spread of plague during the 3<sup>rd</sup> pandemic compared to more ancient pandemics, the role of rapid human movement and trade cannot be underestimated; it continues to be an important factor in today's world and highlights the need for adherence to international sanitation and safety standards.

Within the past three subsections we described three important components of human activities that should be considered as contributing factors to the occurrence of infectious disease outbreaks and epidemics, including plague. We furthermore provided that such factors have likely played an important role for historic plague outbreaks in various places, worldwide. Estimates by the United Nations indicate that as a result of continued human migration, approximately 65% of the world's population will live in large cities and urban centers by the year 2025 [102]. Considering the impact of human migration on disease outbreaks and epidemics in history, it seems only reasonable to predict that such massive human migration in today's world coupled with unprepared and/or deteriorating public health infrastructure in some regions could once again provide the starting point of epidemics; plague will be no exception to this rule. Therefore, human activity factors can only serve as warnings for today's challenges in our ever so closely connected world. But human factors are not just related to trade as we will further explore in the next paragraph. Other factors, such as natural disasters and climate change, could not only increase the amount of human migration on the planet, but perhaps in related ways directly or in part related to a society's response to a disaster contribute to infectious disease outbreaks.

### **Natural Factors Contributing to Outbreaks: Climate Change and Natural Disasters**

During the recent decade, global changes in climate and severe weather conditions have been observed more frequently compared to the previous 100 years and are believed to have a growing and significant influence on human health [103-106]. From a public health standpoint, climate change has now been recognized as a contributing factor to changes in ecology and epidemiology of infectious diseases [105,106]. Although it may be difficult and almost impossible to quantify the exact risk posed by climate change with respect to a specific infectious disease, the complex interactions between the human host population and the causative agents of infectious diseases have been studied in various settings including climate change models, and the importance of the ability of human society and public health systems to adapt has been clearly recognized [107-109]. The influence of climactic factors on the epidemiology of plague was perhaps recognized as early as the 1960s when some investigators began to analyze patterns of increased plague outbreaks in Vietnam and India, recognizing that the timing of outbreaks was strongly influenced by temperature and rainfall patterns [107,110]. In more recent studies several investigators described a dependence of flea vectors and rodent hosts on various climate factors such as periods of drought, intense rainfall, and specifically winter-spring precipitation in areas of plague endemicity (e.g. New Mexico, Arizona, and Colorado) [110-115]. From these few studies, it appears that increases of rainfall in otherwise semi-arid regions lead to increased food sources for rodents, resulting in heightened rodent reproduction and numbers which are then likely to result in a greater risk of plague epizootics and transmission of the disease to humans. Other studies demonstrated that high temperatures or low humidity may influence the behavior of the vector, namely the rat flea; other studies demonstrated that some species of fleas are able to live unfed in rodent burrows and survive for several months to a year [107]. Still

other studies suggested that the change in climate in the U.S. may also influence the distribution and further spread of plague, away from its current predominant area of occurrence, the "Four Corners Region" (i.e. New Mexico, Colorado, Arizona, Utah) perhaps further eastward or toward higher latitudes and/or even higher altitudes [112]. Other, recent studies, demonstrated that environmental factors such as high levels of precipitation and flooding events resulted in increased spread velocity of plague in China and Vietnam [116,117]. The effects of global climate change have been previously described in great detail for many other vector-borne diseases, such as malaria and dengue fever [118,119] considering this evidence, it would be reasonable to assume that climate change can similarly affect the spread and dissemination of plague within the vector and rodent population, ultimately affecting the occurrence of plague within the human population as well. Understanding the microenvironment of plague (pathogen and flea life-cycle) and the complex interrelationship of the macroenvironment, the pathogen-vector-host cycle, studies have demonstrated how climate and climate change has the ability to influence the persistence and dissemination of plague [120]. Therefore, the threat of outbreaks may be elevated in regions where humans live in close proximity to natural enzootic plague reservoirs. However, the ability to develop better models for risk assessment and mitigation heavily depends on further research of plague dynamics. While some studies on the effects of climate change on plague ecology have been reviewed here, there is clearly a need for further and ongoing research to better understand the interplay between the rodent reservoir, the vector, and the human host.

