Temperature, toponyms and thresholds.

A modelling approach to understanding the spread of plague during the second pandemic

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Dissertation presented for a degree of

Philosophiae Doctor (PhD)

2020

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Series of dissertations submitted to the
Faculty of Mathematics and Natural Sciences, University of Oslo
No. 2365

ISSN 1501-7710

Cover: Hanne Baadsgaard Utigard.
Print production: Reprosentralen, University of Oslo.

Acknowledgements

It is not without irony to finish a PhD thesis on a pandemic during a pandemic. In the past months, I have observed many parallels in the ways people react to the global threat of the COVID-19 pandemic and how they reacted during the historical plague pandemics. I have seen ignorance, rumours, denial, panic and people making profits with useless treatments and services. But I have also seen solidarity and hope. And I have come to understand what it really means to live in isolation and trying to carry on with life, when disease and contagion surrounds you. I more than ever appreciate the work of numerous physicians, scholars and scientists during the second plague pandemic who understood the importance of collecting data during an epidemic, and of those who passed the information down so it can be used by scientists like me.

I foremost would like to thank my supervisors Nils Chr. Stenseth, Boris V. Schmid and Hildegunn Viljugrein for supporting me in many ways and believing in me and my work, even when I didn't. A special thank you goes to Ottar Bjørnstad and Andrew JK Conlan for helping me to improve my modelling skills and my work. Thank you also to all the friends who have accompanied and supported me on this rocky journey: Katie, Fränzi, Xiaoyan, Amine, Damie, Lulu, Anneke, Giada, Stefaniya, Flora, Meriam, Oliver, Claudio, and many more. I am also very grateful for funding and administrative support from CEES and the Kristine Bonnevie Travel Stipend at UiO.

But most of all, I would like to thank my family for encouraging, supporting and loving me no matter what.

For my dad.

Table of Contents

List of papers

Paper I
The influence of temperature on the seasonality of historical plague outbreaks
Fabienne Krauer, *Hildegunn Viljugrein, Katharine R. Dean.*

Manuscript under review at Proceedings of the Royal Society B: Biological Sciences

Paper II
The seasonal abundance of *Pulex irritans* and its correlation with historical plague: insights from mathematical simulations
Fabienne Krauer, *Katharine R. Dean, Ottar N. Bjørnstad, Nils Chr. Stenseth, Boris V. Schmid*

Manuscript.

Paper III
The human flea and the seasonality of plague in pre-industrial Europe: a modelling study using historical data from 17th century London
Fabienne Krauer, *Katharine R. Dean, Ottar N. Bjørnstad, Andrew J. K. Conlan, Nils Chr. Stenseth, Boris V. Schmid*

Manuscript.

Paper IV
Mapping the plague through natural language processing
Fabienne Krauer, *Boris V. Schmid*

Manuscript

Summary

Plague is one of the most infamous infectious diseases. For centuries, the disease caused by the bacterium *Yersinia pestis* has ravaged the world and caused millions of casualties. Three pandemics are historically recorded, but the second was by far the largest in terms of numbers of deaths and duration. The second pandemic began around 1346 at the conjunction of Europe and Asia with the Black Death period, and lasted until the 18th century. During this time, multiple plague waves swept across Europe and the Mediterranean, and thousands of outbreaks were recorded in historical sources. Despite a richness of records on plague, some of the key epidemiological aspects such as the seasonality, the vector(s) involved or the contribution of pneumonic plague have not been uncovered yet. This thesis aims to address these knowledge gaps using mathematical and statistical approaches.

Paper I systematically investigates the seasonality of second pandemic outbreaks. I studied the epidemic peak timing and growth rates of newly digitised outbreaks across Europe and the Mediterranean, and their association with temperature and precipitation. The results show that some second pandemic outbreaks exhibited a distinct seasonal pattern, which could be partially explained by the existence of an optimal temperature range conducive of epidemic growth.

In paper II, I investigate potential mechanisms underlying the findings from paper I by studying the role of a highly debated, potential plague vector: the human flea (*Pulex irritans*). I use published experimental data to model the temperature-dependent life cycle of *P. irritans* and predict the resulting seasonal flea abundance for Europe and the Mediterranean. These results were correlated with historical plague mortality from paper I. The findings suggest that the flea abundance coincides with plague outbreaks for many places in the temperate climate zone, but less so for the Mediterranean region.

In paper III, I synthesize the results from paper I and II. I developed a deterministic, compartmental disease transmission model that accounts for seasonal human-to-human transmission by a human ectoparasite vector as well as direct, pneumonic transmission. The results show that the optimal flea abundance must peak several weeks before the plague mortality in order to explain a causal relationship. Furthermore, this paper confirms findings from modern outbreaks that the average contribution of pneumonic plague is only minor compared to bubonic plague. Hence, the human flea as a plague vector could indeed explain the seasonal mortality pattern if the vector-to-host ratio and the bacteraemia of the hosts were large enough.

Finally, in paper IV, I digitised a historical plague treatise and generated a novel geocoded dataset of plague outbreaks during the second pandemic. I compared the performance of several natural language processing algorithms for the extraction of geographical places with plague, and explored how simple text mining techniques can help to understand qualitative plague narratives. The integration of my novel data with an existing re-digitised dataset shows that the spatio-temporal extent of the second pandemic was larger than often referred to, and that the focus may have shifted from western Europe to southeastern Europe and western Asia in the 17th century.

In summary, this thesis provides further insight into the hypothesis of human ectoparasites as potential plague vectors during the second pandemic by exploring the relationship of temperature, the human flea and the seasonality of outbreaks. This work also contributes to the effort to building of global plague database with one novel and one improved dataset of plague outbreaks for the second pandemic.

Introduction

Background

Plague is a zoonosis caused by the bacterium *Yersinia pestis.* It has been classified as a re-emerging and notifiable disease by the World Health Organization (WHO). Since the 1950s more than 80,000 cases and almost 7000 deaths have been reported globally [1]. As of today, seven countries are regularly affected by outbreaks among humans (Brazil, the Democratic Republic of the Congo, Madagascar, Myanmar, Peru, the United States and Vietnam). Three plague pandemics are historically and biologically documented: the first pandemic in the 6^{th} – 8^{th} century, the second pandemic during the 14^{th}-19^{th} century and the third pandemic that started in the 19^{th} century in Asia [2]. All three pandemics together resulted in millions of casualties, which makes plague one of the most infamous infectious diseases. The era of large epidemics is mainly over now, but *Y. pestis* is considered a category A bioterrorism agent by the Centers for Disease Control and Prevention (CDC) because it is highly lethal if untreated [3].

Microbiology and evolution

Y. pestis is a gram-negative rod-shaped coccobacillus bacterium. The virulence of *Y. pestis* is determined by multiple mechanisms, which all contribute to host immune evasion and facilitate extracellular replication. *Y. pestis* possesses a type three secretion system (T3SS), which it uses to inject effector proteins (Yops, encoded on the plasmids pYV and pCD1) into the host cell [4]. The purpose of the Yop effector proteins is to inhibit phagocytosis by macrophages, downregulate the expression of proinflammatory cytokines and trigger the death of the host cell [4, 5]. The plasmid pFra/pMT encodes Yersinia murine toxin (Ymt), which blocks β-adrenergic receptors in hosts and promotes the survival of the bacterium in the midgut of the flea vector [6]. The Pla protein, encoded on the plasmid pPla/pPCP, activates host plasmin, which leads to the destruction of extracellular matrix and facilitates the invasion and migration of *Y. pestis* within the host [4]. *Y. pestis* in its current form evolved from its progenitor *Yersinia pseudotuberculosis* around 5000 years ago by acquisition of the virulence plasmids and inactivation of the virulence-associated gene pde3 [7]. These steps enabled *Y. pestis* to colonize fleas and thus promoted the flea-borne transmission route [8]. The genomic population structure of *Y. pestis* has five phylogenetic branches (0-4) with branches 1-4 radiating from branch 0 (big bang event) [9]. Ancient DNA (aDNA) samples from the Bronze Age and the 6^{th} century AD are placed on branch 0, while all later aDNA samples from the second and third plague pandemic are placed on branch 1 [9].

Pathogenesis and clinical forms

There are three major clinical forms of plague: Bubonic plague, septicaemic plague, and primary and secondary pneumonic plague. Another, rare clinical form is pharyngeal or gastrointestinal plague, which can occur after the ingestion of infected animals [10].

Bubonic plague, which is characterised by lymphadenopathy, is the most frequent form and accounts for approximately 65-90% of all plague cases [2, 11, 12]. After the bacterium is deposited in the skin through a flea bite or another cutaneous lesion, *Y. pestis* bacteria colonize the local lymph node, where they grow rapidly and trigger an immune response resulting in a large swelling of the lymph node (bubo) [13]. Buboes occur mostly inguinal and femoral resulting from infection sites in the lower body, but they can also be found axillary, supraclavicular or cervical [2, 12]. Infected patients develop symptoms of fever, malaise, chills and lymphadenopathy after an average incubation period of two to six days [14]. Other cutaneous manifestations include carbuncles (ulcerations) or petechiae (hemorrhages). The pus produced in necrotic infected lymph nodes is highly infectious [14]. The case fatality ratio of untreated bubonic plague was estimated around 66% [11].

Septicaemic plague occurs when the infection spreads from a lymph node through the lymphatic system into the bloodstream and disseminates systemically. Many patients with bubonic plague have low-level, intermittent bacteraemia, but when the bacterial growth cannot be controlled by the immune system, septicaemia develops leading to multiple organ failure and death [15]. The level of bacteraemia detected in plague patients can range from <10 to $4x10^7$ CFU/ml, and larger amounts of bacteria in the blood are associated with higher mortality [16]. The threshold of bacteraemia leading to death in most cases is unclear, but data from the Indian Plague Commission show that more than half of all fatal septicaemic cases had levels of >100 CFU/cc of cultured blood [17]. The average survival of untreated, septicaemic patients is short (2 days, range 1-10 days) [17, 18]. Septicaemic plague can also occur without apparent lymphadenopathy [19], but the main route of infection is still considered a cutaneous lesion, and the swelling of the lymph node may be missed because of fast dissemination or deep lymphadenopathy [14].

Primary pneumonic plague occurs through inhalation of infectious droplets. The bacteria colonize the alveoli of the lung and cause a massive inflammatory response, which manifests with coughing and the production of bloody sputum. The incubation period is short (2-4 days) and most patients die 1-3 days after

symptom onset [20]. Pneumonic transmission requires close contact of infector and infectee, and outbreaks of primary pneumonic plague are thus usually small in size [21]. Large pneumonic outbreaks like 1911 in Manchuria [22] or 2017 in Madagascar [23] are rare. Occasionally, infectious droplets can be transmitted from cats to their owners [2]. The infection of the lungs can also occur after bubonic and subsequent systematic infection (secondary pneumonic plague), which occurs in about 10% of the cases [24]. Primary and secondary pneumonic plague cases account for about 8-35% of all plague cases depending on the setting [2, 11, 12]. The case fatality ratio of pneumonic plague is about 93% [11].

The plague transmission cycle

The rodent-flea scenario

The transmission cycle of plague involves many actors, and may include different phases such as the enzootic, epizootic and epidemic phase (Figure 1). In the traditional transmission model, *Y. pestis* is transmitted between rodent hosts by a flea vector in a enzootic cycle with low fatality and partial resistance of the hosts [25]. These enzootic cycles occur mainly in sylvatic rodent populations, called plague foci, and several different species may act as reservoirs that maintain plague at low levels (maintenance hosts) [26]. Alternative theories propose that the rodent fleas or soil components such as Protozoa may also act as disease reservoirs [26]. Such enzootic plague foci exist on every continent except Australia, many of which were seeded in the past century during the global expansion of plague. The known foci are located mainly in semi-arid to arid areas and low-humidity forest zones [2, 27]. Rodent species involved in the enzootic phase include for prairie dogs, ground squirrels or great gerbils [28]. When plague spreads to more susceptible rodent populations (amplifying hosts), such as commensal (domestic) rodents, large epizootics occur where the majority of the rodents succumb to the disease [2, 25]. The most famous commensal rodents involved in the epizootic phase are the black rat (*Rattus rattus*) and the brown rat (*Rattus norvegicus*) [14]. The vector that is most often associated with the black rat and plague epizootics is the oriental rat flea, *Xenopsylla cheopis*, however many other flea species are capable of transmitting the bacterium [29]. Epizootic phases might also occur in sylvatic populations, but the circumstances and the distinction from the enzootic phase are unclear [26]. These die-offs in the rodent populations lead to the release of a large number of fleas looking for new hosts in other species [30]. Humans are infected if they are bitten by these free, infectious fleas. A spillover of plague to the human population is generally a rare event and humans are considered incidental host [31]. However, epidemics may occur if the number of free infectious rodent fleas is large enough to infect multiple persons. Livestock or pets,

including dogs, cats [32], cattle and camels [33], can also become infected if bitten by infectious fleas.

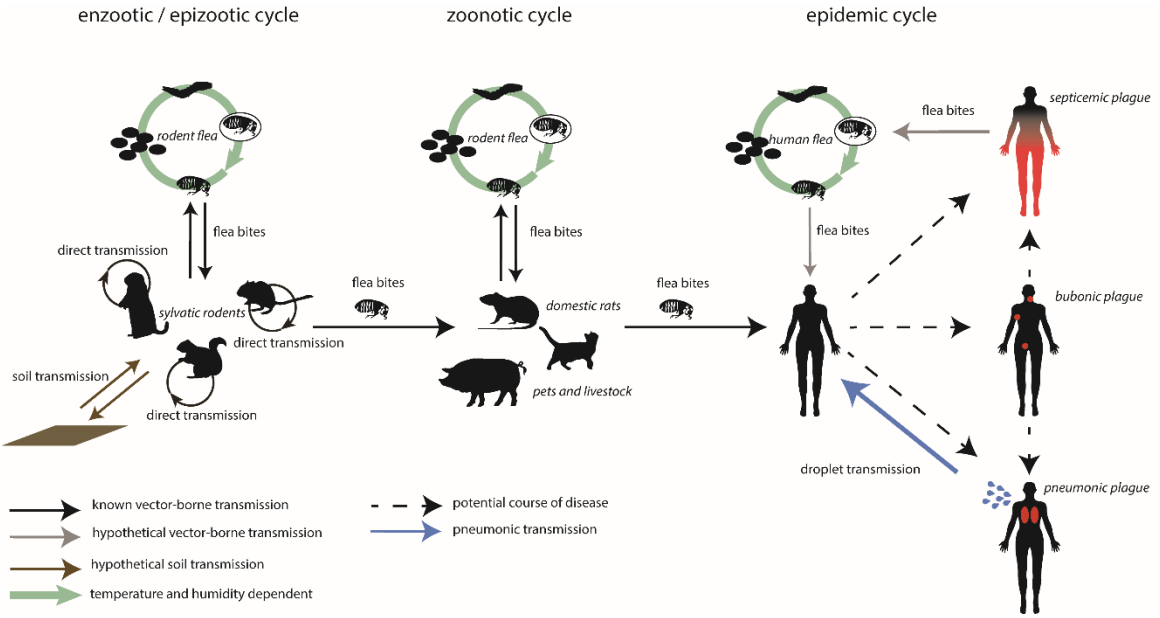

Figure 1. The plague transmission cycle with known transmission routes (black solid arrows), hypothetical transmission routes (grey solid arrows) and courses of disease in humans (black dotted arrows).

The human ectoparasites scenario

Alternative transmission routes of plague through human ectoparasites have been proposed for the second and the third pandemic [34-37]. This transmission cycle does not require an intermediate rat host and plague would be transmitted directly between humans. A sick rodent would only be required to introduce the disease in the human population. In the human ectoparasite scenario, humans are not dead-end hosts and must transmit back to the vector to complete the cycle. Candidate vectors include the human flea (*Pulex irritans*), the head louse (*Pediculus humanus capitis)* or the body louse (*Pediculus humanus corporis*). Particularly the human flea has been suggested repeatedly, but little research has been done to confirm its capacity as a plague vector.

In the past century, *P. irritans* has repeatedly been associated with plague outbreaks. In rural Tanzania, the human flea was found to be a common domestic parasite, and its density was significantly higher in places with high plague activity [38]. Similarly, in Peru the human flea was the most common domestic ectoparasite and its density was positively associated with plague activity [39]. During an earlier outbreak in 1934, 80-90% of fleas collected from households and belongings were *P. irritans* and head lice isolated from the head of a plague victim

were found to induce bubonic plague in a guinea pig upon inoculation [40]. The author also note that the local population habitually crushed their flea and lice between their teeth suggesting pharyngeal inoculation as a possible transmission route. *Y. pestis* was also isolated from human fleas found in a plague focus in Madagascar in a house with a known plague case [41].

