The epidemiology of plague in Europe:
inferring transmission dynamics from historical data

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Proceedings of the National Academy of Sciences USA, doi: 10.1073/pnas.1715640115

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Summary

Throughout history, plague (*Yersinia pestis*) has caused devastating outbreaks in human populations around the world, however, the mechanisms that have given rise to plague epidemics are still poorly understood. With an emphasis on transmission, this thesis investigates the epidemiology of plague outbreaks in Europe using quantitative methods.

Several hypotheses have been proposed to explain the rapid spread of plague in Europe during the Black Death and throughout the Second Pandemic. The first paper in this thesis develops a novel mechanistic model for plague transmission by human ectoparasites, namely body lice and human fleas. By fitting the model to historical mortality data using Markov Chain Monte Carlo simulations in a Bayesian framework and comparing it to other candidate models, we demonstrate that human ectoparasite transmission could explain the development of large plague epidemics under certain conditions.

A challenge of modeling historical plague epidemics is that there are very few studies which have estimated parameters for untreated plague cases. In the second paper, we provide a detailed analysis of plague in the pre-antibiotic era using an outbreak from Glasgow, Scotland in 1900 as a case-study. Using a machine learning method (Expectation-Maximization), we reconstruct the transmission network for the outbreak from clinical and contact-tracing records. We provide estimates for several epidemiological parameters for bubonic plague, most likely spread between humans, possibly through a human ectoparasite vector.

Although often overlooked, plague outbreaks in Europe during the Third Pandemic may be used to better understand those during the Second Pandemic. In the third paper, we compile reports of internationally notified plague cases in Europe during the Third Pandemic. We show that there were more than 1,600 suspected cases of plague in Europe between 1899 and 1950. We found that most of these cases were distributed in coastal and inland ports, suggesting that the main source of

plague was from maritime shipping, not a local reservoir. Furthermore, we highlight the international efforts used to prevent the spread of infectious diseases and the improved hygienic conditions in Europe, which ultimately led to disappearance of plague.

In conclusion, this thesis improves our understanding of the mechanisms underlying the spread of plague in Europe using epidemiological models and historical outbreak records.

Introduction

Plague is a vector-borne zoonotic disease caused by the gram-negative bacterium *Yersinia pestis*, which primarily affects rodents. *Y. pestis* is maintained in a natural cycle, driven by transmission between rodent hosts and flea vectors [1]. During epizootics, plague can spread rapidly among highly susceptible hosts, including humans and other mammalian species [2]. In humans, the disease progresses quickly and is often fatal if treatment is inadequate or delayed [3]. Plague is infamous as the cause of three major pandemics in human history, including the Black Death, when it killed an estimated 30-60% of the European population, causing long-lasting social and economic repercussions [4]. Today, the distribution of plague is geographically widespread, and outbreaks still occur in countries liked Madagascar, where plague is endemic [5]. Natural foci are typically found in latitudes between 55 degrees North and 40 degrees South, mainly in tropical or sub-tropical regions, and occasionally in warmer temperate regions [6]. Epidemiological studies of plague, both modern and historical, have improved our understanding of the transmission, distribution, and control of the disease.

Ecology

The cycle of *Y. pestis* in the natural environment is characterized by periods of enzootic and epizootic activity [Figure 1]. During enzootic cycles, plague is maintained at low levels in the environment and transmitted between partially resistant rodents, which have low mortality for the disease, and their fleas [1; 2]. Epizootics occur when plague spreads from reservoir hosts to more highly susceptible hosts, called amplifying hosts [7]. Since amplifying hosts do not exhibit resistance to plague, the disease can spread rapidly and may lead to large die-offs [7]. In some areas, the distinction between the enzootic and epizootic periods is not always clear because a single host species may be involved in both maintenance and increased periods transmission [1].

There is no consensus as to how plague is maintained during endemic periods; although, it is generally accepted that heterogeneous responses to plague infection

in hosts may allow the disease to persist at low levels over long periods of time [1; 2; 8]. Other proposed mechanisms for the maintenance of plague include hibernation of hosts [9; 10], flea diversity [11], and persistence in the soil [8; 12; 13]. In particular, long-term persistence of *Y. pestis* in soil could explain the geographic distribution of plague foci [8; 14]. However, more research is needed to determine if *Y. pestis* can survive in natural soil samples, as either a free-living organism or as an intracellular parasite, and the steps involved in such a transmission pathway [12; 13; 15].

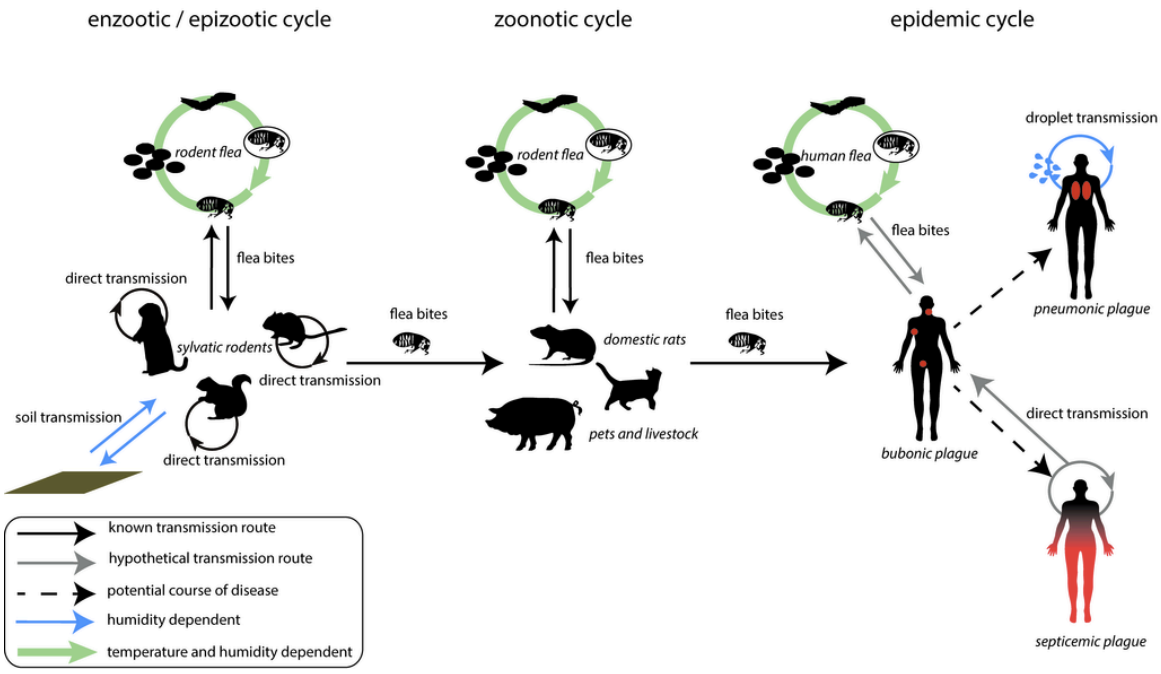

Figure 1. Plague transmission cycles: enzootic/epizootic cycle, zoonotic cycle, and epidemic cycle. Figure by Fabienne Krauer.

Epizootics are defined by an increase in secondary transmission above a critical threshold [2; 16]. Several studies have found associations between epizootics and host abundance, flea burden, and climatic factors [17-23]. This has led to the "trophic cascade hypothesis" to explain the relationship between increased precipitation and plague epizootics [17; 24]. The hypothesis predicts that increased rainfall leads to more plant growth, which in turn provides more food for expanding host populations [24; 25]. However, further studies have shown that the trophic

cascade hypothesis may apply in some foci, but not universally to all [17; 26]. In addition to climate fluctuations, there are numerous other factors that can impact epizootics, such as the *Y. pestis* strain [27], species of flea vector [28], genetic composition of the host population [29], and mechanisms for flea transmission [30].

Humans are most at risk for plague during epizootic periods, when the disease is amplified by highly susceptible hosts living in close proximity to human settlements [Figure 1]. In particular, epizootics among black rats (*Rattus rattus*) living in urban centers have been the most common cause of human cases during the Third Pandemic [6; 9]. As susceptible rats die of the infection, their fleas (*Xenopsylla cheopis*) seek alternate hosts for blood meals, leading them to bite humans and other mammals [6]. In addition to rats, there have been reports of plague cases from several species of domesticated animals including cats [31-34], dogs [35; 36], camels [37-41], goats [40], sheep [42], and rabbits [43]. Transmission from domestic animals to humans may occur through wounds, ingestion of infected meat, inhalation of infectious droplets, or by a cosmopolitan vector, such as the human flea (*Pulex irritans)* or the cat flea (*Ctenocephalides felis*) [6]. Once infected with plague, humans may further transmit the disease to other people [6]. This can occur directly, through primary pneumonic plague transmission, or indirectly through a vector, both creating the potential for large, rapidly spreading epidemics.

Transmission

In the last 5,000-9,000 years, *Y. pestis* evolved from a common ancestor of *Yersinia pseudotuberculosis*, and adopted a flea-borne route of transmission [44; 45]. In order for transmission to occur, flea vectors must acquire the bacteria during feeding, harbor the infection until a subsequent bloodmeal is taken, and further transmit the bacteria to a new susceptible host [46]. *Y. pestis* has evolved mechanisms in both hosts and fleas, including hypervirulence, to maximize the probability of transmission [2].

Experimental studies have shown that hosts need high levels of bacteremia ($\geq 10^6$ CFU/ml) in order to reliably transmit *Y. pestis* to fleas [47; 48]. Consequently, it is

thought that *Y. pestis* has developed high virulence in order to maintain transmission by fleas, which are inefficient vectors [49]. Studies have demonstrated that concentrations of *Y. pestis* in the blood of experimentally infected rats and mice can reach a maximum of 10^7-10^9 CFU/ml [50-52]. However, such high levels of bacteremia in hosts can lead to death within hours [30; 48]. Since fleas may feed multiple times a day on a single host, this short window of time is sufficient for a flea to become infected [49]. Furthermore, the death of a host encourages further transmission as fleas seek alternate sources for blood meals [49].

Once fleas are infected, they have several mechanisms for plague transmission, typically divided into biofilm-dependent transmission (BDT, or 'blocked' transmission) and early-phase transmission (EPT, or 'unblocked' transmission) [53]. Blocked transmission was first described by Bacot and Martin in 1914 [54]. During BDT, *Y. pestis* multiplies in the flea gut, forming a dense biofilm that eventually blocks the proventriculus [55]. The process of block formation can take as little as five days post infection, but more commonly occurs after two to three weeks [30; 49; 50]. A complete blockage prevents blood from entering the midgut, leading to starvation and frenzied attempts to feed [49]. Transmission occurs when the inflow of blood mixes with bacteria in the proventriculus and is regurgitated back [56-58]. Blocked *X. cheopis* can have a transmission rate as high as 50% for each feeding [49; 50; 57]. Although BDT is highly effective, individual fleas and many flea species, including known vectors for plague, will not form blockages [46]. Furthermore, studies have shown that that BDT alone cannot explain rapidly spreading epidemics due to both the long extrinsic incubation period and the short infectious period between blockage formation and the death of the flea due to starvation [59; 60].

Unlike BDT, early-phase transmission can occur hours or days after an infectious bloodmeal in most flea vectors [30; 59]. EPT was first discovered during experiments conducted by the India Plague Commission and others in 1904-1907 [53; 61; 62]. They observed that fleas could infect naïve rodents within days of feeding on a host with terminal bacteremia, but with a low rate of transmission,

with the highest rates being after the first bloodmeal and around 5-15% per flea bite [53; 61; 62]. Although EPT, previously termed mass transmission, is less efficient than BDT, it could explain rapidly spreading plague epizootics [30; 53].

Despite the importance of EPT, the exact mechanism for transmission is not known. Some studies point towards 'mechanical transmission,' meaning simply that bacteria are transferred while feeding with contaminated mouth parts [59]. However, others have noted that *Y. pestis* can only survive for 3 hours on exposed surfaces [63]. Another mechanism that has been suggested involves a biomechanical pathway, which would allow the survival of the bacteria in residual blood on the grooved surfaces of feeding and salivary canals of the flea mouthparts [30; 53]. A recent study by Bland et. al. (2018) has further suggested that EPT results from a phenomenon termed post-infection esophageal reflux (PIER), whereby *Y. pestis* is regurgitated from a partially obstructed flea foregut [57]. Interestingly, they also reported that EPT efficiency was influenced by the source of the host blood, post-infection esophageal reflux, and digestive tract obstruction, and may occur with BDT [57].

Early-phase transmission has opened up the possibility that flea species that do not efficiently form blockages may still act as vectors for plague, with potentially significant ecological and epidemiological repercussions [59]. In particular, the human flea (*Pulex irritans*) has been suggested as possible vector for interhuman transmission during the medieval period [8; 9; 64-66], despite its inability to participate in BDT. Even today, human fleas have been found infected with *Y. pestis* during recent outbreaks in Africa [67-69], although their ability to further transmit the disease under natural conditions has yet to be proven [59]. Limited experimental evidence suggests that *P. irritans* may transmit through EPT. In particular, a study by Blanc and Baltazard (1941) demonstrated that human fleas, which fed on terminally-ill patients, could infect guinea pigs with plague [65].

Overall, the relative importance of BDT and EPT in plague transmission in different contexts remains a subject of opinion [53]. Most agree that BDT is important for

the enzootic maintenance of plague and that EPT is most relevant during epizootics, when populations are highly susceptible (i.e., they develop high levels of bacteremia) [9; 50; 53]. However, some studies have argued that the role of EPT has been generally underappreciated in terms of plague ecology [53; 70]. For now, it seems likely that BDT and EPT are both important in a variety of situations. It is also clear that additional work is needed to further elucidate the transmission efficiency of both mechanisms under different scenarios.

Epidemiology and Clinical forms

Humans are highly susceptible to plague infection and cases of plague are internationally notifiable to WHO [6]. Long-term studies of plague have shown that the incidence, distribution, and clinical forms of plague have changed dramatically over time [71-74]. Today, the distribution of human plague cases is closely linked to the distribution of natural foci, which are presently found in North and South America, Africa, and Asia (Figure 2) [6]. Humans are most commonly infected after either direct or indirect contact with animals and their fleas. Moreover, studies have shown that the most important risk factors for plague are behaviors and conditions that increase these contacts, regardless of other socioeconomic factors [71; 72]. In areas where plague is endemic, human cases also show a marked seasonality throughout the year, with the highest incidence of cases corresponding to the timing of epizootics [75].

Plague is typically diagnosed by clinical features and laboratory testing. Symptoms of plague depend on the route of infection. The most common primary forms of the disease are bubonic, pneumonic, and septicemic plague (described in detail below) [71; 72]. Rare clinical forms of the disease include meningeal, pharyngeal, gastrointestinal, and ocular plague [76]. In cases where plague is suspected based on symptoms, the WHO recommends that specimens should be collected for diagnosis and patients should receive appropriate antimicrobial treatment prior to definitive confirmation [6].

A diagnosis of plague is typically confirmed on the basis of laboratory testing. Since the discovery of the bacterium in 1894, a culture of the bubo aspirate, blood, or sputum has been the traditional method of diagnosis, with the advantage of being both highly specific and sensitive [75]. Over time, newer methods for rapid detection have been developed using both immunoassays and PCR [75]. For post-exposure treatment, streptomycin, along with tetracycline, gentamicin, and fluoroquinolone antibiotics are recommended because they are effective against most *Y. pestis* isolates [77].

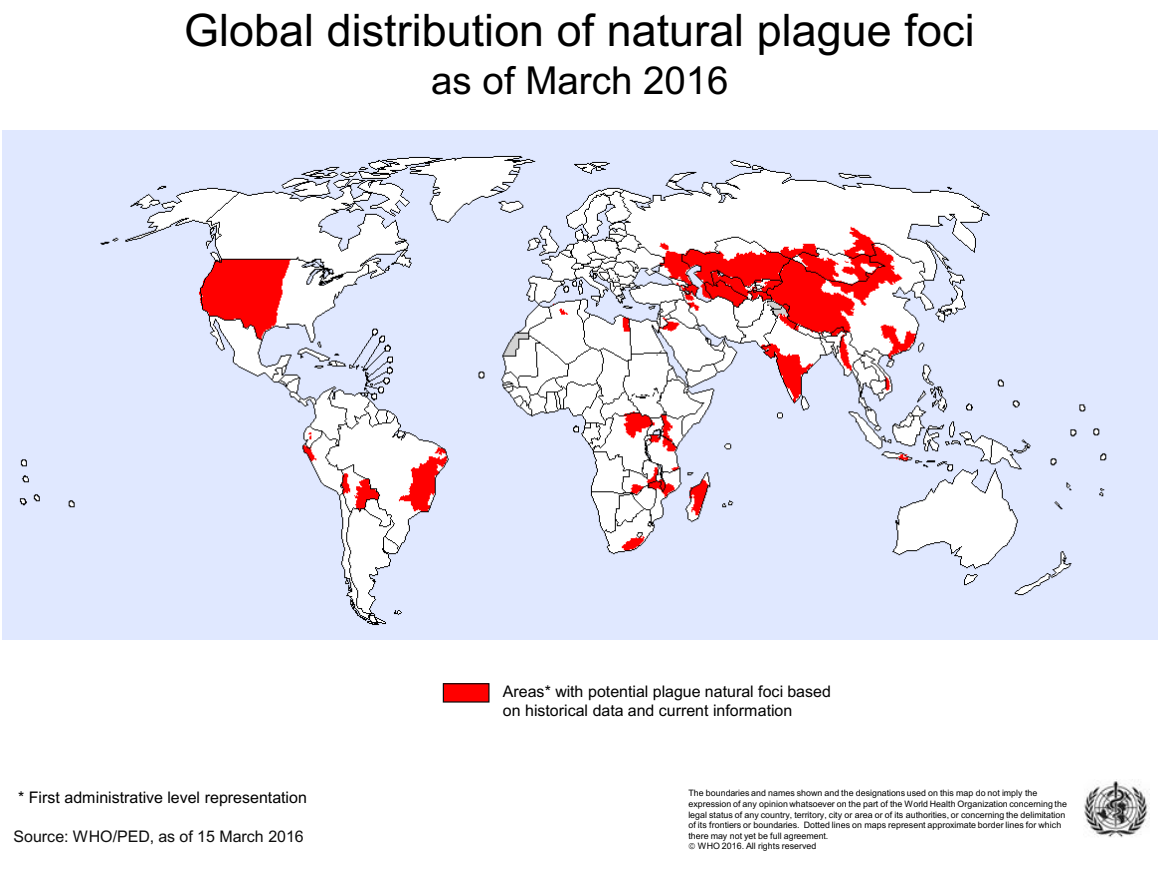

Figure 2. Geographical distribution of potential plague foci based on historical data. Image available from: World Health Organization. Global distribution of natural plague foci [image on the Internet]. 15 Mar 2016 [cited: 4 Mar 2009]. Available from: https://www.who.int/csr/disease/plague/Plague-map-2016.pdf?ua=1

Bubonic plague

Bubonic plague is the most common form of plague infection in humans, constituting approximately 80-90% of reported cases in the United States and

Madagascar [71; 72]. Bubonic plague occurs when *Y. pestis* enters the body through the skin, typically from the bite of an infected flea vector. From the bite site, bacteria are transported to the draining lymph node, where they multiply and cause swelling or 'buboes.' Symptoms of bubonic plague typically appear after an incubation period of two to six days and include fever, headache, chills, and tender and/or sore lymph nodes [78]. Patients also reported gastrointestinal symptoms and, less commonly, skin lesions at the infection site [79; 80]. If left untreated, symptoms of bubonic plague typically last three to seven days [81]. The disease can progress rapidly causing secondary pneumonic and septicemic infections in roughly 21% of cases [82]. In the pre-antibiotic era, bubonic plague had a case fatality rate of 60-90% [71]. However, since the introduction of antibiotics in the 1940s, the mortality rate in the United States has declined to 13% [71].

Pneumonic plague

Pneumonic plague, which accounts for around 10% of all reported plague cases, occurs when bacteria infect the lungs, either as a primary or secondary infection [71; 72]. Primary pneumonic plague is caused by inhalation of infectious droplets. Secondary pneumonic plague can occur if bacteria spread to the lungs during a bubonic or septicemic infection. An estimated 5-20% of bubonic patients develop secondary pneumonic plague, which can further transmit through the respiratory route, leading to primary cases among close contacts [82; 83]. As a result, pneumonic plague can be transmitted from person-to-person without an intermediate vector [83]. Human cases of pneumonic plague have also been linked to close contact with dogs [36; 84], cats [31; 85; 86], and one report of a mountain lion carcass [87].

Pneumonic plague has a short incubation period, on average around three days (range 1-6) [83; 88-90], in which patients may be asymptomatic for the first 20-24 hours [3]. Symptoms include sudden illness, coughing, headache, fever, chills, and increased heart rate [83; 88; 90]. Following the latent period, patients were infectious for an average of two to three days [89; 90]. The case-fatality rate (the

probability of dying from plague upon infection) for pneumonic plague is close to 100%, however antibiotic treatment is effective if administered in the first 20 hours of the infection [91]. The use of antibiotics since the 1950s has reduced the mortality rate of pneumonic plague to 35% [71]. Outbreaks of pneumonic plague since 2000 have been characterized by small, localized clusters, and, in general, the disease is not highly transmissible compared to other communicable diseases [89; 92].

Septicemic plague

Patients with primary septicemic plague have bacteremia, but an absence of apparent lymphadenopathy, following cutaneous exposure [6; 78]. Primary septicemic plague is relatively rare compared to bubonic and pneumonic forms, generally occurring in less than 10% of cases [71; 78], although it has been as high as 25% during some outbreaks [80]. Septicemic plague more commonly occurs as a secondary form of bubonic or pneumonic plague [72; 78]. Additionally, there is some debate as to whether or not septicemic plague should be regarded as a primary form of plague [78]. Clinical symptoms of septicemic plague, including chills, headache, weakness, and gastrointestinal distress, typically resemble those of sepsis caused by any gram-negative bacteria [78]. Death from septicemic plague occurs as the result of the endo-toxemic consequence of large numbers of bacteria in the blood and it can be fatal within 24 hours [59; 78]. From a study of 490 cases of plague in the United States in the antibiotic period, 38.9% of cases presenting with primary septicemia were fatal [59]. However, septicemia was found in 96.5% of all fatal cases based on positive cultures and smears [59]. Although it is not known, the proportion of untreated patients achieving septicemia and the duration that high levels of bacteremia are maintained, has important implications for interhuman early-phase transmission [59].

History of plague

Genetic studies have revealed that plague most likely evolved in Central Asia and spread globally on multiple occasions [93]. Distinct strains of plague are responsible

for at least three known pandemics in human history: the First Pandemic (6th-8th C.E.), the Second Pandemic (14th-19th C.E.), and the Third Pandemic (beginning in the 19th C.E.). Recently, an ancestor of *Y. pestis* was identified in archaeological remains from prehistoric times, suggesting that plague affected humans prior to the First Pandemic [94; 95]. Thus far, historical, genomic, and modeling studies have only begun to uncover the past distribution of plague, the transmission routes, and the populations that were affected by this epidemic disease. Here these aspects are presented with a particular emphasis on plague in Europe.

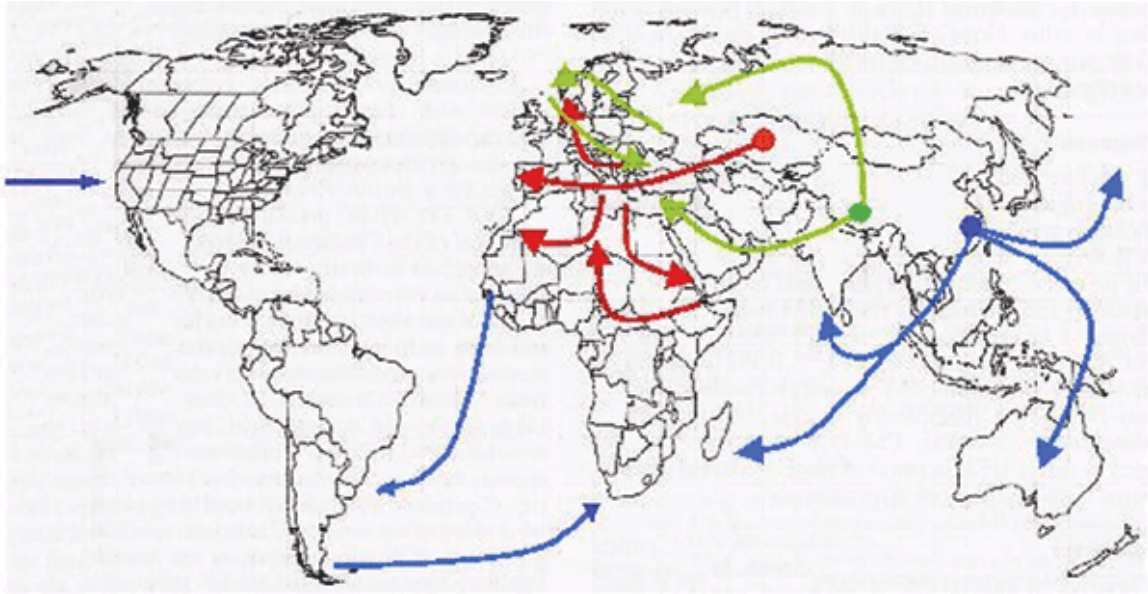

Figure 3. Geographic origin and routes of spreading of three historical plague pandemics labeled in red (First Pandemic), green (Second Pandemic), and blue (Third Pandemic). Image available from: Drancourt M, Roux V, Dang L, et al. Genotyping, Orientalis-like Yersinia pestis, and Plague Pandemics. [Figure appendix 4]. Emerging Infectious Diseases. 2004;10(9):1585-1592. doi:10.3201/eid1009.030933. Available under a Creative Commons Attribution License (CC-BY).

First pandemic

The earliest known records of the First Pandemic come from the summer of 541 AD, when an infectious disease resembling plague broke out in the Egyptian port city of Pelusium. By the next spring, it had spread to Constantinople, and eventually to Syria, Anatolia, Greece, Italy, Gual, Iberia, and North Africa [96]. The initial

spread of plague at the beginning of the First Pandemic is often called the "Plague of Justinian," referring to the concurrent reign of Emperor Justinian [96].

Evidence of the First Pandemic comes from historical narratives, as well as archaeological and ancient DNA studies. Historical narratives in Syriac, Arabic, Greek, and Latin document dozens of epidemics throughout the Mediterranean, reaching as far inland as Persia and as far north as the British Isles [96]. Witnesses describe a disease that killed entire towns and regions, leaving behind abandoned dwellings and farms [96]. They also wrote about symptoms of the infection, which progressed rapidly and caused sores and swollen glands [96]. Many places were hit multiple times by the disease over a 200-hundred-year period; the last known plague outbreak attributed to the First Pandemic was from 749-750 in Naples and in Sicily [96].

The analysis of ancient DNA from human remains has confirmed that plague was the etiological agent of the First Pandemic. Early studies using PCR approaches were able to positively identify *Y. pestis* in samples from multiple sites in Germany, dated to the 6th century [97; 98]. The latter study also confirmed previous phylogenetic analyses, which placed the origin of the First Pandemic in Asia [93; 98; 99]. Whole genome sequencing of *Y. pestis* strains further revealed that the First Pandemic was caused by a genetically distinct lineage [100; 101].

Second pandemic

The Second Pandemic began in the middle of the 14th century. The exact origin of the plague strain responsible for the Second Pandemic is not known; however, ecological and genetic evidence suggests that the disease came from Asia along the Silk Road and through the Caucuses [93; 102]. Historical evidence suggests that plague was introduced to Europe in 1346, when Mongols besieged the city of Caffa (now Feodosija, Ukraine), which was a major point of trade along the Don River for Genoese merchants [103]. A narrative of the events asserts that plague-infected corpses were hurdled over the walls of the city, infecting the thousands of

inhabitants, who in turn fled, spreading the disease throughout the Mediterranean basin and eventually the rest of Europe [103].

The initial introduction and spread of plague throughout Europe is known as the Black Death (1347-1352). From Crimea, plague spread along shipping routes in the Mediterranean basin, eventually reaching western Europe through Messina, Sicily in October 1347 [104; 105]. By the beginning of 1348, plague had affected the coastal areas around the Mediterranean, including Alexandria and Tunis, Sardinia, Toulouse, and Marseilles [104]. The disease soon reached the Atlantic coast of France, where it then spread to the United Kingdom, and eventually through the North Sea to Scandinavia [104]. Plague continued to travel in Denmark and Germany, and epidemics extended as far as Poland in 1951 and Russia in 1952 [104]. By the end of the Black Death, plague had killed millions of people in Europe, North Africa, and the Near East [104].