In addition to climate factors, it is equally important to recognize that the occurrence of other natural events and disasters associated with a subsequent disruption of ecosystems and public health infrastructure have often been linked to local and regional disease outbreaks. Natural disasters (e.g. hurricanes, flooding, earthquakes, and landslides) are likely to result in displacement and redistribution not only of large human populations, but also disease-carrying reservoirs of rodents and other small mammals [121,122]. While there is still a general debate whether such perceived association between plague epidemics and natural disasters is merely a coincidence or has a true causal relationship, some studies examined the historic evidence to support the theory of causality: historic accounts recorded during the times of the Justinian Plague mentioned disease outbreaks that followed earthquakes by up to 12 months [123]. Such historic records could then be used to document natural foci of plague during antiquity up to modern times, and several studies suggested that the neglect to acknowledge and monitor such foci could be at the root cause of plague epidemics following high-magnitude earthquakes in these regions. To support such a theory, one might take a look at the plague outbreak in Surat, India, in 1994. One year prior to the 1994 plague outbreak in India, a major earthquake occurred in the Latur region, where the first cases of bubonic plague were reported [4]. A similar observation was made for the plague epidemic in Algeria [56,124]. Perhaps the earthquakes in areas of plague endemicity resulted in the disruption of a previously more stable ecologic system, and forced rodent populations to leave their burrows/habitats and come in closer contact with human settlements ultimately leading to these smaller plague epidemics and outbreaks. Yet another study suggested a link between volcanic eruptions and plague epidemics [125], the author suggests that volcanic dry fogs and successive climate cooling were closely linked with famine and plague epidemics at least on 5 accounts during the past 2000 years. While the geographic and timely proximity of these events in relation to the historic plague outbreaks in both scenarios is intriguing, the absolute proof of causality remains difficult to establish.

## Other Factors to be Considered in the Re-Emergence of Plague and Future Directions

In the previous paragraph we discussed the importance of such baseline surveillance with respect to achieving a better understanding of infectious disease outbreaks following natural disasters or severe weather events. In recent years, some new theories on the transmission of plague and factors surrounding the sudden rise in both animal and human cases of plague have been developed; such theories not only consider the importance of surveillance systems, but also suggest alternate vectors and transmission models. In the following paragraph, we will first highlight the importance of establishing and maintaining a continuous surveillance system for enzootic infectious diseases such as plague, using historic and current examples of plague surveillance and reported outbreaks. Lastly, we will describe some of the recently proposed alternate models for disease transmission.

The occurrence of plague in Madagascar can be used as a great example to illustrate the importance of disease surveillance [97]. Plague was apparently brought to Madagascar from India by steamboat around 1898, and since then spread along the coastal port cities of the island, and ultimately reached the center-island highlands in 1921 [97,126,127]. Since the 1920s, plague gradually disappeared from the coastal regions and was ultimately limited to the High Plateau of the inner island; as a result, surveillance efforts in the coastal regions were eventually reduced and/or discontinued altogether [126]. Coinciding with political unrest and economic changes that lead to increased poverty and disorganization of public services and overall decreased disease surveillance, the number of human plague cases increased in Madagascar since the 1980s. In other areas of the world, namely India and Algeria, surveillance efforts were also substantially decreased and/or discontinued since the 1960s; as a result, plague reemerged in the recent decades in form of smaller outbreaks to regional epidemics: 1994 in India, 2003 in Algeria [56,70,72,73,126]. In the simplest way, one might describe this problem of “re-emerging human plague” as the problem of the forgotten ancient foci of plague. Complacency toward historic knowledge coupled with discontinued surveillance in light of financial hardship, would inevitably become the foundation upon which dormant, yet persistent enzootic infectious diseases such as plague could “re-emerge”, ultimately resulting in human cases of plague. In these examples of India, Madagascar, and Algeria, the lack of continuous baseline surveillance resulted in an undetected sudden increase of the disease incidence in an enzootic/endemic region of the world, and a sudden outbreak of human cases, what was then considered a re-emerge of the disease. On the other hand, human cases of plague have occurred regularly in Kyrgyzstan and Kazakhstan, which are also considered countries where plague is enzootic [128], however, no large-scale outbreaks have been reported to date [128-132]. The perhaps better controlled plague occurrences in Kyrgyzstan and Kazakhstan, with a substantially lower number of cases compared to other outbreaks during the past 50 years, are likely an attestation to the importance and functionality of a well-designed plague surveillance system; Kyrgyzstan and Kazakhstan likely inherited such a surveillance system from the times when these countries were a part of the Soviet Union. For a detailed description of the history and function of the USSR plague surveillance system, we refer the interest reader to related literature [78]. In two other countries with enzootic plague foci, the disease in humans is considered to be a public health notifiable disease. In addition, plague remains a WHO notifiable disease if cases occur outside endemic areas or the numbers of cases reach the threshold of initiating an epidemic. Based on the understanding that plague is a