In the 1940s, Blanc and Baltazard investigated plague outbreaks in Morocco, and found that houses were often infested with *P. irritans* [34, 42]. They collected 200 of the fleas from the house of a plague victim and let them feed on a shaved guinea pig. The animal died days later of bubonic plague. They also used 200 fresh fleas and let them feed on a septicaemic human plague victim. The fleas were then crushed and inoculated into the skin of a guinea pig, that later developed bubonic plague and died. Blanc and Baltazard subsequently hypothesized that direct transmission between humans through human ectoparasites was the dominant route of transmission [43, 44]. Earlier experiments in 1902 by Verjbitski showed that *P. irritans* can be infected when feeding on a plague infected rodent host [45]. He also demonstrated that the fleas could transmit the disease back to animals during the first six days after they were infected. Their faeces were also shown to be infectious for five to six days. The survival of the flea did not appear to be influenced by infection with *Y. pestis*. Burroughs later conducted similar experiments with a range of flea species [46]. He confirmed with mass transmission experiments that infected *P. irritans* could transmit to guinea pigs. These observations show that transmission is possible both from hosts to the human flea and vice versa, which is crucial for a complete vector-borne cycle. However, the probability of transmission seems to be low particularly from fleas to hosts [46].

Mechanisms of the vector-borne transmission act

In 1914, Bacot and Martin discovered that upon feeding on infected animals, *X. cheopis* developed a biofilm of plague bacteria that blocked the proventriculus (foregut) [47]. They observed that during feeding, the plague bacteria in the block would come into contact with fresh host blood, some of which would be contaminated and regurgitated back into the bite wound. Complete blockage of the proventriculus could occur in some cases leading to the starvation of the flea, which would increase the biting rate and thus the transmission of plague. This mechanism requires the prior development of a block, which may take several weeks, and there is thus an obligatory extrinsic incubation period in the flea before transmission can occur [48]. This theory was later named biofilm-dependent transmission (BDT) and became a popular explanation for transmission through rodent fleas [48]. However, the theory of BDT is not completely compatible with

other observations. Firstly, not all flea species that transmit plague develop a block [29]. Secondly, the requirement of the extrinsic incubation period is not consistent with the rapid dynamics during epizootics [49]. Early transmission experiments with *X. cheopis* and other species at the beginning of the third pandemic had already shown that fleas are able to transmit immediately after infection (early-phase transmission, EPT) [45]. Recent experiments have confirmed that EPT is as efficient as BDT for plague transmission by *X. cheopis* [50] and other flea species [51]. *P. irritans* also rarely develops a proventricular block [46]. The exact mechanism of EPT is unclear. Possible explanations include mechanical transmission from contaminated mouthparts of the flea [46] or a post-infection esophageal reflux, where a portion of the blood and the bacteria flows from the midgut back to the proventriculus within 24 hours post infection [52]. Further transmission then occurs, when fresh blood is mixed with the refluxed portion in the proventriculus and regurgitated back into the bite wound, as suggested for BDT.

Plague and climate

Climatic factors are known to have a large influence on plague activity in animals and humans at different geographical and temporal scales [27]. Both hosts and vectors depend on favourable meteorological conditions. Fleas are highly susceptible to changes in temperature and humidity [53-55]. They have adapted to various ecological niches with different meteorological profiles, and the preferred temperature or humidity ranges depend on the species [56]. Extreme conditions are fatal for all flea species. Rodents are likewise sensitive to climate. For example, the plague prevalence in a population of great gerbils in Kazakhstan was shown to increase by >50% following an increase of just one degree Celsius in spring [57]. Precipitation and temperature are thought to act on vegetation growth, which in turn increases the density of rodents due to increased availability of food (trophic cascade model) [58, 59]. However, this model may not apply to every ecosystem of plague hosts [59, 60]. The interplay between climate, fleas, rodents and human plague has been found to be governed by a threshold system, where the spillover to the human population occurs only if the flea density of rodents surpasses a critical level [30]. The effects of climatic factors can also be observed through plague activity in the human population. In northern China, plague cases increased with wetness, whereas in southern China the inverse was observed [61]. This effect is likely due to the differential response of the rodents in the North (arid climate) compared to the South (humid climate). Anomalies in pacific surface temperatures (Pacific Decadal Oscillation PDO) and the El Niño Southern Oscillations (ENSO) have been linked to human plague incidence in the western United States of 1950-2005: warm phases of the PDO and ENSO, which lead to milder and wetter

conditions on the continent, were associated with an increase in human cases [62]. The same positive correlation between ENSO and human plague incidence was also found in Madagascar [63]. Apart from large-scale, inter-annual changes in climatic conditions, intra-annual meteorological conditions that determine the seasons also play a role in shaping the seasonality of plague. Many modern plague foci including Tanzania [64], Madagascar [65], Vietnam [66, 67], India [68] and the United States [11] had a distinct seasonal pattern of plague activity in humans in the past century, which can be linked to specific temperature and/or humidity conditions. In the Democratic Republic of the Congo, where the annual temperature oscillates in a narrow range, no clear plague season was observed, but the incidence was higher in the tropical mountain ecosystem than at lower altitude or drier conditions [69].

History of plague

The first pandemic

For the first pandemic, there is little written evidence. Historical sources mention an emerging pestilence that caused swellings in the groin or armpit and appeared first in Pelusium and Alexandria (Egypt) in 571 AD [70]. The same year, the disease is mentioned also in the Levant, a year later it was in Constantinople and in 543 it had reached the western Mediterranean (Carthago, Rome and Arles). After this first wave called the Justinian plague, it reoccurred periodically at approximately 8-15 year intervals [2]. Many transmission chains were connected to Constantinople, the capital of the Eastern Roman Empire [70]. The causative pathogen of this disease was unknown, but many scholars suspected it to be plague. Molecular methods later confirmed the presence of *Y. pestis* in human remains found in multiple burial sites in Germany, England, France and Spain [71-73]. The magnitude of this pandemic is unknown, but a recent study refuted the claim of millions of deaths [74]. Nevertheless, the detection of *Y. pestis* across Europe suggests a wide dispersal throughout the Roman Empire. The same strain that caused the Justinian plague was also found recently in the Tian Shan mountain focus in Kyrgyzstan suggesting that the first plague pandemic may have originated somewhere in the border region of Kyrgyzstan and China [75].

The second pandemic

According to historical sources, the second pandemic in Europe started with a fulminant wave called the Black Death that lasted from 1346 to 1353 and killed approximately 30-60% of the population [2, 76]. The early events leading up to the Black Death can be reconstructed from the account of the notary Gabriele de Mussi [77]. In 1346, when the Mongols laid siege to the Genovese trade city of

Caffa on the Crimean Peninsula (presently Feodosija), a mysterious illness broke out among them, and the corpses of the deceased were allegedly catapulted into the city. The mysterious illness was plague, and soon thereafter the habitants of Caffa became infected. Genovese merchants fled the town on their ships and imported the disease to Europe. Constantinople was first affected in 1347, from where it spread further along trading routes to Messina (Sicily) and later Genova [78]. Another ship brought the disease to Venice. In the following years, plague spread along trading routes through central Europe towards the North of the continent in a clockwise manner. The first plague wave ended in 1353 in north-western Russia and the Baltics. The velocity of spread has been calculated as average 0.66 – 6 km/day [76, 79-81]. In the following centuries, many smaller and larger outbreaks occurred throughout Europe often with distinct chains of transmission between highly connected places. The last large epidemics were observed in the 18th century.

The identification of plague as the disease of the second pandemic is now generally accepted [78, 82-84]. Some have argued against *Y. pestis* as the causative agent of the second plague pandemic because of the fast spread during the Black Death period compared to the third pandemic [85]. Alternative diseases such as anthrax [86] or a hemorrhagic filovirus [87] have been proposed, but both claims have since been refuted [88]. Differences in the historical descriptions of clinical plague symptoms were used to argue that the causative agent of the second pandemic was different from the third pandemic [85] but also this claim did not withstand scientific scrutiny [89]. In the past few years, molecular methods have definitely confirmed the presence of *Y. pestis* in burials across Europe dating to the 14th century: Barcelona (ES), London (UK), Bolgar (RU), Abbadia San Salvatore (IT), Saint-Laurent-de-la-Cabrerisse (FR), Bergen op Zoom (NL), Oslo (NO), Laishevo (RU), Manching-Pichl (DE), Nabburg (DE) and potentially Toulouse (FR) [7, 9, 90, 91]. Further burial sites with *Y. pestis* dating to the 15th – 18th century include Ellwangen (DE, dating 1486–1627), London (UK, dating 1560-1635), Brandenburg an der Havel (DE, dating 1618-1648), Landsberg am Lech (DE, 1455-1632), Cambridge (UK, dating 1475-1536), Starnberg (DE, dating 1423-1523), Stans (CH, dating 1485-1635) and Marseille (FR, dating 1722) [7, 91, 92].

The long duration of the second pandemic raises the question of how exactly it persisted in Europe for several centuries. There are two nonexclusive mechanisms: repeated reintroductions of the disease from outside Europe, and the persistence in local rodent reservoirs [93]. The existence of local reservoirs in Europe during the second pandemic is controversial [7, 92-95]. A recent analysis of outbreak data

from several centuries has shown that most local outbreaks occurred in space-time clusters suggesting more or less continuous spread between cities without involving local reservoirs [94]. The analysis also suggested that plague may have been introduced from Asia to European and Mediterranean maritime ports on at least 16 occasions between 1346 and 1837 following climatic fluctuations in Asia. The number of plague outbreaks was also found to be associated with the distance to navigable rivers: The closer a place was to a river and the wider the river was, the more outbreaks occurred [96]. A similar analysis suggested that proximity to overland trade routes increased the number of outbreaks [97]. Cities that were highly connected through trade activities or pilgrimage were also found to be affected more often and have higher plague mortality than poorly connected settlements [98]. A further analysis using the same plague dataset suggested an association with temperature and aridity index at a lag of minus five years: an increase in drought conditions and a decrease in temperature would lead to an increase in plague outbreaks [99]. In a separate analysis of the same data, the continental spatio-temporal synchrony of these outbreaks was attributed to the occurrence of drought at a lag of minus four years [100]. Another important driver of spread was the movement of large masses of people during war times [78]. The arrival of soldiers was often associated with outbreaks, particularly in the 18th and 19th century. In summary, climate, trade and warfare were likely drivers of long-distance spread. The hypothesis of distinct introductions into Europe followed by temporary regional spread is also supported by the genotypic analysis of *Y. pestis* extracted from burial samples ranging from the 14th to the 17th century across Europe [9, 101, 102]. However, there is no consensus about how many introductions took place, from where they happened and whether this mechanism could have resulted in the observed pattern of outbreaks in the second plague pandemic.

The alternative hypothesis for the persistence of plague in Europe is that the disease established local rodent reservoirs after a single introduction [7] and caused recurrent outbreaks due to occasional and independent spillover events. Such reservoirs could be located in an urban environment [103] or in wildlife rodents, such as marmots [93]. Wildlife reservoirs of plague are common throughout Asia and in Northern Africa, and persist for decades if not centuries. To date, no past or present reservoir of plague has been discovered in Europe to support the hypothesis that similarly, highly stable local reservoirs played a role in the persistence of plague. However, more transient animal reservoirs could well have existed.

The third pandemic

Early outbreaks recorded in Yunnan province (southwest China) in the 18th century are believed to be the origin of the third pandemic [104]. From Yunnan, plague spread to Taiwan in 1869 and Hainan in 1882, and to Guangzhou Province and Hong Kong in 1894. From Hong Kong it spread globally mainly through steamships [78, 105]. These exportations have led to the establishment of many of the current plague foci [2]. In Europe alone, 1692 cases and 457 deaths were recorded between 1899 and 1947 [105]. These introductions however mainly occurred in port cities and never led to epidemics as large as during the second pandemic [105]. The last outbreaks occurred 1946 in Malta and 1947 in Kaliningrad. The third pandemic was also the time when the most important discoveries around plague were made. In 1894, the Swiss and French bacteriologist Alexandre Yersin was requested by the Institute Pasteur to investigate the plague epidemic in Hong Kong. He was credited as the first to identify and describe the causative pathogen of plague [106]. Yersin named the bacterium *Pasteurella pestis*, which was later renamed in his honour as *Yersinia pestis*. Three years later, Paul-Louis Simond, a French physician at the Institut Pasteur in Paris, was sent to India to study the ongoing plague epidemic there. He noticed that epidemics in humans were usually preceded by epidemics in rats [107]. With simple experiments, he discovered that plague was transmitted between rats through their fleas. He was the first to postulate the vector-borne transmission aspect. In India, *R. rattus* and *X. cheopis*, were the main actors involved in transmission. Subsequent to Simond's publication, the black rat and its flea became a synonym for plague.

Knowledge gaps and controversies

The epidemiology of historical plague outbreaks, particularly during the second pandemic, is still unresolved despite decades of research. The following section highlights some of the current gaps in knowledge and questions that are highly debated among scholars.

The seasonality

The seasonality of second pandemic plague outbreaks has long been contemplated. Many scholars have noted that outbreaks in France, Switzerland and England stopped at the arrival of winter [80, 82, 84, 108], while in Italy plague season was earlier with peaks in summer [85, 109]. However, the seasonal pattern across Europe has not been studied systematically. A recent attempt at comparing selected epidemiological curves from the Black Death period to the end of the 19th century concluded that second pandemic outbreaks peaked in summer, while third pandemic outbreaks peaked in winter [110]. This "inverse seasonal peak" was explained with the Black Death outbreaks being caused by a viral disease and not *Y. pestis*. The major problem with this approach is the disregard for the underlying meteorological conditions in these places. The terms summer and winter do not carry much of the same meaning across the globe, and the summer temperatures in temperate Europe are in the same range as the winter temperatures in India. Moreover, the small sample size with less than 20 epidemiological curves makes any further statistical analysis problematic. This example also highlights the need to look beyond simple pattern recognition, and to explore potential drivers of the seasonality of historical plague. Not every seasonal disease incidence is necessarily the result of meteorological condition. For example Campylobacter infections in Switzerland peak every winter due to the traditional consumption of meat fondue around Christmas [111]. However, vector-borne diseases in particular are strongly influenced by climate due to the sensitivity of the vectors to temperature, humidity or precipitation [112, 113]. Thus, the question of the seasonality of second pandemic plague is directly linked to the question of the transmission routes and the vector.

The vector

After Simond published his theory on rodent fleas as plague vectors [107], many scholars assumed the same mechanism of transmission for the second pandemic in Europe without questioning its plausibility (see [85, 88, 114]). Although some have argued early on that Simond's theory may not be appropriate everywhere and human ectoparasites were repeatedly postulated (e.g. [34, 37, 115, 116]), the idea of an alternative transmission framework did not gain much popularity. It is only recently that researchers have started to challenge the traditional plague

transmission framework again [36]. There are multiple arguments against the conventional transmission model in preindustrial Europe. Firstly, the evidence for the conventional rodent plague hosts in Europe is sparse. There is a lack of historical or archaeological evidence about massive rodent die-offs during the epidemics, which are considered a hallmark of epizootic plague [37, 115]. Some authors argue that the ecological environment in northern Europe may have not been suitable for the black rat [86, 95] and there is little archaeological evidence for its presence in Europe [117]. The other commensal plague rodent, the brown rat, was supposedly not present in Europe before 1700 [14, 95, 117]. Secondly, the most famous plague vector, *X. cheopis*, thrives mainly in tropical and subtropical climate zones and could probably not establish itself in northern Europe [118]. Thirdly, the Black Death has spread much faster across Europe than modern plague epidemics in the US, China or India that were known to involve rats as an intermediate host [79]. These arguments suggest that alternative routes of transmission must have played a role in preindustrial Europe. *P. irritans* was present in various places in Europe since the Neolithic, including France [119], the UK [120], the Netherlands [121] and Norway [122]. The results of a recent modelling study fitted to second pandemic plague data show that early-phase transmission through human ectoparasites is mathematically possible if the vector-to-host ratio is large enough, even if the transmission probabilities are low [123]. However, a biologically more realistic modelling approach is needed to further investigate this hypothesis. Firstly, the seasonality of the human flea must be considered explicitly to better understand the threshold of vector-to-host ratio needed for the establishment of an outbreak, as well as the effect of seasonal changes on the shape of the outbreak. Secondly, the inclusion of pneumonic transmission is necessary to understand the contribution of the different transmission routes (see below).