While the Black Death was particularly devastating, it was only the beginning of the Second Pandemic, which lasted up until the late-19th century. Successive waves of plague hit areas in Europe and the Middle East repeatedly, and although the overall mortality was less than during the Black Death [104], the European population did not recover until the 15th and 16th centuries [106]. But even after the 16th century, many cities still experienced severe plague outbreaks, including the Italian Plague (1629-1630), the Great Plague of Seville (1647-1652), the Great Plague of London (1665-1666), the Great Plague of Vienna (1679), the Great Northern War outbreaks (1700-1721), the Great Plague of Marseilles (1720-1722), and the Russian plague (1770-1772) [107-110].

Unlike the First Pandemic, the waves of plague during the Second Pandemic are documented by a rich historical record [105]. The sources from this time period include hundreds of chronicles, as well as thousands of last wills and testaments, necrologies, burial records, doctors' records, ecclesiastical vacancies, and court rolls [105]. These surviving documents have given us a glimpse of the plague during the Second Pandemic, including the mortality patterns, seasonal fluctuations, and

symptoms and details about the victims, such as age, sex, occupation, lifestyle, living conditions, and wealth [105].

Despite the large number of records from the Second Pandemic, several aspects about plague during this time are still hotly debated. For more than a half-century, scholars have questioned the etiological agent of the Second Pandemic (e.g., [105; 111; 112]), the origins and maintenance of the disease (e.g., [102; 113]), searched for rodent reservoirs in Europe (e.g., [114; 115]), and proposed alternate pathways for transmission (e.g., [8; 66]). Over the past few decades, the analysis of ancient DNA has confirmed the presence of *Y. pestis* during the Second Pandemic and, currently, there are nearly a dozen published genomes [116-119]. However, these studies have failed to definitively answer the question of whether plague remained in Europe in a wildlife or soil reservoir, or if it was continually introduced through travel and trade from Asia, as suggested by others [102; 120-122]. Distinguishing between the two scenarios using genetic data is complicated by the fact that *Y. pestis* has low genetic diversity due to its recent origin and slow mutation rate [99; 116].

Rats are often regarded as both a potential reservoir species for plague in Europe as well as transmitters of the disease to humans. However, clarifying the role of rats during the Second Pandemic has not yet been possible with the archaeological and historical evidence currently on hand. Numerous studies have raised doubts that rats played a large role during plague transmission, on the basis that Europe has never had a large black rat population because of the temperate climate [123-127]. Others argue that the epidemiology of plague in Europe is not consistent with outbreaks involving black rats, with respect to the seasonality [105; 128], rate of spread [129], and household infections [130; 131]. In response, several researchers have proposed the transmission of plague by human ectoparasites, such as body lice or fleas, as an alternative mechanism for the spread of plague during the Black Death and throughout the Second Pandemic, as reviewed by Drancourt et. al. (2006) [8].

Third pandemic

The earliest records of the Third Pandemic come from the Yunnan region of southwest China, where plague caused regular outbreaks beginning in 1772 along the Yunnan-Tibetan trade route [14; 132; 133]. The exact timing of the Third Pandemic in China is not known, and there is some indication that outbreaks began as early as the 17th-century [132]. Plague spread from Yunnan to nearby provinces Guangxi and Guangdong by the latter half of the 19th century, and eventually to the Leizhou Peninsula and Hainan Island [133]. The disease eventually reached the Pearl River Delta by the 1890s, and by the spring of 1894, it was in Hong Kong and Canton [133]. From Hong Kong, plague continued to spread by steamships to major ports around the world, and for this reason 1894 is generally thought of as the beginning of the Third Pandemic [132; 134; 135]. Today, reservoirs seeded by introductions of plague during the Third Pandemic continue to affect countries in Africa, Asia, and the Americas.

At the beginning of the Third Pandemic, India was hit particularly hard by epidemics which killed an estimated 6,000,000 people between 1898 and 1908 [9; 135]. During the outbreaks in India and Hong Kong, scientists used new microbiological and experimental techniques to investigate the cause of the disease and its transmission to man [136]. This led to the discovery of the bacterium, which is credited to Alexandre Yersin in 1894 [136]. Yersin noted that there were many dead rats in Hong Kong, and he observed that they too were infected with the bacillus he found in human buboes [136]. In 1987, Paul-Louis Simond was sent by the Pasteur Institute to Bombay to continue the work that Yersin had started [136]. Two years later, Simond reported on his experiments, which demonstrated that fleas were capable of transmitting plague from infected rats to healthy rats [136; 137]. These early works formed the basis of how plague is understood today, as a vector-borne disease predominantly spread by rodents.

Against this backdrop, the first cases of plague were recorded in Europe in 1897. In the Autumn of 1897, two sailors died of suspected plague on ships, originally

from Bombay, docked in London, on the Thames [138]. From that point on, Europe experienced multiple outbreaks of plague in several major cities, up until the 1940s. The largest of these outbreaks occurred in Porto and Lisbon in 1899-1900, with more than 322 cases and 115 deaths [134]. With better awareness of the disease and its causes, European authorities enacted international regulations on trade and transport, as well as, targeted prevention measures, such as rat-catching and quarantining, in an attempt to stop the spread of plague (e.g., [139-142]). These measures, along with improvements to hygiene, and the lack of a rodent reservoir all likely contributed to the decline and later disappearance of plague from Europe.

Aims

There are many open questions about the spread and maintenance of plague in Europe throughout history, and in particular, during the Second Pandemic. The main objective of my thesis was to gain a better understanding of the epidemiology of plague in Europe using historical data. In **Papers I-III**, I investigate two of these questions, namely how was plague transmitted in Europe and why did it eventually disappear.

Human ectoparasite transmission is often alluded to as a possible mechanism to explain the spread of plague in Europe, without rats. In **Paper I**, we explored the hypothesis of human ectoparasite transmission, to see if a model could fit the observed mortality data for different outbreaks in Europe during the Second Pandemic, and under what conditions.

For many plague outbreaks in Europe, there is very little detailed information about specific cases and how they are connected, which is important for understanding the spread of an infectious disease. In this way **Paper II** represents a continuation of **Paper I**, where we took an in-depth look at an outbreak of plague in Glasgow in 1900 to better understand the pattern of disease transmission.

The Third Pandemic in Europe can be used in other ways to better understand the Second Pandemic. In **Paper III**, we document the outbreaks and cases of plague reported during the Third Pandemic.

Together, these papers shed light on the transmission processes and patterns of plague in Europe throughout history.

Approaches

Mathematical models of infectious diseases are important for understanding the progress of an outbreak and for predicting future outcomes, while at the same time offering insights into transmission parameters and their uncertainties [143]. The modeling approach in **Papers I and II** is for the purpose of increasing our understanding of the transmission processes of plague in Europe. The choice of models, in particular, was largely driven by the availability and quality of data.

Compartmental models, like those in **Paper I**, are commonly used to study infectious diseases and range from exceedingly simple to highly complex, depending on the nature of the question being addressed. The SIR model, introduced by Kermack and McKendrick (1927), is one of the simplest examples of a compartmental model, which divides the population into three compartments: susceptible, infectious, and recovered [143; 144]. In this particular example, there are two transmissions between the classes, the rate of transmission (S to I) and the rate of recovery (I to R), both assumed to be constant. The transmission rate, or β, encapsulates both the contact rate between S and I classes and the likelihood of transmission given a contact, and can be expressed as either frequency-dependent or density-dependent term based on how it scales with population size [145]. This coefficient is usually estimated due to the fact that it is difficult to obtain from field data [145]. Statistical estimation of the transmission coefficient, and other parameters, is generally accomplished by fitting models to epidemiological data, such as incident cases or mortality, as in **Paper I**.

The transmission rate is generally of interest because it is used to calculate the basic reproduction number, as we do in **Paper I**, using the next-generation matrix method [146]. The basic reproduction number, R_0, is by definition the number of secondary infections produced by a primary case in an entirely susceptible population [147]. It is also the critical threshold for disease invasion, whereby an $R_0 = 1$ denotes the endemic equilibrium and an $R_0 > 1$ can result in an epidemic [147].

While most infectious disease studies estimate the reproduction number, the generation interval is also needed to calculate the rate of spread at the population level [148]. The generation interval is defined as the time between two infections: the infection of the infector and the infection of the person that they infected [148]. Generation intervals are typically difficult to observe [149]; therefore, the serial interval is more commonly used, as shown in **Paper II**, which is the time between the symptom onsets of two infections. For vector-borne diseases, such as bubonic plague, the serial interval includes time spent in the vector [150].

Both the reproduction number and the serial interval can be inferred from the transmission tree of an outbreak, as shown in **Paper II**. The transmission tree or network can be reconstructed using clinical and contact tracing information, although, in practicality, only partial information is obtained for most outbreaks [151]. Therefore, it is often necessary to infer plausible trees from the available data, as in **Paper II**, or to use additional data such as spatial or genomic data [152]. With reconstructed trees, it is possible to directly calculate the time-varying reproduction rate, as done in **Paper II**, and to reconstruct the serial interval distribution for the outbreak.

A general challenge of mathematical modelling is to determine the underlying processes that gave rise to the observed dynamics, and to simplify these into rules in order to produce accurate representations of the data [149]. In this way, models are highly dependent on the biological assumptions behind choices in both model structure and the specification of priors. A large effort was made in both **Papers I and II** to use the findings of epidemiological and experimental studies to inform model assumptions. However, there is significant room to improve these models, in particular with a better understanding of human ectoparasite transmission efficiency, seasonality, and behavior, as well as, more information about plague septicemia in humans, and better ways of incorporating time-varying contact rates [149].

Paper Summaries

Paper I. Human ectoparasites and the spread of plague in Europe during the Second Pandemic

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In Paper I, we investigated the potential role of human ectoparasite transmission during the Second Pandemic. To do so, we developed a compartmental SIR model for human ectoparasite transmission, and we compared this to models for primary pneumonic plague transmission and bubonic transmission with black rats (*R. rattus)* and their fleas (*X. cheopis)*. We fit the models using Bayesian inference and MCMC simulations to mortality data from nine outbreaks in Europe during the Second Pandemic and three outbreaks worldwide during the Third Pandemic. From the fitted models, we obtained estimates for the basic reproduction numbers and the transmission parameters. Our results show that our model for human ectoparasite transmission could not be excluded for any of the outbreaks during the Second Pandemic, and in most cases was preferred over models for pneumonic or rat transmission. Although we could not definitively conclude that human ectoparasites contributed the spread of plague in Europe during the Second Pandemic, we do provide support that this is a possible mechanism under certain assumptions.

Paper II. Epidemiology of a bubonic plague outbreak in Glasgow, Scotland in 1900

Royal Society Open Science, 2019, DOI: 10.1098/rsos.181695

In Paper II, we used a well-documented outbreak of bubonic plague in Glasgow in 1900 as a case-study for the epidemiology and transmission of plague in Europe during the Third Pandemic. The outbreak in Glasgow was documented in a report, containing information about 35 patients, including their age, sex, residence, contacts, and symptom onset and death dates. We used this information to reconstruct possible transmission trees for the outbreak, using a likelihood-based

method. We found that the mortality rate was 43%, the median symptomatic period from fatal cases was 6 days (range 2-44), and the median age at infection was 22 years (range 0-66). From the simulated trees we inferred that the mean serial interval was 7.4-9.2 days, depending on the assumptions of the model. We also found that the mean effective reproduction number dropped below one following the identification of plague and implementation of control measures. The sanitary authorities that originally investigated the outbreak noted that new cases could be connected by contacts with previous ones, consistent with a disease that spreads between people. Our results show that there was a high rate of secondary transmission within households, which further supports that the disease was likely spread by human ectoparasite transmission.

Paper III. The third plague pandemic in Europe

Proceedings of the Royal Society B, DOI: 10.1098/rspb.2018.2429 (in press)

In Paper III, we document outbreaks of plague in Europe during the Third Pandemic by digitizing and geocoding hundreds of internationally reported case records and using supplemental information from previous studies and gray literature. We found that there were 1,692 cases of plague reported in Europe between 1899 and 1947, with more than 250 cases in 1899 and 1920. The geographic distribution of cases shows that plague was mainly introduced by ship to major port cities. Despite the many introductions, these outbreaks did not spread further and were usually of small size. In light of scientific advancements during the Third Pandemic, we discuss the role of rats and other documented sources of plague. With no evidence of a plague reservoir in Europe, we argue that international public health measures and improved hygiene led to the disappearance of plague entirely.

Discussion

Mechanisms of plague transmission in Europe

Over the last decade, studies using mathematical models have begun to uncover some of the patterns and processes of plague transmission throughout European history. Many of these studies have highlighted the importance of human agency in the introduction and spread of plague during the Second Pandemic [102; 116; 121; 122; 129; 130]. In particular, Schmid et. al. (2015) found a significant association between climate fluctuations in Asia, as indicated by tree-ring growth, and recorded plague outbreaks in Europe, suggesting that plague was not present in a European reservoir, but was instead introduced multiple times from outside [102]. Yue et al. (2016, 2017) further supported this claim by showing that plague outbreaks in Europe were positively correlated with their proximity to major ports, consistent with a scenario that plague was continually introduced through trade and travel [121; 122]. In **Paper III**, we found this pattern for the Third Pandemic, by showing that plague outbreaks in Europe mainly occurred in coastal or inland ports cities, with no evidence of a rodent reservoir. Collectively, these studies have underscored the importance of human-mediated disease spread.

Compartmental disease models have been widely used to study the transmission of plague during individual outbreaks during the Second Pandemic [131; 153-158]. The majority of these studies focus on the spread of plague by black rats (*R. rattus*) and rat-fleas (*X. cheopis*), despite little ecological or historical support for their role during the Second Pandemic as discussed in **Papers I, II, and III** [154-158]. More recent studies have begun to consider the contribution of alternate transmission mechanisms, such as pneumonic plague or bubonic plague spread by human ectoparasite vectors [131; 153]. In **Paper I**, we compared three different transmission routes for plague in Europe, using mortality data from nine outbreaks. Our results from **Paper I** showed that a model for human ectoparasite transmission could explain the pattern of observed mortality for all of the outbreaks, while models for rat-borne and pneumonic transmission, in almost all

cases, could not. **Paper II** supported this result by showing that bubonic plague most likely spread through human contacts in an epidemic in Glasgow in 1900. Future work should focus on further investigating human ectoparasite models of transmission, and other mixed-transmission models, that have been proposed in **Paper I**.

The plausibility of human ectoparasite transmission remains under question for two main reasons. The first reason is a lack of experimental evidence that human fleas and body lice can act as efficient vectors for plague. The human ectoparasite model in **Paper I** was based primarily on an experimental study that demonstrated plague could be transmitted between body lice and rabbits [13; 159]. However, given that transmission of *Y. pestis* by vectors is dependent on blood source, strain, vector species, and transmission mechanism, additional experimental studies are an important step to evaluate the assumptions for the model in **Paper I**. A second reason human ectoparasite transmission is controversial is that there is limited information about disease progression in humans. This is important because experimental studies have shown that high levels of bacteremia, consistent with terminal septicemia, are required for vectors to become infected [48]. In both **Papers I and II**, we estimated that the majority of transmissions occurred from moribund cases, as expected. However, in **Paper II** we found evidence that a few individuals who were thought to have transmitted plague ultimately recovered from their infections. Even so, the level and duration of bacteremia required for humans to efficiently transmit to vectors remains an open question. In any case, we found in **Paper I** that a high vector to host ratio could potentially compensate for poor vector competency.

Characteristics of European plague epidemics

In **Papers I, II, and III**, we touch upon important characteristics of European plague epidemics, providing both quantitative and qualitative information regarding various outbreaks. In **Papers I and II**, we estimated the basic reproduction number to range between 1.48-1.91, assuming a model of human ectoparasite

transmission. All of the estimates were greater than one, and thus above the critical threshold for disease invasion in the population [148]. We showed in **Paper II** that a drop in the effective reproduction number below one during the plague outbreak in Glasgow coincided with the implementation of intervention measures, suggesting that they were effective in stopping the spread of the disease. In **Paper II**, we also estimated the serial interval. We found that the average serial interval between successive cases was 7.4-9.2 days, although this is somewhat hard to interpret for a vector-borne disease because it includes time spent in the vector [150].

Mortality and case-fatality rates for plague are often discussed in reference to the Second Pandemic, as points of demographic interest, population health, and virulence (e.g., [106; 112; 160; 161]). From **Paper I**, it is clear that plague had a high mortality rate during the Second Pandemic, meaning that a large fraction of the population died. However, the case-fatality rate could not be determined because of a lack of case information. Several studies have speculated about the sex-selective mortality of plague (e.g., [107; 162-164]); however, it is not known if observed increases in female mortality are due to biological factors or differential exposure [164]. In **Paper II**, we found that the case-fatality rate in Glasgow was 43%, with no difference in the rates between males and females, which supports that observations of sex-selective mortality may be due to other factors, such as differences in exposure. Although **Paper II** investigates a very limited number of cases, it does provide a reliable estimate of fatality for untreated plague cases, which is difficult to obtain for most outbreaks due to a lack of historical case data.

Finally, several studies have reported that previous cases in a household appear to be a risk factor for plague during European outbreaks [130; 131; 164-167]. Household clustering of plague cases can be attributed to direct or indirect human transmission, either through pneumonic plague or through a flea vector. This is supported by the fact that household transmission was not observed during outbreaks of plague caused by rats in Bombay, Sydney, or New Orleans [168-170]. In **Paper II**, we found weak evidence of household clustering during the outbreak

in Glasgow. Unlike previous studies, we had the advantage of knowing that the cases in **Paper II** were bubonic plague, supporting the hypothesis of human ectoparasite transmission and, in part, the conclusions of **Paper I**.

The decline of plague in Europe

While the Third Pandemic marked a rise in plague incidence following recent introductions in the United States, Madagascar, and the Congo, we show in **Paper III** that plague cases declined in Europe compared to the Second Pandemic. The decline of plague in Europe during the 20th century compared to other parts of the world is invariably tied to a lack of rodent reservoirs for the disease, the primary source of human plague cases today. In **Paper III**, we show that there is currently no evidence that a rodent reservoir was present in Europe at the time of the Third Pandemic. Furthermore, in **Papers II and III**, we found that effective intervention measures and increased hygiene were likely key to stopping plague when it was introduced from abroad.

Challenges of using historical data

Papers I, II, and II, and the majority of other modelling studies of plague in Europe, rely on the use of historical data about plague cases. The use of historical data, although widely available now in digitized format, is inherently problematic. A review by Roosen and Curtis (2018), in particular, has criticized studies for using digitized datasets without acknowledging potential biases in data collection, the representativeness of the data itself, and potential errors in the original sources [171]. In **Papers I, II, and III**, we have tried to overcome or acknowledge challenges in the use of historical data. For instance, in **Paper I**, we have used outbreak data from a wide temporal and geographic range to reflect that of plague during the Second Pandemic. Ideally, all of the cases and deaths in **Papers I and III** would be bacteriologically confirmed as plague. However, at least for the Second Pandemic, verifying the presence of plague is difficult because it relies on the recovery of ancient DNA, which has thus far been found in very few locations and, typically, with high uncertainty in the dating of samples. In **Paper II**, we used an

outbreak that was bacteriologically confirmed, however, an assumption of the analysis was that all cases of plague were observed. While the sanitary authorities at that time made a strong effort to discover all of the cases, this is difficult to verify even during a modern outbreak investigation. Despite these challenges, historical data does provide a wealth of information about plague epidemics if used with caution.

Conclusions and future perspectives

In light of recent technical advances in microbiology, mathematical modelling, and ancient DNA analysis, our view of historical plague epidemics is changing. By combining historical data with mathematical epidemiology approaches, this thesis sheds light on some of the interesting characteristics of plague in Europe during the Second and Third Pandemics. The studies in this thesis show that plague in Europe was characteristically a human-mediated disease in Europe. We show that the patterns of mortality during the Second Pandemic are consistent with a model for human ectoparasite transmission. We further provide a detailed account of the epidemiology of plague in Glasgow in 1900 that supports a disease that spread through human contacts. Finally, we demonstrate that plague disappeared from Europe during the 20th century despite frequent re-introductions due improved intervention measures and the lack of a suitable rodent reservoir. These results have improved our understanding of historical plague in Europe, while creating new possibilities for future work.

In particular, modelling approaches provide a means to investigate questions about seasonality, acquired immunity, and mixed transmission routes during the Second Pandemic. Given that **Papers I, II, and III** promote a hypothesis of human ectoparasite transmission of plague, rather than rat-borne transmission, it would be interesting to investigate these questions from this new perspective. In general, the seasonality of plague outbreaks in Europe is poorly understood, in part due to an incomplete understanding of the transmission mechanisms. Modeling the effects of seasonality on human flea dynamics by incorporating a seasonality component to

the model in **Paper I**, could be used to answer questions about the timing of epidemics. Further incorporating acquired immunity in populations would be useful for understanding differences in general and age-specific mortality rates for recurrent outbreaks. Finally, it is clear that a model for human ectoparasite transmission cannot account for primary pneumonic plague cases. Therefore, it would be interesting to explore models for mixed-transmission for historical outbreaks. Given that primary pneumonic plague does not always occur in certain regions [172], it is necessary to determine the environmental conditions associated with pneumonic plague cases and use those to predict when and where pneumonic plague would have occurred in the past.

Interdisciplinary work is important for answering many of the remaining questions about plague. In particular, modeling studies rely on experimental and ecological data for human ectoparasites for more accurate and precise parameter estimates. Furthermore, integrating genetic and historical information is crucial to address questions about a historical rodent reservoir in or near Europe. To this end, the data in **Paper III** can be incorporated into existing global outbreak records and combined with genetic data to model the spread of plague worldwide during the Third Pandemic. In the future, it may be possible to do a similar study for the Second Pandemic, however, such work hinges upon obtaining a wider representation of plague outbreak data from Asia, the Middle East, and North Africa.

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Chapter I

Human ectoparasites and the spread of plague in Europe during the Second Pandemic

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Plague, caused by the bacterium *Yersinia pestis*, can spread through human populations by multiple transmission pathways. Today, most human plague cases are bubonic, caused by spillover of infected fleas from rodent epizootics, or pneumonic, caused by inhalation of infectious droplets. However, little is known about the historical spread of plague in Europe during the Second Pandemic (14–19th centuries), including the Black Death, which led to high mortality and recurrent epidemics for hundreds of years. Several studies have suggested that human ectoparasite vectors, such as human fleas (*Pulex irritans*) or body lice (*Pediculus humanus humanus*), caused the rapidly spreading epidemics. Here, we describe a compartmental model for plague transmission by a human ectoparasite vector. Using Bayesian inference, we found that this model fits mortality curves from nine outbreaks in Europe better than models for pneumonic or rodent transmission. Our results support that human ectoparasites were primary vectors for plague during the Second Pandemic, including the Black Death (1346–1353), ultimately challenging the assumption that plague in Europe was predominantly spread by rats.

Yersinia pestis | Black Death | SIR modeling | Bayesian analysis | Monte Carlo Markov chain

Plague, caused by the bacterium *Yersinia pestis*, has been extensively studied due to its modern and historical significance. In the past, plague has famously caused at least three pandemics in human history: the First Pandemic beginning with the Justinianic Plague (6th to 8th centuries), the Second Pandemic beginning with the "Black Death" (14th to 19th centuries), and the Third Pandemic (beginning in the 19th century) (1). Today, plague persists primarily in rodent reservoirs in Asia, Africa, and the Americas, where it poses a recurrent threat to nearby human settlements (2).

The most common forms of plague infection are bubonic and pneumonic (2). Bubonic plague occurs when bacteria enter the skin, usually from the bite of an infected flea vector. The bacteria are then transported to the lymph nodes, causing characteristic swelling, or "buboes." Bubonic plague is typically transmitted to humans from wild or commensal rodents (3), but transmission between people is also thought to occur by human ectoparasites, such as human fleas (*Pulex irritans*) or body lice (*Pediculus humanus humanus*) (4). Primary pneumonic plague occurs when aerosolized bacteria enter and infect the lungs. Pneumonic plague can also arise as a complication of bubonic or septicemic infections (2), known as secondary pneumonic plague. Individuals with pneumonic plague can transmit the disease through the respiratory route, although outbreaks of pneumonic plague are typically small because infected persons die rapidly without treatment (5). Septicemic plague occurs when bacteria infect the bloodstream, commonly from a primary pneumonic or bubonic infection (2).

A central focus of historical plague research has been to understand the spread and persistence of plague in Europe. Little is known about the transmission of plague in Europe, the Middle East, and North Africa during the Second Pandemic, including the Black Death, when the disease killed an estimated one-third of the population. Many studies (4, 6, 7) have suggested that human ectoparasites, like human fleas and body lice, were more likely than commensal rats to have caused the rapidly spreading epidemics. Proponents of the "human ectoparasite hypothesis" argue that plague epidemics during the Second Pandemic differ from the rat-associated epidemics that occurred later, during the Third Pandemic. Specifically, the geographic spread and total mortality of the Black Death far exceeds that of modern plague epidemics (8). While contemporaneous accounts of symptoms during the Second Pandemic are consistent with those of plague (7), there are no descriptions of rat epizootics, or "rat falls," that often precede epidemics in the Third Pandemic (7–9). Some have noted that the climate of northern Europe could not have fostered the widespread distribution of *Rattus rattus* (10), a claim that is supported by a scarcity of rats in the archaeological record (6). Finally, epidemiological characteristics of plague in Europe, such as a high rate of household transmission (11), are suggestive of a more direct transmission route (12).

Despite support for human ectoparasite transmission, it has been difficult to assess their historical contribution because their role in modern plague epidemics appears to be relatively minor. Today, human ectoparasite diseases have declined in most developed countries, but they are still associated with poverty and unhygienic conditions (13). In the past, human ectoparasites

Significance

Plague is infamous as the cause of the Black Death (1347–1353) and later Second Pandemic (14th to 19th centuries CE), when devastating epidemics occurred throughout Europe, the Middle East, and North Africa. Despite the historical significance of the disease, the mechanisms underlying the spread of plague in Europe are poorly understood. While it is commonly assumed that rats and their fleas spread plague during the Second Pandemic, there is little historical and archaeological support for such a claim. Here, we show that human ectoparasites, like body lice and human fleas, might be more likely than rats to have caused the rapidly developing epidemics in pre-Industrial Europe. Such an alternative transmission route explains many of the notable epidemiological differences between historical and modern plague epidemics.

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Table 1. Summary of the Second Pandemic mortality data

Location	Date (MM/YYYY)	Population	Recorded mortality	Refs.
Givry, France	07/1348–11/1348	1,500	636	22
Florence, Italy	05/1400–11/1400	60,000	10,215	23
Barcelona, Spain	04/1490–09/1490	25,000	3,576	24, 25
London, England	06/1563–01/1564	80,000	16,886	26
Eyam, England	06/1666–11/1666	350	197	26
Gdansk, Poland	03/1709–12/1709	50,000	23,496	27
Stockholm, Sweden	08/1710–02/1711	55,000	12,252	27
Moscow, Russia	07/1771–12/1771	300,000	53,642	28
Island of Malta, Malta	04/1813–11/1813	97,000	4,487	29

The present-day location, date (month/year), preplague population size, and recorded plague deaths, for nine plague outbreaks during the Second Pandemic.

have been efficient vectors for diseases such as epidemic typhus (14) and relapsing fever (15). In 1941, plague-infected body lice and human fleas were found on septicemic patients during an outbreak in Morocco (16), indicating that humans can transmit the disease to lice and human fleas. In addition, recent experimental studies have demonstrated that body lice can transmit the bacteria to naive rabbits (4, 17–19). However, the transmission from body lice and human fleas to humans has not yet been documented, and thus the importance of human ectoparasite transmission in current and historic settings remains an open question. Our theoretical analysis demonstrates that human ectoparasites may indeed play such a role.

Mathematical modeling can provide strong insight into mechanisms of plague transmission for past epidemics. Previous epidemiological models of plague during the Second Pandemic are focused mainly on modeling the spread of the disease by commensal rats during a single outbreak (20, 21). In this study, we developed a susceptible–infectious–recovered (SIR) model for plague transmission with a human ectoparasite vector and compared it to models for pneumonic and rat–flea transmission. We applied these models to nine outbreaks during the Second Pandemic, to gain a broad understanding of the transmission dynamics of plague in European epidemics. We identified the best-fitting model for each outbreak and estimated the basic reproduction number, R_0.

Methods

Historical Data. We used data on the daily and weekly disease-induced mortality for nine plague outbreaks during the Second Pandemic (Table 1). These data were publicly available in secondary sources including published articles, books, and government reports. We digitized the epidemic data from printed tables and graphs, using the entire duration of each outbreak, apart from Eyam, which had two mortality peaks. The deterministic models we used cannot account for the stochasticity of infectious disease processes during the early phase of an epidemic; thus, for the outbreak in Eyam, we removed the first 279 data points and considered only the second, larger epidemic peak. To validate the models for pneumonic and rat-associated plague epidemics, we used three additional mortality curves from epidemics with known transmission routes during the Third Pandemic (Table S1).

Parameters. The parameter values and initial conditions used in the models are shown in Table 2 and Table S2. Fixed values were taken from field, experimental, or epidemiological case studies when available. Unobservable parameters were estimated using Bayesian inference.