zoonotic disease with a complex transmission cycle, wildlife surveillance has therefore been recognized as a critical component to better understand the pathogen and to detect the occurrence of epizootics in early stages of their development. Again, both the United States and China developed complex wildlife surveillance systems to monitor the prevalence of vectors and plague in rodents in endemic regions of their respective countries [133]. In a recent review, the authors showed that both countries, and China in particular demonstrated through their programs the ability to implement early warning systems for increased plague risk, when closely monitoring the levels of fleas and rodent hosts [133].

While the complexity of the ecoepidemiology of plague and other infectious diseases has been highlighted in recent publications [92,130], it is of interest to note that as early as 1963, researchers suggested that *Y. pestis*, is in fact capable of remaining alive for several years in the burrows of dead rodents [134,135]. Mollaret and his colleagues demonstrated that in addition to the well-established disease transmission cycle between rodents and fleas, another cycle existed: the “burrow-rodent-burrow” cycle. These investigators described an interepizootic maintenance phase of plague in the endemic foci around the world [135,136]. Other, more recent publications have reintroduced the concept of alternate transmission cycles of plague, aside from the rodent-flea-rodent cycle. One study describes the fact that *Y. pestis* has the ability to persist in soil, albeit the exact mechanisms remain elusive at this point [137]. It is furthermore important to consider the results of these studies when discussing the need for implementation and maintenance of a plague surveillance system; the fact that *Y. pestis* is capable of survival in the natural environment.

Finally, we want to complete the discussion on emerging and alternate concepts for plague transmission by mentioning potential alternate host- and risk-factors for human plague, including the potential role of pet animals, such as cats and dogs, serving as alternate hosts, and the possibility of plague as a telluric, human-ectoparasite-borne disease. The role of pet animals, such as cats and dogs, in transmission has been suggested in past studies and anecdotally reported on several occasions [138-140]. Yet a more recent study provides supportive evidence that pet animals may play a more significant role in transmission of plague in endemic regions (e.g. New Mexico and Colorado) [141,142].

In plague endemic areas, domestic cats and dogs may be frequently exposed to *Y. pestis* and become infected via predation on infected animals or through flea bites. While dogs typically experience a milder form of the illness, presenting with nonspecific signs like lethargy, pyrexia, and purulent skin lesions, cats are highly susceptible to plague, presenting with a disease spectrum similar to that in humans and mortality in untreated cats is equally high [143]. Studies evaluating the serologic response to plague demonstrated that dogs in enzootic areas are frequently exposed to either infected rodents or rodent-fleas [139], cats are more likely to be exposed via predation on diseased animals and rodents. In both instances, caring for a diseased pet (cat or dog), or allowing close contact with a diseased pet dog (e.g. sleeping in the same bed) have been identified as risk factors for acquisition of plague by humans. While most of the human plague cases result from bites by infected fleas, acquisition of the disease via direct contact with a diseased animal cannot be underestimated. Considering that some authors described a paucity of dog and cat fleas in the Southwestern United States [143], and others described a low level of utilization of flea control products [144], it seems reasonable recommend regular use of flea-control products, specifically for domestic out-door pets, in plague-endemic regions. Furthermore, considering the plague seroprevalence

in dogs [142], having a sick dog or cat in the household could be used as an indicator for the presence and risk assessment of peridomestic plague, in the western regions of the United States. While there is sufficient evidence to support the concept of dog- and cat-associated human plague, additional studies are warranted to establish a better understanding of the risk factors and plague-prevention measures, as those differ from the traditional models of plague transmission.