The contribution of pneumonic plague

The phenomenon of repeated plague outbreaks in many northern countries, where *X. cheopis* would probably not have survived, has been explained with several alternative theories. One of these explanations is pneumonic transmission. Historical sources often explicitly mention pneumonic symptoms such as chest pain, coughing and bloody expectorate [89]. This has prompted some scholars to hypothesize that second pandemic outbreaks were mainly the result of purely primary pneumonic transmission [124, 125]. The case of Iceland was used to postulate a pneumonic plague that killed half of the population during two winter epidemics in the 15th century based on the low temperatures and the potential description of pneumonia in contemporary Icelandic annals [124]. However, the historical descriptions of pneumonia do not usually provide any evidence whether

it was a case of primary or secondary pneumonic plague, and retrospective diagnoses are thus problematic. Both secondary and primary pneumonic plague lead to violent coughing and death if untreated. The most important clinical difference between primary and secondary pneumonic plague is the more rapid course of the disease after infection through inhalation. Large epidemics of primary pneumonic plague are rare. A recent modelling study suggested that primary pneumonic transmission alone was implausible for the Black Death period because of the low reproduction number [126]. Under certain conditions, pneumonic transmission may be predominant as in the case of a large outbreak in Manchuria in 1910/11, where at least 5009 cases occurred [22]. Crowded and poorly ventilated housing conditions, a large proportion of migrant workers, and the construction of the Manchurian Railway had contributed substantially to the rapid spread of the disease [127]. The population density of Iceland – and many other pre-industrial European settlements – must have been much lower than Manchuria in 1910, and it is questionable whether such a large epidemic of pure primary pneumonic plague could have occurred. Modern outbreaks are often mixed: the majority are bubonic cases, some of which develop secondary pneumonia and infect other through droplets, which will result in a small proportion of pneumonic cases [12, 128]. These observations suggest that second pandemic outbreaks were likely also mixed and included both bubonic and pneumonic transmission through primary and secondary pneumonic cases. However, the contribution of pneumonic transmission under the assumption of a human ectoparasite vector has not yet been studied.

The spatial and temporal extent of the second pandemic

The second plague pandemic – and particularly the Black Death period – has undoubtedly affected most of Europe and the Mediterranean. Numerous historians have studied and transcribed thousands of historical documents and other archival material. Many have synthesized and compiled information from various sources in an attempt to describe the extent of the second pandemic systematically (for example [78, 80, 129]). These data have been used to map the spatio-temporal spread of the second pandemic and to show that the first wave (i.e. the Black Death) propagated like a wave-front through Europe in a clockwise manner [79, 130, 131]. These compilations have also shown that plague disappeared from central Europe after the 17th century (with occasional outbreaks until the 18th century) [132]. However, these data collections suffer from gaps in the spatial coverage in some regions such as Eastern Europe [133] and overrepresentation in others such as France. Ignoring the selection bias in the data has led some to draw false conclusions about the epicentres of plague activity (see [134]). There is broad agreement among plague scholars that the spatio-temporal extent of historical

plague must be updated with a systematic and interdisciplinary approach [135-137]. Better insights into where and when plague outbreaks happened will contribute to understanding further aspects of transmission such as environmental or socio-economic drivers, potential vectors or the role of reservoirs vs. repeated introductions. However, the systematic generation of global plague data from primary or secondary source data is a massive undertaking. Automated processes such as machine learning and natural language processing are potentially useful to facilitate this task, but their application in historical epidemiology is in its infancy.

The available data

The epidemiological curve is the cornerstone of every epidemiological outbreak analysis. It is commonly composed of the number of incident cases collected at regular time intervals. The shape of the curve comprises information about the speed of spread and the average number of secondary cases. Unfortunately, the majority of information passed down from the second pandemic is of qualitative nature and systematically collected epidemiological outbreak data in the modern sense are rare. However, some places, particularly cities with repeated outbreaks, have early recognised the value of specifically tracking plague deaths across time to understand the progress of the epidemic. The London Bills of Mortality are a weekly collection of deaths of a large variety of causes for each parish (transcribed and published in [138] and [83]). They were published for the first time in 1562 and continued until 1840 with some minor interruptions [139, 140]. The numbers were based on information collected by the searchers, commonly elderly women. When notified about a death, the searchers would visit the home to authenticate the death and collect information about the name, age and cause of death for a fixed fee [139]. The trustworthiness of the numbers has been questioned for various reasons [140], but overall there is a good agreement of the all-cause deaths reported in the Bills and the parish burial records [141]. In Barcelona, the Consell de Cent Jurats (the council of the hundred jurors) commissioned a similar collection of the daily number of plague deaths between 1457 and 1590 (transcribed and published in [142]). The data collection was delegated to the letter-carriers [143]. For the 14th and 15th century, few other epidemiological time series with explicit plague deaths are known, for example Florence (see [144]). For the 16th to 18th century, some data from Spain and Portugal [145, 146], the UK [82, 83], France [147], Poland and Russia [148] and some more have been transcribed and published, but many more numbers may be still be undiscovered somewhere in the archives.

Whether plague victims could unequivocally be identified as such in times when microbiological diagnostics were not yet invented, is debatable. Historically, the word “plague” was often used ubiquitously to describe any disease with high mortality [149]. The description of buboes can be found in many sources from the 14th century until the end of the second pandemic [78, 89]. Some have argued that the distribution of buboes according to second pandemic sources differed from records of the third pandemic, and that these were different diseases [150]. However, the position of the bubo depends on the location of the flea bite, and buboes on the upper body suggest that people were bitten while lying down [89]. Given the similarity of some of the symptoms, it is also conceivable that some of these outbreaks reported as plague were in fact epidemic typhus [82]. This inherent

uncertainty in historical epidemiology can only be reduced with aDNA confirmation for *Y. pestis*, but a situation where both molecular and epidemiological data are available is rare.

Besides designated plague records, the official registration of all-cause deaths is useful for the reconstruction of plague outbreaks. Burial or other all-cause death counts are often more readily available from parish or other town registers than plague-specific data. These records may also contain other useful demographic information such as the name, age, sex, profession and place of residence, and sometimes the cause of death. These additional information were recently used to reconstruct a large outbreak in Venice in 1630-31 and to show a spatial heterogeneity in the spread at the end of the outbreak [151]. A general limitation of these data is that if the background mortality and the cause of death is not known and cannot be subtracted, the actual number of plague deaths is difficult to approximate. However, epidemiological curves from all-cause death counts can still be used to estimate the epidemic peak or the growth rate as long as the background mortality is constant.

Other surrogate data to study plague outbreaks include testaments or wills and vacant benefices. Both data types have been used to determine the peak timing, duration and growth rates of epidemics [82, 85, 126, 150]. However, the agreement of testaments or benefice data with plague mortality, and thus their usefulness as surrogates for epidemiological curves is not well known. Most of these datasets contain only a few dozen observations per time unit and vary substantially over time (i.e. few signal and much noise), which makes statistical inference problematic. Besides, only a fraction of the population made a last will, and the sample is hardly representative of the population. As shown with the example of London, testaments probated at two different courts can yield substantially different numbers for the same year [152]. A recent study comparing the Bills of Mortality to wills data from the same years has shown only a weak correlation between the two time series and a lag of several weeks between the peaks [126]. Vacant benefices are even more questionable as surrogate data, because of the generally low numbers and because the level of random fluctuations due to other reasons than death by plague is unknown.

The majority of information on plague outbreaks are simple occurrence data for a given year and place. Two of the largest compilations that cover most parts of Europe include the works of Sticker in 1908 [78] and Biraben in 1975 [80]. The latter has been digitized twice [153, 154], but the resulting datasets are both incomplete. Despite the apparent gaps in the digitized data, they have been used

extensively to analyse drivers of transmission [94, 96-100]. There is a need to update and expand the existing dataset (see “Knowledge gaps and controversies”) to reduce the risk of interpreting biased data.

Aims

The aim of this thesis is to improve our understanding of the spread of plague during the second pandemic with a focus on the identified knowledge gaps and controversies, and to increase and improve the body of epidemiological plague data. To address these questions, I use a combination of statistical and mathematical modelling as well as text mining approaches.

Paper I focuses on the seasonal aspect of second pandemic outbreaks. In this project, I generate a novel, large dataset of weekly or monthly plague and all-cause mortality data from multiple places across Europe and the Mediterranean. The aim of this study is to establish whether a seasonal pattern is detectable in the data, and how meteorological factors impact the peak timing and the epidemic growth rate.

Paper II investigates potential mechanisms underlying the findings in paper I by exploring the hypothesis of the human flea as a plague vector. I use published entomological data on the temperature sensitivity to simulate the seasonal abundance of the human flea with a deterministic, compartmental model. Finally, this paper explores the correlation of the seasonal flea abundance with the seasonal pattern of human plague mortality from paper I.

Paper III builds on findings from paper I and II, and proposes a novel dynamic transmission model that incorporates the seasonal abundance of the human flea as well as the contribution of pneumonic plague. I use the example of 17th century London to demonstrate how seasonal plague mortality can be explained with the seasonal vector abundance and show under which biological conditions the hypothesis of the human flea is plausible.

Paper IV aims to extend the available data on the spatio-temporal occurrence of second pandemic plague outbreaks. I digitise the plague treatise by Sticker and compare the performance of different natural language processing (NLP) tools for the automated extraction of location data from the text. In addition, I explore salient plague topics in the book to gain contextual information beyond the simple place and time of outbreaks. The final product is a geocoded dataset for the second and the beginning of the third pandemic in Eurasia, as well as an updated, re-digitized version of Birabens plague list. The integration of the two datasets aims to update the spatial and temporal extent of the second plague pandemic.

Paper summaries

Paper I: The influence of temperature on the seasonality of historical plague outbreaks

The seasonality of second pandemic outbreaks has not been investigated systematically. Anecdotal evidence from historical sources suggests that there was a distinct plague season in some places, but it is not known how the plague seasons differed geographically and what its drivers were. This study aimed to 1) detect whether a seasonal pattern existed for places with multiple outbreaks, 2) investigate whether temperature and precipitation influenced the epidemic peak timing and 3) quantify how temperature influenced the epidemic growth rate. The results of a GLM regression model with a negative binomial error structure show that four of the five places with at least four outbreaks had a statistically significant seasonal pattern. Moreover, the percentage distribution of monthly plague deaths of the complete dataset showed a clear latitudinal gradient with a shift of the cases towards the end of the year the farther North a place was. There was also a strong negative association between the peak week and the average annual temperature: a decrease by one degree Celsius delayed the epidemic by 1.4 weeks. Precipitation on the other hand was not associated with the epidemic peak timing. The result of a GAMM regression model showed that the time-varying growth rate of these outbreaks was influenced by temperature. The maximum growth was observed at 17.3°C, positive growth was predicted only between 11.7°C and 21.5°C. This study showed for the first time that 1) a seasonal pattern existed for second pandemic outbreaks and 2) temperature may be one driver among other factors. These findings warrant a closer investigation into potential mechanisms that link temperature and plague mortality in Europe and the Mediterranean.

Paper II: The seasonal abundance of *Pulex irritans* and its correlation with historical plague: insights from mathematical simulations

The seasonality of vector-borne diseases is mainly influenced by the seasonal abundance of the vectors. Insect vectors are generally highly susceptible to ambient temperature and humidity or precipitation. The findings of a distinct seasonal pattern of second pandemic outbreaks raises the question about the seasonality of the human flea and how it agrees with the observed plague mortality patterns in humans. The aim of this study was threefold: 1) to estimate the temperature-dependent mortality rates of pre-adult and adult flea stages, the transition rate between the stages, and the reproduction rate based on published experimental data, 2) to simulate the seasonal abundance of the human flea with a deterministic, compartmental model using the temperature-dependent life cycle

parameters estimated in the first step, and 3) to investigate the correlation of the predicted flea abundance and the observed plague mortality. The estimated mortality function for pre-adult and adult fleas showed the longest lifespan at a temperature around 13.8° C and 15.8°C, respectively. The transition and reproduction rate both increased with increasing temperature. The simulated flea abundance showed a clear, unimodal peak in autumn for temperature profiles as in central and northern Europe (temperate climate). For hot temperature profiles as in Egypt, the flea peak occurred in spring. For the transition zone in between (most of the Mediterranean), two peaks were predicted in spring and autumn. The predicted flea seasonality correlated well with human plague mortality for places in temperate Europe and in Egypt, but the abundance with two peaks for places in the Mediterranean was not confirmed in any of the outbreaks. These findings raise the question of what shape the seasonal flea abundance must have been in order to explain a causal relationship between human fleas and plague.

Paper III: The human flea and the seasonality of plague in pre-industrial Europe: a modelling study using historical data from 17th century London

Although the seasonality of human plague correlates with the predicted seasonal abundance of human fleas in some places, the role of the human flea as a potential plague vector is not proven. Specifically, the exact peak timing of the fleas in relation to the peak in plague and the necessary vector-to-host ratio is unclear. The aim of this study was 1) to determine the shape of the flea abundance under the assumption of a causal relationship, 2) to quantify the contribution of pneumonic transmission in addition to vector-borne plague and 3) to establish the conditions necessary for plague to invade the population. This was established with a novel, deterministic, compartmental disease model, which explicitly estimated a time-varying function for the susceptible fleas as well as the proportion of cases with the different clinical forms of plague (bubonic, septicaemic, primary and secondary pneumonic). The model was fit to a plague mortality time series from the Bills of Mortality from London 1639-1647. The results of this study show that the optimal flea abundance peaks ten weeks before the peak in human mortality, and that pneumonic plague contributed about 30% of the cases. The invasion of plague was not possible below a vector-to-host ratio of 7.7:1, unless the vectors increased rapidly enough after the introduction to push the basic reproduction number above unity.

Paper IV: Mapping the plague through natural language processing

The core aspects of infectious disease epidemiology are place, time and person. The places and times of plague outbreaks during the second pandemic have been collected and compiled by many historians. However, the most popular dataset is

incompletely digitized and suffers from a regional selection bias. The aim of this study was to improve and expand the existing data by digitising a plague treatise published by Sticker in 1908. Specifically, this study aimed to 1) investigate the performance of different natural language processing (NLP) tools to extract toponyms (place names) automatically, 2) to explore the use of text mining to gain additional information about salient topics, and 3) to compare the new Sticker dataset to a re-digitized version of the existing Biraben dataset to update the information on the spatial and temporal extent of the second pandemic. Of the tested NLP algorithms, spaCy had the highest sensitivity (0.92). The exploratory text mining approach showed that clothes and rats were among the most frequently used nouns. While clothes appeared regularly throughout the text, the discussion of rats occurred mainly in the section of the third pandemic. The word for clothes was also often linked to bedding, equipment and people. Compared to the existing Biraben dataset, this study found 1404 new outbreaks, most of which were located in south eastern Europe and southern Russia, the Caucasus, Iran and India. This new dataset represents a valuable addition to the existing corpus of plague data.

Discussion

Why epidemics grow and decline

Many factors determine the growth and decline of epidemics. Formally, the reduction in the force of infection to humans, regardless of whether they are vector-borne or not, can occur because of the exhaustion of susceptibles, the removal of the infectious agents, the reduction in the contacts between them or the reduction of the duration of infectiousness [155]. The availability of susceptible hosts depends, among other things, also on the pre-existing level of immunity in the population. The concept of herd immunity was published in the early 20th century and describes the status when the proportion of immune individuals in a population surpasses a certain threshold, such that the number of susceptibles becomes insufficient for successful transmission and the epidemic declines [155]. This concept is mainly used for planning vaccination strategies, but the recent COVID19 pandemic has compelled some scientists to propose herd immunity as a strategy to mitigate the spread of the SARS-CoV-2 virus [156]. Factors that remove the infectious agents (vectors or other humans) or reduce the contact rates between them include the implementation of control measures, changes in human behaviour, and external environmental forcing that acts on the vectors and/or hosts, for example meteorological conditions such as temperature or precipitation. Environmental forcing is an important aspect of vector-borne diseases, and affects both the seasonal as well as the inter-annual variation in disease incidence [113]. For example the resurgence of many mosquitoe-borne diseases, such as Dengue virus or Malaria, is influenced by changes in temperature, humidity and/or precipitation [157, 158]. The main underlying mechanism is the sensitivity of the various developmental stages as well as the biting behaviour of the vectors to meteorological factors. For example, the transmission of Zika, Dengue and Chikungunya virus by the mosquito species *Aedes aegypti* and *Aedes albopictus* is highest between 25°C and 36°C [159-161]. Seasonal climate also influences host behaviour. For directly transmitted respiratory diseases, indoor crowding in winter may lead to an increase in infectious contacts [113]. For vector-borne diseases, seasonal activities such as harvesting may increase the infectious contacts beyond the effect of climate on the vector directly. Due to the complex interplay of climate, host and vector biology, human behaviour and demographic effects, climatic and meteorological factors alone cannot explain disease incidence [162]. Thus, a dynamic model for historical plague transmission ideally incorporates different factors that could influence the transmission process, in particular if the disease process is fitted or simulated over a longer time period.

Structure of historical plague models

The state-of-the-art method to study the transmission dynamics of infectious diseases is the mathematical SIR-type model [163]. The choice of model structure and the underlying assumptions can influence the outcome of the model substantially. In order for models to be both informative and realistic, we need to find the right balance between complexity and abstraction. In the context of a vector-borne disease, due diligence is owed to representing the dynamics of the vector itself in a biologically meaningful and interpretable manner, especially in the context of seasonal epidemics.