Table 2. Parameters for three SIR models of plague transmission

Parameter	Value	Definition	Refs.
Humans			
β_{low}	$U(0.001, 0.05)$	Transmission rate for bubonic plague from mildly infectious humans to body lice	
β_{high}	$U(0.001, 1)$	Transmission rate for bubonic plague from highly infectious humans to body lice	
β_p	$U(0.001, 1)$	Transmission rate for pneumonic plague	
β_h	$U(0.001, 0.2)$	Transmission rate for bubonic plague from rat fleas to humans	
σ_b^{-1}	8.0 (d)	Average low infectious period for bubonic plague	
γ_b^{-1}	2.0 (d)	Average high infectious period for bubonic plague	
γ_p^{-1}	2.5 (d)	Average infectious period for pneumonic plague	5
γ_h^{-1}	10.0 (d)	Average duration of infection for bubonic plague	30
g_h	0.4	Probability of recovery from bubonic plague	3
Lice (*P. humanus humanus*)			
r_l	0.11 (per d)	Natural lice growth rate	31
K_l	15.0 (per person)	Lice index at carrying capacity	32, 33
β_l	0.05	Transmission rate for bubonic plague from body lice to humans	
γ_l^{-1}	3.0 (d)	Average infectious period for bubonic plague	17
Rats (*R. rattus*)			
β_r	$U(0.001, 1)$	Transmission rate for bubonic plague from rat fleas to rats	
γ_r^{-1}	5.2 (d)	Average infectious period for bubonic plague	34
g_r	0.1	Probability of recovery from bubonic plague	34
Fleas (*X. cheopis*)			
r_f	0.0084 (per d)	Natural flea growth rate	35, 36
K_f	6.0	Average number of fleas at carrying capacity	37, 38
d_f^{-1}	5.0 (d)	Death rate of fleas	39
a	$3.0/S_r(0)$	Searching efficiency	35, 36

Single numbers are fixed values and distributions (U = uniform) are priors.

Human–Ectoparasite Model. The transmission of bubonic plague by a human ectoparasite vector, such as human fleas or body lice, is modeled by seven differential equations:

$$\frac{dS_h}{dt} = -\beta_l \frac{S_h I_l}{N_h},$$

$$\frac{dI_{\text{low}}}{dt} = \beta_l \frac{S_h I_l}{N_h} - \sigma_b I_{\text{low}},$$

$$\frac{dI_{\text{high}}}{dt} = (1 - g_h)\sigma_b I_{\text{low}} - \gamma_b I_{\text{high}},$$

$$\frac{dR_h}{dt} = g_h \sigma_b I_{\text{low}},$$

$$\frac{dD_h}{dt} = \gamma_b I_{\text{high}},$$

$$\frac{dS_l}{dt} = r_l S_l \left(1 - \frac{N_l}{K_l}\right) - \left[\left(\beta_{\text{low}} I_{\text{low}} + \beta_{\text{high}} I_{\text{high}}\right)\frac{S_l}{N_h}\right],$$

$$\frac{dI_l}{dt} = \left[\left(\beta_{\text{low}} I_{\text{low}} + \beta_{\text{high}} I_{\text{high}}\right)\frac{S_l}{N_h}\right] - \gamma_l I_l.$$

The five compartments for humans that are functions of time t: susceptible (S_h), infectious with mild bacteremia (I_{low}), infectious with high bacteremia (I_{high}), recovered (R_h), and dead (D_h). The total living population is given by $N_h = S_h + I_{\text{low}} + I_{\text{high}} + R_h$. The transmission of plague from vectors to humans occurs at rate β_l. The model assumes that humans are mildly infectious for an average of 8 d ($\sigma_b{}^{-1}$), and transmission is unlikely at rate β_{low}. Humans with mild bacteremia may recover at rate g_h, which is around 40% for untreated bubonic plague. Experimental studies have shown that fleas must feed on hosts with high levels of bacteremia for reliable transmission (40). Therefore, the model assumes that moribund humans transmit plague at a high rate to vectors β_{high} for an average of 2 d ($\gamma_b{}^{-1}$). Given the short duration of the outbreaks, we did not model natural births and deaths in the human population.

Human ectoparasite vectors are modeled in two compartments (S_l, I_l). The susceptible vector population grows at the intrinsic growth rate r_l. The growth of the vector population is limited by the carrying capacity K_l, which is the product of the parasite index and the number of human hosts N_h. Modern studies show that the rate of body louse infestation and abundance in affected human populations ranges from 10.5 to 67.7 lice on average per person (33, 41).

There are a limited number of studies that evaluate human fleas and body lice as vectors for plague (17–19). These studies have shown both vectors have similar transmission cycles for *Y. pestis*, and this makes it difficult to distinguish between the two species with either model structure or parameter values (17–19). Our model uses parameters specific to body lice; however, the ranges for the lice and flea parameters overlap. The duration of infection $\gamma_l{}^{-1}$ has been shown experimentally for both species, and is on average 4.5 d for human fleas and 3 d for body lice (17–19). The model assumes that infected human fleas and body lice do not recover. The transmission of plague by human fleas is hypothesized to occur through early phase transmission, an alternative to blocked transmission observed in rat fleas (*Xenopsylla cheopis*) that does not require a lengthy extrinsic incubation period (42).

Pneumonic Plague Model. The direct human-to-human transmission of plague is modeled by three differential equations:

$$\frac{dS_h}{dt} = -\beta_p \frac{S_h I_h}{N_h},$$

$$\frac{dI_h}{dt} = \beta_p \frac{S_h I_h}{N_h} - \gamma_p I_h,$$

$$\frac{dD_h}{dt} = \gamma_p I_h.$$

There are three compartments for humans (S_h, I_h, D_h) and the total human population is $N_h = S_h + I_h$. There is no compartment for recovered individuals because the case fatality rate of untreated pneumonic plague is close to 100% (43). The human-to-human transmission of pneumonic plague occurs at rate β_p. The disease-induced mortality occurs at rate γ_p per day and is equal to the inverse of the infectious period, which is a mean of 2.5 d for pneumonic plague (5).

Rat–Flea Model. Based on a metapopulation model for bubonic plague by Keeling and Gilligan (35, 36), the transmission of plague in a rodent epizootic, and the spillover to humans is modeled by 10 differential equations:

$$\frac{dS_r}{dt} = -\beta_r \frac{S_r F}{N_r}\left(1 - e^{-aN_r}\right),$$

$$\frac{dI_r}{dt} = \beta_r \frac{S_r F}{N_r}\left[1 - e^{-aN_r}\right] - \gamma_r I_r,$$

$$\frac{dR_r}{dt} = g_r \gamma_r I_r,$$

$$\frac{dD_r}{dt} = (1 - g_r)\gamma_r I_r,$$

$$\frac{dH}{dt} = r_f H\left(1 - \frac{H}{K_f}\right),$$

$$\frac{dF}{dt} = (1 - g_r)\gamma_r I_r H - d_f F,$$

$$\frac{dS_h}{dt} = -\beta_h \frac{S_h F}{N_h}\left[e^{-aN_r}\right],$$

$$\frac{dI_h}{dt} = \beta_h \frac{S_h F}{N_h}\left[e^{-aN_r}\right] - \gamma_h I_h,$$

$$\frac{dR_h}{dt} = g_h \gamma_h I_h,$$

$$\frac{dD_h}{dt} = (1 - g_h)\gamma_h I_h.$$

There are four compartments for rats (S_r, I_r, R_r, D_r) and the total rat population is $N_r = S_r + I_r + R_r$. As epidemics within the rat population can only occur when a large proportion of the rats are susceptible to the disease, we assumed an initial black rat (*Rattus rattus*) population that was entirely susceptible. Although the expected ratio of urban rats to humans is about 1 rat to every 5 people (44), we allowed the prior in the model to have a maximum ratio of 1:1 rats to humans. Increasing the rat population in medieval cities allowed the simulated rat-borne plague outbreaks to more easily reach the mortality levels observed in humans during the Second Pandemic.

Rat fleas (*X. cheopis*) are modeled as the average number of fleas per rat, H, and the number of free infectious fleas, F. The flea population has a natural growth rate, r_f, that is limited by the carrying capacity K_f. We assumed that the flea population is limited by the number of rat hosts, because *X. cheopis* does not reproduce on humans (45). Plague is transmitted to rats at rate β_r by free infectious fleas searching for a host with searching efficiency a. We further assumed that fleas can transmit plague in the early phase (42). Rats die at a rate equal to the inverse of the infectious period $\gamma_r{}^{-1}$, or recover with probability g_r. When an infected rat dies, a number of free infectious fleas are released into the environment, depending on the average number of fleas per rat. Free infectious fleas die at rate d_f. The model assumes that plague is a rodent disease and that human cases are a consequence of mortality in the rat population. Therefore, susceptible humans S_h become infected by free infectious fleas at rate β_h. Humans remain infected for an average of 10 d ($\gamma_h{}^{-1}$), at which point they either recover at rate g_h or die.

In the model by Keeling and Gilligan (35, 36), it is assumed that the force of infection from free infectious fleas is divided exclusively between rats and humans. However, the authors note that the true force of infection to humans is less because not every flea will find and infect a human (35). For our model, we sought to establish a range for β_h that would accurately lower the force of infection to humans. To establish this range, we fitted the model to observed mortality for both rats and humans in Hong Kong in 1903 (Fig. S1) and found that the mean estimate for β_h was 0.1 (Table S3). Using simulations, we found that β_h should be less than 0.2 to preserve the characteristic delay and higher peak mortality of the rat epizootic compared with the human epidemic. Based on these observations, we constrained the prior for

the transmission rate to humans β_h to 0.0–0.2, which enabled us to use this model for outbreaks where only human mortality was available.

Bayesian Inference and Markov Chain Monte Carlo. We fitted the deterministic models to the observed data using Bayesian inference and estimated unobservable parameters of interest. The models had a time-step of 1 d and were fitted to daily mortality or weekly mortality. Denoting the set of model parameters as $\Theta = \{S_0, \beta, \ldots\}$, the probability p of the observed data $D_{1\ldots m}$ given Θ is calculated as the product of a series of Poisson random variables with mean λ_T equal to the human mortality in the model at times $T_{1\ldots m}$:

$$p(D|\Theta) = \prod_{T=1}^{m} e^{-\lambda_T} \frac{(\lambda_T)^{D_T}}{D_T!}.$$

The parameters that we fitted were the transmission rates for each model (β_{low}, β_{high}, β_p, β_r, β_h) and the size of the initial primary host population that was at risk [$S(0)_h$, $S(0)_r$] or infected [$I(0)_h$, $I(0)_r$]. We assumed uniformly distributed priors and obtained posterior distributions using Markov chain Monte Carlo (MCMC) simulations with an adaptive Metropolis–Hastings algorithm implemented in PyMC2 (46) (for examples of the implementation, see https://zenodo.org/record/1043924). We ran the MCMC simulations for 180,000 iterations with a burn-in of 80,000 iterations and a thinning of 10. We assessed convergence for each model by running three independent MCMC chains and verifying that the Gelman–Rubin statistic (47) was <1.05 for each parameter. We performed model comparison using the Bayesian information criterion (BIC) from the maximum-likelihood estimates of the model parameters (48). The model with the lowest BIC value was the unique preferred model if the second-best model had a BIC value of at least 10 larger (49).

Estimation of the Basic Reproduction Number. We estimated the basic reproduction number in each model for the primary host using the next-generation matrix method (50).

Reporting Error. We conducted the analysis again considering different levels of underreporting (10%, 25%, and 50%) for each outbreak. To do so, we incorporated a constant probability of reporting into the likelihood function.

Results

Model Fit and Selection. We used Bayesian MCMC and the mortality data to fit the three transmission models: human ectoparasite plague (EP), pneumonic plague (PP), and rat-borne plague (RP) (Fig. 1). The posterior means and 95% credible intervals for the fitted parameters in each model are given in Table S3. Fig. 1 shows the fit of each model to the observed mortality. For the smallest outbreaks, Eyam and Givry, it is difficult to visually distinguish between the models because the credible intervals are overlapping. In general, the human ectoparasite model fit the pattern of the observed data for the Second Pandemic outbreaks. However, the model could not account for irregularities in the observed mortality from Malta and Moscow, which have two peaks. For the pneumonic plague model, the mortality curve is right skewed compared with the observed mortality. Mortality in the rat model tended to grow slowly while plague spread through the rat population, and peaked higher than the observed mortality.

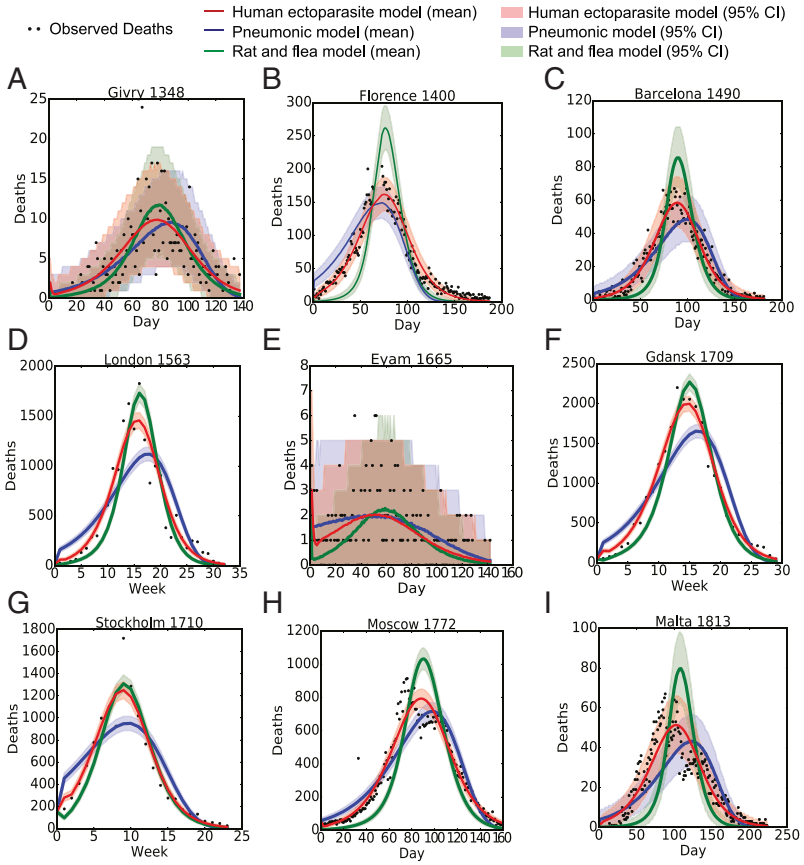

Fig. 1. Fit of three models of plague transmission to mortality during Second Pandemic outbreaks. The observed human mortality data (black dots) and the fit (mean and 95% credible interval) of three models for plague transmission [human ectoparasite (red), pneumonic (blue), and rat–flea (green)] for nine plague outbreaks: (*A*) Givry, France (1348), (*B*) Florence, Italy (1400), (*C*) Barcelona, Spain (1490), (*D*) London, England (1563), (*E*) Eyam, England (1665), (*F*) Gdansk, Poland (1709), (*G*) Stockholm, Sweden (1710), (*H*) Moscow, Russia (1772), and (*I*) Island of Malta, Malta (1813).

We compared the three competing models using the BIC. Our results (Table 3) show that the human ectoparasite model had the lowest BIC value for all outbreaks, except Eyam and Givry. For the remaining outbreaks, the difference in BIC for the human ectoparasite model and the other candidate models was greater than 10, which provides strong evidence against the pneumonic and rat–flea models (50). For Eyam and Givry, the difference between the human ectoparasite model and another model was less than 10; therefore, neither model could be excluded.

To verify our model comparison method, we fitted the models to three additional Third Pandemic outbreaks with known transmission routes (Fig. S2). We found that the model with the lowest BIC matched the known modes of transmission for the outbreaks in Hong Kong (rats) and Harbin (pneumonic) (Table S5). However, we could not distinguish between two of the models for a small outbreak of rat-associated plague in Sydney, suggesting together with the results from Eyam and Givry, that our model comparison method is better suited for sufficiently large outbreaks (>750 deaths).

Basic Reproduction Number R_0. By definition, the basic reproduction number, R_0, is the average number of secondary cases produced by a primary case, given an entirely susceptible population. In practice, R_0 is an important threshold for disease invasion. For each of the three models, we calculated R_0 from the posterior estimates of the fitted parameters (Table 3). For all of the models, R_0 was greater than 1, which is above the threshold for disease invasion. Using the human ectoparasite model, the estimated R_0 was 1.48–1.91 for all pre-Industrial outbreaks.

Table 3. Comparison of transmission models and posterior estimates for the basic reproduction number for different plague models and outbreaks

Location	Model	BIC	ΔBIC	R_0
Givry (1348)	EP	1,287	**0**	1.82 [1.82, 1.82]
	PP	1,333	46	1.10 [1.10, 1.10]
	RP	1,287	**0**	1.61 [1.61, 1.61]
Florence (1400)	EP	2,662	**0**	1.76 [1.76, 1.76]
	PP	4,569	1,907	1.09 [1.09, 1.09]
	RP	10,157	7,495	2.03 [2.03, 2.03]
Barcelona (1490)	EP	1,942	**0**	1.91 [1.91, 1.91]
	PP	2,410	468	1.09 [1.09, 1.09]
	RP	3,392	1,450	2.04 [2.04, 2.04]
London (1563)	EP	1,585	**0**	1.64 [1.64, 1.64]
	PP	4,647	3,062	1.06 [1.06, 1.06]
	RP	3,882	2,297	1.52 [1.52, 1.52]
Eyam (1666)	EP	1,171	**0**	1.48 [1.48, 1.49]
	PP	1,174	**3**	1.04 [1.04, 1.04]
	RP	1,205	34	1.24 [1.24, 1.24]
Gdansk (1709)	EP	797	**0**	1.64 [1.64, 1.64]
	PP	3,841	3,044	1.06 [1.06, 1.06]
	RP	2,212	1,415	1.46 [1.46, 1.46]
Stockholm (1710)	EP	726	**0**	1.75 [1.75, 1.75]
	PP	2,118	1,392	1.06 [1.06, 1.06]
	RP	1,062	336	1.30 [1.30, 1.30]
Moscow (1771)	EP	3,912	**0**	1.79 [1.79, 1.79]
	PP	6,789	2,877	1.09 [1.09, 1.09]
	RP	15,946	12,034	1.76 [1.76, 1.76]
Malta (1813)	EP	2,761	**0**	1.57 [1.57, 1.57]
	PP	3,580	819	1.06 [1.06, 1.06]
	RP	6,445	3,684	1.79 [1.79, 1.79]

The models are designated as human ectoparasite (EP), primary pneumonic plague (PP), and rat–flea (RP). Values in bold represent the best-fitting models that were within 10 points of the lowest BIC. The R_0 (mean [95% confidence interval]) was estimated using the next-generation matrix method.

Reporting Error. We considered the impact of different levels of constant underreporting of deaths throughout the epidemics on model selection (Table S6). We found that underreporting of 10% and 25% did not change the results of the model selection; under these conditions, the human ectoparasite model was the best fit for all outbreaks in Europe except Eyam and Givry. Underreporting of 50% changed the best-fitting models of Gdansk and Givry to pneumonic plague. For these cities, 50% underreporting resulted in the death of more than 90% of the population, giving preference to a pneumonic plague model where all infected individuals die from plague.

Discussion

Our study supports human ectoparasite transmission of plague during the Second Pandemic, including the Black Death. Using recent experimental data on human fleas and body lice as plague vectors, we have developed a compartmental model that captures the dynamics of human ectoparasite transmission. We have shown that, in seven out of nine localities, the human ectoparasite model was the preferred model to explain the pattern of plague mortality during an outbreak, rather than models of pneumonic and rat–flea plague transmission (Table 3). The small size of the plague outbreaks in Eyam and Givry made it difficult to distinguish transmission routes based on mortality data. For Eyam, both the human ectoparasite model and the pneumonic model produced a similar quality fit for the observed mortality. This agrees with a previous modeling study of Eyam (1665), which found that the dominant mode of transmission was an unspecified route of human-to-human transmission, rather than rodent transmission (11). Overall, our results suggest that plague transmission in European epidemics occurred predominantly through human ectoparasites, rather than commensal rat or pneumonic transmission.

The strength of our study is that we compared three plague transmission models, each representing a known or hypothetical mode of plague transmission, for nine plague outbreaks across the spatial and temporal extent of the Second Pandemic in Europe. Our study thus provides a more general understanding of plague epidemics in Europe than previous modeling studies that focus on single outbreaks, or single transmission routes (11, 20, 35, 36, 51). However, since we considered nine outbreaks over several centuries, we were limited to using simple models that could be applied systematically. Consequently, these models did not account for local conditions that can affect disease transmission, like war, famine, immunity, and public health interventions. Additionally, we did not model mixed transmission routes, and this makes it difficult to fully assess the contribution of pneumonic plague, which commonly occurs during bubonic outbreaks (52). Secondary pneumonic plague develops in an estimated 20% of bubonic cases, and this creates potential for primary pneumonic spread, even if it is not the dominant transmission route (52). Finally, we do not consider events leading up to the introduction of the disease and our results cannot be extended to plague transmission between localities, which may have involved different transmission mechanisms.

Recent studies have found human ectoparasites during plague outbreaks in the Democratic Republic of Congo (41), Tanzania (53), and Madagascar (54), but their role in these outbreaks is not clear. In the absence of modern studies on human ectoparasites as vectors for plague, our results yield inferences about the conditions necessary to produce outbreaks driven by human ectoparasite transmission. Our estimated values for R_0 using the human ectoparasite model were consistently between 1.5 and 1.9 for all nine cities. The main components of R_0 in the human ectoparasite model are the ectoparasite index and the transmission rates ($\beta_l, \beta_{\text{low}}, \beta_{\text{high}}$). From the fitted models, we obtained estimates for the transmission rates ($\beta_{\text{low}}, \beta_{\text{high}}$) from humans to ectoparasites during the early and late stages of plague infection.

We found that the majority of ectoparasite infections occurred during the period of high infectivity in humans, consistent with experimental evidence (40). Inferences like these not only improve our understanding of human ectoparasites as plague vectors in the past but also have important implications for limiting the size of plague outbreaks today.

Many studies have sought to clarify the mechanisms underlying the spread and maintenance of plague during the Second Pandemic. Mathematical modeling is an important tool to examine the role of different transmission mechanisms, particularly in the absence of definitive experimental, historical, and archaeological information. Here, we demonstrate that human ectoparasites appear to have been the dominant transmission mode for plague during the Second Pandemic. This alternative mode of transmission could account for many of the epidemiological differences between the Second Pandemic and those caused by rats during the Third Pandemic. Plague is undeniably a disease of significant scientific, historic, and public interest, and is still present in many parts of the world today. It is therefore crucial that we understand the full spectrum of capabilities that this versatile, pandemic disease has exhibited in the past.

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Supporting Information

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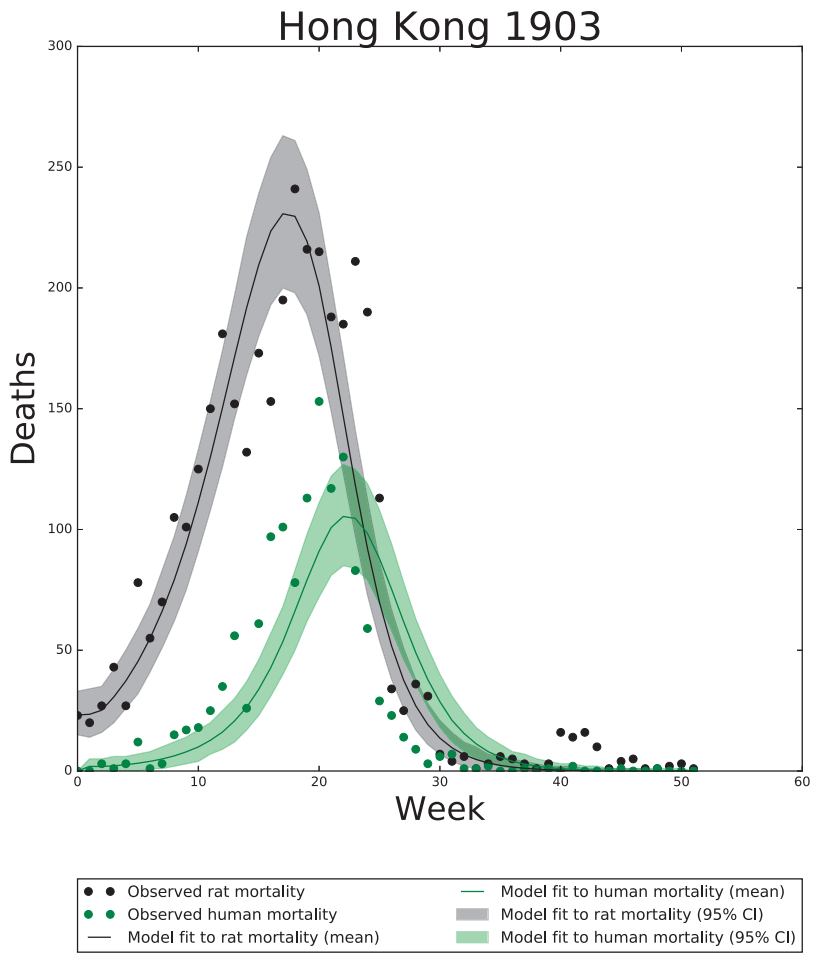

Fig. S1. Fit of the rat–flea model to observed rodent and human mortality during the 1903 plague outbreak in Hong Kong. The observed rat mortality (black dots), the observed human mortality (green dots), and fit (mean and 95% credible interval) of the rat model for plague transmission to both the rat (black) and human (green) mortality. The mortality peak for humans from the model is delayed compared with the observed data. However, the model captures the dynamics of the rat mortality and the relationship between the epizootic and the epidemic well by showing the characteristic higher rat mortality and the delay in the onset of the epidemic in humans.

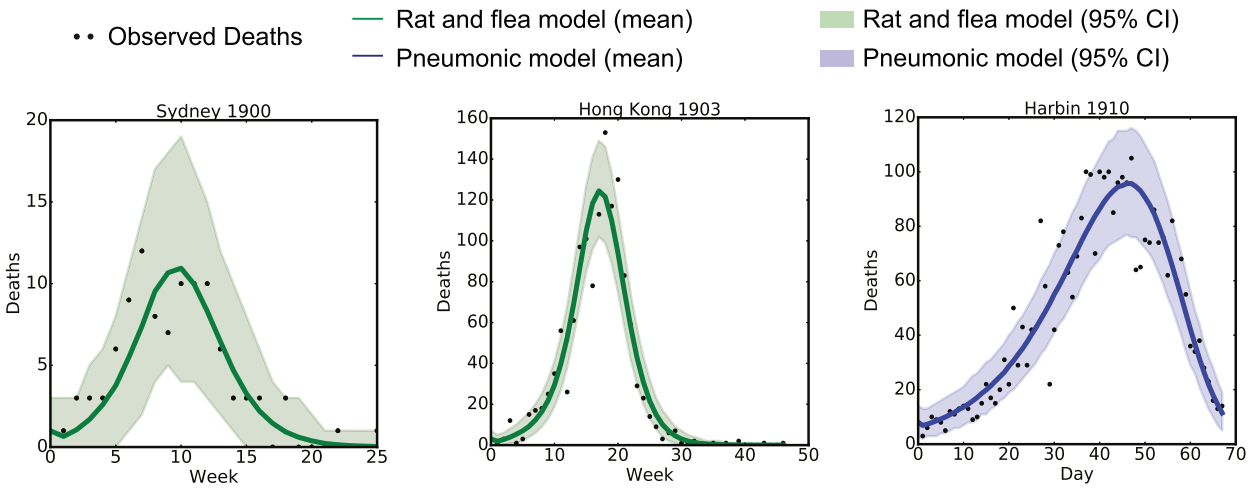

Fig. S2. Fit of the pneumonic and rat–flea models of plague transmission to mortality during Third Pandemic outbreaks. The observed human mortality data (black dots) for plague outbreaks and the fit (mean and 95% credible interval) of the relevant model for plague transmission in each plague outbreak: pneumonic (blue) and rat–flea (green). Both the rat–flea model of plague transmission and the pneumonic plague transmission are well capable of fitting observed human mortality patterns for plague outbreaks that these models describe.

Table S1. Summary of the Third Pandemic mortality data

Location	Date, MM/YYYY	Population	Recorded deaths	Transmission mode	Ref.
Sydney, Australia	02/1900–08/1900	400,000	103	Rat–flea	1
Hong Kong, China	01/1903–12/1903	250,000	1,308	Rat–flea	2
Harbin (Fuchiatien), China	12/1910–02/1911	25,000	3,223	Pneumonic	3

The present-day location, dates (month/year), preplague population size, and recorded plague deaths, and known transmission mode for three plague outbreaks during the Third Pandemic.