In review of the recent publications on plague epidemiology, it is apparent that a thorough understanding of this disease and its epidemiology will require an open-minded approach, allowing

for reevaluation of the observations and conclusions made by the scientists investigating plague during the late 1800s and early 1900s. Traditionally, the rat flea, *Xenopsylla cheopis*, has been described as the main vector for transmission of plague. Transmission of *Y. pestis* by *X. cheopis* occurs through the flea's mouthparts rather than through contamination of the feeding site by flea feces, and is facilitated by a rather complex process that leads to blockage of the proventriculus of the infected flea subsequently leading to *Y. pestis* – contaminated blood being flushed from the fleas distended esophagus back into the feeding site [5]. Various fleas are known to react differently to the infection with

		Geographic region and/or country	Vector	Host reservoir	Comment
Established mode of transmission		<b>Global</b>	<i>Xenopsylla cheopis</i>	<b>Black rat (<i>Rattus rattus</i>)</b>	Originally described as the main vector for plague transmission; most important and common vector for epidemic and sylvatic plague for many rodent species.
		<b>Africa</b> (Democratic Republic of the Congo, Tanzania, Kenya, Zambia, Zimbabwe, Mozambique, Madagascar, Libya)	<i>Xenopsylla brasiliensis</i> , <i>Dinopsyllus lypusus</i>	<i>R. rattus</i> , <i>R. norvegicus</i> , gerbils; pouched rat	
			<i>Leptopsylla segnis</i>	Field mice	
			<i>Ctenocephalides felis</i> , and <i>C. canis</i>	Cats, dogs, humans	
		<b>Arabian Peninsula</b> (Iran, Yemen)	<i>Xenopsylla buxtoni</i> , <i>Stenoponia tripectinata</i>	<i>R. rattus</i> ; gerbils	
			<i>Xenopsylla astia</i> , <i>Neopsylla fasciatus</i> , <i>Monopsyllus anisus</i> , <i>Leptopsylla segnis</i> , <i>Ceratophyllus tesquorum</i> , <i>N. setosa</i> , and various <i>Xenopsylla</i> spp.	Great gerbils, ground squirrels, marmots	Many vectors are typically specific to commensal rodents; some of these vectors can potentially transmit <i>Y. pestis</i> to humans and may be associated with the occurrence of clusters of human plague
		<b>Asia</b> Northwest Caspian focus, Ural mountains, Central Asian desert focus		<i>R. rattus</i> , <i>R. norvegicus</i> , bandicoot rats, gerbils, shrews, and mice	
		India, Indonesia, Myanmar, Nepal, Vietnam	<i>X. cheopis</i> , <i>X. astia</i> , <i>X. brasiliensis</i> , and other <i>Xenopsylla</i> spp.	<i>R. rattus</i> , <i>R. norvegicus</i> , <i>R. flavipectus</i> , marmots, ground squirrels	
		China		<i>R. rattus</i> , <i>R. norvegicus</i> , cotton rat, mice	
		<b>South America</b> Bolivia, Brazil, Ecuador	<i>X. cheopis</i>	<i>R. rattus</i> , <i>R. norvegicus</i>	Urban foci of rodent and human plague
	Peru	<i>X. cheopis</i> <i>Polygenis litargus</i> , <i>Hectopsylla</i> spp., <i>Tiamastus</i> spp.	Tree squirrel, mountain field mouse, cottontail rabbit, oricetine rat	Rural foci; tree squirrels are the principal reservoir	
	<b>USA</b> (California, Oregon, Arizona, New Mexico, Colorado, Utah, Montana, Wyoming, Texas, Oklahoma, Kansas)	Various host-specific flea vectors (e.g. <i>Diamanus</i> spp., <i>Opisocrostis</i> spp., <i>Thrassis</i> spp., <i>Neopsylla</i> spp.)	Prairie dogs, rock squirrels, fox squirrels, ground squirrels, chipmunks, ferrets; domestic cats and dogs	Predominantly rodent plague; occasional human cases associated with occupational exposure to infected rodents, or transmission by infected domestic cats and/or dogs	
Possible / probable route of transmission	<b>Africa</b>	Probable vector in Angola, Tanzania, Burundi, Democratic Republic of the Congo, Brazil, Iran, Iraq, and Nepal	<i>Pulex irritans</i> (human flea)	Parasitizes wide range of hosts: humans, foxes, badgers, ground squirrels, guinea pigs, rats, domestic pigs, goats, dogs, cats	Potential vector for small cluster of human plague associated with poor sanitary and housing conditions
	<b>Ancient plague pandemics</b> (specifically 2 <sup>nd</sup> pandemic, "Black Death")		<i>Pulex irritans</i> ; <i>Pediculus humanus corporis</i> and <i>P. humanus capitis</i> (human body louse and head louse)	Humans; during large and rapid epidemic spread of plague (e.g during the "Black Death" epidemic in Europe)	Despite the presence of <i>R. rattus</i> in northern Europe, there is no archeological evidence of <i>X. cheopis</i> as a flea vector; The European rat flea ( <i>Nosopsyllus fasciatus</i> ) is rarely encountered in humans; Rapid diffusion during 2 <sup>nd</sup> epidemic argues against sole rat-driven epidemic (which has slow diffusion); Observation of plague transmission via clothing during the 2 <sup>nd</sup> epidemic
	<b>Global persistence of plague foci</b>		soil reservoir	Several unresolved issues regarding the potential persistence of <i>Y. pestis</i> in soli still exist; some studies proposed the concept of persistence as a gut symbiont of a telluric nematode	Mollaret introduced the telluric (saprophytic) model of plague transmission as a possible route for <i>Y. pestis</i> to persist in rodent burrows; survival of <i>Y. pestis</i> in soil for 16 months was experimentally confirmed; suggested model for silent plague foci in various geographical regions with enzootic plague foci