The classical model of rat-borne plague transmission in humans was published in 2000 by Keeling and Gilligan [103, 164]. In their epizootic model, the disease persists in a local rat population. When the rat density is low, free infectious fleas search and infect human hosts with some searching efficiency. However only large outbreaks among rats lead to a substantial number of human cases. The force of infection to humans depended linearly on the number of free fleas, but decayed exponentially with the number of rats. The model was extended to include a seasonally forced carrying capacity for the number of rats. However, as the authors note, the seasonal dynamics were "averaged out" at the time scale of one year or more, and the oscillations in their model trajectory are mainly due to the changing susceptibility of rats and humans. The same model was later adapted by Monecke et al. to describe a single outbreak in Freiberg (Germany) [165]. Their results suggest that the human deaths increased only after the rat population collapsed to a sixth of the original size. They assumed disease importation from outside, and the survival of fleas was estimated as 18 weeks. Another, simplified version of this model was published by Didelot for the large outbreak in Cairo in 1801 [166]. The free fleas were not modelled explicitly but the transmission from rats to humans was substituted with a force of infection from rat carcasses. Most of these models have in common that the modelled outbreak stops because of the collapse of the rat population, and a new outbreak is only possible once the rodent population has regenerated enough susceptible individuals. A different approach was chosen by Whittles for the outbreak in Eyam (UK) in 1665-1666, where transmission occurred both from an unlimited pool of rodents and between humans directly (although the mechanism was not specified and theoretically could include pneumonic and ectoparasites transmission) [167]. In their model, the outbreak would stop due to the structured contacts of people within and between households and stochastic extinction. The authors hypothesized a change in transmission route to explain the seasonal pattern with peaks in autumn. White and Mordechai later combined the rat model with secondary pneumonic transmission to simulate the

expected number of deaths and the duration of epidemics during the first pandemic [168]. Lazzari et al. recently reconstructed the large epidemic in Venice in 1630-31 and investigated various rat models and models for direct transmission to explain the epidemic shape with a large peak and a long tail with temporary small surges [151]. They showed that a stochastic delayed behavioural SIR model could explain the shape of the curve, and a change in transmission from bubonic to pneumonic as hypothesized by others may not be required. Dean et al. were the first to model the transmission through human ectoparasites without the involvement of rodent hosts [123]. The problem of the epidemic decline was solved by estimating the proportion of the population that was exposed. Once this partitioned exposed population was depleted of susceptibles, the outbreak would stop.

The seasonal aspect of plague transmission was explicitly modelled only in recent studies. Bacaer published a modified version of the Keeling-Gilligan model in 2012, where the transmission probability from flea to host was modelled with a hyperbolic tangent function of the temperature [169]. This parametrization was based on the finding that fleas are less likely to transmit *Y. pestis* when the temperature was hot. The abundance of fleas however was kept constant throughout the year. In their model, the epizootic in rats and the outbreak in humans largely overlap with a small delay between the peak of a few weeks. Lewnard and Townsend approached the seasonality problem with a seasonal forcing of the mortality function of the free, infectious fleas in the form of a harmonic cosine function [170]. In addition, the rat population was modelled with a hereditary resistance to plague to explain the long-term seasonal phase shift and decline of cases over time. A similar approach was chosen by Ngeleja et al. with sinusoidal transmission rates between rodents, fleas and humans [171]. However, the model system did not result in a seasonal pattern and the periodicity was at a larger scale suggesting that it was driven mainly by the availability of susceptible hosts. Nguyen modelled the outbreak in Madagascar in 2017 with a sinusoidal function to describe the temperature-dependent density of the rat population [23]. In their model, the outbreak stopped because of the implemented control interventions.

In **paper III** I have chosen a different approach. I focused on the seasonal abundance of the vector and its effect on plague transmission while accounting for the development of population immunity and renewal of the susceptibles through immigration and birth processes. I modelled the seasonal abundance of susceptible fleas directly to gain more information about the vectors, instead of calculating a seasonal force of infection only to humans. I also made less assumptions about the shape of the curve (compared to a sinusoidal forcing), and the function allows for a

more flexible seasonal abundance. In addition, I modelled the contribution of pneumonic transmission both from primary and secondary pneumonic plague. Mixed epidemics occurred often, but this circumstance has rarely been considered in models of historical plague.

Temperature, human fleas and the seasonality of plague

In **paper I,** I have shown that temperature played an important role in the timing and growth of second pandemic outbreaks. Temperatures around 17°C were associated with the largest epidemic growth and no growth was observed below 4°C. The temperatures in Europe and the Mediterranean differ substantially, and thus the minimum temperature threshold conducive of positive epidemic growth was attained at different time points of the year for different places. As a result, the epidemic peak timing shifted increasingly towards the end of the year the colder the annual average temperature was. These findings prompted me to investigate the temperature-sensitivity of *P. irritans*, an often hypothesized but hardly studied potential plague vector. As I have shown in **paper II**, the lifespan of *P. irritans* is also longest at ~16°C, and the reproduction rate started to increase dramatically in this range. The modelled seasonality of the human flea coincided also with the human plague mortality for outbreaks in the temperate climate zone and in Egypt. Because the temperature threshold that is beneficial for flea growth was attained earlier in the year in warmer places, the flea abundance also peaked earlier. As I have shown in **paper III**, the invasion potential for plague in London was a direct function of the vector-to-host ratio, which in turn was a function of the temperature (**paper II**). In warmer places, the temperature stayed above the threshold and in a favourable range for longer, and thus the vector-to-host ratio was generally larger (**paper II**). The observation that plague seasonality was more consistent in Central and Northern Europe than in the Mediterranean (**paper I**) may thus be a direct effect of the length of the window with the optimal vector-to-host ratio needed for transmission. Outside the periods of favourable temperatures (and thus outside plague season), transmission would not occur because the number of vectors available was too low. Anecdotes from the second pandemic report that people who returned to their houses after a plague epidemic and would sleep in the beds of plague victims, but would not become sick as long as the plague season was over [84]. In **paper III** I predicted the peak in the fleas to occur ten weeks before the peak in plague mortality, which is inconsistent with the results from **paper II**, where I predicted the fleas to peak simultaneously with plague mortality. As discussed in **paper III**, there are several possible explanations for this discrepancy, including biased entomological data, modelling assumptions that are too simplistic, and the influence of factors other than the environmental forcing on the vector.

Other factors that influence seasonality

Besides the temperature-dependent seasonality of the human flea, other factors could have potentially played a role in shaping the seasonality of second pandemic outbreaks.

Pre-existing immunity can influence the dynamics and determine how an epidemic grows and declines. As I show with my model in **paper III**, the best fit to replicate the periodic plague mortality was obtained with a distinct seasonal fluctuation of the fleas. This suggests that the fluctuations of the susceptible humans alone due to the immunity and demographic process are not sufficient to explain plague seasonality. The estimated proportion of the population that was infected could range from a few percentages to the whole population (**paper I**). Interestingly, these attack rates declined non-linearly with the population size. In very large populations such as London in the 17th century, the proportion infected may have never surpassed 30% based on the collected data (not considering underreporting of deaths). Assuming a basic reproduction number of 1.5 to 2 [123] and homogeneous mixing, a minimum of 33% to 50% of the population would be required to be immune in order to reach the herd immunity threshold. Given the high case fatality, large populations were unlikely to attain a level of herd immunity that would lead to an epidemic decline. Small populations may have reached herd immunity temporarily, but population turnover due to natural deaths and births as well as immigration would compensate rapidly for the loss of susceptibles. Overall, population immunity may have played a role in some settings, which needs to be studied further. However, the theory that the second pandemic declined because of full population immunity in Europe is highly implausible [172].

Changes in human behaviour and thus contact rates due to mitigation measures or fleeing of people are well known and described for historical outbreaks during the second pandemic [78, 173]. In fact, the now famous concept of the quarantine was implemented in the 14th century following the Black Death period [174]. The word is derived from the Italian word for “40”, which refers to the 40 days, during which incoming travellers with suspected plague had to isolate themselves from the population. As shown in **paper IV**, “quarantine” is among the most frequently discussed topics related to plague transmission in historical sources. Other measures included the isolation of cases in “Pesthouses” and the fumigation and disinfection of objects and dwellings [78]. However, it is unclear, how effective these measures were and what the effect on the plague seasonality was. Quarantine and isolation may be effective at the beginning of an outbreak when case number

are manageable, and the early implementation must have prevented some outbreaks from growing into large epidemics. However, many of the outbreaks studied in **paper I** were quite large, and the systematic and successful separation of infectious and susceptible agents (hosts or vectors) at this scale seems unlikely. As observed during the COVID19 pandemic in 2020, the systematic implementation of control measures is challenging even in the 21st century with modern means of communication and improved knowledge about pathogens. Also, the connection of plague and fleas was discovered only a century ago [107], and historical control measures were thus not very targeted. In the case of London, but also other places with recurrent outbreaks and a distinct seasonality (see **paper I**), a consistent implementation of control measures that would lead to a similar peak timing and epidemic shape every year seems unlikely. Anecdotal evidence for the predominance of factors other than control measures also comes from rodent-borne outbreaks in Malta, where transmission usually ended independently of whether measures to kill the rats or their fleas were taken or not [175]. Due to a lack of good data, I have not considered the effect of control measures in the model in **paper III**. However, future models will ideally address both aspects to confirm the effect of the flea seasonality on plague while controlling for the effects of mitigation measures.

Finally, seasonal changes in human behaviour could have contributed to the spread of plague. Seasonal plague incidence due to seasonal harvesting activities has been observed in several regions with active foci plague [176-178]. However, in the alternative transmission framework of human ectoparasites, this effect is less relevant for the growth of an epidemic and may only have played a role for disease introduction into the human population. However, this would require the presence of plague foci in pre-industrial Europe, which is controversial (see introduction). In the case of pneumonic plague, crowding and poor ventilation may occasionally lead to large pneumonic outbreaks, but this seems to be a rare event [22, 23]. Indoor crowding during winter may have led to an increase in the rate of successful, infectious contacts between humans directly. However, as shown in **paper I**, winter was not the predominant plague season in many places, and the contribution of pneumonic plague was estimated to be as low as 30% (**paper III**), which is consistent with modern outbreaks.

Further evidence for human ectoparasites

In **paper IV**, I have investigated the qualitative aspects of plague narratives by extracting word associations in a plague treatise published in 1908 [78]. One of the findings of paper IV was that the discussion of clothes and bedding in the context of transmission featured prominently throughout the book and epochs. This

phenomenon is indicative of ectoparasites residing in clothes, beds or equipment. Until the early 20th century, the infestation of dwellings with fleas was not uncommon [105]. In Norway, beds were humorously called “flea boxes” [88]. Not all domestic fleas might have been *P. irritans*, but the human flea was often the predominant species in flea infested households [34, 38, 40, 114]. Clothes had also been recognized as a source of transmission already at the beginning of the third pandemic in India [179]. During a plague outbreak in Java at the beginning of the 20th century, the clothes and bags of almost 57,000 persons were disinfested, and several hundred human fleas were found but only a handful of *X. cheopis* [114, 180]. All these observations suggest that human ectoparasites played a part in historical plague transmission.

The second plague pandemic was not exclusively a European, but rather a Eurasian-African phenomenon [181-183], which is also confirmed in **paper IV** with the (re-)digitization of two plague treatises. The large spatio-temporal extent and the occurrence in many different climate zones demands a critical investigation into the drivers and routes of transmission beyond the traditional narrative of the black rat and the oriental flea. The findings that temperature may partially drive plague transmission (**paper I**), that the human flea shows a similar seasonal behaviour as plague mortality (**paper II**) and that seasonal plague transmission is possible when the seasonal vector-to-host ratio is above a certain threshold (**paper III**) provides further evidence in favour of the human ectoparasites transmission framework for the second pandemic.

A proposal of the mechanism of historical plague transmission

How do human ectoparasites fit in the grand scheme of the second plague pandemic plague? The spillover of plague from an animal reservoir is commonly believed to occur through rodent fleas. However, *P. irritans* is also known to feed on various mammals including rats [184], albeit reluctantly [46]. Once the disease was introduced into the human population near a plague focus (either through rodent or human fleas), transmission between humans could have occurred through a mix of human fleas, rodent fleas and pneumonic transmission. Human fleas are mostly confined to a household, and thus the dispersal within a town was likely due to passive transport in clothes or other fabric, or belongings from a deceased person. For places far away from plague foci, trade activities were crucial for the disease introduction. Specific commodities, including clothes, other fabric, grain but also fur [9] infested with both human or rodent fleas were an optimal vehicle for long-distance dissemination [78]. Rodents on board of ships could maintain the cycle and keep the fleas alive. Once infested commodities arrived in Europe, the rodent or human fleas could potentially infect humans who came in contact with

merchandise. The subsequent development of local outbreaks would be possible if the local population of human fleas that infested the human population was large enough to spread the disease further. If the lifespan of the human fleas was long enough, long-distance trade within Europe could have further disseminated plague through the flea, without ever infecting a local rodent population or seeding a new reservoir.

Perspectives

This thesis has shed some light on the circumstances of the second plague pandemic and the potential contribution of human fleas. However, many questions are still unanswered. The life cycle of the human flea under varying meteorological conditions could be investigated with more systematic entomological studies. Moreover, experimental studies on the transmission probability from human fleas to mammal hosts and vice versa, as well as the level of septicaemia required for transmission could clarify whether human fleas are indeed suitable vectors. These insights can be used to parametrize an entomological-epidemiological transmission model that combines the approaches in paper II and paper III. Given the sparsity of true epidemiological data for historical plague, the usefulness of surrogate or proxy data to infer the epidemiological curves should be investigated further. Particularly the agreement of wills data with plague mortality in terms of growth rates and peak timing must be quantified given that their use has gained popularity in historical epidemiology. Finally, the question of the plague reservoirs in Europe, which is also linked to the question of the vector, should be studied further. This requires a good knowledge of where and when outbreaks occurred. The datasets I have provided in this thesis could be supplemented with additional data from selected regions particularly in eastern Europe, the Levant and western Asia. Such a dataset could provide some additional insight into where the reservoirs closest to Europe were, and how trade activities linked them to the spatio-temporal pattern we observed.

Acknowledgements

I thank Katharine R. Dean, Franziska Franeck and Hildegunn Viljugrein for proofreading this thesis.

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Paper I

The influence of temperature on the seasonality of historical plague outbreaks

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Abstract

Modern plague outbreaks exhibit a distinct seasonal pattern. In contrast, the seasonality of historical outbreaks and its drivers has not been studied systematically. Here, we investigate the seasonal pattern, the epidemic peak timing and growth rates, and the association with latitude, temperature and precipitation using a large, novel dataset of plague- and all-cause mortality during the second pandemic in Europe and the Mediterranean. We found that average annual temperature was negatively associated with peak timing: a decrease of the annual average temperature by 10°C delayed the peak timing by average 14 weeks. We further show that the predicted epidemic growth rates exhibit a non-linear relationship with temperature and are maximal at 17.3°C. These findings suggest that the pre-industrial outbreaks in our dataset were governed by the same underlying temperature thresholds. Our study provides a first systematic insight into the seasonality of historical plague in the northern hemisphere, as well as consistent evidence for a temperature-related process influencing the timing and growth of these epidemics. Given the importance of understanding past epidemics to prepare for future outbreaks, our study warrants further investigation into potential mechanisms.

Keywords: climate, temperature, seasonality, epidemic growth, second plague pandemic, Yersinia pestis

Introduction

Seasonality is a salient feature of many infectious diseases [1]. For example, in the Northern hemisphere influenza is known to occur almost exclusively in winter, chickenpox peaks mainly in spring, West Nile Virus circulates mostly in summer [2]. The drivers of seasonality are manifold and depend on the type of transmission. Directly transmitted childhood diseases like measles are strongly affected by seasonal changes in social behavior like school terms or household clustering. The seasonality of vector-borne diseases depends heavily on the seasonal abundance of the vector and additional hosts, which is a function of local

climate including temperature and precipitation. The seasonality of respiratory diseases is influenced by climatic factors that affect the transmissibility of the pathogen, the susceptibility and the contact patterns of humans [3]. Influenza and respiratory syncytial virus both show a clear latitudinal gradient with peak activity being shifted towards the end of the year for increasing latitudes and decreasing average temperatures [4].

Modern plague is another example of a highly seasonal disease. This zoonosis is maintained in rodent reservoirs, and is transmitted between the animals through various flea species. Recurrent epizootic outbreaks may occasionally lead to spillover to the human population. Humans develop bubonic plague when bitten by infectious rodent fleas, which is usually fatal in about 66% of the cases if untreated [5]. They may also develop secondary pneumonic plague if the disease spreads to the lungs. Direct human-to-human transmission through infectious droplets lead to primary pneumonic plague, which is almost always fatal if not treated immediately. Many of the biological components of the plague system – including the bacteria, vectors and animal hosts – are sensitive to environmental factors [6-8]. The influence of temperature on plague activity has already been noticed in 1917 in India, where each year the outbreaks peaked between February and April and ceased completely when the temperature rose above 80° F (26.7°C) [9, 10]. A recent study has shown that during 1898-1949 outbreaks were more likely to occur when the annual humidity was moderate (60-80%) compared to lower or higher humidity levels [11]. Temperature ranges between 15-27° C have also been associated with plague incidence in many African countries [12]. In Tanzania, bubonic plague cases in the 1980s peaked mainly in December to February two months after the short rains between October and December [13]. In the highlands of Madagascar, cases occur in the warm, wet season between September and April [14]. In the United States, plague season is mainly from July to September [5]. In all of these cases, the sensitivity of the vectors and hosts to meteorological conditions also influences the plague incidence in humans.