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Table S2. Initial conditions for three SIR models of plague transmission

Parameter	Value	Definition
Human ectoparasite model		
$S_h(0)$	$U(0.001, 1)$*population size	Initial susceptible humans
$I_{low}(0)$	$U(1, 10*D_h(0))$	Initial infected (low) humans
$I_{high}(0)$	$2*D_h(0)$	Initial infected (high) humans
$R_h(0)$	0	Initial recovered humans
$D_h(0)$	Observed deaths at $T = 0$	Initial dead humans
Pneumonic plague model		
$S_h(0)$	$U(0.001,1)$*population size	Initial susceptible humans
$I_h(0)$	$U(1, 10*D_h(0))$	Initial infected humans
$D_h(0)$	Observed deaths at $T = 0$	Initial dead humans
Rat–flea model		
$S_r(0)$	$U(0.001, 1)$*population size	Initial susceptible rats
$I_r(0)$	$U(1, 15*D_h(0))$	Initial infected rats
$R_r(0)$	0	Initial recovered rats
$D_r(0)$	0	Initial dead rats
$S_h(0)$	$S_r(0)$	Initial susceptible humans
$I_h(0)$	$1.5*D_h(0)$	Initial infected humans
$R_h(0)$	0	Initial recovered humans
$D_h(0)$	Observed deaths at $T = 0$	Initial dead humans
$H(0)$	K_f	Initial fleas on host
$F(0)$	$K_f*D_h(0)$	Initial free infected fleas

Single numbers are fixed values and distributions (U = uniform) are priors.

Table S3. Initial parameter values and posterior estimates for the rat–flea model fitted rat and human mortality in Hong Kong

Parameter	Parameter value/prior distribution	Posterior estimate, mean [95% highest posterior density interval]
$S_h(0)$	$S_r(0)$	Fixed
$I_h(0)$	5.0	Fixed
$R_h(0)$	0	Fixed
$D_h(0)$	Observed deaths at $T = 0$	Fixed
β_h	$U(0.001, 1)$	0.11 [0.10, 0.12]
$S_r(0)$	$U(0.001, 1)$*population size	0.018 [0.017, 0.018] * 250,000
$I_r(0)$	$U(1, 23)$	22.8 [22.6, 23]
$R_r(0)$	0	Fixed
$D_r(0)$	Observed deaths at $T = 0$	Fixed
β_r	$U(0.001, 1)$	0.053 [0.053, 0.053]

Single numbers are fixed values, and distributions (U = uniform) are priors.

Table S4. Posterior means and 95% highest density posterior intervals for estimated parameters in three plague models for Second and Third Pandemic outbreaks

Location	Model	Population at risk (proportion)	Initial infected $[I_{low}(0), I_h(0), I_r(0)]$	Transmission rate $(\beta_{low}, \beta_{high}, \beta_p, \beta_r, \beta_h)$
Givry (1348)	EP	0.75 [0.69, 0.81]	2.21 [2, 2.61]	0.04 [0.02, 0.05] 0.39 [0.32, 0.53]
	PP	0.42 [0.38, 0.45]	1.85 [1.41, 2.32]	0.44 [0.43, 0.44]
	RP	0.73 [0.64, 0.81]	28.81 [26.60, 29.99]	0.06 [0.06, 0.06] 0.19 [0.18, 0.2]
Florence (1400)	EP	0.36 [0.35, 0.36]	79.65 [78.99, 80]	0.049 [0.04, 0.05] 0.32 [0.31, 0.38]
	PP	0.17 [0.17, 0.17]	79.79 [79.39, 79.99]	0.42 [0.42, 0.42]
	RP	0.19 [0.19, 0.19]	119.91 [119.76, 120.0]	0.084 [0.083, 0.085] 0.2 [0.199, 0.2]
Barcelona (1490)	EP	0.28 [0.27, 0.28]	8.68 [7.54, 9.97]	0.032 [0.007, 0.05] 0.49 [0.35, 0.67]
	PP	0.14 [0.13, 0.14]	9.90 [9.73, 10.0]	0.43 [0.43, 0.43]
	RP	0.14 [0.13, 0.14]	14.95 [14.87, 15.0]	0.08 [0.08, 0.08] 0.2 [0.19, 0.2]
London (1563)	EP	0.42 [0.41, 0.42]	32.45 [29.68, 35.62]	0.04 [0.04, 0.05] 0.27 [0.26, 0.28]
	PP	0.21 [0.20, 0.21]	50.85 [48.81, 52.99]	0.43 [0.43, 0.43]
	RP	0.30 [0.30, 0.31]	254.80 [254.43, 255]	0.06 [0.059, 0.06] 0.2 [0.2, 0.2]
Eyam (1666)	EP	0.97 [0.92, 1.0]	3.76 [3, 4.97]	0.032 [0.01, 0.05] 0.32 [0.2, 0.5]
	PP	0.56 [0.48, 0.63]	3.80 [3, 4.82]	0.41 [0.41, 0.42]
	RP	0.96 [0.90, 1.0]	38.08 [29.53, 44.97]	0.04 [0.04, 0.05] 0.19 [0.18, 0.2]
Gdansk (1709)	EP	0.93 [0.92, 0.94]	51.3 [49, 54.6]	0.049 [0.046, 0.05] 0.28 [0.26, 0.3]
	PP	0.46 [0.46, 0.47]	79.11 [76.56, 81.95]	0.42 [0.42, 0.42]
	RP	0.92 [0.90, 0.93]	734.48 [733.36, 735]	0.04 [0.04, 0.05] 0.2 [0.2, 0.2]
Stockholm (1710)	EP	0.42 [0.41, 0.42]	159.63 [153.01, 168.35]	0.04 [0.03, 0.05] 0.33 [0.30, 0.38]
	PP	0.22 [0.21, 0.22]	145.36 [139.14, 151.28]	0.42 [0.42, 0.42]
	RP	0.36 [0.35, 0.36]	2,290.65 [2,282.25, 2,294.99]	0.069 [0.069, 0.069] 0.2 [0.2, 0.2]
Moscow (1771)	EP	0.34 [0.34, 0.35]	157.41 [150.41, 164.44]	0.04 [0.04, 0.05] 0.34 [0.32, 0.39]
	PP	0.17 [0.17, 0.18]	148.31 [144.46, 152.12]	0.43 [0.43, 0.43]
	RP	0.20 [0.20, 0.21]	659.86 [659.57, 660.0]	0.069 [0.069, 0.069] 0.2 [0.2, 0.2]
Malta (1813)	EP	0.09 [0.09, 0.09]	18.09 [16.47, 19.9]	0.04 [0.04, 0.05] 0.26 [0.23, 0.31]
	PP	0.04 [0.04, 0.04]	9.96 [9.90, 10.0]	0.43 [0.43, 0.43]
	RP	0.045 [0.044, 0.046]	14.98 [14.939, 15.0]	0.06 [0.06, 0.06] 0.2 [0.2, 0.2]
Sydney (1900)	EP	0.49 [0.003, 0.95]	7.49 [5.48, 9.77]	0.024 [0.0, 0.04] 0.15 [0.0, 0.3]
	PP	0.001 [0.0, 0.001]	1.46 [1, 2.06]	0.42 [0.41, 0.42]
	RP	0.001 [0.0, 0.001]	13.559 [10.637, 15.0]	0.05 [0.04, 0.05] 0.18 [0.14, 0.2]
Hong Kong (1903)	EP	0.011 [0.011, 0.012]	3.05 [3, 3.17]	0.048 [0.044, 0.05] 0.24 [0.22, 0.26]
	PP	0.01 [0.01, 0.01]	2.88 [2.41, 3.35]	0.42 [0.42, 0.42]
	RP	0.011 [0.009, 0.013]	36.66 [27.63, 44.99]	0.05 [0.05, 0.05] 0.16 [0.13, 0.2]
Harbin (1910)	EP	0.02 [0.02, 0.021]	33.93 [27.09, 41.58]	0.03 [0.01, 0.05] 0.88 [0.76, 1.]
	PP	0.12 [0.12, 0.13]	16.99 [14.9, 18.98]	0.48 [0.48, 0.48]
	RP	0.11 [0.11, 0.11]	119.25 [117.66, 119.99]	0.14 [0.13, 0.14] 0.19 [0.19, 0.2]

Posterior estimates for initial conditions for different plague models and outbreaks. Models are designated as human ectoparasite (EP), primary pneumonic plague (PP), and rat and rat–flea (RP). Posterior estimates (mean [95% highest density posterior interval]) for the proportion of the initial population at risk, the initial number of infected [$I(0)$], and the transmission rate (β).

Table S5. Comparison of transmission models and estimates for the basic reproduction number for different plague models and Third Pandemic outbreaks

Location	Model	BIC	ΔBIC	R_0
Sydney (1900)	EP	235	46	0.86 [0.86, 0.87]
	PP	196	**7**	1.05 [1.05,1.05]
	RP	189	**0**	1.36 [1.36,1.36]
Hong Kong (1903)	EP	611	107	1.52 [1.52, 1.52]
	PP	900	396	1.06 [1.06,1.06]
	RP	504	**0**	1.41 [1.41,1.41]
Harbin (1910)	EP	851	31	2.98 [2.98, 2.98]
	PP	820	**0**	1.21 [1.21,1.21]
	RP	1,606	786	3.62 [3.62,3.62]

The models are designated as human ectoparasite (EP), primary pneumonic plague (PP), and rat and rat–flea (RP). Values in bold represent the best-fitting models that were within 10 points of the lowest BIC. The R_0 (mean [95% confidence interval]) was estimated for each model using the next-generation matrix.

Table S6. Comparison of transmission models with different levels of underreporting

		BIC		
Location	Model	10% underreporting	25% underreporting	50% underreporting
Givry (1348)	EP	**1,288**	**1,280**	1,395
	PP	1,333	1,333	**1,331**
	RP	**1,292**	1,370	1,439
Florence (1400)	EP	**2,729**	**2,876**	**3,392**
	PP	4,668	4,928	5,877
	RP	10,568	11,264	12,752
Barcelona (1490)	EP	**1,942**	**1,951**	**2,121**
	PP	2,418	2,453	2,610
	RP	3,482	3,640	3,991
London (1563)	EP	**1,582**	**1,577**	**1,575**
	PP	4,630	4,629	4,629
	RP	4,256	4,954	6,743
Eyam (1666)	EP	**1,176**	**1,175**	**1,243**
	PP	**1,174**	**1,174**	**1,238**
	RP	1,210	1,228	1,304
Gdansk (1709)	EP	**825**	**1,803**	No convergence
	PP	3,817	3,817	**3,817**
	RP	2,176	4,447	No convergence
Stockholm (1710)	EP	**718**	**709**	**688**
	PP	2,180	2,109	2,110
	RP	1,238	1,612	2,759
Moscow (1771)	EP	**3,916**	**3,916**	**3,931**
	PP	6,790	6,790	6,790
	RP	17,604	22,612	No convergence
Malta (1813)	EP	**2,760**	**2,775**	**2,864**
	PP	3,653	3,850	4,244
	RP	6,632	6,953	7,656

The models are designated as human ectoparasite (EP), primary pneumonic plague (PP), and rat and rat–flea (RP). Values in bold represent the best-fitting models that were within 10 points of the lowest BIC.

LETTER

REPLY TO PARK ET AL.:

Human ectoparasite transmission of plague during the Second Pandemic is still plausible

Katharine R. Dean[a,1], Fabienne Krauer[a], Lars Walløe[b], Ole Christian Lingjærde[c], Barbara Bramanti[a,d], Nils C. Stenseth[a,1], and Boris V. Schmid[a,1]

In their letter, Park et al. (1) raise several concerns and question our conclusion (2) that human ectoparasites could have caused plague epidemics during the Second Pandemic.

First, Park et al. (1) state that our study cannot provide evidence that human ectoparasite transmission was more likely than a mixed pneumonic and rat-flea transmission. We have acknowledged this limitation in our discussion, where we wrote that "we did not model mixed transmission routes, and this makes it difficult to fully assess the contribution of pneumonic plague, which commonly occurs during bubonic outbreaks." They assert that this scenario is "highly plausible." We note that while secondary pneumonic infections are common, primary pneumonic transmission through droplets may only occur under particular environmental conditions such as specific temperature or humidity ranges, poor ventilation, and high-density housing (3, 4). For two of the epidemics we used, Moscow and Stockholm, detailed contemporary descriptions of symptoms are available; they indicate bubonic plague with only a few sporadic cases of pneumonic disease (5, 6).

Second, Park et al. (1) criticize the omission of an incubation period in both humans and vectors in all three models and the values of point priors in the human ectoparasite model. Plague can be transmitted by fleas in various ways, not all of which warrant an incubation period (7). Our assumption of early-phase transmission (EPT) is based on current literature stating that EPT provides a better explanation for rapidly spreading epidemics than biofilm-dependent transmission (8). For pneumonic plague, the incubation period is extremely short and it is unlikely that including it in our model would change the fitted dynamics substantially. Furthermore, we demonstrated that the models for pneumonic plague and rat-flea transmission fit well to the outbreaks of known transmission mode during the Third Pandemic, which confirms their individual validity. Point priors used in the human ectoparasite model were largely taken from experimental studies (9, 10). Estimation of all of the parameters in all of the models is problematic due to high parameter correlation, which leads to identifiability problems.

Finally, Park et al. (1) raise an important issue that several technical assumptions such as point priors, uniform priors, and deterministic dynamics may have led to an underestimation of the uncertainty, which could have been better captured using a stochastic model. We agree that the uncertainty in our models could have been larger under different assumptions, which may reduce the possibility of distinguishing between the models based on fit alone. In this situation, we can consider the biological reasonableness of the fitted models. For example, to fit the European mortality curves, the rat-flea model requires a large, highly susceptible rat population and a high transmission rate, which is difficult to justify in Nordic countries (11).

We would like to emphasize that we do not provide evidence against rat-borne plague transmission but explore an alternative explanation of human ectoparasites, which has been suggested by many plague researchers for decades. Our results support our conclusion that human ectoparasites are a plausible and likely vector of plague epidemics during the Second Pandemic. However, we are open to alternative scenarios that could similarly explain the epidemiology of plague in preindustrial Europe under biologically reasonable assumptions.

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The authors declare no conflict of interest.

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Chapter II

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Epidemiology of a bubonic plague outbreak in Glasgow, Scotland in 1900

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On 3 August 1900, bubonic plague (*Yersinia pestis*) broke out in Glasgow for the first time during the Third Pandemic. The local sanitary authorities rigorously tracked the spread of the disease and they found that nearly all of the 35 cases could be linked by contact with a previous case. Despite trapping hundreds of rats in the area, there was no evidence of a rat epizootic and the investigators speculated that the outbreak could be due to human-to-human transmission of bubonic plague. Here we use a likelihood-based method to reconstruct transmission trees for the outbreak. From the description of the outbreak and the reconstructed trees, we infer several epidemiological parameters. We found that the estimated mean serial interval was 7.4–9.2 days and the mean effective reproduction number dropped below 1 after implementation of control measures. We also found a high rate of secondary transmissions within households and observations of transmissions from individuals who were not terminally septicaemic. Our results provide important insights into the epidemiology of a bubonic plague outbreak during the Third Pandemic in Europe.

1. Introduction

Plague is a zoonotic disease, caused by the bacterium *Yersinia pestis*, which is well known as the cause of at least three pandemics in human history: the First Pandemic (sixth to eighth centuries), the Second Pandemic (fourteenth to nineteenth centuries) and the Third Pandemic (beginning in the nineteenth century). At the beginning of the Third Pandemic, *Y. pestis* spread from Asia to Europe, Africa, Australia and the Americas along maritime transport networks [1]. These introductions led to the establishment of plague reservoirs in rodent populations around the world, which today pose a recurrent threat to nearby human populations [2].

The most common form of plague infection in humans is bubonic plague, caused by the bite of an infected flea vector [3,4]. Today, cases of bubonic plague typically arise through contact with sylvatic or commensal animals and their fleas [3,4]. In the

past, large epidemics of plague in Asia were caused by epizootics in the susceptible urban rat population, which led infected rat-flea vectors to seek alternative mammalian hosts [5]. However, there is some evidence that bubonic plague may also spread between people through human ectoparasite vectors such as body lice (*Pediculus humanus humanus*) or human fleas (*Pulex irritans*). This is supported by experimental and epidemiological studies that have shown that human ectoparasites are potential vectors for plague and have been found infected during modern outbreaks in Africa [6–9].

In general, the epidemiology of plague outbreaks in Europe is poorly understood [10]. Even though there were hundreds of plague notifications during the Third Pandemic, research on the disease in Europe has mainly focused on the large outbreaks during the Second Pandemic. However, records from mediaeval and early-modern Europe provide limited information about the nature of the outbreaks and lack the scientific awareness of the bacterium and its transmission that was formed during the investigation of plague outbreaks in India at the end of the nineteenth century. Therefore, there is an opportunity to better understand the epidemiology of plague outbreaks in Europe during the Third Pandemic. Although these outbreaks cannot simply be assumed to be representative of the Second Pandemic, they can provide a valuable point of comparison for future studies.

Here we use an official government report of plague in Glasgow, Scotland in 1900 to study the epidemiology of plague in Europe [11]. During this remarkably well-documented outbreak, investigators observed that many cases of plague could be linked by contact with a previous case and they found no evidence of a rat epizootic. The information in the report can be used to partially reconstruct the transmission tree; however, some transmission events are not known. To address this problem, we applied a robust likelihood-based method to reconstruct probable transmission trees, from which we estimated several disease transmission parameters [12].

For disease spread at an individual level, we estimated the serial interval, which is defined as the time between the symptom onset of a case and the symptom onset of their infector [13]. To understand how the disease spreads on a scale of disease generations, we calculated the effective reproduction number R_e defined as the average number of secondary cases produced by a primary case [13]. We compared R_e before and after notification of the disease to assess the impact of intervention measures on controlling the outbreak. Finally, we discuss different aspects of transmission, including the number of secondary cases arising within the same household and the possibility of those arising from individuals who ultimately recovered from the disease (non-septicaemic transmission).

2. Material and methods

2.1. Description of the outbreak

On 25 August 1900, the sanitary authorities of Glasgow were notified of several suspected cases of bubonic plague, despite no known cases of plague in Britain at the time [14]. By the following day, they confirmed their initial diagnosis of *Y. pestis* infection from cultures taken on glycerin agar, and later in the week by animal experiments at the University of Glasgow [14]. Upon the identification of the plague, the Medical Officer of Health in Glasgow opened an immediate investigation into the spread of the disease. The investigation led to the identification of the index cases, known as Mrs B., a fish hawker, who sickened along with her granddaughter, on 3 August (Day 0 of the outbreak) [14]. The sanitary authorities searched for contacts associated with Mrs B. or who had attended her wake, leading to the examination and quarantine of more than one hundred people in a 'reception house' for observation [14].

In addition to contact tracing and quarantining, the sanitary authorities implemented several other measures to control the spread of plague including (1) removal of cases to the hospital, (2) cessation of wakes for deaths attributed to plague, (3) fumigation of infected homes with liquid sulfur dioxide and disinfection with a formalin solution, (4) removal and treatment of clothing and sheets, (5) disinfection of all homes and communal areas in infected tenements with chloride of lime (chlorine powder) solution, (6) emptying of ashpits and (7) dissemination of information about the disease to the public and health professionals [15].

Two years prior to the outbreak in Glasgow, Paul-Louis Simond had discovered that rats and their fleas could transmit plague to humans [16]. Consequently, the sanitary authorities in Glasgow were particularly interested in the role of rats in spreading the disease. They noted that rats were numerous in the infected tenements; however, there was no evidence that the mortality among rats was abnormal [15]. The authorities undertook an extensive trapping and extermination campaign, which included the examination of 326 rats [11,17]. Despite their efforts, they found no evidence of plague in

the rat population at any time during the outbreak, leading them to conclude that plague may have spread directly between humans through clothing among other means, and possibly by 'the suctorial parasites of mankind' [11]. Notably, rats were caught and examined for plague in Glasgow during the period between 1900 and 1907, and a small number of infected rats were found in the years after the 1900 outbreak: 1901 (122 of 1641), 1902 (30 of 6492) and 1907 (1 of 140) [17].

In the official report of the outbreak published in 1901, the local authorities identified 37 cases of plague in and around Glasgow between 3 August and 24 September 1900 [11]. By March 1901, the city had a population of 761 712, but the cases were primarily located in the densely populated Gorbals area, on the south bank of the river Clyde [11]. Most of the cases after notification were identified as a primary bubonic or septicaemic plague by the presence of external buboes [11]. However, we excluded one of these confirmed cases, called 'Govan boy', for whom there was no case information [11]. The additional suspected case presented with primary pneumonia, but it was noted that the survival of the patient and failure to retrieve the bacteria discredited the assumption of plague pneumonia [11]. Thus, our analysis included 35 cases with information about their date of symptom onset and possibly their contacts with previous cases. We broadly defined a contact to be any individual that lived at the same address as the case; any individual who visited the house of a case; or any individual who provided formal or informal care to the case.

2.2. Likelihood of possible transmission pairs and estimation of the serial interval distribution

Using the notation in Hens *et al.* [12], we assigned each case a unique case identifier (i) [12]. We numbered the cases by the symptom onset date (t_i) and if the symptom onset dates were equal we used the original order from the case reports [12]. For each case i, except the index cases, we denoted the unique infector as $v(i)$ or contacts as $w(i)$, if known. With no missing information for $v(i)$, the serial interval can be calculated as a positive number for each case i as $t_i - t_{v(i)}$, which is the difference between the symptom onset of case i and the symptom onset of the infector $v(i)$. The observed serial intervals can be used to describe the serial interval distribution $g(t_i - t_{v(i)}|\theta)$ and the effective reproduction number, R_e. However, for the outbreak in Glasgow, the transmission tree is not fully resolved, and information about the infectors is often missing.

To find the missing transmission pairs, we used the method in Hens *et al.* [12], which finds the probability $p_{ij}(v, w)$ that case i was infected by case j, given the estimated serial interval distribution (described below), and given any prior information on the infectors in v ($1 \times n$ matrix) and the contacts w ($n \times n$ matrix). The total log-likelihood of the data is then given by summing the total log-likelihood of all cases, excluding the index cases,

$$E\{\ell(\theta|t, v, w)\} = \sum_{i=3}^{n} \sum_{j=1}^{n} p_{ij}(v, w) \log g(t_i - t_j|\theta). \tag{2.1}$$

We assumed a gamma distribution to describe the probability density of the serial interval distribution for bubonic plague. Maximizing the expected log-likelihood yields estimates for the parameter set $\hat{\theta} = \{a, b\}$, where a is the shape parameter and b is the scale parameter of the gamma distribution.

The probability that case i was infected by case j, p_{ij}, is the product of the probability of observing the serial interval between two cases, $g(t_i - t_j|\theta)$, and the probability of an infectious contact between i and j, $\pi_{ij}(v, w)$, normalized by the probability of case i being infected by any other case k,

$$p_{ij}(v, w, \hat{\theta}) = \frac{g(t_i - t_j|\hat{\theta}) \times \pi_{ij}(v, w)}{\sum_{k \neq i} g(t_i - t_k|\hat{\theta}) \times \pi_{ik}(v, w)}. \tag{2.2}$$

The probability of an infectious contact between cases i and j, $\pi_{ij}(v, w)$, is informed by the contact information collected during the outbreak, such that:

— $\pi_{ij}(v, w) = 1$, if case j is the only possible infector of case i;
— $\pi_{ij}(v, w) = 1/m$, if case j is one of m contacts and a possible infector of case i;
— $\pi_{ij}(v, w) = 1/(i - 1)$, if there are no contacts for case i and it is not an index case.

We used the prior-based expectation maximization (PEM) algorithm described by Hens *et al.* [12] to obtain the maximum expected log-likelihood value [12]. By this process, the probability of infectious contacts based on information collected during the outbreak is evaluated first (P-step), then the probability of transmission is evaluated given the current estimate of the serial interval parameters θ

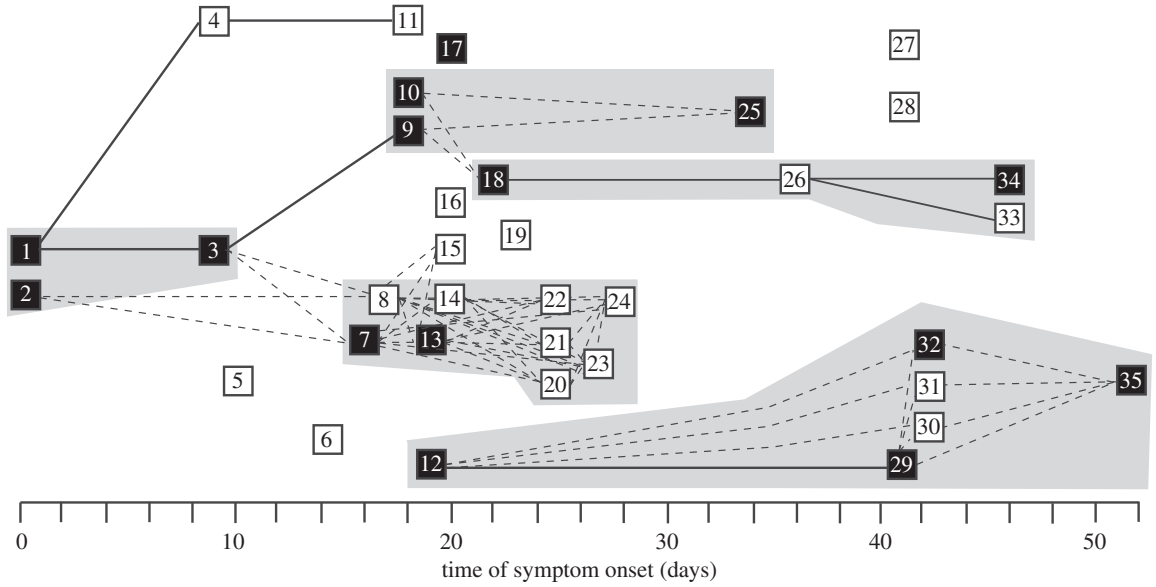

Figure 1. Recorded transmission events during a plague outbreak in Glasgow, Scotland, from 3 August 1900 to 24 September 1900. Cases are represented by squares (solid = dead) and ordered by the date of symptom onset. Solid lines indicate transmission events between cases with a known infector. For cases without a known infector, dashed lines indicate reported contacts between cases. Grey shaded boxes indicate cases in the same household.

(E-step), and then the parameters of θ are found that maximize the likelihood given the probabilities of transmission (M-step), repeating the E-step and M-step until the results converge to the maximum log-likelihood estimate [12].

To examine the effect of potentially false information for the known pairs on the estimated serial interval distribution, we repeated the analysis by leaving out information for the infector $v(i)$ for each pair one by one. The resulting change in the expected log-likelihood estimate for the parameter set θ for case i is called the 'global influence measure' and can be written as $GI_i = E\{\ell(\hat{\theta}_{[-i]})\} - E\{\ell(\hat{\theta})\}$ [12]. Additionally, we considered the extreme case that all recorded contact information was unreliable and repeated the PEM algorithm using only the symptom onsets. We also considered the scenario that only moribund cases, with high levels of septicaemia, were capable of infecting vectors and we repeated the analysis restricting the possible infectors to those that died from the plague.

2.3. Reconstruction and analysis of possible transmission trees

From the likelihood procedure, we obtained probabilities that any case i was infected by any case j. Using these probabilities to specify a multinomial distribution, we sampled a single infector $v(i)$ for each case i (excluding the index cases) to produce a fully reconstructed transmission tree. We repeated this process to produce 1000 possible transmission trees for each model. For each simulated tree, we calculated the average serial interval for all cases, for household transmission, and for community transmission. For the trees simulated from the model that allowed for any individual to be an infector, we calculated the number of secondary cases produced by each case. We calculated the effective reproduction number as the average secondary infections for cases with symptom onsets on day t: $R_e(t) = \sum_j \sum_{i=} p_{ij}(v,\ w, \hat{\theta})$. Additionally, we counted the number of cases with infectors in the same household and the number of cases with infectors that ultimately survived their infections (i.e. that spread the disease without being terminally septicaemic).

3. Results

Thirty-one (88%) suspected cases of plague in Glasgow were diagnosed by the presence of external buboes; and 17 (48.5%) of these cases were confirmed by bacteriological examination [11]. The median patient age was 20 years (range less than 1–60 years): 21 (60%) of the cases were female and 14 (40%) were male. The case-fatality rate for the outbreak was 42.8% for both men and women. From the 15 fatal cases, we found that the median symptomatic period was 6 days (range 2–44 days). There was not enough information in the patient histories to calculate the symptomatic periods for non-fatal cases.

The observed transmission tree for the outbreak is shown in figure 1. The report included contact information for 24 (69%) of the cases; and for 8 of these, they identified a single known infector. From

the eight observed pairs, we found that the mean serial interval was 11.5 days (95% confidence interval (CI): 9.0, 20.6) (figure 2*a*).