Table 2: Recognized and suggested vectors and host reservoirs for transmission of *Yersinia pestis*.

Scenario	Description of Epidemiology	Expected extent of cases	Current and historic examples
1	Wild rodent plague in the absence of human ectoparasites	Rare, sporadic cases (flea-borne plague)	United States in endemic areas (e.g. New Mexico)
2	Wild rodent plague in the presence of human ectoparasites	Rare, limited clusters of human cases (ectoparasite-borne plague)	Syria, Iraq, Turkey during the 1950s
3	Plague in wild rodents and (urban) rat populations	Slowly spreading plague in animals with regular occurrence of human cases	India, during the 20 <sup>th</sup> century
4	Plague in wild rodents and (urban) rat populations in the presence of human ectoparasites	Clusters of human cases that progressively affect larger and numerous settlements	Morocco, during the 1940s
5	Pure rat plague	Typically observed in port cities, involving numerous human cases associated with limited extension in time and place	
6	Rat plague, in the presence of human ectoparasites	Severe epidemics of plague	
7	Rat plague, in the presence of human populations heavily infested with ectoparasites	Progressive expansion of previous scenario, leading to severe plague pandemics with significant human mortality	Historic plague epidemics and pandemics (e.g. Black Death during the 14 <sup>th</sup> and 15 <sup>th</sup> century)

**Table 3:** A new and alternative model for plague epidemiology.

*Y. pestis*, and differences in blocking rates among fleas may account for the differences in their effectiveness of transmitting the organism between hosts [5]. Compared to other fleas, *X. cheopis* is an unusually effective and dangerous vectors; however, in recent years more evidence is being found that other flea species such as *Xenopsylla orientalis* and *Oropsylla montanus*, and even other types of ectoparasites and/or endoparasites (including the human flea, *Pulex irritans*) may be capable of being efficient vectors for the transmission of *Y. pestis* [5-7,145-147]. Some of the currently proposed vectors in addition of *X. cheopis* are summarized in (Table 2).