Contrary to the rich evidence for the seasonal behaviour of modern day plague, the seasonality of plague during the Second Pandemic (14th to 19th century) has not been studied systematically. Anecdotal evidence suggests that also historical outbreaks in Europe may have followed a typical seasonal pattern. Parish records in Switzerland show that mortality during plague years was highest in November [15]. In the British Isles, plague season was predominantly in autumn [16], whereas in the Mediterranean region plague outbreaks peaked mainly in spring to summer [17]. Some have argued that historical plague in Europe peaked in the "warm season" whereas modern plague in Asia peaks in the "cool season" and speculated these discrepancies may be due to different causative agents [18].

However, molecular methods have shown unequivocally that second and third pandemic plague was indeed the same disease caused by *Y. pestis* [19]. Nevertheless, the question of whether there was a consistent plague season, and how it related to meteorological conditions is still unaddressed. Quantifying the seasonality of an infectious disease and its drivers may also provide insight into the mechanisms of historical plague in Europe. The existence of local reservoirs in pre-industrial Europe is controversial, and the vectors and hosts involved in disease transmission are not known [20]. Nowadays, the risk of another plague pandemic is fairly low due to the availability of antibiotics and reduced exposure to ectoparasites. Nevertheless, plague is still active in many parts of the world, and understanding the seasonality of historical outbreaks may contribute to understanding and preventing future epidemics.

Thus, we here investigate the seasonality of plague outbreaks across Europe and the Mediterranean during the second plague pandemic. We collected and digitized epidemiological curves from published literature and established whether a seasonal pattern was present in the data. We then estimated the peak timing and the growth rates and studied how these measures related to temperature and precipitation. We show that temperature could partially explain both the epidemic peak timing and the concurrent epidemic growth rate. We conclude our analysis with a discussion about potential mechanisms and limitations of our work.

Methods

Plague and all-cause mortality data

We first established a dataset of plague outbreaks through a combination of systematic and opportunistic literature search. We searched three major literature databases (jstor, pubmed and the internet archive) using a pre-specified search strategy (Table S1). The details are given in Text S1. We collected time series data of incident plague and all-cause mortality during plague outbreaks at daily, weekly, bi-weekly or monthly time intervals. We focused on pre-industrial outbreaks during the second plague pandemic (14^{th} – 19^{th} century) in Europe (including Russia) and the Mediterranean Region. An epidemic was defined as uninterrupted plague activity for a period of at least 3 months for a given place. Epidemics with zero cases for four or more months in between were considered two different epidemics and split into two datasets. Some datasets had continuous plague activity during multiple years (recurrent peaks). For the calculation of the epidemic peaks, we split these epidemics into annual outbreaks at the minima between the peak to assess the seasonality for each outbreak separately. We also calculated the estimated attack rates (i.e. the proportion of the population infected

at the end of the epidemic, also known as final size) of all outbreaks, for which we could retrieve initial population sizes. The attack rates were calculated as

$$attack\ rate = \frac{n_{deaths} * \frac{1}{p(dying \mid infected)}}{population\ size} \quad \text{Eq. 1}$$

where n_{deaths} is the cumulative number of deaths at the end of the epidemic and p(dying | infected) is the case fatality ratio (CFR), which is around 0.66 in untreated cases [5]. Wherever possible, dates were converted to the Gregorian calendar prior to analysis. The raw data and the R code for data preparation and analysis are available in a public repository [21].

Climatic, geographical and demographic data

Geographical coordinates of all locations with plague data were obtained from Google Maps. To investigate the effect of temperature and precipitation, we used the CRU TS 4.03 dataset, which are global, monthly-averaged climate raster data [22]. From this dataset, we extracted the monthly temperature and precipitation values for the years 1901 to 1939. We first calculated the annual mean precipitation and temperature for each place and used these point estimates as predictors to model the timing of the epidemic peak. We then used the monthly temperature data and fitted a Fourier series model of the form

$$Temperature = a + b \times \sin\frac{2\pi}{365}t + \mathrm{c} \times \cos\frac{2\pi}{365}t + \mathrm{d} \times \sin\frac{4\pi}{365}t + \mathrm{e} \times \cos\frac{4\pi}{365}t \quad \text{Eq. 2}$$

where t is the day of the year. This model allows for a harmonic smoothing of temperature data without the constraints of vertical symmetry as in a simple sine function. We used the resulting coefficients to predict the average, daily temperatures, which were used as a covariate to model the growth rates.

Detection of seasonal pattern

We first investigated whether seasonality was present in our dataset. For this, we selected all plague-specific mortality data from places with at least four outbreaks. We first examined the distribution of the number of deaths by month for each place separately. We then grouped months into seasons and fitted a generalized linear model (GLM) with a negative binomial error structure and a log link function and with the season as a categorical covariate for each place:

$$\ln\left(\frac{y}{population}\right) = \beta_0 + \beta_1 \cdot season \quad \text{Eq. 3}$$

where *y* is the number of deaths, the natural log of the population is an offset and β_0 is the intercept. The exponential of the β_1 coefficients resulting from this type of model give an estimation of the incidence rate ratio (IRR), which is the increase in incidence compared to a baseline (winter in our model). This model was then compared to a null model with an intercept only and without season by means of a likelihood ratio (LR) test.

Influence of latitude, temperature and precipitation on the epidemic peak timing

To investigate the association between latitude and plague mortality, we aggregated all plague mortality data monthly and calculated the annual average percentage (AAP) for each month *i* as

$$AAP_i = \frac{n_i}{\sum_1^{12} n_i} \times 100\% \qquad \text{Eq. 4}$$

where n_i is the number of plague deaths in month *i*, and examined the distributions with a plot. Since latitude itself is a proxy measure for climatic variables, we then investigated the influence of annual average temperature and precipitation on the observed patterns of mortality. For this, we looked at the timing of the mortality peak, which is a more convenient indicator for seasonality of historical outbreaks than the start or end points, which are often not well recorded. We aggregated all daily and weekly plague mortality data by ISO week and calculated the calendar week in which most deaths were reported. Some places had multiple outbreaks and these data points are potentially stronger correlated than measurements from other places. We thus fitted two linear, univariable GEE (generalized estimating equations) models for the effect of temperature and precipitation, respectively, using the R package geepack [23]. The GEE model is a population-averaged model that can deal with clustering of observations [24]. It treats the within-subject covariance as a nuisance effect but yields a parameter estimate and robust standard errors adjusted for the clustering. We specified an exchangeable working correlation structure, i.e. assuming the correlation of observations within the same cluster is constant across all clusters. For each model, we calculated the variance explained given by the coefficient of determination adapted to GEE models (R^2_{marg}, for the calculation see [25]). We also conducted four sensitivity analyses by extending the dataset to include also 1) monthly plague data, 2) weekly all-cause mortality data during known plague outbreaks, 3) monthly plague and all-cause mortality data during known plague outbreaks, and 4) by excluding data from small outbreaks.

Influence of temperature on the epidemic growth

Based on the findings from the model of temperature and peak timing, we were interested in how temperature determined the epidemic growth. To calculate the growth rates we used all weekly plague mortality data with complete epidemiological curves. We then established the actual epidemic curve (i.e. the number of incident infections over time) by taking into account the probability of dying when infected and the delay between infection and death. For the prior, we divided the weekly incident deaths by the average case fatality ratio CFR of 0.66. For the latter, we subtracted the average time from infection to death from all the dates, which is around 7 days according to data from the third plague pandemic in India [26]. We then modelled the epidemic growth rate for each outbreak by regressing the log-transformed incident cases on time in days. To account for variations of the growth rate over time, we partitioned the data into rolling time windows of four weeks and fitted each segment separately. This resulted in a time-varying, moving average of growth rate. To reduce the influence of random fluctuations when case numbers were low, we excluded the beginning and the tail of the epidemics when the incident number of cases were smaller than 21 (i.e. 3 cases per day). To explore the potential function that links temperature to the time-varying growth rates (r), we fitted a univariable generalized additive mixed model (GAMM) with a Gaussian error structure and an identity link function of the form:

$$r = \beta_0 + f(temperature) + \varepsilon \qquad \text{Eq. 5}$$

where β_0 is the intercept and ε are the residuals. To account for the remaining autocorrelation of data points from the same outbreak, we assumed an AR1 gaussian correlation structure for the residuals with $\varepsilon_i = \varepsilon_{i-1} + \rho e_i$, where ρ is the correlation parameter and $e_i \sim N(0, \sigma^2)$. The advantage of a generalized additive model is that it allows for a nonlinear relationship between predictor and outcome without making an explicit a-priori assumption about the shape of this relationship (see [27]). We used the R package mgcv for the fitting prodecure [27].

Results

Description of plague and all-cause mortality data

With the systematic search strategy, we retrieved 2450 references (Table S2). After screening the full texts of 246 references (10%), we included nine publications that contained useful data. We also included 36 publications from an opportunistic search strategy resulting in 45 publications containing useful data for our analysis. Eighteen publications contained data on two or more epidemics, which resulted in 130 datasets in total, with 76 datasets for plague mortality and 54

datasets for all-cause mortality during plague outbreaks (Tables S3 and S4). Some of the epidemics consisted of multiple years resulting in totally 157 annual outbreaks from 87 unique locations. Of these, 100 (64%) were plague mortality data and 57 (36%) were all-cause mortality data. The location and epidemiological curves of all outbreaks are shown in Figures S1 and S2. The interval at which the plague deaths were recorded was weekly (28.6%), monthly (36.4%), daily (33.8%) or bi-weekly (1.3%). The majority of the plague mortality datasets were from the UK (35.1%), followed by Spain (18.2%), Egypt (10.4%) and other places (36.3%). Most dated from the 17th century (32.5%), followed by the 16th century (23.4%) and the 19th century (18.2%). The median duration of the plague outbreaks was 9 months (range 4-103). The median cumulative number of deaths was 1352 (range 38-68,596) and the median number of deaths at peak was 429 in a month (range 14-31,036). The median attack rate was 11% (0.11, range 0.0009-1) and decayed non-linearly with increasing initial population size (Figure S3). Above a population size of 100,000 the proportion of infected people never exceeded 0.25 (25%). The year of the outbreak was not associated with the attack rate (Pearson correlation coefficient -0.05).

Detection of seasonal pattern

As shown in Figure 1, the monthly distribution of plague deaths in places with at least four outbreaks (Alexandria, Algiers, Barcelona, London and Vienna) suggests a distinct seasonal pattern for all places but different peak times. A model including season explained the data better than a model without a season covariate for all places except Algiers (Table 1, see p-values of LR tests). Compared to the baseline of winter, the maximum increase in the incidence was observed in spring (March-May) for Alexandria (IRR 4.75, 95% CI 1.7-12.54) and Barcelona (IRR 8.1, 95% CI 3.31-18.61), and in autumn (September-November) for London (IRR 10.66, 95% CI 6.85-16.57) and Vienna (IRR 5.11, 95% CI 2.03-12.55). In Algiers, the maximum incidence was also in spring but the difference to the other seasons was statistically not significant (IRR 2.66, 95% CI 0.82- 8.47). These results indicate that the historical outbreaks in our data exhibit a consistent seasonality pattern.

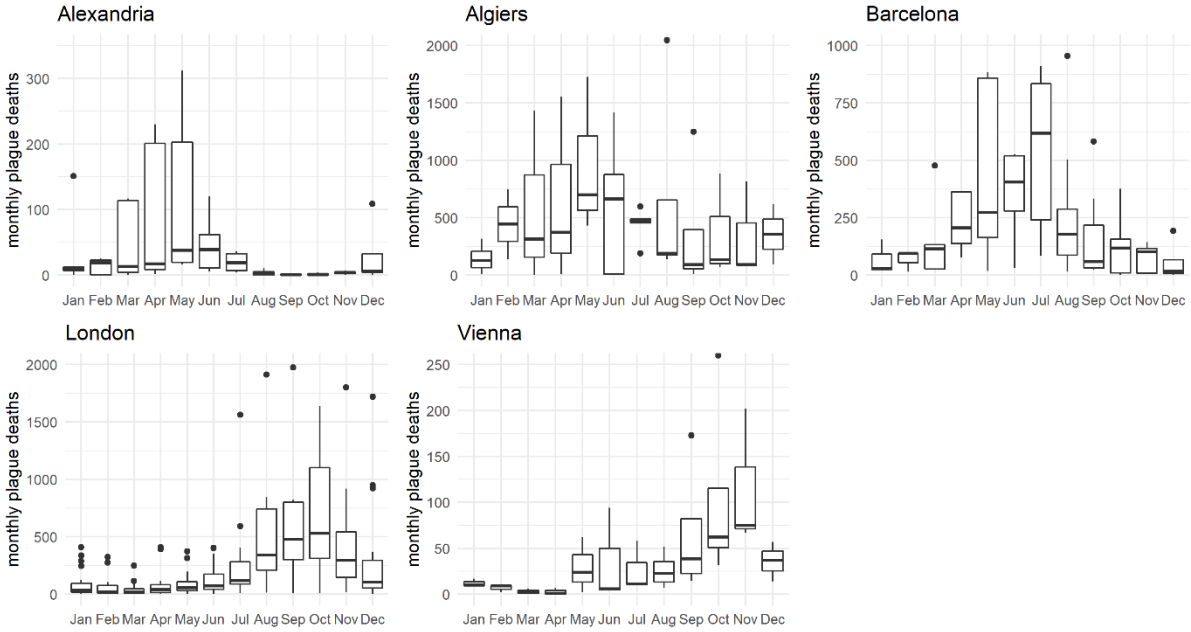

Figure 1. The distribution of plague deaths by months from all recorded plague years shows a distinct seasonality pattern for all five places with multiple outbreaks. The boxes encompass the 25th to 75th percentile, the whiskers extend to the maximum or to maximally to 1.5 times the interquartile range. The vertical lines denote the medians. Few outliers (dots) have been omitted from the plot for clarity.

Table 1. Results from a univariable GLM model with a negative binomial error structure. The incidence rate ratio (IRR, with 95% CI) is the increase in incidence rate compared to the baseline. The p-values are from an LR test comparing the model to a null model without seasonality.

Place	spring IRR [95% CI]	summer IRR [95% CI]	autumn IRR [95% CI]	p-value (LR test)
Alexandria	4.75 [1.7 - 12.54]	0.35 [0.12 - 0.95]	0.03 [0.01 - 0.11]	<0.001
Algiers	2.66 [0.82 - 8.47]	2.03 [0.67 - 5.58]	1.29 [0.4 - 3.94]	0.329
Barcelona	8.1 [3.31 - 18.61]	7.1 [3.07 - 14.88]	1.85 [0.77 - 4.09]	<0.001
London	0.44 [0.28 - 0.68]	4.66 [3 - 7.23]	10.66 [6.85 - 16.57]	<0.001
Vienna	0.63 [0.24 - 1.68]	1.57 [0.61 - 3.99]	5.11 [2.03 - 12.55]	<0.001

Influence of latitude, temperature and precipitation on the epidemic peak timing

The findings from the previous model not only suggest that historical plague showed a distinct seasonality, but also that the typical plague season differed by

latitude. We therefore investigated this aspect further by assessing the monthly percentage distribution of plague deaths for all places in our dataset. Figure 2 suggests a latitudinal gradient with a shift of the cases towards the end of the year for increasing latitude.