Using the likelihood-based method, we obtained the probabilities (table 1) for the missing transmission pairs based on the date of symptom onset and the contact information. To check the influence of the known serial intervals on the results, we calculated the global influence measure for the observed pairs, shown in table 2. We found that one pair (case 29-case 12) had a relatively high *GI* measure, but the impact of this pair on the mean serial interval was negligible.

To estimate the serial interval for the outbreak, we used the probabilities from the likelihood-based approach to simulate transmission trees for different models. The mean serial intervals estimated from the simulated trees were 7.4 days (95% CI: 6.5, 8.6) assuming non-terminal cases could transmit and 9.2 days (95% CI: 7.9, 10.6) assuming only terminal cases could be infectors (figure 2*b* and figure 3). There were no significant differences between the average serial intervals for household and community transmissions across the models (figure 3).

From the simulated trees allowing non-terminally ill infectors, we estimated the time course reproduction numbers. We found that the effective reproduction number declined throughout the duration of the outbreak, shown in figure 2*c*. Before notification of the outbreak on day 22, the average reproduction number was 1.6 (95% CI: 0.9, 2.9). Following notification and implementation of control measures, the average reproduction number was 0.6 (95% CI: 0.0, 2.5).

We also estimated the proportion of secondary household transmissions and the proportion of transmissions from non-septicaemic infections (figure 4). From the observed data, we found from that 62.5% of infections occurred between household contacts. Using both the symptom onset dates and the contact information, we found that the proportion of secondary household infections was 51.5% (95% CI: 51.5, 51.5). When simulating trees using only the symptom onset data and ignoring known contact information, we estimated that 24.4% (95% CI: 18.1, 34.6) of the transmission pairs occurred within a household (figure 4*a*). Next, we identified transmission pairs where the infector had a non-lethal infection. Based on the eight known pairs in the data, 37.5% of cases were infected by persons who survived their infection (non-septicaemic transmission). The proportions of non-septicaemic transmission were 51.7% (95% CI: 39.3, 66.6) and 38.9% (95% CI: 27.3, 48.6), using the trees with and without contact information, respectively (figure 4*b*).

4. Discussion

Our study reports on the epidemiological characteristics of an outbreak of bubonic plague in Glasgow in 1900. From the information in the report, we found that the symptomatic period for bubonic plague in fatal cases was 6 days, which agrees well with the estimate of 5.5 days reported for 100 fatal cases in India [18]. The case-fatality rate was around 40% and this is consistent with other reports of bubonic plague in the pre-antibiotic era [4]. These estimates support the diagnosis of bubonic plague made by the sanitary officials.

We used the contact-tracing information from the official report and applied a likelihood-based method to infer plausible transmission trees. With the reconstructed trees, we directly inferred the serial interval and the effective reproduction number for the outbreak. We estimated that the mean serial interval was on average 7.4–9.2 days (95% CI: 6.5, 10.6), depending on the model assumptions, which was shorter than the mean observed serial interval of 11.5 days (95% CI: 9.0, 20.6). The difference in the means, although not significant, could be attributed to the small number of observed serial intervals or a bias towards observing longer intervals. To our knowledge, there are no other estimates of serial intervals for bubonic plague, thus the reliability of either estimate is difficult to assess. The serial interval for a vector-borne disease is longer than for directly transmitted diseases because they include time in the host as well as in the vector. Given that bubonic plague is transmitted by vectors and that *Y. pestis* can be cultivated from the serum on average 5 days post-infection, and as early as 2 days, an estimate of one to two weeks seems biologically plausible [19].

The reproduction number decreased after notification of the disease. Our estimate of 1.6 before notification is within the range reported (1.4–1.8) for nine outbreaks of plague in Europe during the Second Pandemic with suspected human ectoparasite transmission [20]. The small size and short duration of the outbreak suggest that quarantining and sanitation were effective in stopping the spread of plague, which is also reflected in the drop in R_e below 1 after the implementation of control measures.

Many studies have reported household clustering of cases during Second Pandemic plague outbreaks in Europe [21–26]. For Glasgow, we found that more than half of the secondary cases arose from

Table 1. The most likely infectors and their probability according to the likelihood procedure based on the time of symptom onset (EM algorithm), the time of symptom onset augmented with the contact information (PEM algorithm) and the time of symptom onset augmented with the contact information and with only terminally ill infectors (PEM algorithm). Source cases for which the probability was lower than 0.1 were omitted from the table.

case (***i***)	likely infectors ***j*** based on symptom onset	likely infectors ***j*** based on symptom onset and contacts	likely infectors ***j*** based on symptom onset and contacts (only terminal infectors)
5	v1, v2 (0.274)	v1, v2 (0.192)	v1, v2 (0.285)
	v3, v4 (0.225)	v3, v4 (0.307)	v3 (0.428)
6	v3, v4 (0.273)	v3, v4 (0.277)	v1, v2 (0.218)
	v5 (0.276)	v5 (0.299)	v3 (0.563)
7	v3, v4 (0.220)	v2 (0.185)	v1, v2 (0.207)
	v5 (0.240)	v3 (0.818)	v3 (0.584)
	v6 (0.203)		
8	v3, v4 (0.183)	v2 (0.178)	v1, v2 (0.204)
	v5 (0.203)	v3 (0.821)	v3 (0.591)
	v6 (0.224)		
	v7 (0.116)		
10	v3, v4 (0.144)	v3, v4 (0.117)	v1, v2 (0.104)
	v5 (0.163)	v5 (0.136)	v3 (0.310)
	v6 (0.211)	v6 (0.210)	v7 (0.480)
	v7 (0.167)	v7 (0.206)	
	v8 (0.103)	v8 (0.161)	
12	v5 (0.107)	v6 (0.133)	v1, v2 (0.104)
	v6 (0.155)	v7 (0.148)	v3 (0.310)
	v7 (0.149)	v8 (0.141)	v7 (0.480)
	v8 (0.124)	v9, v10, v11 (0.110)	
13	v5 (0.107)	v7 (0.512)	v7 (1.0)
	v6 (0.155)	v8 (0.487)	
	v7 (0.149)		
	v8 (0.124)		
14	v6 (0.115)	v7 (0.492)	v7 (0.532)
	v7 (0.123)	v8 (0.507)	v13 (0.467)
	v8 (0.117)		
15	v6 (0.115)	v7 (0.492)	v7 (0.532)
	v7 (0.123)	v8 (0.507)	v13 (0.467)
	v8 (0.117)		
16	v6 (0.115)	v7 (0.113)	v7 (0.177)
	v7 (0.123)	v8 (0.117)	v9 (0.179)
	v8 (0.117)	v9, v10, v11 (0.111)	v12, v13 (0.155)
17	v6 (0.115)	v7 (0.113)	v7 (0.177)
	v7 (0.123)	v8 (0.117)	v9 (0.179)
	v8 (0.117)	v9, v10, v11 (0.111)	v12, v13 (0.155)
18	($<$0.100)	v9, v10 (0.500)	v9, v10 (0.500)

(*Continued*.)

Table 1. (*Continued.*)

case (***i***)	likely infectors ***j*** based on symptom onset	likely infectors ***j*** based on symptom onset and contacts	likely infectors ***j*** based on symptom onset and contacts (only terminal infectors)
19	(<0.100)	(<0.100)	v7 (0.111) v9, v10 (0.131) v12, v13 (0.139) v17 (0.143) v19 (0.122)
20	(<0.100)	v7(0.188) v8 (0.217) v13 (0.281) v14 (0.312)	v7 (0.428) v13 (0.571)
21	(<0.100)	v7(0.188) v8 (0.217) v13 (0.281) v14 (0.312)	v7 (0.428) v13 (0.571)
22	(<0.100)	v7(0.188) v8 (0.217) v13 (0.281) v14 (0.312)	v7 (0.428) v13 (0.571)
23	(<0.100)	v13 (0.124) v14 (0.142) v20, v21, v22 (0.187)	v7 (0.419) v13 (0.580)
24	(<0.100)	v14 (0.111) v20, v21, v22 (0.177) v23 (0.131)	v7 (0.415) v13 (0.584)
25	v23 (0.113) v24 (0.126)	v9, v10 (0.500)	v9, v10 (0.500)
27	v25 (0.212) v26 (0.224)	v25 (0.230) v26 (0.255)	v18 (0.105) v25 (0.476)
28	v25 (0.212) v26 (0.224)	v25 (0.230) v26 (0.255)	v18 (0.105) v25 (0.476)
30	v25 (0.161) v26 (0.175)	v29 (0.945)	v12 (0.113) v29 (0.886)
31	v25 (0.161) v26 (0.175)	v29 (0.945)	v12 (0.113) v29 (0.886)
32	v25 (0.161) v26 (0.175)	v29 (0.945)	v12 (0.113) v29 (0.886)
35	v30, v31, v32 (0.101) v33, v34 (0.158)	v29 (0.220) v30, v31, v32 (0.259)	v29 (0.471) v32 (0.528)
mean (95% CI)	8.28 (6.81, 9.72)	7.4 (6.48, 8.63)	9.2 (7.9, 10.6)

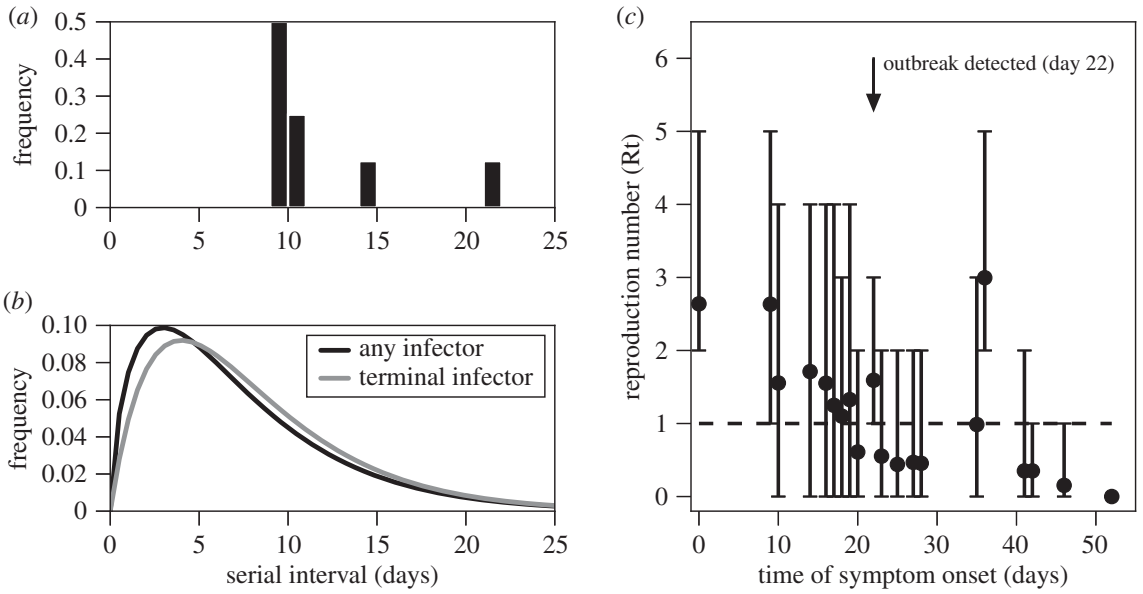

Figure 2. Reconstruction of transmission events for a plague outbreak in Glasgow, Scotland, from 3 August 1900 to 24 September 1900. (*a*) Relative frequency of the serial intervals, based on eight observed transmission events, (*b*) Relative frequency of the serial intervals, based on 8 observed transmission events and 27 reconstructed transmission events. The black line shows the distribution with any infector, mean = 7.4 days [95% CI: 6.5, 8.6]. The grey line shows the distribution with only terminally ill infectors, mean = 9.2 days [95% CI: 7.9, 10.6]. (*c*) Average effective reproduction number ($R_e(t)$) per day (dots) and 95% bootstrap percentile confidence interval (bars).

Table 2. Global influence of the observed serial intervals.

case (***i***)	infector (***v***(***i***))	global influence measure (GI_i)
3	1	0.0
4	1	0.0
9	3	0.42
11	4	0.42
26	18	0.46
29	12	2.85
33	26	0.49
34	26	0.49

infectors in the same household, which was higher than expected based only on the symptom onsets (figure 3*a*). Household clustering of plague cases in historical outbreaks may be attributed to pneumonic plague, which spreads directly between people [23]. However, our results show that a high rate of secondary transmission within households can also occur during bubonic outbreaks. A similar finding was reported for a plague outbreak in Nepal in 1967, with suspected human ectoparasite transmission [27]. By contrast, household clustering was not a feature of plague epidemics spread by rats, as observed in Bombay, Sydney and New Orleans [28–30].

For many vector-borne diseases, like plague spread by rats, it may be difficult or impossible to trace successive cases and establish transmission chains. However, human ectoparasites are tightly associated with their hosts or host environment, and switching hosts may require close and prolonged contact, such as staying in the home or sharing clothes [31,32]. Under these conditions, the transmission of bubonic plague through a human ectoparasite vector would in theory exhibit a household clustering. Given the absence of evidence for plague in the rat population and the observed case pattern, the bubonic plague outbreak in Glasgow is likely to be the result of human-to-human transmission, possibly by a human ectoparasite vector, as already noted by the original investigators of the outbreak.

Human ectoparasite transmission is controversial because there is very limited information about the levels of bacteraemia required for humans to transmit plague to fleas [33]. Experimental studies suggest

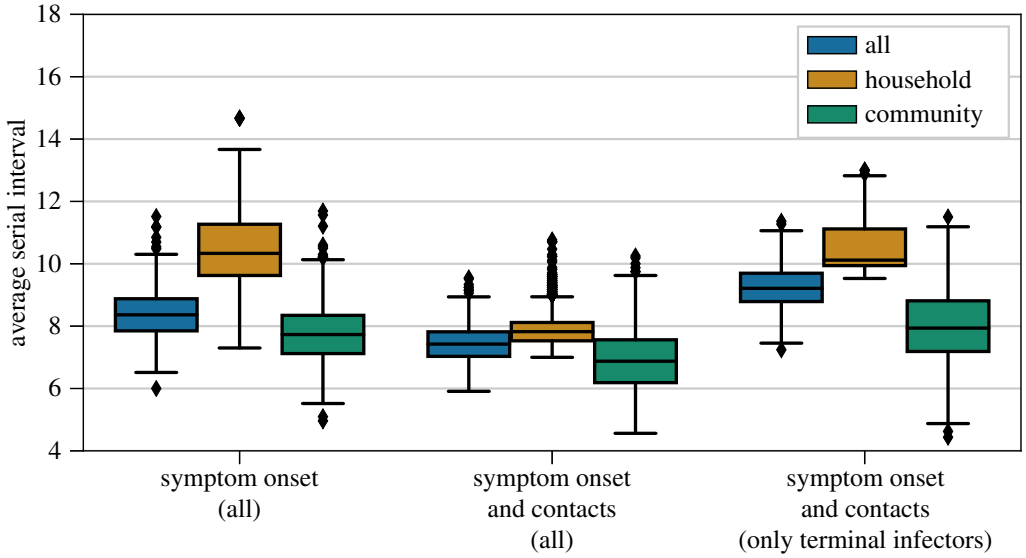

Figure 3. Average serial interval for all cases, community cases and household cases in 1000 simulated trees reconstructed using only the symptom onset dates, the symptom onset dates and the contact information with any infector, and the symptom onset dates and contact information with only terminally ill infectors.

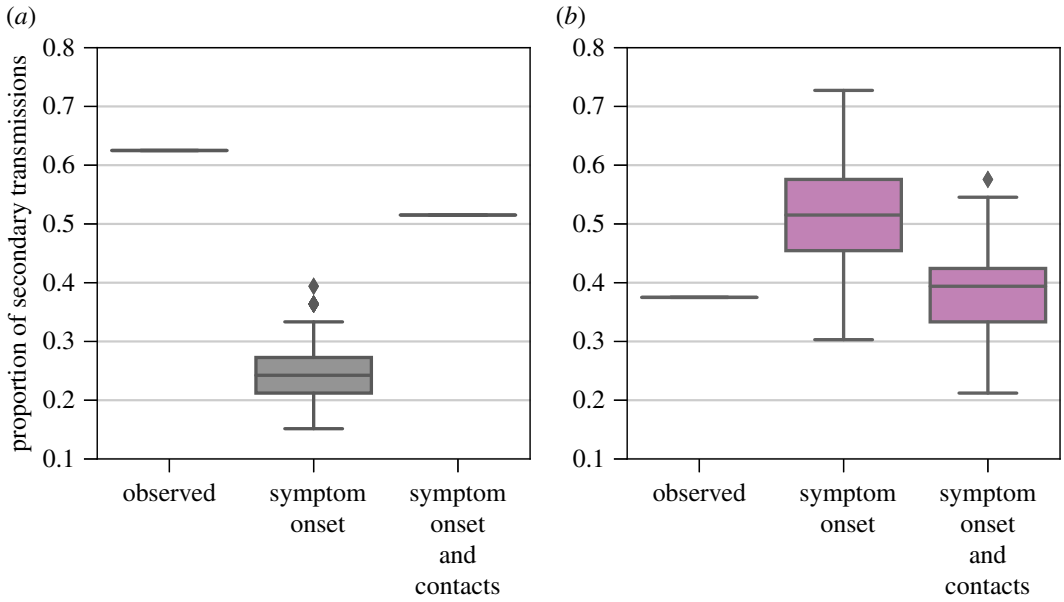

Figure 4. Proportion of secondary cases arising from (*a*) primary cases within the same household for observed pairs, simulated trees using only symptom onset information and simulated trees using symptom onset and contact information, and (*b*) primary cases that ultimately recovered from their infection for observed pairs, simulated trees using only symptom onset information and simulated trees using symptom onset and contact information.

that high levels of bacteraemia, consistent with terminal septicaemia, are necessary for hosts to reliably infect certain flea vectors [34]. However, we observed from the eight known pairs that three secondary transmissions occurred from two individuals who ultimately recovered; this agrees with observations that mild bacteraemia may be exhibited by individuals that are resistant to the disease or those that eventually recover [19,34,35]. Based on the above, we allowed recovered individuals to be potential infectors in one of the models. Even with this assumption, we found that the majority of secondary infections in the reconstructed trees occurred from moribund individuals, as expected. Nonetheless, individuals that survive their infections may also transmit the disease.

The likelihood-based method we used makes three assumptions about the outbreak to fully resolve the transmission trees [12]. The first assumption is that all cases during the outbreak are observed. During this outbreak, underreporting of cases is unlikely given both the thorough nature of the outbreak investigation and the overt and unequivocal course of the disease in humans. At the time of the outbreak, the symptoms for bubonic plague in humans were known, easily recognizable and cases could be confirmed with early bacteriological methods. Moreover, the plague was an extremely rare disease in Scotland at the beginning

of the twentieth century, yet officials were acutely aware of the plague pandemic spreading in India [11]. The second assumption is that all cases, excluding the index cases, are infected by another case. Humans were the only known source of the infection during the outbreak; there were no known local reservoirs for plague in Scotland and there was no evidence of plague in the rat population at the time [11]. The third condition, that the distribution of the serial interval remains stable over the course of an outbreak, is more difficult to evaluate. To our knowledge, there are no studies reporting on the temporal heterogeneity of the serial interval distribution for the plague. Thus, we consider our approach valid for the given outbreak. As shown in the sensitivity analysis, our estimates of the serial interval distribution are unchanged when the contact information is reduced, and this method is thus robust enough to deal with potential contact misclassifications.

In conclusion, our study describes an outbreak of bubonic plague in Glasgow in 1900 and uses transmission tree reconstruction to better understand the epidemiological characteristics of the outbreak. Based on the clustering of cases, bubonic plague most likely spread from human to human, possibly through a human ectoparasite vector. Without diminishing the role of rats in plague transmission during the Third Pandemic, it is important to consider that other models of transmission may apply in different historical contexts. In a modern context, the information in this study can be used to model plague outbreaks where the asymptomatic and symptomatic periods for untreated bubonic cases may be relevant.

Data accessibility. The epidemiological data used in this study are available in the report by A.K. Chalmers, 'Report on certain cases of plague occurring in Glasgow in 1900' (https://archive.org/details/b21359167/) [11]. The code used to analyse the data can be found in the supplement of Hens *et al*. [12].

Authors' contributions. K.R.D. and F.K. conceived and designed the study. K.R.D. performed the analysis; K.R.D., F.K. and B.V.S. interpreted the results; K.R.D. wrote the paper with input from F.K. and B.V.S. All authors gave final approval for publication.

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Chapter III

The Third Plague Pandemic in Europe

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Abstract

Plague has a long history on the European continent, with evidence of the disease dating back to the Stone Age. Plague epidemics in Europe during the First and Second Pandemics, including the Black Death, are infamous for their widespread mortality and lasting social and economic impact. Yet, Europe still experienced plague outbreaks during the Third Pandemic, which began in China and spread globally at the end of the 19th century. Digitization of international records of notifiable diseases, including plague, has enabled us to retrace the introductions of the disease to Europe from the earliest reported cases in 1899, to its disappearance in the 1940s. Using supplemental literature, we summarize the potential sources of plague in Europe and the transmission of the disease, including the role of rats. Finally, we discuss the international efforts aimed at prevention and intervention measures, namely improved hygiene and sanitation, that ultimately led to the disappearance of plague in Europe.

Introduction

Ancient DNA studies have identified *Yersinia pestis,* the etiological agent of the Third Pandemic, as the cause of the previous plague pandemics: the First Pandemic (6-8th centuries)[1–3], and the Second Pandemic (14-19th centuries) [4–8]. During all three pandemics, distinct strains of *Y. pestis* were introduced to Europe causing epidemics of plague, including the infamous Black Death (1346-1353); the strains from the first two pandemics are now extinct. Recently, researchers have identified the earliest known strains of *Y. pestis* in Europe dating as far back as the Stone Age [9–11].

While plague clearly has a long history in Europe, there are no known reservoirs for the disease today [12], which has generated debate surrounding how the ecology and epidemiology of plague has changed over time [13,14]. Here we investigate plague during the Third Pandemic in Europe, as it differs from other parts of the world, in order to characterize the unique epidemiology of the disease during this time period.

The Third Plague Pandemic originated in the Yunnan region of southwest China, where plague caused multiple outbreaks since 1772 [15–17]. In 1894, plague reached Canton and then spread to Hong Kong, where Alexandre Yersin identified the bacterium. It was then carried by ships to Japan, Singapore, Taiwan, and the Indian subcontinent [18,19]. Over the next few years, plague spread to many cities around the world: Bombay, Singapore, Alexandria, Buenos Aires, Rio de Janeiro, Honolulu, San Francisco and Sidney, among others [20]. The earliest known European cases occurred in September and October of 1896, when two sailors from Bombay died of plague on ships docked in London on the Thames [21].

Case records and outbreak reports for the Third Pandemic are numerous and have improved our understanding of the historical epidemiology and distribution of plague. These reports have been compiled and summarized for several regions: North America [22,23], South America [23,24], Africa [23,25], and Asia [23]. However, a similar account for Europe is missing, making it difficult to compare local and global transmission patterns. Europe is also the only region for which we have extended records and accounts on the previous plague pandemics, in particular those of the Second Pandemic. Thus, having documented outbreaks of the Third Pandemic can enable comparisons with historical ones, especially considering that the Third pandemic in Europe was restricted to the pre-antibiotic era.

Here we compile the reported plague cases for Europe during the Third Pandemic from digitized records of notifiable diseases, previous studies, and gray literature. We describe important cases and outbreaks that took place during the Third Pandemic and the international efforts enacted to prevent the importation and spread of the disease. We also investigate the role of rats and other sources of plague, which contributed to decades of small outbreaks. Finally, we discuss the eventual disappearance of plague in Europe due to increased hygiene and a lack of a long-term rodent reservior.

Methods

We systematically collected data for plague cases in Europe from the *Public Health Reports* (formerly *Bulletins of the Public Health* and *Weekly Abstract of Sanitary Reports*) between 1879-1950 accessed through PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/). In the original reports, cases in the period before September 1927 were recorded mainly as outbreaks with start-end dates and those after September 1927 were recorded as weekly or monthly incidence. For some of the early outbreaks, such as those in Porto (1899) and Glasgow (1900), the cases are more temporally resolved. We present these raw data in Table S1 (1899-1927 in blue, 1927-1947 in green), with the highest resolution available from the reports. For overlapping reports, we used the most recent in time, corresponding to the highest number of cases and deaths. Our study area was continental Europe, excluding Russia, but including the Mediterranean islands. We excluded Russia because their reporting of cases internationally has been sparse and irregular. We converted city and country data to latitudes and logitudes for mapping using GeoPy (https://geopy.readthedocs.io/en/stable/).

We used narrative and scientific reports in four languages (English, French, Italian, and German) to supplement the case data. These reports are translated and summarized in ESM. The reports consisted of primary accounts, secondary accounts, and scientific reports, which are mainly found in gray literature.

Results

There were 1,692 cases and 457 deaths from plague reported in Europe between 1899 and 1947 (Figure 1, Table S1), with the largest number of cases in the years 1899 and 1920. Cases were geographically widespread, although they were primarily found in coastal

or inland port cities (Figure 2). Plague was reported in 11 countries, and many cities including Lisbon, Marseille, Paris, and Pireas, experienced multiple outbreaks (Table 1). Plague was notably absent in some parts of Europe. For instance, the Nordic countries, which reported infectious diseases such as polio and cholera, did not report any plague case during the Third Pandemic.

From a comparison with the gray literature summarized in the ESM, it is evident that not all cases have been reported in the *Public Health Reports*. For instance, the last oubreak in Taranto in 1945, with 30 cases and 15 deaths, was hidden due to military reasons, and possibly other cases were not reported in times of war. We see that cases were mainly notified in large cities and ports, which had more traffic from trade but also may have had more resources and established practices for detecting infectious diseases. Some regions, such as the Nordics and Eastern Europe, did not report any case of plague. While plague may be truly absent in these areas, we cannot exclude the possiblity that plague was undectected or unnotified. Nevertheless, overreporting may have occurred if cases were misdiagnosed as plague. While early bacteriological methods were used to identify plague in some instances, to our knowledge, most of the cases in Table S1 were not confirmed. Official reports and accounts of individual outbreaks such as those in Oporto, Glasgow, and Taranto (summarized in ESM), offer more detailed information about case numbers, symptoms, transmission, and mortality, which may differ from the information in the *Public Health Reports* and Table S1.

Discussion

During the later part of the 19th century, diseases such cholera and later plague were spreading throughout the world, partly due to the advent of steamships [26]. This necessitated the development of adequate measures to prevent the introduction and spread of infectious diseases to Europe. The European sanitary authorities responded by meeting often to discuss preventative measures against plague and other diseases. International conferences were held in Venice in 1892, in Dresden in 1893, and in Paris in 1894 [21].

Two events emphasized the re-emerging threat of plague to Europe in the late 1800s. The first was an outbreak of pneumonic plague in Vetlianka, along the Volga River, in Russia [21]. Three commissions were sent to nearby Astrakhan by European governments

(French, British, and joint Austrian-German) to study the outbreak which resulted in more than 400 cases [21,27–31]. The second event was the discovery of two sailors from Bombay who died of plague on a ship in London in 1896 [21,32]. These events prompted European officials to convene an international sanitary conference in February of 1897 in Venice to specifically discuss the spread of plague [21]. Another key international plague conference was held in Shenyang (old name, Mukden) in April 1911, with epidemiologists and scientists from 11 countries (China, Japan, United States of America, Great Britain, France, Germany, Italy, Austria-Hungary, Netherlands, Russia, and Mexico) [33]. The conference was chaired by Dr. Wu Lien Teh, who had stopped the great epidemic of pneumonic plague in Manchuria and Mongolia (about 60,000 victims) by 1910 [33].

Following the international conferences, regular reporting of infectious diseases in Europe began in 1890s [34]. For plague, detailed records of cases and deaths appear in the *Public Health Reports* beginning in 1899 (Table S1). These reports show that plague was continually introduced to European ports throughout the Third Pandemic by ships arriving from abroad, often from former European colonies such as Bombay, Buenos Aires, and Alexandria (Table S1). Ships arriving in European ports, such as those in the United Kingdom, were checked for early signs of plague at arrival and filled out a 'Declaration of Health' [35]. These early signs of plague included suspicion of human or rat cases onboard, as well as unexplained rat mortality [35], which was also noted in many of the case reports (Table S1). It appears that plague was also transported by other means, as there are several accounts relating to specific cargo, such as clothing, rags, grain and other merchandise likely containging infected rats or fleas [20,21,32,36–44].

It is clear from the prevention measures enacted that the authorities were aware of the role of maritime trade in the spread of plague (e.g., [21,35]). For instance, in Venice in 1897, they organized quarantines, controlled maritime traffic from infected areas without stopping trade, and regulated the hygenic condition of ships, travelers, crew, and goods entering Europe. It was noted by Proust that, "As in the previous meeting about cholera, it was decided that the treatment applicable to ships must be regulated by their sanitary condition at the arrival and not by the state of the port of provenance which gives only indications, which may be valuable indications but which are only indications. This is the new principle underlying modern international prophylaxis" [21]. The recommendations of the conference to governments resulted in a complex system of regulations that controlled

carriers coming by land and sea from infected regions [21]. Despite the regulations in place, Europe experienced several outbreaks of plague during the Third Pandemic, but the vast majority of these outbreaks were small (Table S1).