After recognizing the existence of alternate arthropod vectors for transmission of *Y. pestis* among various rodents and mammals, some authors described the early findings on transmission of *Y. pestis* to humans exclusively by *X. cheopis* likewise as a “somewhat limited classic model” for plague transmission [148]. While many investigators previously considered a six-stage concept for plague transmission, Drancourt and colleagues recently added a seventh scenario to this model, in the attempt to explain the occurrence of large pandemics in history [148]. The original model introduced by Baltazard in 1956 includes six scenarios accounting for the occurrence of human plague cases (Table 3) [148,149]. Drancourt and colleagues, while acknowledging the previous 6 scenarios explaining the occurrence of human plague, proposed the addition of a 7<sup>th</sup> scenario evolving in situation where rodent/rat plague exists in the presence of human ectoparasites, such as the human body louse (*Pediculus humanus*) [148]. These investigators postulated that in situations of humans living in crowded spaces in the presence of heavy ectoparasite infestation, transmission of *Y. pestis* is easily facilitated leading to large-scale epidemics and even pandemics. The occurrences of large-scale epidemics in history could be more easily explained through this transmission model. Additional experimental studies confirmed the possibility of human lice being an effective vector for transmission of *Y. pestis* in humans and mammals [150,151]. The investigators acknowledge, however, that additional studies on this topic will be necessary to validate these emerging concepts of plague transmission cycles.

## Final Discussion and Conclusions

Considering the complexity of factors contributing to the occurrence of plague outbreaks described in this review, one must recognize that not all factors dictating disease transmission and epidemiology are based on active functions of the contributing circumstances (e.g. increase in vectors or rodents). Some aspects, like the breakdown of public health services or lack of disease surveillance, are inherently passive in nature,

and are not typically viewed as key components of disease transmission and spread. In developing countries, however, where public health services are often ill-funded (if not absent) the lack of funding options for treatment and preventative care have always been highlighted as factors in the spread of communicable diseases. In addition, the overall worldwide decline in plague incidence since the 1950s resulted in decreased financial support, lesser interest, and ultimately the deterioration of laboratory-based surveillance systems in many countries, worldwide. In this regard, several lessons can be learned and perhaps re-learned from the 1994 outbreak in India: i. the importance of thorough investigations using appropriate microbiology laboratory and epidemiological tools; ii. prevention of mass hysteria and public fear, which may be nurtured by inappropriate public media reporting; iii. appropriate management of all confirmed and suspected cases [72]. The recent plague outbreak in Kyrgyzstan in 2013 highlights several of these measures: official outbreak response teams were dispatched to first confirm the presence of plague, assess all clinical cases, and study local rodent populations, then administer antimicrobials to diseased individuals and those with confirmed exposure, and finally quarantine all afflicted individuals [152,153].

In this review, we provided several examples for plague occurrences throughout human history; the absence of or partial to complete breakdown of existing public health services has been commonly a problem associated with outbreak scenarios. More specifically, such lack of public health services has been a frequently expected and documented problem associated with infectious disease (and plague) outbreaks in developing countries. However, the difficulties imposed on public health infrastructure by financial hardship, insufficient funding, political struggle, and the need for specialized and trained personnel are obstacles that are not just unique to the developing world. Even in developed countries, community outreach and public health workers have frequently alluded to the importance of these issues during the past decades. In a recent review by Bevins and colleagues, the importance as well as success of robust, well-designed and funded surveillance systems has been highlighted, using the plague surveillance systems in the USA and China as examples [133]. Another extremely successful plague surveillance system existed during the time of the Soviet Union; this “anti-plague” system, founded on the basis of the plague surveillance infrastructure of the Russian Empire, was considered an important adjunct component to the Soviet Bioweapons program [78]. After the dissolution of the Soviet Union, parts of this plague surveillance system have been inherited with different levels of success by various, now independent countries formerly part of the Soviet Union; among these countries are Kazakhstan and Kyrgyzstan, which operate their

systems at a fairly successful level. In general, the implementation of such a comprehensive disease surveillance system is essential not only for a better understanding of zoonotic diseases, but also for developing strategies for treatment and prevention. Accurate diagnosis and disease reporting of human infections is usually considered to be at the core of such public health surveillance systems.