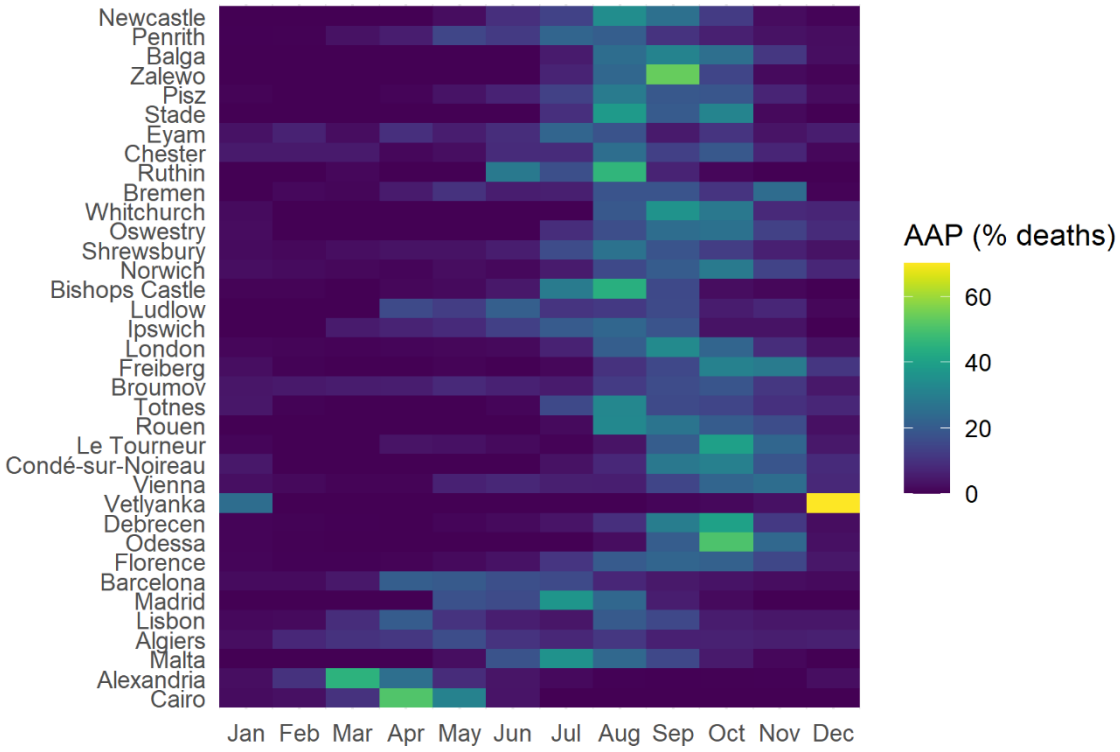

Figure 2. The annual average percentage (AAP) of monthly plague deaths sorted by latitude suggests a latitudinal gradient with a shift of epidemic activity towards the end of the year for increasing latitude. The northern places until Odessa cover an area between 45° and 55° N, the southern places encompass the latitudes 30° to 45° N.

Latitude alone may not explain the seasonality of plague mortality mechanistically, but it is a rough proxy measure for climatic conditions. We thus investigated the association between the seasonal epidemic peak timing and average, annual temperature and precipitation, respectively. For this, we used weekly plague mortality data from 65 outbreaks from 22 unique places, of which 73% had data for only one outbreak. A third of the outbreak data came from London. The median peak was observed at week 35 (range 11-52), which falls usually at the beginning of September (range mid-March to end December). Overall, we found a negative association between week of the year and annual temperature, and no association between week and precipitation (Figure 3). A decrease in average temperature of one degree Celsius delayed the epidemic peak by 1.4 weeks (β=-1.39, SE=0.232, $p<0.01$). Temperature was a significant predictor in the model, but overall the model explained only 44% of the variance in the data (R^2_{marg}=0.44).

Average annual precipitation was not associated with peak month (β=0.124, SE=0.130, p=0.34, R^2_{marg}=0.075) and did not improve the fit when added to the model with temperature (R^2_{marg}=0.43).

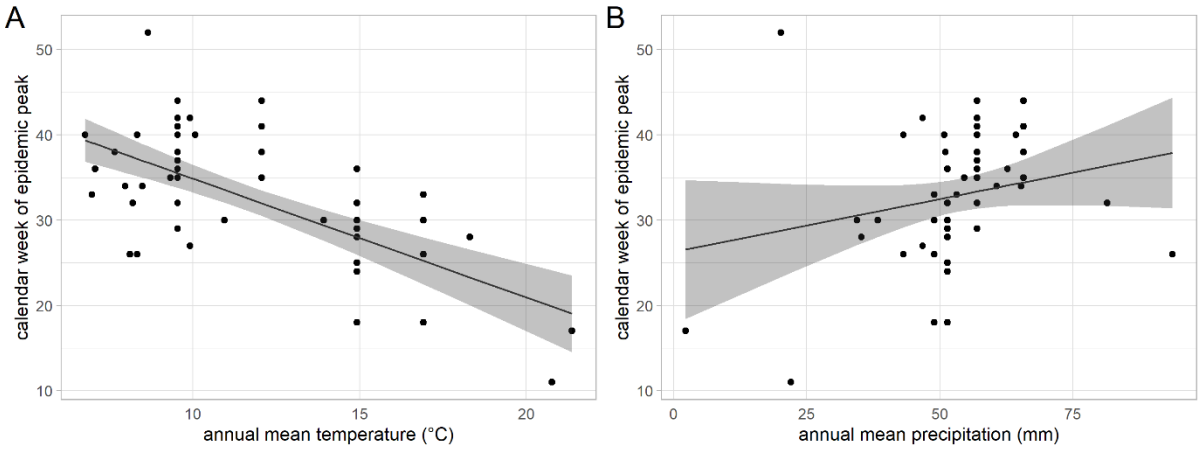

Figure 3. Association of annual mean temperature (A) and annual mean precipitation (B) with epidemic peak week. The bands show the 95% confidence intervals for the fit from a univariable, linear GEE model.

To investigate the robustness of our findings, we repeated the analysis including additional data points. As shown in Figure S4 the negative association between temperature and peak timing was confirmed when extending the dataset with monthly plague data (beta=-0.31, SE=0.03, R^2_{marg}=0.497), weekly all-cause mortality (beta=-1.33, SE=0.177, R^2_{marg}=0.429) and monthly all-cause mortality (beta=-0.286, SE=0.029, R^2_{marg}=0.43). Excluding smaller outbreaks with less than 100 deaths at the peak improved the model fit slightly (beta=-1.55, SE=0.22, R^2_{marg}=0.556). These results corroborate the finding that annual mean temperature had an effect on the peak timing of historical plague epidemics in Europe and the Mediterranean: The epidemic activity occurred later in the year as the mean temperature decreased and the latitude increased. Of note, the peaks represent the maximum mortality and not the maximum in epidemic activity. However, if we assume that the average time from infection to death was constant across all places and throughout the outbreaks, the epidemic peak is simply shifted to the left by a constant, which does not affect the results from the regression analysis.

Influence of temperature on the epidemic growth

Based on the finding that peak timing was associated with annual temperature (and its proxy latitude), we further investigated this aspect by examining the temperature-dependence of the epidemic growth rates. For this, we used the plague mortality data from 49 outbreaks (13 unique places) and estimated the instantaneous time-varying growth rates for each outbreak separately (Figure S5).

These calculated growth rates ranged from -0.097 to 0.098 with a median estimate of 0.02 for the increasing phases and -0.02 for the decreasing phases. We then explored the relationship of the instantaneous growth rates with the concurrent local temperature. The distribution of growth rates by temperature is noisy, but a non-linear relationship with unequal distributions for positive and negative growth rates was detectable (Figure 4A). The temperatures measured at the 13 places ranged from -3.8°C to 27.2°C, but no positive growth was observed below 4°C or above 26°C. The prediction from a GAMM model showed that this relationship takes the form of a single peak curve with a maximum at 17.3°C (Figure 4B). Positive growth was predicted only for temperature between 11.7°C (95% CI 9.8-13.4°C) and 21.5°C (95% CI 20.3-22.5°C). This model explained 28% of the variance in the data (R^2_{adj}=0.28). The model fit substantially better than a model without a AR1 correlated error structure (LR test p-value <0.0001).

We also conducted two separate sensitivity analyses for the effect of temperature on the growth rates by 1) including only large outbreaks with at least 500 weekly deaths at peak, and 2) omitting the data from London. The prior addresses the issue of imprecise measurements of the growth rates in small outbreaks due to random fluctuations in cases, the latter addresses the predominance of London in the dataset. Using only large outbreaks, the non-linear, unimodal relationship was still detectable (Figure S6A). The maximum growth was predicted marginally lower at 16.2°C, and the model fit marginally better than with the full dataset (R^2_{adj}=0.30). Fitting the model without the data from London still resulted in the same relationship between temperature and growth rates (Figure S6B) with a peak at 16.5°C. However, the variance explained was lower than in the model with the full dataset (R^2_{adj}=0.20). We also performed the same analysis with precipitation as a predictor of the time-varying growth rate and found a weak, unimodal association ($R^2_{adj=}$0.19) (Figure S7A). However, this association was driven entirely by the data from London; when we omitted these data points, there was no association between precipitation and the time-varying growth rate (R^2_{adj}=0.03, Fig. S7B). Model diagnostics showed that the residuals were approximately normally distributed and the variance was constant for all models.

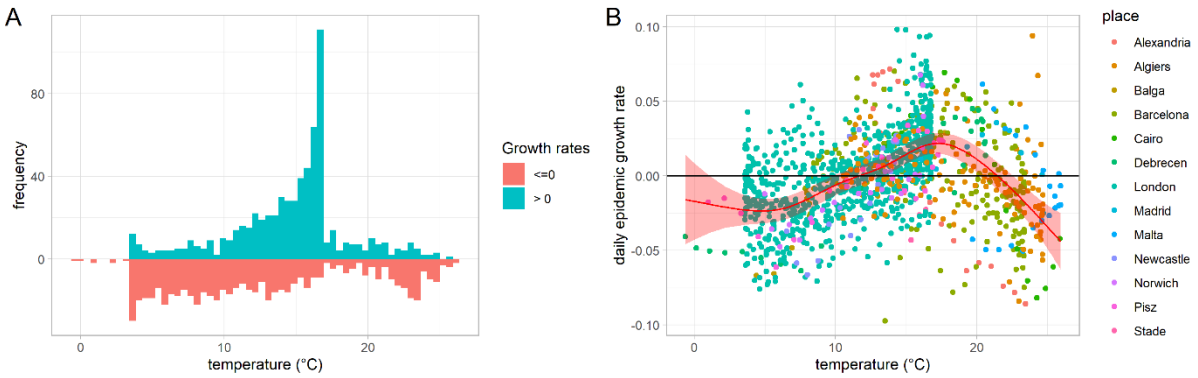

Figure 4. Distribution of predicted time-varying growth rates by temperature. (A) Histogram of positive (green) and zero or negative growth (red) and (B) scatter plot of time-varying growth rates for the full data set. The red line and ribbon indicate the fit and 95% CI from a univariable GAMM model. The maximum growth was predicted at 17.3°C.

Discussion

In this study, we investigated the epidemiological characteristics and the seasonality of pre-industrial plague outbreaks in Europe and the Mediterranean. We show that on average, an outbreak lasted for 9 months, caused a total of 1352 deaths with 429 deaths at peak month, and infected 11% of the population. The attack rate also depended on the population size: the larger the initial population size, the lower the attack rate. This suggests that there was a limiting factor that prevented large populations from being infected completely, unlike small populations which could be wiped out almost completely. We further show that places with repeated outbreaks had a consistent plague season and that epidemic peak timing followed a latitudinal gradient. This same gradient was also observed when modelling the annual mean temperature as a predictor: The colder the mean temperature and the more north a place, the later the epidemic peak occurred. Moreover, we show that the predicted epidemic growth of all outbreaks was positive between 11.7°C and 21.5°C with a maximum at 17.3°C. Hence, our study provides evidence that the growth of plague epidemics across the whole study region depended on similar absolute temperature thresholds. The minimum temperature threshold also explained the shift in peak timing with decreasing temperature (see Figure 3): the lower the annual mean temperature in place, the later in the year the threshold was reached (Pearson correlation coefficient -0.90, Figure S8) and thus the later in the year the epidemic peaks occurred. Overall, our findings from the different analyses provide consistent evidence for a temperature-related process that influenced the dynamics of pre-industrial plague outbreaks. Precipitation on the other hand seemed not associated with neither peak timing nor epidemic growth. This finding contradicts ecological studies, which show that

precipitation influences plague incidence among rodents through effects on vegetation, fleas and hosts (trophic cascade hypothesis) [28]. Because the inter-annual variation is generally larger for precipitation than for temperature, true effects may be concealed due to the use of modern, averaged precipitation data. The relationship between precipitation and epidemic peak timing may also not be linear as suggested by few outliers, but it was not possible to test this with the present data. We did not observe an effect of precipitation in our analysis, but we cannot exclude that precipitation played a role in addition to temperature.

Our findings warrant a closer investigation into potential mechanisms. Bubonic plague is linked to climate through the sensitivity of vectors and hosts to meteorological conditions [6, 8]. The mortality rates and development of various flea species are known to increase with rising temperatures leading to a characteristic seasonal abundance, but the favourable temperature ranges differ by flea species [29]. For some flea species the microclimate in the fur or the burrow of their host may play a larger role than the air temperature [30]. Moreover, the plague bacterium, *Yersinia pestis*, was shown to be transmitted from fleas to rodents at temperatures ranging from 23°C to 30°C but not at 10°C [31]. Nowadays, bubonic plague transmission in humans happens mainly at the interface between the human population and wildlife and its temperature dependence is thus mainly due to the temperature sensitivity of the wildlife plague system. For second pandemic outbreaks, there is an ongoing debate about which vectors and rodent hosts or reservoirs were present in Europe and which transmission routes dominated the spread [32-34]. The involvement of human ectoparasites, such as human fleas, has been hypothesised [34]. However, the influence of temperature on human ectoparasites and the resulting effect on plague in humans has not been studied. Another potential mechanism is the influence of temperature on human-to-human transmission of pneumonic plague. The main driver of primary pneumonic transmission seems to be close contact between infectee and infector during the final stage of the disease [35], which is why pneumonic outbreaks are usually small. The contribution of climatic conditions to pneumonic transmission has not been studied systematically. However, the occurrence of pneumonic outbreaks in many geographically and climatically diverse places such as Madagascar in August to September ([36] average temperature 15-20°C), Manchuria in December to January ([37], average temperature around -10°C) or Rangoon (Myanmar) in September ([38], average temperature 25-30°C) suggests that the suitable temperature range is very large, and that other factors such as crowding and the influx of susceptibles may be more influential. Of note, the outbreak in Vetlyanka in our dataset had a large proportion of cases with pneumonia. Interestingly, the peak occurred about two months later than what we would expect given the geographical location (see Figure 2). This observation may

support the hypothesis that outbreaks of substantial or complete pneumonic nature are not as dependent on temperature as vector-borne plague.

Temperature did not fully explain the variance in our data, and additional factors or alternative explanations for the plague seasonality must be considered. The growth and decline of human plague outbreaks commonly depends on a disease introduction event in the human population, the level of susceptibility in the human population and the availability of and contacts with vectors. The latter may additionally be influenced by other meteorological factors such as relative humidity or vapour pressure [6], which we have not considered here given the lack of association with precipitation. These measures exhibit large inter-annual variation, and their contribution is better modelled with contemporaneous meteorological data instead of modern, averaged data. The use of averaged data may also affect the association between temperature and epidemic peak timing and growth. As we show, the historical temperatures differed up to a few degrees (Text S2, Figure S9), and our results are thus an approximation of the general, meteorological process. The use of contemporaneous temperature data would allow to take into account inter-annual variation in the seasonal temperature, which might explain a larger proportion of the variance in peak timing and growth rates. The occurrence of plague outbreaks in Europe during the second and third pandemic has also been linked to maritime trade activities to explain outbreaks in the absence of permanent local plague reservoirs [20, 39]. Ship trade in pre-industrial times was highly seasonal due to weather conditions and seasonal availability of commodity. However, favourable local conditions are a prerequisite for an outbreak to grow beyond a few dozen cases after disease introduction (irrespective of the assumption about the transmission routes). Most of the data in our analysis are from large epidemics with hundreds of casualties, thus conditions must have been suitable for transmission. Hence, disease introduction is a necessary but not a sufficient condition for the establishment of an outbreak. In fact, during the third pandemic, only around 5% disease introductions in Europe through maritime trade activities led to the establishment of a sizeable outbreak with more than 20 cases (see supplement in [39]). This suggests that the local conditions were not conducive of epidemic growth or that mitigation strategies were very successful.

Other factors such as the fluctuation of susceptibles due to population immunity and demographic turnover of the human population are also known to influence the periodicity of some infectious diseases. This periodicity arises mostly in directly transmitted childhood diseases, where the interplay of population immunity and replenishment of susceptibles through births leads to an endemic-epidemic cycle [40]. However, plague is a highly fatal disease and many of these

outbreaks were several years to decades apart. The increase in immune hosts over time may have been counteracted by the rapid natural population turnover due to a short lifespan and a high birth rate. Thus, we expect that population immunity played only a minor role in the periodicity of most of these outbreaks. Seasonal human behaviour such as harvesting may periodically increase the contact between humans and wildlife, and may lead to seasonal plague outbreaks as observed in Argentina [41]. However, this would require the existence of plague reservoirs all over Europe, which is debatable. Finally, reporting errors in plague mortality may influence the peak timing and growth rates. The extent of missing plague deaths and the effect on our analysis is difficult to assess in the absence of contemporaneous all-cause mortality data. We expect underreporting of deaths to be an issue mostly for very large epidemics with several hundred casualties per week. Particularly in London, a systematic undercounting of plague deaths was reported [42]. However, constant underreporting does not affect the estimation of the growth rate or the peak timing even if the absolute death counts are false.