Role of rats and other sources of plague

At the beginning of the Third Pandemic, physicians and scientists used new methods to increase their knowledge of plague, including microbiological and experimental techniques [45]. From the late 1800s, J.H. Lowry [46], E. Rocher [47], A. Yersin [48], among others, observed a connection between human and rat plague mortality during epidemics in India and China, suggesting that black rats were involved in transmission. This observation was later confirmed by P. L. Simond, who demonstrated in 1897 that rat-fleas were vectors for the disease [49,50]. The prevailing view among researchers in the Indo-Pacific region, including J.A. Thompson [51] who observed plague outbreaks in Sydney, W. Hunter who reported on plague in Hong Kong [52], and those of the Indian Plague Commission [53], was that black rats played an important role in the spread of plague, both as hosts in the chain of transmission and as carriers of the disease on ships [54]. When plague was introduced to Europe during the Third Pandemic, rats were heavily scrutinized by European health authorities (Figure 3) when plague cases were discovered [e.g., [36,37,55], see also ESM].

There were two species of commensal rats present in Europe during the Third Pandemic, the black rat (*Rattus rattus*), also called the ship rat or the roof rat, and the brown rat (*Rattus norvegicus*), also called the sewage rat. The black rat has a history in Europe dating back to medieval times, but it has never been present in large numbers, since the climate in Europe is too cold for it to be able to live and reproduce outside heated buildings [56]. The brown rat came to Europe from Russia during the early part of the 18th century and was abundant in all European cities around 1900 [57,58]. The two species are similar in appearance, but they have very different behavior, as first described in a German zoological journal in 1952 by I. Eibl-Eibesfeldt [59] and later in great detail by H.-J. Telle [60]. The American zoologist D.E. Davis [56] described similar differences in articles from the mid-1950s. The British zoologist G. Twigg later describes these differences in his book on 'The Black Death' [61][ww]. These sources state that the black rat is an efficient climber, which makes nests in the walls and roofs of buildings, while the brown rat may live outdoors

in the European climate, is an efficient swimmer, and makes nests in borrows in the soil, in cellars or in sewage pipes [58,59]. The two species of rats carry the same species of fleas. Due to their different behavior, black rats are living closer to humans than brown rats. During the Third Pandemic, plague was transported around the world by black rats on ships. At this time black rats were not generally found in Europe, except in warehouses in ports and in a few towns [62].

From the first reports of plague, European sanitary authorities actively searched for dead rats in cities [39,63–66], urban districts [36,44], isles [67–70] and on ships [19], and they used early bacteriological methods to test for the plague bacterium in the local black and brown rat populations [e.g. [36,39,43,63–67,69,70]]. For instance, when plague broke out in Glasgow in 1900 (see ESM) the Medical Officer of Health caught and examined 326 rats, but found no evidence of plague in the rat population [39,63]. They wrote after the outbreak that "inquiry failed to discover any evidence that rat-mortality prevailed to an unusual extent" [63]. However, in the years following the outbreak they found some evidence of plague in the rat population: in 1901 (122 of 1,641), in 1902 (30 of 6,492), and in 1907 (1 of 140) [55].

Rats were also examined during and after outbreaks in East Suffolk [36,44], Malta [67–69], Italy [66], Corsica [70], Spain [65] and France [64] (see ESM). After a small outbreak of plague in Taranto, Italy, in 1945, there was a large-scale anti-rodent campaign, which killed aound 5,000 rats [42]. Of these, 60% were *R. norvegicus* and 40% were *R. rattus* in the docks, while all of the rats in the city were black rats. In 1945, they found only two rats tested positive [66] and, in 1946, none were infected [43]. There was a similar outbreak in Ajaccio, Corsica on May 12th, 1945, with 13 cases of plague reported over ten weeks [71]**.** It was rumored that dead rats were observed before the outbreak, but none were examined. Following the outbreak, the authorities trapped 148 rats, 14 were *R. rattus* and the rest were *R. norvegicus*, but they found no evidence of plague [70]. Rat monitoring was also carried out in Marseille, France, where 132 cases of plague were reported from 1919-1929 [64]. The largest rat epizootic found in Marseille occurred in the poor downtown areas in 1930, where 42 infected rats were discovered out of the 7,275 that were examined [64].

Perhaps the most extensive rat surveys carried out during the Third Pandemic in Europe were in and around East Suffolk, Britain, where cases appeared regularly from 1906 to 1918 [36,44]. The pattern of recurrent cases in East Suffolk led researchers John and

Dorothy Black to assume that plague was endemic in this region [36]. Surveys for plague were carried out over an area of more than 2,000 km^2 [36,44]. However, only 60 plague infected rats were found out of more than 266,000 rats that were caught during the 3-year survey [36,44]. In addition to rats, the authorities found some ferrets, cats and rabbits that died of plague [44]. The local authorities concluded that the infected rats were most likely brought by grain ships which unloaded their cargo in the area to lighten their draught before continuing onwards [36,44].

Other documented sources of plague in Europe were from direct human transmission of pneumonic plague [e.g., [36,44,63]] and the transportation of infected vectors [e.g., [36,63]] (SI and Table S1). Pneumonic plague occurs when plague infects the lungs, either primarily by the spread of infectious droplets or secondarily as a complication of bubonic plague. Cases of pneumonic plague were reported during many of the outbreaks in Europe (SI and Table S1) and often spread within households and among close contacts [36,44]. For example, in East Suffolk, a 9-year-old girl became ill with pneumonic plague and died in a cottage five miles from Ipswich on the 13th of September 1910 [36,44]. Her mother also contracted the disease and died three days after her daughter's death, followed by her stepfather and a neighbor who nursed her mother. To prevent further spread, the funeral services of the victims were held in open air and the contacts of the deceased were isolated [36,44].

There are also accounts of bubonic plague transmission without a clear association with rats, likely from infected vectors [e.g., [39,63,72]]. Many different flea species can carry and transmit plague, such as those commonly found on rats (*Xenopsylla cheopis*), cats (*Ctenocephalides felis*), and humans (*Pulex irritans*) [21]. Ectoparasites were so abundant in Europe that the Third International Congress on School Hygiene held in Paris in 1910 advised to fight against them, since one out of every three children was infested [73]. As it is still the case for today, vermin infestations back then were associated with poverty and unhygenic living conditions [e.g. [36,63,64,69,74]], often in the poorest quarters of cities, where majority of cases were found during outbreaks such as Oporto (1899), Glasgow (1900), and Marseille (1900-1921). Scheube wrote that, "The development and spread of plague is influenced in a great measure by the unfavorable hygienic conditions, essentially connected with social misery"[75]. In some cases, it appears that infected vectors transmitted the disease between people in close contact. For example, during the plague in

Glasgow in 1901, a woman who had fallen ill with the plague was visited by two friends from Liverpool [38] (see ESM). Weeks later in Liverpool, a chain of deaths from plague began among the relatives and neighbors who handled the clothes worn by the two girls in Glasgow [38]. Indeed, infected ectoparasites in clothing, rags, grain sacks, and other textiles could explain the appearances of plague even in the absence of infected rats [e.g. [21,38,63]].

Overall, the connection between urban rodents and human plague in Europe during the Third Pandemic is less clear than for outbreaks in India and China [21,46,48–50,54,75–78]. However, it was often proposed that other sources of plague, such as infected human-specific or human-biting parasites, like fleas and lice, were important for transmission in Europe during the Third Pandemic [21,36,63,64,74]. The low numbers of plague infected rats found during European outbreaks suggests that they played relatively minor role in plague transmission. However, some researchers have argued that the authorities were unlikely to find plague infected rats because they would go into hiding [51], thus differing in their behaviour from the rats in Hong-Kong during the outbreak of 1894, which were described as dead "in abundance on the streets and in the houses" [48]. The low number of human plague cases in Europe during the Third Pandemic could be explained by a low number of infected rats, but it could also be a reflection of effective public health intervention measures that reduced the contact between humans and infected vectors, such as isolation of patients and contacts, prohibition of gatherings, and improved hygiene [e.g. [21,63,72]].

Disappearance of plague

Plague is not a disease that is found in Europe today, and we found no mention of plague outbreaks after 1950. The disappearance of plague in Europe during the Third Pandemic can be attributed to two main factors, improved hygiene and the lack of a present-day sylvatic reservior for the disease.

At the end of the 19th century, the newly established discipline of microbiology found causative relationships between germs and diseases. In 1897, Proust observed that, "It is no matter of doubt that the plague cannot produce nowadays the disasters of the Black Death in the 14th c. Fortunately, the general hygienic conditions have much changed" [21]. Indeed, during the 19th c., the spread of several diseases like tuberculosis, smallpox,

cholera, and yellow fever, prompted extensive campaigns in European cities to improve hygienic conditions [79]. In many places in Europe, this work included the destruction of slums, improvement of sewage systems, and the widespread development of safe water supply systems [79].

Contemporary scholars regarded cleaning and disinfecting as an essential part of plague control measurements [21,69,80]. Proust described in Bombay that in places where it was possible to clean dwellings, houses, and streets, plague outbreaks could be contained or avoided [21]. Indeed, from the 1950s, the introduction of baths in the majority of European dwellings, and the use of vacuum cleaners and washing machines, strongly enhanced personal hygiene and that of the domestic environment [e.g. [81]]. In addition, from the middle of the 20th c., the number of pests and parasites was reduced by the introduction of insecticides like DDT, which was used heavily in many places like Malta from 1946 onwards [68]. In Taranto in 1945, the allied forces, contributed noticeably to the fight against the epidemic by spraying large quantities of DDT against “fleas, but also bugs, lice and ticks” [66].

Although the existence of a rodent reservoir for plague in the past is heavily debated [7,14,17,56,82–84], there is no evidence that plague is endemic to Europe today or was at any time during the Third Pandemic. Introductions of plague during the Third Pandemic led to the formation of plague reserviors in the United States [22,23], South America (Peru, Bolivia, and Brazil) [23,24], and Africa (Democratic Republic of the Congo, Tanzania, Uganda, and Madagascar) [23,25], where ecological conditions have favored the persistence of the bacteria in sylvatic rodent communities. Today, the spillover of plague from these reservoirs leads to the thousands of cases of plague reported every decade [85]. However, not all introductions of plague led to the formation of reservoirs, typically found in arid and semi-arid highlands [17], which are not present in Europe. The lack of a rodent reservoir in Europe is the fundamental reason why plague is no longer a public health threat today on the continent. The unfavorable environmental conditions in Western Europe make it very unlikely that there has been a wild plague reservoir there. Even in Malta, where the environment is much more favorable to rodent reproduction [69], Barnett oberved that “plague outbreaks always come to an end even if nothing is done to kill rats or their fleas” [69]. It is possbile that future ancient DNA studies will demonstrate that all of the different

lineages of *Y. pestis* involved in historic outbreaks went extinct after their introduction into Europe (see also Namouchi et al. [8]).

Conclusion

Although plague is no longer a public health issue in Europe today, the threat of the disease remains close in both space and time. Plague was in Europe until the middle of the last century, just two generations ago. The disease has recurred in Algeria [86] and Lybia [87] less than a decade ago, in places that are less than 300 miles from European boarders. Moreover, plague is currently present in 11 countries around the world [85]; at a time of globalization, characterized by the increased mobility of people and goods, diseases can easily spread from endemic or enzootic regions (i.e., foci and reservoirs) to the rest of the world in a short time [88]. A recent paper [89], which analyzed plague cases reported since the end of the last century, has proposed classifying plague as a re-emerging disease. Indeed, in the last years, the frequency of plague outbreaks in developing countries in Africa should not be overlooked; industrialized countries must react promptly to plague outbreaks as well as other epidemic diseases, in order to inform the population and help fight against them.

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Figures' and table's captions

Figure 1. Reported suspected plague cases per year in Europe (1899-1950) from the *Public Health Reports*. See also Table S1.

Figure 2. Map of reported plague cases in Europe (1899-1947) from the *Public Health Reports* and ESM including the number of outbreaks in each location (see also Table S1).

Figure 3. 'Liverpool Port Sanitary Authority rat-catchers dipping rats in buckets of petrol to kill fleas for plague control. Liverpool, England. Photograph, 1900/1920.' image courtesy of Wellcome Collection. Credit: Wellcome Collection. CC BY 4.0.

Table 1. Locations and years of reported plague outbreaks in Europe (1899-1950) from the *Public Health Reports* and ESM. Only locations with multiple plague outbreaks are shown (see also Table S1). Country ISO code in parentheses.

Data, code and materials

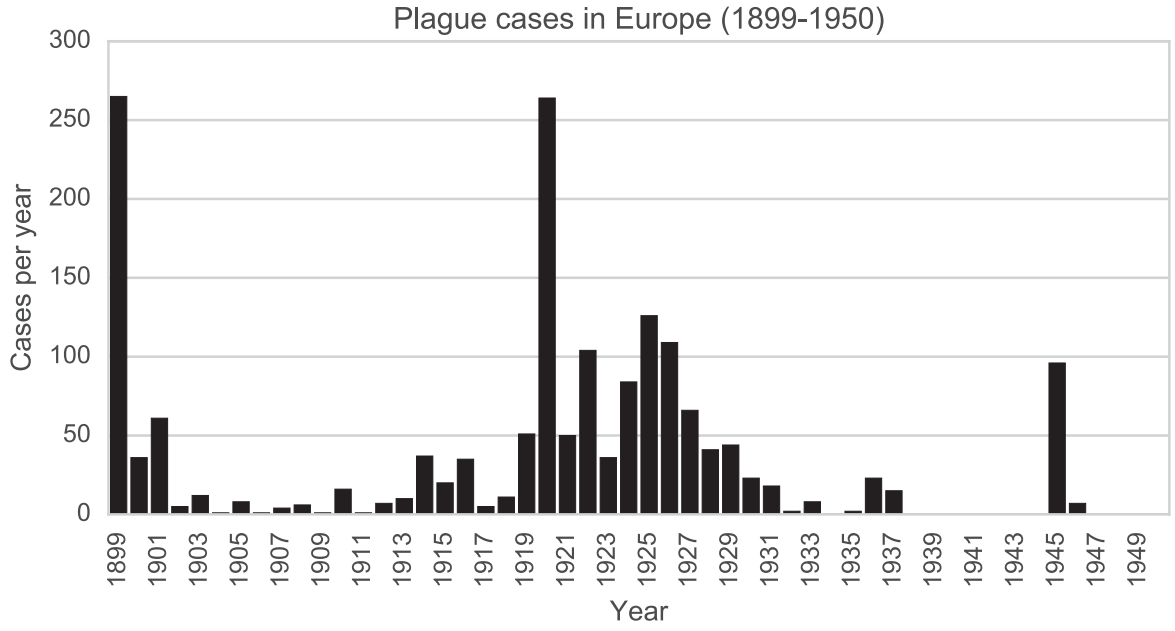
The datasets supporting this article have been uploaded as part of the supplementary material (Table S1).

Competing interests

The authors declare no competing intersts.

Author Contributions

BB and LW conceived the work; BB, LW and NCS designed research; BB carried out the research of the historical texts with help of LW; KRD collected data and performed analyses; BB and KRD wrote the paper with contribution of the other authors.



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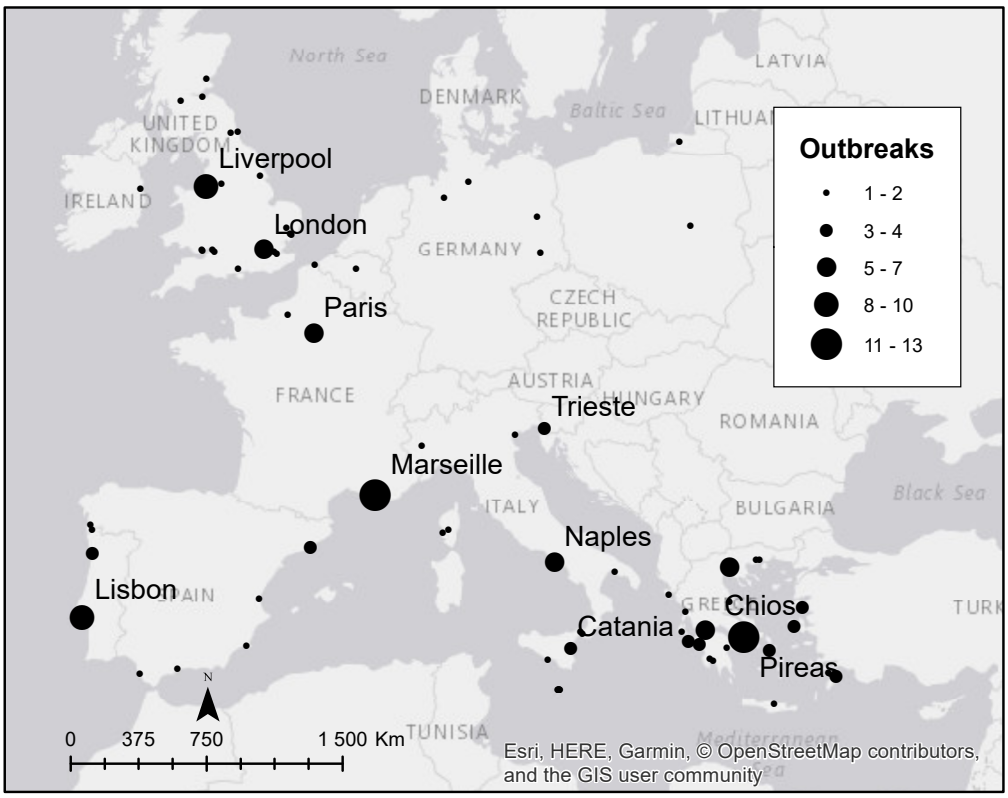

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Table 1. Locations and years of reported plague outbreaks in Europe (1899-1950) from the *Public Health Reports* and ESM. Only locations with multiple plague outbreaks are shown (see also Table S1). Country ISO code in parentheses.

Location	Years
Athens (EL)	1913, 1915, 1919, 1920, 1925, 1926, 1927, 1928
Avonmouth (UK)	1919, 1931
Barcelona (ES)	1902, 1919, 1922, 1931
Catania (IT)	1914, 1920, 1921, 1922
Chios (EL)	1893, 1914, 1916, 1920
Dublin (IE)	1920, 1921
Dunkirk (UK)	1902, 1922
Glasgow (UK)	1900, 1901, 1907, 1908
Hull (UK)	1901, 1916
Lisbon (PT)	1899, 1910, 1914, 1920, 1921, 1922, 1923, 1924, 1926, 1928
Liverpool (UK)	1901, 1905, 1908, 1912, 1914, 1916, 1919, 1920, 1926
London (UK)	1900, 1905, 1910, 1917, 1918, 1919, 1920
Marseille (FR)	1902, 1903, 1907, 1919, 1920, 1924, 1925, 1926, 1930, 1932, 1933, 1935, 1936
Mytilene (EL)	1927, 1928, 1929, 1930
Naples (IT)	1901, 1921, 1922, 1924, 1929
Paris (FR)	1920, 1921, 1922, 1923, 1924, 1926, 1929
Patras (EL)	1922, 1924, 1925, 1926, 1927
Pireas (EL)	1913, 1914, 1915, 1916, 1919, 1920, 1921, 1922, 1925, 1926, 1927, 1929, 1930
Porto (PT)	1899, 1900, 1923
Pyrgos (EL)	1925, 1929, 1930
Rhodes (EL)	1910, 1921, 1925
Saint-Ouen (FR)	1926, 1930
Syros (EL)	1914, 1916, 1923
Taranto (IT)	1927, 1945
Thessaloniki (EL)	1914, 1915, 1919, 1920, 1924, 1925
Trieste (IT)	1906, 1908, 1912, 1913
Zakynthos (EL)	1915, 1920, 1926

Electronic Supplementary Material

The Third Plague Pandemic in Europe

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ACCOUNTS OF PLAGUE IN EUROPE DURING THE THIRD PANDEMIC

London 1896. This outbreak is the first known importation of plague into Europe during the Third Pandemic. Proust[1] reported that plague was discovered on two vessels docked on the River Thames. The disease spread, and on the 26th or 27th of September, a storekeeper's helper fell ill and later died on the 3rd of October. A second helper also became ill on the 26th of September and died on the following day. Another infected ship arrived on the Thames on the 7th of September. After taking on crew a few months earlier in Bombay, the ship left Calcutta and stopped at Colombo, Aden, and several other ports before arriving on the Thames. On the 16th of September, an Indian crewmember fell ill and his condition worsened for two or three days until he died on the 19th at hospital.

Conference of Venice on February 16th 1897. Details of the public health measures proposed at the Health Conference of Venice on February 16th 1897 are given in a renowned and comprehensive report by Proust[1]. Many of these measures were targeted specifically at preventing the spread of plague to Europe. For instance, regions outside of Europe that were under the threat of plague, i.e., plague foci, were to be monitored. In particular, this included areas of Iraq and Iran. Ports were also kept under surveillance, as well as border crossings, where plague could be imported from Russia, India, Afghanistan, and Pakistan (Belochistan). For ports, the conference suggested strong measures, including compulsory daily medical examination of all people on board ships, by a doctor delegated by a public authority. In addition, the measures suggested rigorous disinfection of any objects that were suspected of harboring plague. For overland travel, measures were to be taken during transport through provinces with plague and were meant to comply with the rules accepted in Venice in 1892, in Dresden in 1893, in Paris in 1894, and in Venice in 1897. Modern sanitary practices were to replace quarantine for travelers, including placing ovens and other disinfection stations

along well-traveled routes and railways. Goods were to be disinfected according to the principles adopted by the Conference of Venice of 1897. The conference agreed to rigorous measures of border closure in exceptional cases, with the option for governments to close their borders to passengers and cargo.

Vienna 1898. Three people died of plague after cultivating bacteria in the laboratory, brought from Bombay and confirmed to be *Y. pestis*[2].

Oporto 1899. Two weeks after plague was officially declared in Alexandria, Egypt, plague arrived in Oporto and gave rise to the first large European outbreak during the Third Pandemic[3]. Plague had vanished from Oporto for two centuries. The disease was reintroduced to the city by goods[2] or rats, imported by a ship from Bombay[4]. The first five patients were Galician laborers, who unloaded a shipment of wheat of unspecified origin on the 5th of June[2,3]. Five women who had been hired to sew and mend the grain sacks also died of plague[3]. It was not until the 20th of July that plague was confirmed by bacteriological examination for the first time. This was reconfirmed on the 8th of August, but the government did not declare a public health emergency until the 23rd of August[3]. As a result, plague spread until the beginning of February 1900, and the official statistics cited a total of 322 cases and 115 deaths. The number of deaths was likely higher, given that the total mortality in Oporto rose from an average of 4,650 deaths to 5,520 in 1899[3]. The outbreak in Oporto caused considerable alarm, as evidenced by the many medical commissions sent from around the world to assist with the outbreak[5]. Those working to stop the outbreak were among the victims, including the famous physician Luís da Câmara Pestana[6], a Professor of Anatomo-pathology and Legal Medicine in Lisbon, who had been in Oporto studying the nature and symptoms of plague.

The majority of the victims were from poor waterfront neighborhoods, including: Sao Nicolau, A Sé, Sao Ildefonso, Victoria and Miragaya, and surrounding villages. In the more prosperous commercial and residential quarters of the city, fewer cases were reported and, among those, nearly all were domestic servants, day laborers, and shop clerks[3]. It was written that, "Porto offered horrendous living conditions for its working poor"[3]. A. Shadwell, an official British medical observer, described the living conditions in Oporto in 1899:

> The city center was overcrowded with recent arrivals who had doubled its population in the last three decades of the nineteenth century: The city had just installed electric lighting and begun building a tram network, but in 1899 a modern sewage system did not yet exist. In its poorest districts closest to the port, the visitor could observe oxcarts, sedan chairs, and wagons drawn by as many as ten mules. Here, residents of the squalid tenements were subjected to some of the highest rates of mortality per thousand recorded anywhere in Europe…In addition to the standard measures used elsewhere, two antiquated and controversial procedures were applied by the Federal Board of Health in Lisbon: the erection of a military cordon sanitaire around Oporto and the imposition of official censorship on all information concerning the plague emergency[3].

The measures enacted against plague were in violation of the Venice protocols of 1897. Citizens reacted against them and some soldiers disobeyed orders and broke the blockade. In a letter dated December 8th, 1899, Surgeon Fairfax Irwin wrote:

> The sanitary cordon around the city is inefficient owing to the poverty of the soldiers and their inability to withstand the bribes offered them by the country people wishing to pass through. It is doubtful if this sanitary cordon now exists, as the people of Oporto were on the verge of revolution on account of the restrictions to trade and travel and the probability that a change of ministry would result in the withdrawal of the cordon[7].

Unsurprisingly, wealthy citizens, numbering as many as 20,000-30,000 people, fled the city. All sanitary restrictions put in place during the months that plague ravaged the city were eventually suspended by decree on the 6th of February, 1900[6].

As the first large outbreak during the Third Pandemic, “Porto was the first city where physicians used extensive serum and vaccine therapy in response to an outbreak of plague”[3]. One hundred forty-two patients received the Pasteur serum to prevent plague and, of them, 21 died. However, it was not known if the vaccine offered protection against the disease because the experiment was not conducted with a control group[3].

Glasgow 1900. In autumn 1900, plague reappeared in Glasgow after two and a half centuries. The outbreak consisted of 36 cases, of which 16 were fatal[8]. The earliest known cases were described in a report about the outbreak:

> A child and its grandmother (Mrs. B.), living in the same house at 71 Rose Street, South-Side, Glasgow, sickened suddenly on the evening of 3rd August — the child dying on the 7th and the grandmother on the 9th — the cause of death of the child being certified as "zymotic enteritis,'' and of the grandmother "acute gastro-enteritis”. […] In both cases a wake was held, and the grandmother was buried on the 11th. Although the husband of this latter patient sickened on the 12th, he was only admitted to hospital on Monday, 27th August, certified "enteric fever," when he was recognized to be suffering from plague[8].

Care was used by the sanitary commission to ascertain the origin of plague, as described in the report:

> The house occupied by the B. family was a single apartment on the ground floor. It is distant at least a quarter of a mile from the river — considerably further from the docks. The father, although a dock laborer, was employed exclusively in vessels engaged in the coasting trade, and no evidence of other association with shipping could be found. The mother was a fish hawker, and took special charge of her grandchild. This is important, because the grandmother took the child with her wherever she went, and they sickened simultaneously. It suggests that they found their infection beyond the limits of their dwelling. […] The only other inmate of this house was a daughter — mother of the baby referred to — and employed, until the date of her mother's sickening, in a rag store. She was not affected. […] Concurrently with the later developments in this household, the following illnesses were appearing in the members of a family (M.), 57 Thistle Street, some of whom had either attended Mrs. B.’s wake, or were present during the illnesses in her house[8].

The sanitary authorities constructed a chain of transmission among the contacts of the initial cases. However, not all cases could be connected to previous ones. In general, the disease spread in the poor quarters of the city, where there was overcrowding in dwellings with poor light and ventilation. However, in one case a woman was infected without any direct contact with these areas. She was the wife of a clothes collector, who cleaned the personal belongings of the plague victims. It was noted in the report that, “the houses of the majority of the cases were hotbeds of vermin, and the clothes collector, like all those who had to deal with the infected houses, frequently complained of the annoyance these insects caused him”[8]. The clothes collector had received a dose of Yersin’s serum and did not develop plague, but it was thought that he transported the parasites home with the clothes[8].

The mechanism for the transmission of plague was not clear to the sanitary authorities. They regarded wakes with particular suspicion, as many of the cases were connected through contacts made during wakes. They wrote that:

> Waking, or watching with the dead, is primarily an act of reverence and of sympathy. But "wakes," as we now mostly know them, are an abuse of this custom. […] Considerably over one hundred persons were present on one or other of the evenings on which these ceremonies were held, and, as the families were related, many attended the “Avakes” in both households. […] Of the persons present at the wakes here, four afterwards sickened. Among those attending the Thistle Street wake, six primary attacks resulted. The first illness in the Thistle Street household was pneumonic in type; and during the wakes three others of the family were sick, one of them of plague septicaemia. Seven families altogether were

> resident at 57 Thistle Street; but attacks occurred only among those who had been present at the wakes, although the importance of this may be to some extent discounted by the recognition of the nature of the disease five days after the death in this household occurred, and the consequent removal of all the known contacts to the reception-house[8].

With this observation, the authorities temporarily prohibited gatherings and visits during wakes.