Human plague is considered to be a public health notifiable disease in many developed countries, including Western European countries, the United States, and in China; in addition it remains a WHO notifiable disease if cases occur outside endemic areas or the numbers of cases reach the threshold of initiating an epidemic. Furthermore, understanding that plague is a zoonotic disease with a complex transmission cycle, wildlife surveillance must be recognized as a critical component to better understand the pathogen and to detect the occurrence of epizootics in early stages of their development. Again, both the United States and China developed complex wildlife surveillance systems to monitor the prevalence of vectors and plague in rodents in endemic regions of their respective countries. China specifically demonstrated through its program the ability to implement an early warning system for increased plague risk, when closely monitoring the levels of fleas and rodent hosts. Understanding that surveillance systems must take unique ecological components of individual countries into account, surveillance strategies may differ among various countries; however, as outlined by Enserink, any successful surveillance strategy should involve a “One Health Approach” [154]. The concept of “One World, One Health” has received increasing attention during the past few years, as zoonoses, including plague, are a growing concern, worldwide [155]. The future success in prevention of zoonotic disease outbreaks and epidemics is intimately linked to the development of sustainable comprehensive surveillance systems, including the monitoring of human and animal health.

While a robust surveillance system is at the core of an effective “anti-plague” system, we outlined the importance to consider several natural occurring factors that contribute to increases in the incidence of infectious diseases; among such factors are natural disasters such as earthquakes, flooding, and perhaps other natural events related to global climate change. The risk of infectious disease outbreaks following such events is often specific to the nature of the disaster itself; however, it is also dependent on numerous other factors, such as the endemicity of the specific pathogens in the disaster-affected region, the type of the disaster itself, and the impact of the event on the existing infrastructure (e.g. sanitation, housing construction). The ability to sustain a functional public health infrastructure during a disaster is furthermore of critical importance. We presented some evidence in this review that certain natural disasters and climate factors may have the potential to not only effect wildlife in general, but specifically rodent and vector populations with respect to the transmission cycle of plague. While post-disaster surveillance systems are critically important to rapidly detect cases of epidemic-prone human disease (e.g. plague), the correct interpretation of such cases and subsequent mitigation strategies are likely to be hampered in the absence of baseline surveillance data. Despite the obvious need to prioritize efforts for mitigation of immediate threats during the acute stages of a disaster event, the knowledge of the baseline, enzootic and endemic background level of a specific disease is critically important for allocation of resources during the acute response phase of natural disasters and to allow for the most accurate risk assessment of infectious disease threats following disasters. Considering that most disasters strike with little warning, we would like to highlight the importance of baseline surveillance system of enzootic infectious diseases. The evidence provided by the above

analyses of historic plague outbreaks, and specifically the 20<sup>th</sup> century outbreaks in India and Algeria, support these conclusions.