Data from outbreaks not included in our study confirms our findings. The last large outbreak in Porto started in June 1899, but the incidence started to increase rapidly only in the second half of September with a peak mid-October [43]. The average temperature oscillated between 20 and 25°C but dropped below 20°C in mid-September when the cases started to increase. The last large plague outbreak globally happened in 2017 in Madagascar [44]. It started in August with few incident cases and increased rapidly towards the end of September with a peak in bubonic cases at the beginning of October when the temperature was favourable for the plague vectors [45]. Of note, 75% of the cases were pneumonic plague, which is an extraordinary large proportion. A recently published study of a large epidemic in Venice in 1630/31 [46] showed that the peak mortality occurred approximately at the end of October (around calendar week 44), which is well within the range of our data for places with a comparable annual mean temperature (12.6°C). The largest expected epidemic growth seems to have occurred at the beginning of September, when the predicted temperature decreased below 20°C (according to the CRU data), which also agrees well with our model prediction. Not all plague outbreaks show a similar temperature threshold behavior. Third pandemic outbreaks in Bombay usually grew rapidly in December to January and peaked in February to April [10, 18]. The average CRU temperature in Bombay drops below 25°C in December and January and rises again above 25°C in March. While this example shows that a favourable temperature and thus a seasonal pattern range exists also for outbreaks in India, the absolute temperature range is somewhat higher than what we found. As shown in a recent study, humidity may have been a larger driver of the seasonality in India than absolute temperature [11].

As with modern plague outbreaks, we argue that local, climatic conditions that acted on the abundance of vectors (and other hosts) were drivers of historical plague seasonality. Further entomological and epidemiological research is needed to investigate the influence of temperature and other meteorological factors on the abundance of various plague vectors. Uncovering the underlying mechanisms of the plague seasonality that we document here will strengthen our understanding of historical and modern plague transmission.

Funding

This work was supported by funding from the Centre for Ecological and Evolutionary Synthesis (CEES), University of Oslo, and the Research Council of Norway (FRIMEDBIO project 288551).

Ethics statement

Not applicable.

Data accessibility statement

The R code and the plague and all-cause mortality dataset is available in a public repository (http://doi.org/10.5281/zenodo.4240204) [21]. The CRU TS 4.03 dataset [22] is available at https://catalogue.ceda.ac.uk/uuid/10d3e3640f004c578403419aac167d82.

Competing interests statement

We declare we have no competing interests.

Authors' contributions statement

F.K. conceived and designed the study; F.K. and K.R.D collected and compiled the data; F.K. performed the analysis; K.R.D., F.K. and H.V. interpreted the results; F.K. wrote the paper with input from K.R.D. and H.V. All authors gave final approval for publication.

Acknowledgments

We thank everyone who helped with finding data or who contributed their own data: The staff at the Science Library (Realfagsbiblioteket) of the University of Oslo, Krásenská Klára (National Library of the Czech Republic), Dr. Daniel Curtis (University of Rotterdam), Filomena Rodrigues (Associação Portuguesa de Demografia), Marie Prusova (Czech Statistical Office).

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Supplemental material for

The influence of temperature on the seasonality of historical plague outbreaks

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Table S1. Search strategies for the systematic search of literature containing plague mortality data

Source	Search terms / Restrictions
Jstor	((plague OR Pest OR peste) AND (epidemi* OR mortalit*) AND (histori*) NOT (India OR Indien OR Madagas*ar OR China OR Mongolia OR Kazakhstan OR United States OR Ameri*a OR Bra*il* OR Argentin* OR Afri*a OR Australi* OR Iran OR Hongkong OR Persi*)) Subjects: Agriculture, Anthropology, Aquatic Sciences, Archaeology, Bibliography, Biological Sciences, Botany & Plant Sciences, British Studies, Classical Studies, Cultural Studies, Development Studies, Ecology & Evolutionary Biology, Economics, Environmental Studies, Environmental Science, European Studies, General Science, Geography, Health Policy, Health Sciences, History, History of Science & Technology, Mathematics, Middle East Studies, Museum Studies, Population Studies, Public Health, Public Policy & Administration, Science & Technology Studies, Statistics, Technology, Urban Studies, Zoology Type: research-article
Pubmed	(plague OR Pest OR peste) AND (epidemi* OR mortalit*) AND (histori*) NOT (India OR Indien OR Madagas*ar OR China OR Mongolia OR Kazakhstan OR United States OR Ameri*a OR Bra*il* OR Argentin* OR Afri*a OR Australi* OR Iran OR Hongkong OR Persi*)
Internet Archive	-title:(India) AND -title:(Indien) AND -title:(Bombay) AND -title:(Ameri*a) AND -title:(Madagas*ar) AND -title:(Persi*) AND -title:(Hongkong) AND -title:(Hong Kong) AND -title:(China) AND -title:(Mesopotamie*) AND -collection:(jstor_publhealrepo1896) AND mediatype:(texts) AND -collection:(inlibrary) AND -collection:(dticarchive) AND ((plague OR Pest OR peste) AND (epidemi* OR mortalit*))

Text S1. Description of data collection

For the establishment of a novel dataset of plague outbreaks, we used a combination of systematic and opportunistic literature search. We systematically searched three major literature databases (jstor, pubmed and the internet archive). We also opportunistically searched a number of selected monographs on plague. We then screened the title (and abstracts if available) of all returned search results and decided for each result whether to screen the full text. From the screened full texts, we extracted all tables, lists and graphs that provided information on plague- or all-cause mortality at a monthly or higher temporal resolution. We extracted the data manually or using WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/) and generated one dataset per plague epidemic.

Table S2. Number of publications retrieved, screened and included from different databases and sources.

Database	N retrieved	N included after title/abstract screening	N included after full text screening
Pubmed	473	117	6
Jstor	1611	81	1
Archive.org	366	48	2
Opportunistic	36	36	36
Total	2486	282	45

Table S3. Metadata of all included datasets. Mortality indicates whether the data are plague specific deaths or all-cause burials or deaths. Interval denotes the time step of the data collection. Source type indicates whether the data were digitized from a graph or a table/list. Values denotes whether the data are counts (deaths) or proportions/percentages. In the latter case, the data were only used for the assessment of the epidemic peak. Data ref gives the literature reference for the mortality data (and the population size if from a different source).

id	country	place	start	end	mortality	interval	calendar	source	value	data ref
1	Syria	Aleppo	1761	1762	all-cause	weekly	jul	t	n	[1]
2	Egypt	Alexandria[1]	1834	1835	plague	daily	greg	t	n	[2]
3	Egypt	Alexandria	1836	1837	plague	monthly	greg	t	n	[2]
4	Egypt	Alexandria	1838		plague	monthly	greg	t	n	[2]
5	Egypt	Alexandria	1840		plague	monthly	greg	t	n	[3]
6	Egypt	Alexandria	1840	1841	plague	monthly	greg	t	n	[3]
7	Egypt	Alexandria	1842	1843	plague	monthly	greg	t	n	[3]
8	Egypt	Alexandria	1842		plague	monthly	greg	t	n	[3]
9	Algeria	Algiers	1817	1819	plague	daily	greg	t	n	[4] ([5])
10	Algeria	Algiers	1821		plague	daily	greg	t	n	[4] ([5])
11	Algeria	Algiers	1822		plague	daily	greg	t	n	[4] ([5])
12	Italy	Arezzo	1390		all-cause	monthly	jul	g	n	[6]
13	Denmark	Asminderød	1711		all-cause	weekly	greg	g	n	[7]
14	Russia	Balga[2]	1710		plague	weekly	greg	t	n	[8]
15	Spain	Barcelona	1457		plague	daily	jul	t	n	[9], ([10])
16	Spain	Barcelona	1475	1476	plague	daily	jul	t	n	[9], ([10])
17	Spain	Barcelona	1483		plague	daily	jul	t	n	[9], ([10])
18	Spain	Barcelona	1489	1490	plague	daily	jul	t	n	[9], ([10])
19	Spain	Barcelona	1494		plague	daily	jul	t	n	[9], ([10])
20	Spain	Barcelona	1501		plague	daily	jul	t	n	[9], ([10])
21	Spain	Barcelona	1515		plague	daily	jul	t	n	[9], ([10])
22	Spain	Barcelona	1520		plague	daily	jul	t	n	[9], ([10])
23	Spain	Barcelona	1530		plague	daily	jul	t	n	[9], ([10])
24	Spain	Barcelona	1558		plague	daily	jul	t	n	[9], ([10])
25	Spain	Barcelona[3]	1589		plague	daily	greg	t	n	[9], ([10])
26	Denmark	Birkerød	1711		all-cause	weekly	greg	g	n	[7]
27	UK	Bishops	1593		plague	monthly	jul	g	n	[11]
28	Germany	Bremen	1713		plague	monthly	greg	g	n	[7]
29	Denmark	Brønshøj	1711		all-cause	weekly	greg	g	n	[7]
30	Czech	Broumov	1632	1635	plague	monthly	greg	t	n	[12]
31	Egypt	Cairo	1801		all-cause	daily	greg	t	n	[13]
32	Egypt	Cairo	1835		plague	daily	greg	t	n	[14]
33	UK	Chester[2]	1604	1604	plague	monthly	greg	g	n	[15]
34	UK	Chesterfield	1586	1587	all-cause	monthly	jul	g	n	[11]
35	UK	Colchester[3]	1665	1666	plague	weekly	jul	g	n	[11]
36	France	Condé-sur-	1626	1627	plague	monthly	greg	t	n	[16]
37	Denmark	Copenhagen	1711		all-cause	weekly	greg	g	n	[7]
38	Hungary	Debrecen	1739	1740	plague	daily	greg	t	n	[17]
39	Denmark	Ejby	1711		all-cause	weekly	greg	g	n	[7]
40	Denmark	Esbønderup	1711		all-cause	weekly	greg	g	n	[7]
41	UK	Eyam	1665	1666	plague	daily	jul	t	n	[18]
42	Italy	Florence	1400		all-cause	daily	jul	g	n	[19]
43	Italy	Florence	1424[4]		plague	daily	jul	g	p	[19]
44	Italy	Florence	1430[4]		plague	daily	jul	g	p	[19]
45	Italy	Florence	1450[4]		plague	daily	jul	g	p	[19]
46	Italy	Florence	1456[4]	1457	plague	daily	jul	g	p	[19]
47	Germany	Freiberg	1613	1614	plague	biweekly	greg	g	n	[20]
48	Poland	Gdansk	1709		all-cause	weekly	greg	g	n	[7]
49	France	Givry	1348		all-cause	daily	jul	t	n	[21]
50	Germany	Halberstadt	1681	1682	all-cause	monthly	greg	t	n	[22]

51	Germany	Halle	1682		all-cause	monthly	greg	t	n	[22]
52	Denmark	Helsingør	1711		all-cause	weekly	greg	g	n	[7]
53	Denmark	Herfølge	1711		all-cause	weekly	greg	g	n	[7]
54	UK	Ipswich	1665	1666	plague	monthly	jul	g	n	[11]
55	Russia	Kaliningrad	1620		all-cause	weekly	greg	t	n	[8]
56	Russia	Kaliningrad	1709	1710	all-cause	weekly	greg	t	n	[8]
57	Denmark	Kildebrønde	1711		all-cause	weekly	greg	g	n	[7]
58	Lithuania	Klaipeda[2,3]	1710		plague	weekly	greg	t	n	[8]
59	Denmark	Køge	1711		all-cause	weekly	greg	g	n	[7]
60	France	Le Tourneur	1635		plague	monthly	greg	t	n	[16]
61	Denmark	Ledøje	1711		all-cause	weekly	greg	g	n	[7]
62	UK	Leeds[3]	1645		plague	weekly	jul	t	n	[23]
63	Netherland	Leiden	1624	1625	all-cause	daily	greg	t	n	[24]
64	Netherland	Leiden	1635		all-cause	daily	greg	t	n	[24]
65	Netherland	Leiden	1655		all-cause	daily	greg	t	n	[24]
66	Netherland	Leiden	1664		all-cause	daily	greg	t	n	[24]
67	Portugal	Lisbon	1569		plague	monthly	greg	g	p	[25]
68	Portugal	Lisbon	1579	1580	plague	monthly	greg	g	p	[25]
69	UK	London	1563	1564	plague	weekly	jul	t	n	[26], ([27])
70	UK	London	1578	1582	plague	weekly	jul	t	n	[26], ([27])
71	UK	London	1593		plague	weekly	jul	t	n	[28], ([27])
72	UK	London	1603		plague	weekly	jul	t	n	[26], ([27])
73	UK	London	1605	1610	plague	weekly	jul	t	n	[28], ([27])
74	UK	London	1625	1626	plague	weekly	jul	t	n	[28], ([27])
75	UK	London	1630		plague	weekly	jul	t	n	[28], ([27])
76	UK	London	1636	1637	plague	weekly	jul	t	n	[28], ([27])
77	UK	London	1639	1647	plague	weekly	jul	t	n	[28], ([27])
78	UK	London	1665		plague	weekly	jul	t	n	[28], ([27])
79	UK	Ludlow	1609		plague	monthly	jul	g	n	[11]
80	Spain	Madrid	1599		plague	weekly	greg	g	n	[29]
81	Germany	Magdeburg	1681		all-cause	monthly	greg	t	n	[22]
82	Malta	Malta	1813		plague	daily	greg	t	n	[30]
83	Switzerlan	Malters	1628	1630	all-cause	monthly	greg	g	n	[31]
84	UK	Manchester	1605		all-cause	daily	jul	t	n	[32]
85	UK	Manchester	1645		all-cause	monthly	jul	g	n	[33]
86	Russia	Moscow	1771		all-cause	daily	jul	g	n	[34]
87	Germany	Mühlhausen	1683		all-cause	monthly	greg	t	n	[22]
88	Denmark	Nakskov	1619	1620	all-cause	monthly	jul	g	n	[35]
89	UK	Newcastle	1636		plague	weekly	jul	t	n	[36]
90	Estonia	Noarootsi	1710	1711	all-cause	weekly	greg	g	n	[7]
91	Italy	Nonantola	1630		all-cause	weekly	greg	g	n	[37]
92	Germany	Nordhausen	1682	1683	all-cause	monthly	greg	t	n	[22]
93	UK	Norwich	1603	1604	plague	monthly	greg	g	n	[38]
94	UK	Norwich	1666		plague	weekly	jul	t	n	[39]
95	Ukraine	Odessa	1812		plague	monthly	jul	t	n	[40]
96	UK	Oswestry	1559	1560	plague	monthly	jul	g	n	[11]
97	Italy	Parma	1630		all-cause	monthly	greg	t	n	[41]
98	UK	Penrith	1597	1598	plague	monthly	greg	g	n	[15]
99	Poland	Pisz[2]	1710		plague	weekly	greg	t	n	[8]
10	Czech	Prague[3]	1680	1681	plague	weekly	greg	t	n	[42]
10	Czech	Prague[3]	1713	1714	plague	daily	greg	t	n	[43]
10	UK	Preston	1630	1631	all-cause	monthly	jul	g	n	[11]
10	Estonia	Reval	1710		all-cause	monthly	greg	g	n	[7]
10	Denmark	Roskilde	1711		all-cause	weekly	greg	g	n	[7]
10	France	Rouen	1668		plague	monthly	greg	t	n	[16]
10	UK	Ruthin	1349		plague	monthly	jul	g	n	[11]
10	UK	Shrewsbury	1650	1651	plague	monthly	jul	g	n	[11]
10	Germany	Stade	1712		plague	weekly	greg	g	n	[7]
10	Sweden	Stockholm	1710	1711	all-cause	weekly	greg	g	n	[7]
11	Denmark	Store	1711		all-cause	weekly	greg	g	n	[7]
11	Denmark	Stralsund	1710	1711	all-cause	monthly	greg	g	n	[7]

11	UK	Stratford-	1564	1565	all-cause	monthly	greg	g	n	[15]
11	Denmark	Tårnby	1711		all-cause	weekly	greg	g	n	[7]
11	Denmark	Tikøb	1711		all-cause	weekly	greg	g	n	[7]
11	Lithuania	Tilsit[3]	1710		plague	weekly	greg	t	n	[8]
11	UK	Totnes	1570		plague	monthly	jul	g	n	[11]
11	UK	Totnes	1590		plague	monthly	jul	t	n	[26]
11	Germany	Uelzen	1566		all-cause	weekly	jul	g	n	[44]
11	Germany	Uelzen	1597		all-cause	weekly	greg	g	n	[44]
12	Germany	Uelzen	1626		all-cause	weekly	greg	g	n	[44]
12	Germany	Uelzen	1627		all-cause	weekly	greg	g	n	[44]
12	Spain	Valladolid[3]	1599		plague	weekly	greg	g	n	[29]
12	Russia	Vetlyanka	1878	1879	plague	daily	jul	g	n	[45]
12	Spain	Vic	1361	1362	all-cause	monthly	jul	t	n	[46]
12	Spain	Vic	1371		all-cause	monthly	jul	t	n	[46]
12	Austria	Vienna	1653	1656	plague	monthly	greg	t	n	[47], ([48])
12	Austria	Vienna	1679		all-cause	monthly	greg	t	n	[49], ([48])
12	Poland	Warsaw	1708		all-cause	weekly	greg	g	n	[7]
12	UK	Whitchurch	1650	1651	plague	monthly	jul	g	n	[11]
13	Poland	Zalewo[2]	1710		plague	monthly	greg	t	n	[8]

Abbreviations: jul=julian, greg=gregorian, t=table, g=graph, n=numbers (counts), p=proportion
1 some days in April 1835 in the original data seem to lack the 100 digit, which has been added in our data set
2 the number for the population size was approximated as the number of hearths/households given in the reference times six persons per household
3 incomplete epidemiological curve (beginning and/or end missing)
4 The y-axis of the original graph indicates number of daily deaths, but the occurrence of numbers smaller than one suggest that the data were interpolated. We therefore converted the curve to proportions

Table S4. Characteristics of datasets included in the main analysis (plague mortality) and the sensitivity analysis (plague and all-cause mortality)

	Plague mortality	All-cause mortality	Total
Yearly peaks, N	100	57	157
Time interval, N			
Daily	25 (32.8)	9 (16.7)	34 (26.2)
Weekly	22 (28.9)	27 (50)	49 (37.7)
Biweekly	1 (1.3)	0 (0)	1 (0.8)
Monthly	28 (36.8)	18 (33.3)	46 (35.4)
Unique locations, N	42	45	87
Century, N (%)			
14^{th}	1 (1.3)	4 (7.4)	5 (3.8)
15^{th}	9 (11.8)	1 (1.9)	10 (7.7)
16^{th}	18 (23.7)	4 (7.4)	22 (16.9)
17^{th}	25 (32.9)	20 (37)	45 (34.6)
18^{th}	9 (11.8)	24 (44.4)	33 (25.4)
19^{th}	14 (18.5)	1 (1.9)	15 (11.5)

Figure S1. Map of the number of available datasets by location and data type.