As was usual for the Third Pandemic, rats were monitored during the outbreak. It was noted that:

> Rats were numerous in many of the infected tenements, and in those in which the type of the disease was pneumonic or intestinal, opportunities of infection, in all likelihood, occurred. On the recognition of the cases, inquiry failed to discover any evidence that rat-mortality prevailed to an unusual extent; and when a definite system of examination was begun, nearly three hundred, killed by trapping, or found dead in ashpits or elsewhere, chiefly within the area of infection, were bacteriologically examined without evidence of pest being discovered in any of them[8].

Interestingly, the authors of this report in 1901 already knew about the mechanisms of transmission mediated by ectoparasites: Fleas "together with flies, lice and ants, are capable of conveying the infection, and indirect contact may thus be established"[8].

While the sanitary commission made every attempt to understand the transmission of plague in Glasgow, the origins of the disease were still unclear. The commission wrote that, "The infection in the first outbreak in Glasgow in 1900 was no doubt imported into the city either by a human carrier of the disease or by infected material, more probably the latter, at a season of the year that was most favorable to the activity of the Bacillus pestis"[9]. They speculated on the origins that, "For this, modern methods of commerce and travel are responsible"[8] and, "Plague means so much to the mercantile and maritime interests of the town or city in which it may appear"[9].

Glasgow and Liverpool 1901. Although small in the number of cases, this outbreak is interesting because Colvin reconstructed the spread of plague between Glasgow and Liverpool, where eight cases occurred with six deaths. The outbreak began in August of 1901, in Glasgow, when it was reported that a 12-year-old boy became, "extremely ill, with a febrile temperature, and a painful swelling in his groin. No wounds or abrasion of any kind were seen on the boy's leg to account for the bubo. Two days later the boy's father took suddenly ill with the symptoms of an acute pneumonia […] He died suddenly after two days' illness. […] The house and his rag-store were disinfected and all the contacts removed to the sanitary reception house"[10]. Nevertheless, "at the end of October, 1901, there was a recrudescence of plague in Glasgow, four patients being found in the Central Station Hotel, while other two in association with them sickened of the same disease"[10]. These cases were connected to the 12-years old boy and his father, the ragman.

On August 15th 1901, a young woman in Glasgow developed a hidden mild form of plague with an iliac bubo, which was first diagnosed as an acute ovaritis[10]. During the week the woman was ill, two friends from Liverpool stayed three days with her. An account of the events stated that:

> Although they did not occupy the same bedroom, for there were five apartments in the house, they were in most intimate contact with the patient. On Sept 21st, or about four weeks later [when they were back to Liverpool], their mother sickened and died from plague after an illness of seven days with buboes in her axillae. On Sept. 22nd one of the girls sickened and died from plague nine days later with axillary buboes. On Sept. 24th the other girl sickened with plague with a bubo in her groin and she recovered. A woman who assisted in laying out the mother's body also died from plague, while four children living in an adjoining house sickened with plague, three of whom died[10].

Since the average incubation time of plague is about 10 days, Colvin could not at first establish a connection between the cases in Glasgow and those in Liverpool. Inquiries uncovered that, "the mother superintended the washing and laying aside of the clothes worn in Glasgow and thus caught the infection, and having evidently developed a virulent form of the disease infected her two

daughters"[10]. The death of the four children in the neighboring house could be explained by the same mean of transmission:

> the very week that two of these children sickened their mother was wearing a blouse that had been given to her by one of the girls who had been to Glasgow, for the girl's mother being dead and the blouse being of a bright colour she could not wear it herself, for she was in mourning. The last time this blouse was worn by the girl was in Glasgow when in immediate contact with her friend, who was ill presumably with plague, for the blouse was never worn by her after she sickened with plague on account of her mother's death. I made strict inquiries whether the blouse had been washed or cleaned before being worn by the mother of the children and received a negative reply, for the blouse was silk and a new one and only worn in Glasgow[10].

Colvin reported other accounts of clothing being a carrier of plague: "many of the cases of plague in China were traced to the practice of the Chinese wearing the cloths of those who had died from the disease"[10]. He conveyed another interesting observation about immunity or asymptomatic cases of plague: a mother who spent 18 days with her daughter, a plague patient, slept with her and ate food handled by her without sickening[10].

Glasgow and Liverpool 1907. The third outbreak in the Scottish port occurred in 1907, again in August. "There were 2 known cases in the plague-infected area of 1900. In my opinion there were more cases, but I do not wish to introduce into this letter any disputed cases"[9]. The account of the outbreak was particularly interesting because it indicated that infected rats were involved:

> For the first time in any of the three outbreaks, infected rats were detected, and the disquieting fact was that they were found in Kinning Park, which is on the same side of the [river] Clyde, but fully a mile from the plague-infected area of 1900. These rats were accidentally discovered by giving rise to an offensive smell. They numbered 51, and had probably died about the same time. Only one of them was fit for bacteriological examination, and Dr. R.M. Buchanan, the city bacteriologist, reported (Local Government Board Report for Scotland, 1907) that the Bacillus pestis was found. A subculture proved virulent for a healthy mouse and a healthy rat within forty-eight and seventy-two hours respectively. Dr. Buchanan adds: 'In view of the absence of any other probable cause of the death of these rats it must be presumed that the others had all succumbed to plague'[…] Finally, we have the second outbreak of plague in Liverpool – and again in autumn. […] Hence I would suggest the following relationship between each of the five outbreaks. There is not the shadow of a doubt that the other two outbreaks resulted from the first one and were not fresh importations into the city. They were a positive proof that the Bacillus pestis, as in all modern outbreaks, had remained in the city since 1900 in spite of all that was done to destroy it. The infection in the first outbreak of plague in Liverpool in 1901 was most probably brought into that city from Glasgow, as I have already described, by infected clothing, and in the absence of proof to the contrary I would now suggest that the infection in the recent three cases of plague in Liverpool is not a fresh importation, but is related in some way with the outbreak in Liverpool in 1901[9].

East Suffolk 1906-1918: John and Dorothy Black[11] reviewed the work of van Zwanenberg[12] on the progress of the small outbreaks that occurred in East Suffolk during 1906-1918. The first victim was a 9-year-old girl, who became ill with pneumonic plague in a cottage located five miles from Ipswich on the 13th of September 1910. Her mother died three days after her death, followed by her stepfather and a neighbor who had nursed her mother. It was written that, "All the victims had similar symptoms. The last two patients were buried on 30 September, the vicar taking the whole service in the open air; all those attending had their clothes disinfected. There were no necropsies or inquests. On 1 October the contacts were removed to isolation accommodation in Tattingstone Workhouse, which had been opened for this purpose."[11]. Some rats, a ferret, and a cat had also died close to the main river and their death was attributed to plague. A rat-survey was carried out in November 1910 and at the end of the year; the findings stated that:

> The investigators examined 568 captured rats; all were brown rats. Seventeen of these rats were found to be infected. […] Dr. Rowland paid particular attention to the flea population and obtained 584 fleas, about half of which were of the species *Nosopsyllus fasciatus*, which they demonstrated will readily bite man in the absence of its normal host. The stomachs of three fleas from rats infected with plague were examined; two contained a considerable number of plague bacilli. 40 rabbits were also examined, 2 of which carried the flea described above; 2 rabbits were found to be infected, one either recovering or suffering from chronic plague and one with acute plague[11].

A second, more extensive survey was carried out in January 1911, but the investigators did not find any infected rats. A third survey was organized between July and October 1911 and they found that, "Of 15 332 rats examined by dissection, 35 were found to be infected; diagnosis was mainly on the basis of post-mortem appearance and was confirmed by bacteriological culture in some cases. […] The surveys had shown that rats on both sides of the Orwell were infected"[11]. On October 10th, 1911, a sailor, based at the Royal Naval Barracks on the HMS Ganges in Shotley, developed severe pneumonia and an investigation of his sputum supported the diagnosis of plague. "He had cut himself while cleaning a rabbit which he had caught on the Ipswich Road […]. He recovered and died at the age of 76, although remained almost completely blind"[11].

Later rat campaigns, from 1912-1914, revealed that plague was sporadic:

> During 1912 a quarter of a million rats were killed but no cases of plague were discovered. In 1913 two parishes in the Shotley peninsula and one in the Woodbridge district were found to have infected rats, and 7 infected ferrets were found in the Woodbridge district. In 1914 no infected rats were found and no further action was taken because of the war[11].

Further inquiries retrospectively disclosed eight probable cases of pneumonic plague in 1906-1907, which had originally been certified as pneumonia:

> Dr Bulstrode was informed by a gamekeeper at Woolverstone Park [on the west bank of the river Orwell] that in 1906±1907 rats were observed to be dying in large numbers on the estate. The gamekeeper at Freston House reported a similar high mortality among rats in the autumn of 1910[11].

Another outbreak of bubonic plague was reported between December 1909 and January 1910.

> The infected family consisted of two adults and their five children, aged from 6 to 18 years. The home circumstances were poor and the house was reported to be infested with fleas. All seven members of the family were affected, of whom three recovered. All the victims developed bubonic plague, at intervals of three to six days between cases […]. Dr Bulstrode concluded that the family had suffered from bubonic plague, with case to case infection, probably by the human flea[11].

The last episodes of plague in East Suffolk concerned two women. The first became ill on Saturday June 8th, 1918[12] and died the following Thursday. Her neighbor who visited her died shortly after of pneumonic plague[12]. Their contacts were quarantined and all of their clothing and bedding was burned.

Due to the long-lasting presence of plague in the area, it was proposed that a reservoir was established in East Suffolk. It was written that, "There is no evidence that plague was in existence in Suffolk before 1906, nor were there any reports, apart from isolated cases in ports, of plague in other parts of the British Isles between 1906 and 1918"[11]. However, another explanation for plague in the area was that larger grain vessels coming from infected regions "off-loaded cargo into barges at Butterman's Bay on the north bank of the Orwell, to lighten their draught sufficiently to enable them to dock in Ipswich. It would have been easy for infected rats to swim ashore or for them to be brought on shore in sacks of grain"[11]. The number of rats coming off of ships was likely less after July 9th, 2012, when an ordinance in the United States introduced the use of rat guards for plague control. It was written that, "A rat guard is a sort of round metal "shield," placed over mooring lines to make it nearly impossible for rats to climb over and get onto or off the vessel when docked. Black rats were very common on all commercial ships from far back in history (and up to 1940s)"[13].

Catania 1914. In the newspaper *La Sicilia*, a short review appeared in 2014[14] about the report "La peste in Catania nel 1914". The report was written in 1917 by S. Privitera, a health official of Catania who helped to stop plague there in 1914. As stated in the report, plague was introduced by the steamer *Polcevera*, returning from Lybia. Infected rats were found on board and Privitera organized an extensive anti-rat campaign in the city. Eleven persons died in this outbreak of bubonic plague, including dockyard workers and their relatives. Among them was the daughter of a longshoreman, who had washed the clothes of her father.

Marseille 1900-1930. The work of Mafart et al.[15] is a valuable, rare account on the plague outbreaks in Marseille during the Third Pandemic:

> In 1900, 6 cases (no death) and 1901, 31 cases (4 deaths) were reported aboard ships coming from China, Egypt, Italy but the town was trusting their quarantine framework. So the first re-emergency of plague inside Marseille, in 1903 was a great surprise and cause for anxiety to local council and even, to national health authorities. […] At the end of August 1903, several deaths occurred among the workmen of a cardboard factory in city suburbs, at Saint-Barnabé district, which sorted old papers from Syria. Previously, rats, usually very many numerous in the factory, had disappeared and many rat corpses had been incinerated by the workmen. September 3th, a doctor noted the presence of bubo among two patients. The analysis of the pus imposed the diagnosis of plague. Most of patients were factory workers or parents of them. Suspects and subjects contacts (27 people) were hospitalized at the Salvator Hospital on September 6th with a rigorous bulk heading (Pons, 1904). An anti-plague serum was injected to the patients and the anti-plague vaccine was injected to 300 people, contacts and paramedical and medical personnel. The use of special garments (overall of fabric and Wellingtons) was imposed to paramedical and medical personnel. A sterilization with the drying oven of clothing was carried out. In spite of these precautions, three cases occurred among the personnel of the hospital. On the whole, 9 people died among 21 patients, 18 contaminated downtowns, three at the Salvator hospital that was opened from September 6th to October 15th. This epidemic of plague in Marseilles was held secret and the national medical authorities sent the general inspector of Health to take the direction of prophylactic measurements. A disinfection of the buildings, houses of the patients and suspects was undertaken. The cardboard factory burned during the disinfection, which fire was recognized as voluntary in 1921. […] In 1913, a new case of plague was declared in the rebuilt factory. […] From 1919 to 1929, 132 cases of human plague were declared and involved 41 deaths […] There were 21 cases of plague (7 deaths) diagnosed among the sailors of the ships arriving or being at anchor […]. The employees working on the quays were exposed as well as the various trade associations, which approached the cargo warehouses (10 patients, 4 deaths). However, the majority of the cases of plague were described downtown among patients not having any relation with the port (101 cases, 30 deaths). These patients lived the unhealthiest districts of the city, at a few hundred miles from the port (Villette and Arenc district). In this part of town, where houses like a shantytown had no hygiene, occupied by poorest people, the rats were abounding […].The epidemics generally began in a house or a slum. A person died with hot fever and some days later, others family members and neighbors were also ill and died. […] The captured or dead rats found in the port were sometimes infected. The presence of *Xenopsylla cheopis* was found among 92,7% among the rats captured on the ships, 33% among those of the quays and 50,4% among the rats captured downtown on a total of more than 9000 chips [*i.e.* fleas] examined in 1908 and 1909. Greatest epizootic was observed downtown in 1930: 28 among 42 infected rats discovered during the year in Marseilles among total amount 7275 examined rats came from the same district[15].

The authors concluded, "It is clearly proved that *Yersinia pestis* was present in urban murine population, contaminated for a long time by infected rodents living on harbor. So, at several time, in city areas were poverty allowed rodent increase, some sporadic bubonic plague human cases could occur with a secondary small outbreak, intensified by lack of hygiene and human fleas"[15].

Paris 1920-1. Although the French capital was already hit in 1917, there was a new outbreak of plague in Paris in 1920 – known as the "plague of the ragmen" (*peste des chiffonniers*). The outbreak was named after the majority of its victims who were ragmen living in conditions of extreme poverty, and it passed relatively unnoticed because of the earlier Spanish flu episode and the aftermath of the First World War[16]. This plague outbreak killed 33 people, with 95 reported cases[17]. The first known cases were children playing on the banks of the Seine, where suspicious barges were lodged[16].

Dublin 1921. We learn from Sir Arthur Ball[18] that he "was called to Sir Patrick Dun's Hospital late in the evening, to a case brought in by the ambulance, supposed to be one of strangulated hernia". He observed symptoms of a serious infection in the patient and decided to surgically remove a "gland" and send the specimen for analysis. Bubonic plague was diagnosed.

> Its mode of spreading may be by direct infection from one human being to another, either by inoculation with some discharge of the sick through a breach of surface in the healthy, or by inhalation of germ-laden atmosphere. By inoculation through the medium of rat fleas--which have left a sick rat and sought temporary sustenance from a human being. Sometimes the inoculation is caused by the bite of a sick rat or other animal. The case under consideration was that of a young woman of about 25 years, who […] lived not far from the shipping quays on the South side of the river, in a single room, alone, with a cat as bed-companion. When I saw her first on the morning of the 18th, I was at once struck with her typhus-like aspect. […] The trunk was covered with the marks of flea-bites, and the nurse informed me that she was in a very dirty state on admission. Careful search was made for the, minute, vesicle, or pustule, frequently seen at the site of inoculation on the macule made by a flea-bite, but nothing of the sort was found, and there was no wound to be found on the body[18].

She recovered after 13 days.

Barcelona 1931. After about 200 years' absence from the Iberian peninsula, plague struck on several occasions in Barcelona during the Third Pandemic: in 1905, with 52 cases and ten deaths; in 1919 with at least seven cases; in 1920 with a unique case; in October and November 1922, with a total of 28 cases; in November and December 1923, with two cases; in 1925, with one case ("in March, a man who brought a cargo of plantains from the Canary Islands"[19]); in October 1930, with four cases and four deaths; and in August-December 1931, with 31 cases, eight of which were fatal. The source of the infection, whether rats, goods or humans, could not be determined[19]. The most heavily hit quarters were the poorest, with unsanitary dwellings and refuse dumps in the vicinity. All measures to contain the outbreak were taken and rats were monitored as well during the outbreaks: 8,074 were examined, of which 4,268 bacteriologically (July 1931-January 1934). Only one rat was apparently infected, but inoculation tests using guinea pigs gave negative results. Of the total rats examined, over 99% were *R. norvegicus*, whereas of their 4,992 caught fleas, 1,985 were *X. cheopis* and 1,643 *C. fasciatus*[19].

Malta 1917. Malta's government, like many other European governments, feared the reintroduction of plague to the island, after the terrible outbreak of 1813[20] at the end of the Second Pandemic. Thus, in 1899, when plague was reported in Egypt and Portugal, the Maltese authorities authorized the Superintendent of Police to pay for every dead rat delivered. Over the course of one year, from November 1899 to November 1900, more than 49,400 rats were killed and delivered to the police[21].
Plague occurred again in Malta in 1917 and the first plague victim was, "infected from a sick rat which he found in a box containing stores coming from Mesopotamia where the disease was epidemic"[22]. With only eight cases and four deaths, the outbreak remained confined to the area around the port and occurred among dockyard workers and their contacts[22] from March 2nd to April 2nd, 1917[23]. "Of these cases, 7 were bubonic in form; 1 case was septicemic. Five of the 8 cases notified occurred at Calcara among a group of laborers from the neighboring island of Gozo, living in two tenements; the remaining cases occurred in contacts with this group"[23]. Over three months, Maj W. Broughton Alcock RAMC and Prof. Themistocles Zammit examined over 1,500 rats from around

the Grand Harbor; of these, 15 rats were found to be infected[24]. The brown rat, *R. norvegicus,* was the predominant species in the neighborhood of the Grand Harbor. Their account stated that, "Other species were *M. rattus* (black rat), of more recent introduction and found also on the shore, and the variety *M. rattus alexandrinus*, which is fairly common in the island"[24]. The 102 fleas associated with the *R. rattus* individuals examined were: *X. cheopis* (60), *Ctenopsytta musculi* (38), *N. fasciatus* (3), and *Ctenocephalus* (1); whereas the 180 fleas taken from *R. decumanus* consisted of *X. cheopis* (118), *Ctenopsytta musculi* (49), *N. fasciatus* (3), and *Ctenocephalus* (10)[24]. Mites were also found on the rats, the most common being *Laelaps echidninus*[24].

Malta 1936-1937. Twenty years after the outbreak in 1917, a further epidemic occurred in Malta at Oormi from April 1936 to May 1937, which spread to Zebbug, with some additional cases in Rabat, Marsa, and Attard. In total, there were 33 cases and 12 deaths[25]. During 1936, the Health Department initiated an anti-rat campaign in the harbor areas, which led to the collection of 750 rats by trapping[21]. Plague was thought to have been imported by rodents that infested the hay and straw from the Barbary Coast[25]. Investigators found that an epizootic among *R. norvegicus* was present before the start of the epidemic[22]. *Leptopsylla segnis* was the most frequently found rat flea (48.75%), followed by *X. cheopis* (37.5%), whereas *N. fasciatus* was less common (13.75%)[22].

Malta 1945-1946. A further outbreak occurred in Malta from 1945-1946, in the commercial port area, which resulted in 80 cases and 22 deaths[26,27]. An account of the outbreak noted the involvement of rats and pets:

> From June 1945 to June 1946, out of 22,902 examined […] 20 rats were diagnosed as infected and of these 15 were *R. norvegicus*. It will be noticed that this species is clearly implicated as an important vector of plague in this outbreak […]. Although there was evidence of a widespread epizootic there was evidently a low incidence of infection; there were no reports of heavy mortality among rats which could be attributed to plague. Plague was also identified in one family of pet cavies and suspected in another. Both of the households concerned had human cases of plague as well[26].

Barnett further reported about the rat surveys carried out in those years:

> The obvious inference is that 4 months' intensive rat destruction had checked the plague outbreak. Unfortunately, it must be admitted that this inference is not safe one, since plague outbreaks always come to an end even if nothing is done to kill rats or their fleas. It cannot be proved that in this instance it was rat destruction that was responsible. However, the fact that the only cases of plague in the summer of 1946 were in an untreated village is suggestive[26].

Barnett described the conditions that led to the spillover of plague:

> As is usual in such outbreaks […], the majority of infected persons were accustomed to walking about in bare feet in filthy surrounding which provided harbourage for fleas. […] In Tower Road, Bubaqra, in which most of the Bubaqra cases lived, there were three privately owned refuse heaps. At one of these three *R. norvegicus* infested with bacteria indistinguishable from *P. pestis* were taken. Of 13 cases in Bubaqra, 3 were refuse collectors, and a fourth was a son of one of the 3; 5 others were associated in work, or topographically, with refuse collection[26].

The Maltese authorities also employed vector control against plague and, "From 1946 on, frequent and abundant use of DDT was introduced in Malta against insect and parasites, in particular against sand-fly which can transmit leishmaniosis and mosquitos. From 1948, the Insect Control section included a team of two labourers and one supervisor for the period April-November"[21].

Ajaccio 1945. The plague outbreak in Ajaccio occurred soon after World War II (May-July 1945), after centuries of absence from the island. The number of cases was limitied[28], but the death toll among the cases was relatively high. The Bull WHO 1951[22] wrote that plague was "apparently imported from North Africa". Additional information comes from a paper published in 1948[28], which said that the outbreak was confined to three small areas, one of which was a military barracks. Control measures

were carried out, including compulsory vaccination for all the 25,000 citizens of Ajaccio. Of the 148 rats trapped after the outbreak, none were found to be infected. Of the rats that were trapped, 14 were *Rattus rattus alexandrinus* and the rest were *R. norvegicus*. They collected 101 fleas from the rats; 42 were *Xenopsylla cheopis*, of which all but eight were found on the 14 *R. rattus* individuals.

Taranto 1927 & 1945. During the Second Pandemic, the city of Taranto was struck by plague, in 1485 and again in 1523[29]. In the period of the Third Pandemic, a first lethal case of plague on a military vessel was reported in 1927 and did not produce any further victims[30,31]. At the beginning of September 1945, some dead mice were found in the harbor's armoury[32]. The first confirmed human plague case was reported on the 6th of September, and the last case was reported on the 29th of November[33]. All of the earliest victims were workers of the parcel office in the armoury[32], and the other cases lived in close proximity[32]. At that time, the official total number of cases was 29, of which 28 were civilian cases and one was among army personnel. With 15 deaths, the mortality rate was 51.7%; all 14 cases with primary septicemia died and one case out of 15 with primary bubonic plague died. No cases of pneumonic plague were reported. Seven of the cases that were reported had been inoculated; of these, three died of septicemic plague, the others with bubonic plague recovered[33]. Schultz[33] suggests that the exact source of infection was not clear:

> The disease may have existed in the form of a dormant epizootic in the Italian naval arsenal dock area for some considerable time before manifesting itself by human infection. Strong suspicion centred on a cargo of imported rags, stored in a shed in the arsenal, from which the infected rodents may have spread to other parts of the arsenal. The first cases notified had all been working in the vicinity of the shed, but, subsequently, infections occurred in persons situated in two other places. One of these persons was a military policeman on duty outside the arsenal, at a place where a broken drain might have given direct access to rodents, and the other was a civilian; it was not possible to trace the source of infection of the latter. The barque "Cherso" came under suspicion because the cargo of rags, which was stored in the shed and was later considered to be the primary source of infection, had been unloaded from it on about 28 July. The origin of the cargo is unknown; the ship may have come from Malta or some other port in an area where plague is endemic. […] Seizure of the ship was carried out when she arrived in Venice harbor on about 8 September. The results of the investigation are not known[33].

Schultz attested to receiving information on the movement of the ship from the Report ADMS 52 Army Area (obtained from UNRRA Health Division, Rome). More recent articles[32,34] summarizing the results of many years of historical research came to different conclusions about the origin of plague in Taranto. They claimed that plague was spread by an English mercantile transporting cotton noil from Malta. During the journey, the ship may have had an onboard fatal case of plague, which was not reported to the Italian authorities. Days before the first notification, the military police was seen at night quickly unloading a coffin onto one of their cars[32]. There were no official reports about the incident, but the British Army unofficially admitted that they had one case of plague[32]. The official number of victims of the epidemic is now considered to be 30.

This episode of plague occurred in Taranto after the end of World War II, when the Italian ports were partially still under the control of the allied military, as well as the civilian public-health organization[33]. The allied forces had imposed a veto on the dissemination of news about the plague outbreak[32,34]. Despite the difficult situation, the outbreak was stopped by officers of the Italian marines in only three months[32], with the help of the British military. A number of anti-plague measures were implemented; these included burning rags suspected of carrying plague, abundant spraying of DDT and notifications to the public[32]. It was written that, "The cases were immediately isolated, contacts were inoculated and kept under surveillance for 10 days, and their houses were sprayed with DDT and cleared of rodents"[33]. Perhaps due to the intervention measures, no relatives of the initial victims became ill. This large-scale anti-rodent campaign killed approximately 5,000 rats in three districts, with the help of two medical officers coming from India and two renowned specialists[32]. Of the rats that were poisoned in the docks, 60% were *R. norvegicus* and 40% were *R.*

rattus. All the rats found in the city were black rats. None of the 308 rats tested for plague in 1946 were positive[33]. It is possible that only two rats tested in 1945 were positive for plague[34].

Reggio di Calabria 1946. At the beginning of January 1946, an isolated case of plague was reported in the port of Reggio di Calabria. Investigations showed that this was a case that was originally from Taranto[33].