Furthermore, we described the importance of travel and trade in ancient, historic, and more recent occurrences of plague. The increasing mobility of human societies coupled with other contributing factors (e.g. international trade, deforestation, and urbanization) has been associated with outbreaks of plague and various other infectious diseases throughout history. In order to prevent future epidemics and pandemics, the adoption of a “One World, One Health” approach will certainly be necessary; such approach combines improved wildlife and human disease surveillance with good governance of human health, veterinary, and food safety services, as well as improved education of human and veterinary healthcare workers. The potentially great threat that plague poses to humans has generated not only the need to develop and maintain sufficient support for diagnosis and treatment of human cases, but also the need to develop preventative vaccines. Unfortunately, to date no infallible plague vaccine exists for use in humans [156,157]. Considering that *Y. pestis* is a highly virulent pathogen, live-vaccines have been appealing as good candidates to balance the level of virulence with a retained ability to still elicit a sufficient immune response. In previous paragraphs, we described early attempts of vaccine development during the late 19<sup>th</sup> and early 20<sup>th</sup> centuries. Such attempts had little success, but it is noteworthy to recognize that the 19<sup>th</sup> century scientists already considered the development of preventative measures against plague. During the most recent decades, there has been a renewed interest in developing plague vaccines, and specifically live attenuated vaccines. The major challenge, however, in developing live-attenuated vaccines lies the process of balancing attenuation and immunogenicity. At this point, such vaccines may be best applicable for laboratory personnel working with *Y. pestis*, or people (e.g. veterinarians and wildlife workers) who reside in geographic areas with enzootic plague where complete avoidance of contact with rodents and fleas in impossible. Future research and studies will hopefully demonstrate progress with vaccine development and clinical trials to implement therapeutic plague vaccines that are safe and widely available [156]. It is of interest to note that one case of multi-drug resistance (MDR) in *Y. pestis* was reported in Madagascar in 1995 [158], the original isolate was resistant to ampicillin, chloramphenicol, kanamycin, streptomycin, spectinomycin, sulfonamides, tetracycline, and minocycline. Streptomycin, chloramphenicol, and tetracycline are typically used for treatment of plague, and sulfonamides and tetracycline are used for prophylaxis, and the occurrence of an MDR *Y. pestis* strain raised initial concerns for treatment and prophylaxis in future plague outbreaks, since the resistance plasmid appeared to be freely transferrable between organisms [159]. Since 1995, in the United States, antimicrobial resistance testing (AST) and monitoring is routinely performed on isolates of *Y. pestis*. However, subsequent studies found apparently little to no selective advantage for *Y. pestis* to maintain the MDR plasmid, and these studies found no evidence of antimicrobial resistance in *Y. pestis* isolates from rodent, flea-vector, and/or human cases from all three continents with plague endemicity [160]. Despite the lack of MDR, it will, however, be in the interest of any robust public health plague surveillance system to continue antimicrobial resistance surveillance of *Y. pestis* in isolates obtained from both rodent and human cases of plague, specifically considering the current increase of antimicrobial resistance, worldwide.

At this point the public health community on a global scale has received unprecedented support for public health emergencies such as pandemic infectious diseases. Since plague is an endemic disease

in many areas of the world, continued efforts to support national and international public health programs are essential to not only maintain, but further develop current capacities, in order to prepare for possible future outbreaks. The International Health Regulations as developed by the WHO are an essential component to achieve this goal [161]. Given its place in history, plague is frequently classified as a problem of the past. However, as demonstrated in this review it remains as an eminent threat to human health in many parts of the world, particularly in Sub-Saharan Africa and Asia. While plague may not be considered equal to the so-called “Big Three Diseases”, i.e. tuberculosis, malaria, and HIV/AIDS, when considering the current global prevalence of human disease, plague far exceeds these other diseases in its pathogenicity and rapid dissemination under the right conditions. One must also remember that plague cannot be simply eradicated, since it is widespread throughout wildlife rodent reservoirs. On a global scale, it is now more obvious than ever before that ancient foci of plague, even if considered to be extinguished at the present time, must be continuously monitored, in order to detect possible surges in disease activity that could lead to further dissemination and spread of this disease. We have illustrated in this review, that the key to the possibility of re-emergence of plague is in the “instability” of the ecosystem, a general concept previously proposed by Epstein in 1995 [162], any major changes in the existing ecology of plague, whether influenced by climate change, natural disaster events (e.g. floods and earthquakes), factors leading to deterioration of living conditions (e.g. wars, financial crisis), or ecological changes (e.g. urbanization, deforestation), should be interpreted as early warning signs to implement or increase surveillance efforts in order to detect the re-emergence of plague in its earliest stages. Therefore, it is our opinion, that plague should not be relegated to the sidelines of infectious diseases nor considered merely as an agent of bioterrorism/biowarfare, but that continued efforts in basic science, teaching of healthcare professionals, and clinical research are necessary to achieve a better understanding of the pathobiology and ecology of this disease in its natural environment. Understanding that surveillance efforts can be costly, it will be important to identify the most reliable, yet easily collectable indicators that allow for the most precise surveillance system to monitor plague and predict possible outbreaks. In addition to the surveillance efforts, it is critically important to build and maintain a resilient public health infrastructure which is necessary to prevent future re-emergences and expansion of this once widely feared disease.

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