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Electronic Supplementary Material

The Third Plague Pandemic in Europe

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Index	Location	Country	Start	End	Cases	Deaths	Notes	Source (PubMed Central ID)
1	Porto	Portugal	16-Aug-1899	31-Oct-1899	223	77		PMC2014162
2	Lisbon	Portugal	16-Aug-1899					PMC2014162
3	Port of Leixões	Portugal	30-Oct-1899					PMC2014162
4	Porto	Portugal	1-Nov-1899	20-Nov-1899	41	17		PMC2014162
5	Lisbon	Portugal	12-Nov-1899		1	1		PMC2014162
6	Porto	Portugal	12-Jun-1900		1			PMC2014148
7	London	United Kingdom	3-Aug-1900		4	2		PMC2014148
8	Glasgow	United Kingdom	31-Aug-1900	6-Oct-1900	28	8		PMC2014148
9	Govan, Glasgow	United Kingdom	4-Sep-1900		1	1		PMC2014148
10	Bremen	Germany	27-Sep-1900	5-Nov-1900	1	1	On a SS from Buenos Ayres	PMC2014148
11	Llandaff, Cardiff	United Kingdom	4-Oct-1900		1	1	From Rosario	PMC2014148
12	Hull	United Kingdom	8-Jan-1901	31-Jan-1901		8	On steamship Friary	PMC1998804
13	Cardiff	United Kingdom	8-Feb-1901		1			PMC1998804

14	Southampton	United Kingdom	21-Mar-1901		1		On SS Simia	PMC1998804
15	Les îles du Frioul	France	7-Jul-1901		15		From steamship Laos from Port Said	PMC1998870
16	Naples	Italy	7-Sep-1901	12-Oct-1901	26	8		PMC1998870
17	Glasgow	United Kingdom	19-Oct-1901	1-Nov-1901	5	1		PMC1998870
18	Liverpool	United Kingdom	26-Oct-1901	7-Nov-1901	5	3		PMC1998870
19	Dunkirk	France	11-Jun-1902	13-Jun-1902		2	Two deaths on SS City of Perth, from Calcutta etc.	PMC1999014
20	Marseille	France	3-Jul-1902		1		One case on SS Espagne from Buenos Ayres	PMC1999014
21	Barcelona	Spain	16-Jul-1902		1		One case on SS Duca di Galliera from Buenos Ayres	PMC1999014
22	Marseille	France	1-Dec-1902		1		On SS Pehio from Batoum	PMC1998972
23	Berlin	Germany	5-Jun-1903	18-Jun-1903	1		Nurse of case previously reported	PMC2129207
24	Licata	Italy	14-Sep-1903	20-Sep-1903	1	1		PMC2129207
25	Marseille	France	15-Sep-1903		10	5		PMC2129207
26	South Shields	United Kingdom	19-Sep-1904		1		On SS Bishopegate from Rosario	PMC1998781
27	Liverpool	United Kingdom	7-Feb-1905			1	From steampship Crewe Hall from Rangoon	PMC2080951
28	Cádiz	Spain	1-Apr-1905	30-Apr-1905		1		PMC2080951
29	Leith, Edinburgh	United Kingdom	7-May-1905	13-May-1905	4	1		PMC2080951
30	Manchester	United Kingdom	12-Jun-1905			1	On SS Hylas from Buenos Ayers via Hamburg	PMC2080979
31	London	United Kingdom	30-Nov-1905		1		On SS Weybridge from the Rio de la Plata	PMC2080951
32	Trieste	Italy	8-Nov-1906			1		PMC2081032
33	Gröden	Germany	28-May-1907		1		On Br SS Warfedale from Buenos Aires	PMC1999365
34	Marseille	France	17-Sep-1907	18-Sep-1907	2		In quarantine at Frioul	PMC1999435
35	Glasgow	United Kingdom	17-Oct-1907	23-Oct-1907	1			PMC1999435
36	Glasgow	United Kingdom	17-Aug-1908	31-Aug-1908	1	1	Received out of date. ??1907	PMC1999472
37	Trieste	Italy	21-Sep-1908		2	1	From SS Erzherzog Frans Ferdinand from Bombay	PMC1999510
38	Liverpool	United Kingdom	23-Oct-1908	8-Nov-1908	3	2	From barge Wesley. Last death occurred Nov. 8	PMC1999510
39	Elstree	United Kingdom	3-Feb-1909	4-Feb-1909	1	1	At plague laboratory	PMC1999252
40	Rhodes	Greece	22-May-1910	28-May-1910			Present	PMC1999343
41	Valletta	Malta	16-Jul-1910		1		In quarantine station on Comino Island, from SS North Wales	PMC1999343
42	Freston, Ipswich	United Kingdom	16-Sep-1910	29-Sep-1910	4	4		PMC1999343
43	London	United Kingdom	18-Oct-1910	19-Oct-1910	2	1	Case Oct. 18 from SS Oceana from Bombay; case Oct. 19 from SS Hindle from Bombay	PMC1999343
44	Lisbon	Portugal	24-Oct-1910	8-Nov-1910	9	2	First case repaired boilers on SS Africa from Mozambique	PMC1999343

45	Suffolk	United Kingdom	10-Oct-1911		1		In Admiralty Barracks, parish of Shotley, Samford rural district	PMC1999129
46	Trieste	Italy	14-Apr-1912	25-Apr-1912	2		In isolation hospital from SS Amphrtrite from Messina via Port Said and Alexandria	PMC1999236
47	Liverpool	United Kingdom	27-Apr-1912	30-Apr-1912	1	1	In the Royal Southern Hospital, from SS Italian	PMC1999173
48	Liverpool	United Kingdom	26-Jul-1912		1			PMC1999236
49	Hamburg	Germany	2-Sep-1912	5-Sep-1912	2		2 cases on SS Bellailsa from Rosario, via Cape Verde Islands	PMC1999236
50	River Tyne	United Kingdom	10-Sep-1912	16-Sep-1912	1	1	From SS Bellailsa from Rosario, via Hamburg	PMC1999236
51	Pireas	Greece	21-Aug-1913	3-Sep-1913	8	2		PMC1999531
52	Athens	Greece	29-Aug-1913		1			PMC1999531
53	Trieste	Italy	1-Nov-1913	8-Nov-1913		1	1 fatal case on a post steaer from Buenos Aires	PMC1999531
54	Chios	Greece	2-Aug-1914				Epidemic, among the military, Sep 30, ended	PMC1999955
55	Pireas	Greece	7-Aug-1914	9-Sep-1914	16	2	Epidemic, among the military, Sep 30, ended	PMC1999955
56	Liverpool	United Kingdom	8-Aug-1914	12-Aug-1914	9	3		PMC1999955
57	Catania	Italy	1-Sep-1914				Since Sep 1, 1914 there have been 17 officially reported cases and unauthenticated rumors of others	PMC1999955
58	Syros	Greece	3-Sep-1914	4-Sep-1914	1	1		PMC1999955
59	Thessaloniki	Greece	15-Sep-1914		3			PMC1999955
60	Lisbon	Portugal	8-Oct-1914	9-Oct-1914	8	8	Pneumonic form	PMC1999955
61	Pireas	Greece	17-Jan-1915	27-Jan-1915	1		Sep 12, present in Drama and Kavala	PMC1999864
62	Thessaloniki	Greece	4-Apr-1915	10-Apr-1915	5	7		PMC1999864
63	Zakynthos	Greece	1-Aug-1915	11-Oct-1915	14	13	Present, Oct. 23	PMC1999899
64	Athens	Greece	8-Dec-1915	20-Dec-1915		1		PMC2013768
65	Syros	Greece	16-Jan-1916		16	10		PMC2013768
66	Pireas	Greece	29-Jan-1916		7	5		PMC2013768
67	Bristol	United Kingdom	18-Aug-1916	31-Aug-1916	3			PMC2013829
68	Hull	United Kingdom	19-Aug-1916	31-Aug-1916	2	1		PMC2013829
69	Liverpool	United Kingdom	22-Sep-1916	6-Oct-1916	6	3		PMC2013829
70	Chios	Greece	29-Sep-1916				Present	PMC2013829
71	Volos	Greece	29-Sep-1916	1-Nov-1916			Slight epidemic. Epidemic declard extinct Nov 1, 1916	PMC2013829
72	Pireas	Greece	9-Dec-1916		1			PMC2013829

73	London	United Kingdom	3-May-1917	8-May-1917	2		2 in hospital at port. From SS Sardinia from Australia and oriental ports	PMC1999778
74	Gravesend	United Kingdom	13-Aug-1917	24-Aug-1917	3	1	From SS Matiana (14 Jul-18 Jul 9 cases, 6 deaths en route for port of London)	PMC1999778
75	Dundee	United Kingdom	19-May-1918		3	1	At Dundee, Scotland from Calcutta. One of cases pneumonic.	PMC1999841
76	Rochester	United Kingdom	2-Jun-1918		1	1	From SS Somali at Gravesend from Bombay (May 19: At Gravesend, England, from Bombay. Further case developed June 2 in member of creat at Rochester, England)	PMC1999841
77	Erwarton, Ipswich	United Kingdom	19-Jun-1918		1	1	Rural district, Sanford, East Suffolk	PMC1999841
78	London	United Kingdom	17-Aug-1918		6		On vessel from Calcutta (Aug 10-Aug 21: SS Hector at Gravesend, port of London, 6 members of crew)	PMC1999841
79	Liverpool	United Kingdom	13-May-1919	17-May-1919	1	1	On vessel SS City of Sparta at Liverpool: Case, a native member of the crew	PMC1996952
80	Avonmouth	United Kingdom	25-Jul-1919		1		On vessel SS Framlington Court from Alexandria, May 30: from Montreal, July 4; from Sydney, Nova Scotia, July 9; at Avonmouth, England July 22, 1919	PMC1996952
81	Liverpool	United Kingdom	30-Jul-1919		1	1	In dock laborer	PMC1996952
82	Marseille	France	16-Aug-1919	2-Sep-1919	5	3	Total number of cases reported to Aug 27, 11; deaths, 3	PMC1996952
83	London	United Kingdom	19-Aug-1919		1		On vessel SS Clan Lamont in dock in port of London, England. Vessel left Calcutta Mar 23; arrived Buenos Aires May 9; sailed June 20; arrived Montevideo and sailed June 21; arrived at St. Vincent, Cape Verde Islands July 10	PMC1996952
84	Barcelona	Spain	15-Sep-1919	6-Oct-1919	10			PMC1996952
85	Thessaloniki	Greece	6-Oct-1919	20-Dec-1920	19	7		PMC1996806
86	Athens	Greece	20-Oct-1919		5	3		PMC1996952
87	Pireas	Greece	20-Oct-1919		2	1		PMC1996952
88	London	United Kingdom	21-Oct-1919	27-Oct-1919	6		On vessel SS Nagoya arrived Oc. 25 at port of London, England. Left Yokohama, Aug 30. Oriental ports of call: Kobe, Shaghai, Hong kong, Penang, Singapore, and Colombo. In Egypt, Port Said. In Europe, Marseille, Gibraltar, and Plymouth.	PMC1996952
89	London	United Kingdom	28-Feb-1920	5-Mar-1920	2	2	On vessel SS Alps Maru at port of London, England. Vessel left Yokohama, Japan Dec 3, 1919; arrived Suez Jan 21, 1920. Destination Hamburg.	PMC1996806

90	Pireas	Greece	25-Apr-1920	20-May-1920	7			PMC1996806
91	Marseille	France	1-Jun-1920	31-Aug-1920	58	20		PMC1996866
92	Paris	France	1-Jun-1920	15-Oct-1920	50	11	In suburbs, June-Nov 2, 1920: Cases, 38; deaths, 19, 1 (Suspect.)	PMC1996866
93	Liverpool	United Kingdom	20-Jun-1920	26-Jun-1920	1	1		PMC1996845
94	Catania	Italy	22-Jun-1920	3-Jul-1920	3	2		PMC1996845
95	Pireas	Greece	29-Jun-1920	20-Sep-1920	13	1		PMC1996845
96	Kavala	Greece	5-Jul-1920	3-Oct-1920	4			PMC1996845
97	Zakynthos	Greece	22-Jul-1920		2			PMC1996845
98	Athens	Greece	19-Aug-1920	14-Oct-1920	3	2		PMC1996845
99	Nafplion	Greece	21-Aug-1920		20			PMC1996845
100	Thessaloniki	Greece	25-Sep-1920	8-Oct-1920	4			PMC1996845
101	Lisbon	Portugal	2-Oct-1920	17-Nov-1920	93	27		PMC1996866
102	Chios	Greece	14-Oct-1920		1			PMC1996845
103	Dublin	Ireland	18-Oct-1920		1		1 case reported Dec 15, 1920: date of occurrence Oct 18, 1920	PMC1996866
104	Kavala	Greece	29-Oct-1920	7-Nov-1920	2			PMC1996866
105	Paris	France	1-Jan-1921	13-Jan-1921	3	1		PMC1996866
106	Lisbon	Portugal	1-Feb-1921	28-Feb-1921	6		Pneumonic; occurring in one family	PMC1999984
107	Lisbon	Portugal	29-Jul-1921	3-Sep-1921	7			PMC1996902
108		Poland	9-Aug-1921		8		In border province, Aug 9, 1921: Cases, 8	PMC1996902
109	Naples	Italy	4-Sep-1921	7-Oct-1921	5		2 were workers in mill; plague-infected rats found on premises	PMC1996902
110	Rhodes	Greece	20-Sep-1921	8-Oct-1921	7	1	1 fatal case reported late in August, 1921	PMC1996902
111	Pireas	Greece	23-Sep-1921		3			PMC1996902
112	Rhodes	Greece	13-Oct-1921		3	1		PMC1999984
113	Catania	Italy	16-Oct-1921	27-Nov-1921	1	1	Total, Oct 16-Nov 27, 1921: Cases, 8 (of which 1 doubtful): deaths, 5. Jan-Feb, 1922: 28 plague-infected rats found.	PMC1999984
114	Torre Annunziata, Naples	Italy	22-Oct-1921	Dec 27 1921	2		17 miles from city of Naples	PMC1999984
115	Catania	Italy	24-Oct-1921	21-Nov-1921	3			PMC1996902
116	Venice	Italy	27-Oct-1921		1			PMC1999984
117	Lisbon	Portugal	15-Dec-1921		1	1		PMC1999984
118	Preveza	Greece	8-Feb-1922				Outbreak. Port on the Ionian Sea	PMC1999984

119	Dunkirk	France	24-Mar-1922			1	In hospital, from steamship City of Genoa, from Bombay. Vessel SS City of Genoa at Suez and Port Said, Egypt, from Karachi and Bombay, India, for Plymouth, England. One fatal case at sea en route to Suez; 1 case on arrival. At Port Said, 2 cases of which 1 fatal. At Dunkirk, France, Mar 24, 1922: Several cases on arrival; 1 fatal case in hospital at Dunkirk.	PMC1999984
120	Patras	Greece	24-Apr-1922	25-Jun-1922	5	3		PMC2000016
121	Catania	Italy	17-Jun-1922		1			PMC2000016
122	Naples	Italy	18-Jul-1922	28-Sep-1922	19		Occuring in suburbs, viz, at Torre Annunziata, July 18-Sept 28, 1922, 18 cases; San Giovanni a Teduccio, July 25, 1922, 1 case	PMC2000016
123	Messina	Italy	19-Jul-1922				On Greek vessel at Messina, Italy. Cases on board. Vessel not allowed to enter.	PMC2000016
124	Lisbon	Portugal	23-Jul-1922	10-Nov-1922	16	16	Aug 1-Oct 23, 1922: Deaths, 10	PMC2000016
125	Pireas	Greece	1-Aug-1922	31-Aug-1922	3	1		PMC2000016
126	Paris	France	11-Aug-1922	18-Aug-1922	4			PMC2000016
127	Barcelona	Spain	24-Sep-1922	14-Nov-1922	23	9	Stated to be confined to factory in which disease first appeared Oct 18,1922: 18 cases present	PMC2000016
128	Cartagena	Spain	18-Oct-1922		2			PMC2000016
129	Valencia	Spain	18-Oct-1922		2			PMC2000016
130	Lisbon	Portugal	10-Nov-1922	29-Nov-1922	4	2		PMC1975895
131	Barcelona	Spain	15-Nov-1922	18-Dec-1922	24	9	Sep 24-Nov 14, 1922: Cases, 23; deaths, 9	PMC1975895
132	Porto	Portugal	21-Jan-1923	27-Jan-1923		1		PMC1975895
133	Málaga	Spain	27-Feb-1923		20		17 suspected cases.	PMC1975895
134	Paris	France	13-Aug-1923		1		Published in Public Health Reports, Sept. 14, 1923, pp. 2189 and 2190	PMC1975922
135	Syros	Greece	10-Sep-1923				Present	PMC1975922
136	Lisbon	Portugal	25-Oct-1923		2	1		PMC1975922
137	Málaga	Spain	1-Dec-1923	31-Dec-1923	4			PMC1975963
138	Lisbon	Portugal	13-Dec-1923	21-Dec-1923	7			PMC1975963
139	Lisbon	Portugal	31-Dec-1923	6-Jan-1924		1		PMC1975963
140	Kalamata	Greece	18-Apr-1924	24-Apr-1924			Several deaths	PMC1975963
141	Patras	Greece	18-Apr-1924	24-Apr-1924			Several deaths	PMC1975963
142	Thessaloniki	Greece	3-Jul-1924	4-Jul-1924	2			PMC1976008

143	Patras	Greece	7-Jul-1924		36			PMC1976008
144	Marseille	France	10-Jul-1924		1		On vessel SS Amboise at Marseille, France; removed to quarantine station. Case occurred in an Arab fireman embared at Aden. Vessel left Yokohama May 30 and Colombo, Ceylon, June 22, 1924.	PMC1976008
145	Kalamata	Greece	15-Jul-1924		29	6	Reported on July 15, 1924: cases, 29; deaths, 6	PMC1976008
146	Symi	Greece	26-Aug-1924		11	2		PMC1976008
147	Naples	Italy	15-Sep-1924		3	1	Including a suburb of Portici, 1 case	PMC1976008
148	Paris	France	1-Oct-1924	31-Oct-1923	2		Bubonic, occurring in suburbs, St. Medard and St. Ouen	PMC1976008
149	Patras	Greece	5-Apr-1925		1			PMC1976009
150	Athens	Greece	1-Jul-1925	10-Oct-1925	64	18		PMC1976039
151	Pireas	Greece	18-Jul-1925	14-Aug-1925	9		2 cases on Steamship Arcadia July 24-27 at Piraeus, Greece, from Alexandria, Egypt. 1 case on Steamship Anatolia Aug 8, at Piraeus, Greece from Alexandria.	PMC1976039
152	Marseille	France	13-Aug-1925	18-Aug-1925	3			PMC1976039
153	Pyrgos	Greece	1-Sep-1925		1			PMC1976039
154	Secondigliano, Napolini	Italy	3-Sep-1925	5-Sep-1925	2		From the Bulletin Quarantenaire Egypt Sept 17, 1925	PMC1976039
155	Rhodes	Greece	12-Sep-1925		1		On Steamship Naxos, at Rhodes from Dodecanese Islands via Alexandria, Egypt. The vessel left Alexandria Sept 9, 1925	PMC1976039
156	Thessaloniki	Greece	22-Sep-1925	12-Oct-1925	2	1		PMC1976039
157	Chateau-Gombert	France	13-Oct-1925		1	1	Distant 8.5 kilometers from Marseille	PMC1976039
158	Athens	Greece	21-Oct-1925	31-Oct-1925	18	3	Including Piraeus	PMC1976039
159	Athens	Greece	1-Nov-1925	30-Nov-1925	18	4	Including Piraeus	PMC2000042
160	Cephalonia	Greece	10-Nov-1925		1		Ionian Islands. Case stated to have originated at Patras	PMC1976039
161	Patras	Greece	13-Nov-1925	12-Dec-1925	4	1		PMC2000042
162	Vilvoorde	Belgium	1-Dec-1925	8-Dec-1925	1	1		PMC2000042
163	Athens	Greece	1-Jan-1926	31-Mar-1926	25	4	On island of Crete	PMC2000042
164	Heraklion	Greece	4-Feb-1926		1			PMC2000042
165	Athens	Greece	1-Apr-1926	31-May-1926	16	4	Including Piraeus	PMC2000087
166	Zakynthos	Greece	17-May-1926		1			PMC2000087
167	Patras	Greece	27-May-1926	12-Jun-1926	4	1		PMC2000087
168	Marseille	France	8-Jul-1926		1	1	Reported on July 24, 1926	PMC2000087
169	Patras	Greece	25-Jul-1926	29-Oct-1926	9	5		PMC2000087

170	Athens	Greece	1-Aug-1926	30-Sep-1926	20	5	Including Piraeus	PMC2000087
171	Saint-Denis	France	2-Aug-1926		1		Vicinity of Paris	PMC2000087
172	Saint-Ouen	France	14-Aug-1926		2		Suburb of Paris	PMC2000087
173	Liverpool	United Kingdom	29-Aug-1926	4-Sep-1926	2	1		PMC2000087
174	Liverpool	United Kingdom	1-Sep-1926		2	2	On SS Zaria at Liverpool, England, from Lago, Nigeria, West Africa	PMC2000087
175	Paris	France	18-Oct-1926		1			PMC2000087
176	Pireas	Greece	1-Nov-1926	31-Nov-1926	19	5		PMC1999045
177	Lisbon	Portugal	22-Nov-1926	26-Nov-1926	3	2		PMC1999045
178	Eleftheroupoli	Greece	27-Nov-1926		1	1		PMC1999045
179	Patras	Greece	28-Nov-1926	4-Dec-1926		1		PMC1999045
180	Pireas	Greece	1-Jan-1927	31-Mar-1927	24	3		PMC1999045
181		Greece	1-May-1927		4	3		PMC1999075
182	Patras	Greece	30-May-1927	5-Nov-1927	10	3		PMC1999075
183	Athens	Greece	1-Jun-1927	29-Aug-1927	3		Including Piraeus	PMC1999075
184	Mytilene	Greece	9-Aug-1927	25-Sep-1927	6			PMC1999075

Index	Location	Country		Week ending	Cases	Deaths	Notes	Source (PubMed Central ID)
1	Patras	Greece		3-Sep-1927	2			PMC1996702
2	Mytilene	Greece		24-Sep-1927	5			PMC1996702
3	Patras	Greece		1-Oct-1927	1	1		PMC1996702
4	Mytilene	Greece		8-Oct-1927	1			PMC1996702
5	Mytilene	Greece		29-Oct-1927	1			PMC1996706
6	Patras	Greece		5-Nov-1927	1	1		PMC1996706
7	Mytilene	Greece		12-Nov-1927	2			PMC1996706
8	Vigo	Spain		19-Nov-1927	3		On SS Aghios Garasimos at Vigo, Spain	PMC1996706
9	Mytilene	Greece		26-Nov-1927	1			PMC1996713
10	Mytilene	Greece		3-Dec-1927	1			PMC1996713
11	Mytilene	Greece		10-Dec-1927	1			PMC1996713
12	Athens	Greece		7-Jan-1928	1		Includes Pireas	PMC1996718
13	Athens	Greece		21-Jan-1928	2	1	Includes Pireas	PMC1996718
14	Corfu	Greece		16-Jun-1928	1			PMC1996747
15	Corfu	Greece		23-Jun-1928	14	3		PMC1996747
16	Lisbon	Portugal		30-Jun-1928	1			PMC1996737
17	Patras	Greece		14-Jul-1928	1	1		PMC1996762
18	Patras	Greece		28-Jul-1928	1	1		PMC1996747
19	Corfu	Greece		4-Aug-1928	1			PMC1996764
20	Patras	Greece		11-Aug-1928	1			PMC1996764
21	Corfu	Greece		1-Sep-1928	1			PMC1996782
22	Patras	Greece		8-Sep-1928	1			PMC1996782

23	Athens	Greece		22-Sep-1928	2		Includes Pireas	PMC1996782
24	Athens	Greece		29-Sep-1928	2		Includes Pireas	PMC1996787
25	Patras	Greece		29-Sep-1928	1			PMC1996787
26	Athens	Greece		6-Oct-1928	2		Includes Pireas	PMC1996787
27	Athens	Greece		13-Oct-1928	1		Includes Pireas	PMC1996787
28	Athens	Greece		3-Nov-1928	4		Includes Pireas	PMC1996787
29	Athens	Greece		10-Nov-1928	1		Includes Pireas	PMC1996787
30	Corfu	Greece		17-Nov-1928	1			PMC1996787
31		Greece		31-Dec-1928	2	1	Monthly data	PMC2000138
32		Greece		31-Jan-1929	3	1	Monthly data	PMC2000138
33		Greece		28-Feb-1929	1		Monthly data	PMC2000161
34		Greece		30-Apr-1929	1		Monthly data	PMC2000161
35		Greece		31-Jul-1929	3	1	Monthly data	PMC2000189
36	Patras	Greece		31-Aug-1929	1			PMC2000189
37	Pireas	Greece		31-Aug-1929	1			PMC2000189
38	Pireas	Greece		7-Sep-1929	1			PMC2000189
39	Patras	Greece		14-Sep-1929	1			PMC2000218
40	Pireas	Greece		14-Sep-1929	1			PMC2000189
41	Patras	Greece		21-Sep-1929	1			PMC2000218
42	Paris	France		28-Sep-1929	1			PMC2000195
43	Naples Province	Italy		28-Sep-1929	2	1		PMC2000218
44		Greece		30-Sep-1929	5	2	Monthly data	PMC2000218
45	Patras	Greece		5-Oct-1929	1			PMC2000218
46	Patras	Greece		12-Oct-1929	1			PMC2000218
47	Patras	Greece		19-Oct-1929	1			PMC2000218
48		Greece		31-Oct-1929	5	2	Monthly data	PMC2000229
49	Messenia	Greece		9-Nov-1929	2			PMC2000218
50	Patras	Greece		9-Nov-1929	1			PMC2000229
51	Patras	Greece		16-Nov-1929	1			PMC2030468
52	Pyrgos	Greece		16-Nov-1929	6			PMC2000229
53	Pyrgos	Greece		23-Nov-1929	2			PMC2000229
54	Pireas	Greece		7-Dec-1929	1			PMC2000229
55		Greece		31-Dec-1929	1		Monthly data	PMC2030488
56	Pireas	Greece		25-Jan-1930	1			PMC2030476
57	Patras	Greece		29-Mar-1930	1			PMC2030488
58	Pyrgos	Greece		5-Apr-1930	1			PMC2030498
59		Greece		30-Apr-1930	1		Monthly data	PMC2030518
60	Patras	Greece		21-Jun-1930	1			PMC2030513
61		Greece		30-Jun-1930	1		Monthly data	PMC2030525

62	Saint-Ouen	France		19-Jul-1930	1	1		PMC2030513
63	Patras	Greece		19-Jul-1930	1			PMC2030513
64	Marseille	France		30-Aug-1930	2			PMC2030522
65	Marseille	France		6-Sep-1930	2			PMC2030522
66	Marseille	France		13-Sep-1930	1			PMC2030522
67	Pyrgos	Greece		4-Oct-1930	2			PMC2030525
68	Marseille	France		18-Oct-1930	4			PMC2030525
69	Marseille	France		25-Oct-1930	2			PMC2030525
70	Marseille	France		1-Nov-1930	1			PMC2030525
71	Marseille	France		15-Nov-1930	1			PMC2030525
72	spitalet de Llobregat, Barce	Spain		22-Aug-1931	5	2		PMC1996665
73	spitalet de Llobregat, Barce	Spain		29-Aug-1931	1			PMC1996674
74	spitalet de Llobregat, Barce	Spain		19-Sep-1931	1	1		PMC1996674
75	spitalet de Llobregat, Barce	Spain		26-Sep-1931	1	1		PMC1996674
76	spitalet de Llobregat, Barce	Spain		3-Oct-1931	1			PMC1996674
77	spitalet de Llobregat, Barce	Spain		10-Oct-1931	1	1		PMC1996674
78	spitalet de Llobregat, Barce	Spain		24-Oct-1931	5	1		PMC1996699
79	Déville-lès-Rouen	France		31-Oct-1931	P			PMC1996699
80	spitalet de Llobregat, Barce	Spain		7-Nov-1931	1			PMC1996699
81	spitalet de Llobregat, Barce	Spain		14-Nov-1931	1			PMC1996699
82	Avonmouth	United Kingdom		27-Dec-1931	1		On vessel SS Marionga de Thermiotis at Avonmouth	PMC1996590
83	Marseille	France		3-Sep-1932	1		On SS Figuig at Marseille from Bona and Philippeville	PMC1995488
84	Marseille	France		31-Dec-1932	1			PMC2016022
85	Marseille	France		12-Aug-1933	8	3		PMC2016800
86	Marseille	France		19-Oct-1935	2		On vessel SS Ipanema at Marseille; One of these cases was a member of the crew and the other was a stevedor believed to have worked on the vessel. Several plague infected rats were reported found on board the vessel.	PMC1996387
87		Malta		18-Apr-1936	3	2		PMC1996513
88		Malta		2-May-1936	1			PMC1996513
89		Malta		6-Jun-1936	3	1		PMC1996530
90		Malta		1-Aug-1936	1	1		PMC1996530
91		Malta		8-Aug-1936	2			PMC1996530
92	Marseille	France		15-Aug-1936	2		1 case on SS Impanema at Marseille from Bone and Philippeville	PMC1996535
93		Malta		29-Aug-1936	1			PMC1996530
94	Marseille	France		5-Sep-1936	1			PMC1996549

95	Marseille	France		12-Sep-1936	1			PMC1996549
96		Malta		19-Sep-1936	1			PMC1996549
97		Malta		24-Oct-1936	1			PMC2024179
98		Malta		7-Nov-1936	1			PMC2024318
99		Malta		14-Nov-1936	3			PMC2024318
100		Malta		21-Nov-1936	1			PMC2024318
101		Malta		28-Nov-1936	1			PMC2024318
102		Malta		9-Jan-1937	2	1		PMC2024498
103		Malta		16-Jan-1937	2			PMC2024498
104		Malta		30-Jan-1937	2			PMC2024498
105		Malta		24-Apr-1937	1			PMC2024692
106		Malta		22-May-1937	4			PMC2024696
107		Malta		26-Sep-1937	2			PMC1996549
108		Malta		3-Oct-1937	2			PMC2024179
109	Corsica	France		19-May-1945	2			PMC1976065
110	Corsica	France		9-Jun-1945	2			PMC1976072
111	Corsica	France		23-Jun-1945	1			PMC1976072
112		Malta		30-Jun-1945	4			PMC1976072
113	Corisca	France		14-Jul-1945	2			PMC1976078
114		Malta		14-Jul-1945	8			PMC1976078
115		Malta		21-Jul-1945	4			PMC1976078
116		Malta		28-Jul-1945	2			PMC1976078
117		Malta		4-Aug-1945	1			PMC1976081
118		Malta		11-Aug-1945	1			PMC1976081
119		Malta		18-Aug-1945	3			PMC1976081
120		Malta		25-Aug-1945	2			PMC1976081
121		Malta		1-Sep-1945	4			PMC1976088
122		Malta		8-Sep-1945	13			PMC1976088
123		Italy		15-Sep-1945	12			PMC1976088
124		Malta		15-Sep-1945	5			PMC1976088
125		Italy		22-Sep-1945	2			PMC1976088
126		Malta		22-Sep-1945	2			PMC1976088
127		Malta		6-Oct-1945	5			PMC1976093
128		Italy		20-Oct-1945	1			PMC1976093
129		Malta		20-Oct-1945	6			PMC1976093
130		Italy		27-Oct-1945	1			PMC1976093
131		Malta		3-Nov-1945	4			PMC1976103
132		Malta		10-Nov-1945	4			PMC1976103
133		Malta		17-Nov-1945	1			PMC1976103
134		Malta		24-Nov-1945	1			PMC1976103

135		Italy		30-Nov-1945	2		Monthly data	PMC1976108
136		Italy		15-Dec-1945	1			PMC1976108
137		Malta		2-Feb-1946	2			PMC1976137
138		Malta		2-Mar-1946	1			PMC1976142
139		Malta		8-Jun-1946	1			PMC1976154
140		Malta		15-Jun-1946	3			PMC1976154
141	Kaliningrad	Russia		1-Jun-1947	??		During the month of June 1947, an outbreak of plague with high mortality occurred in Konigsberge, East Prussia, Germany	PMC1995301