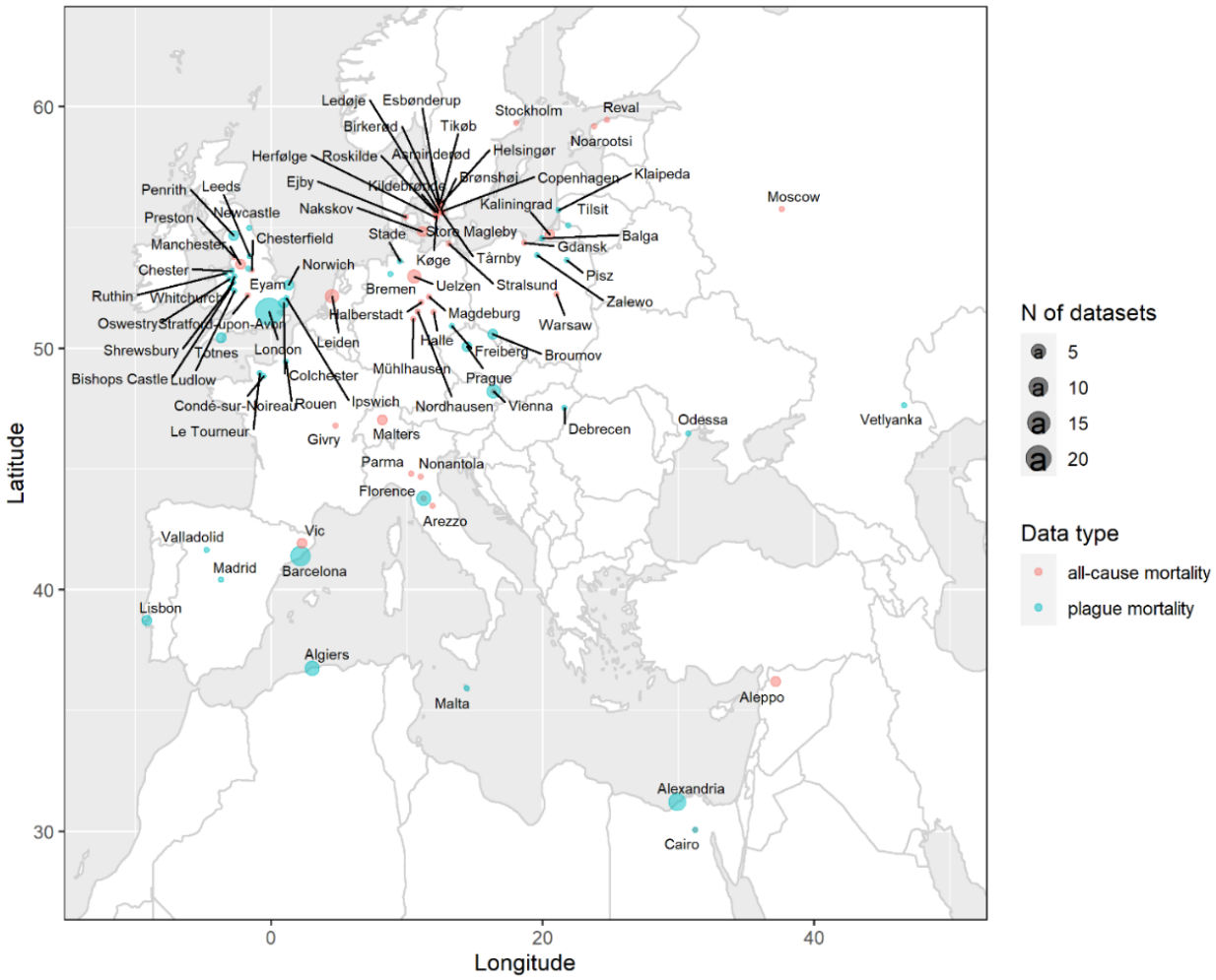


Figure S2. Incident plague (red bars) and all-cause deaths (blue bars) from all the datasets in the analysis

Figure S2 continued. Incident plague (red bars) and all-cause deaths (blue bars) from all the datasets in the analysis

Figure S2 continued. Incident plague (red bars) and all-cause deaths (blue bars) from all the datasets in the analysis

Figure S3. Association of the attack rate (i.e. the estimated proportion of the initial population infected at the end of the epidemic) with the initial population size.

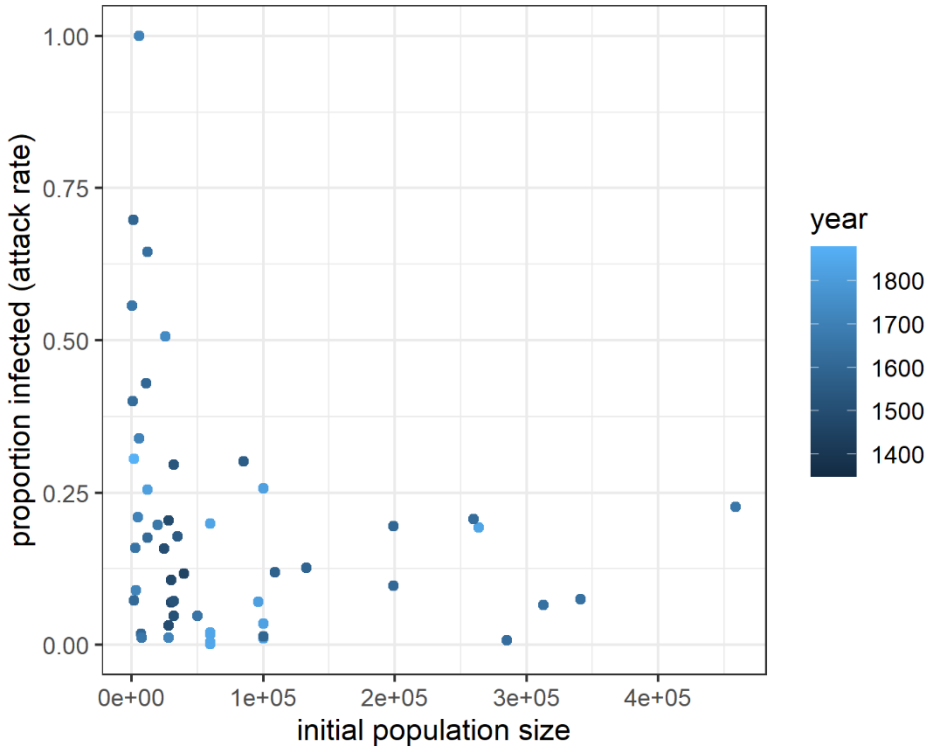


Figure S4. Results of the sensitivity analysis on the association between annual mean temperature and epidemic peak timing using different datasets. (A) monthly plague data, (B) weekly plague and all-cause mortality data during plague outbreaks, (C) monthly plague and all-cause mortality data during plague outbreaks and (D) weekly plague deaths from outbreaks with at least 100 deaths at peak. The line and the shaded areas represent the fit and 95% CI.

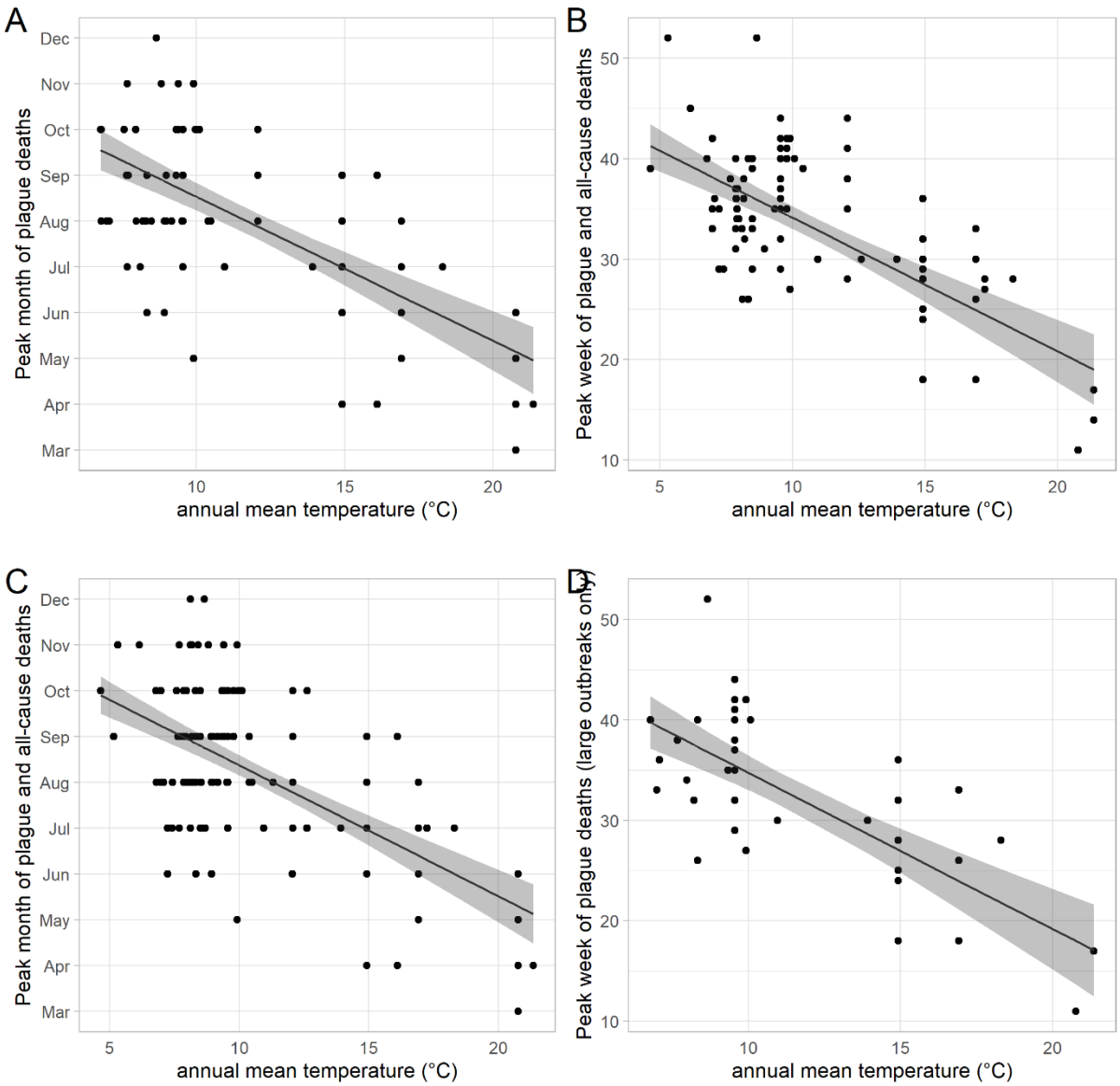


Figure S5. Epidemiological curves and the corresponding time-varying growth rates. The dark grey bars represent the incident plague mortality, the light grey bars represent the incident plague cases calculated from the mortality data. The red line and pink ribbon are the mean estimate and 95% CI for the time-varying epidemic growth rate calculate based on the incident case data (right y-axis). Values below 0 indicate no growth (i.e. a decline of the epidemic). The values on the right y-axis represent the daily growth rate.

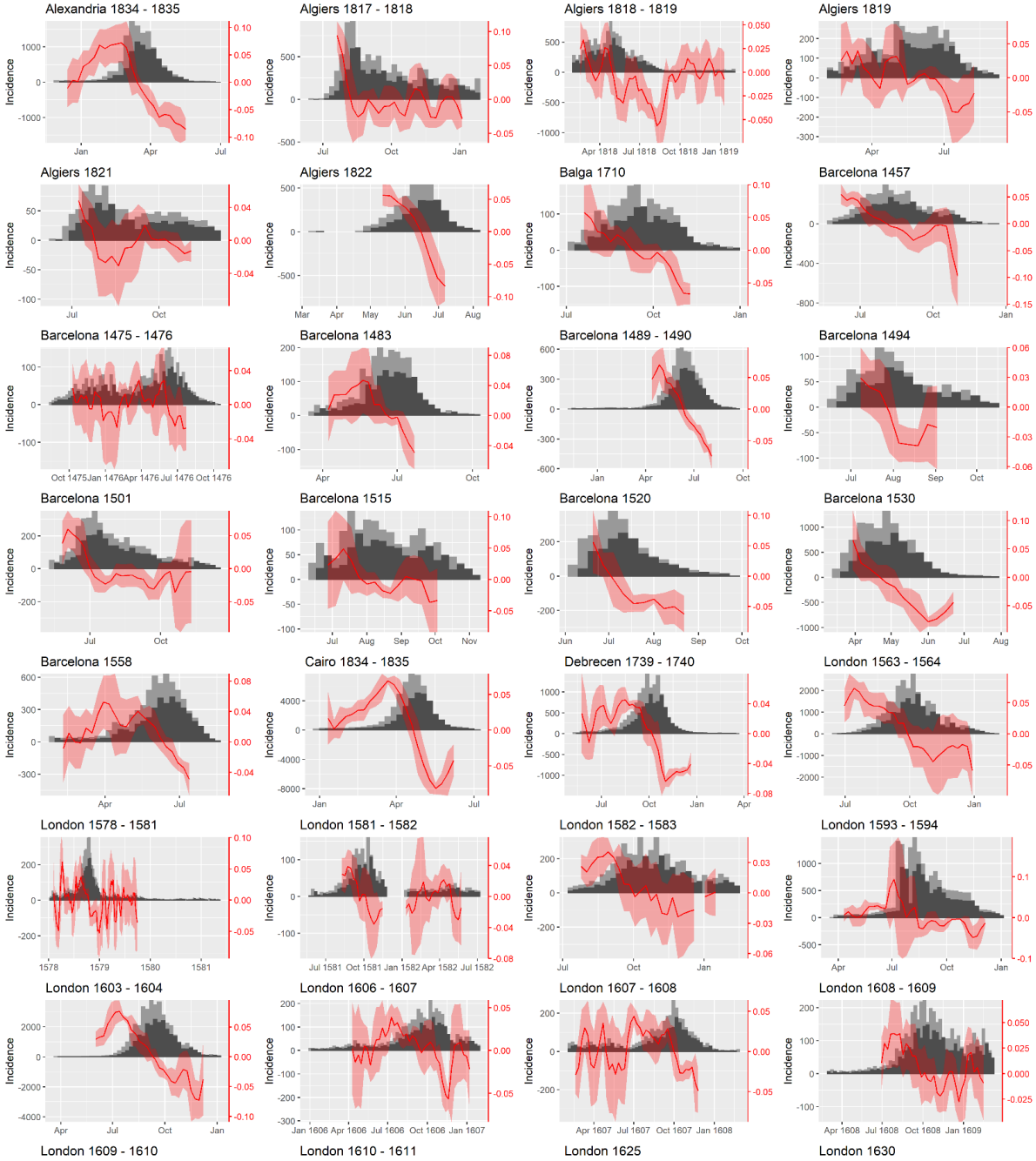


Figure S5 continued. Epidemiological curves and the corresponding time-varying growth rates. The dark grey bars represent the incident plague mortality, the light grey bars represent the incident plague cases calculated from the mortality data. The red line and pink ribbon are the mean estimate and 95% CI for the time-varying epidemic growth rate calculate based on the incident case data (right y-axis). Values below 0 indicate no growth (i.e. a decline of the epidemic). The values on the right y-axis represent the daily growth rate.

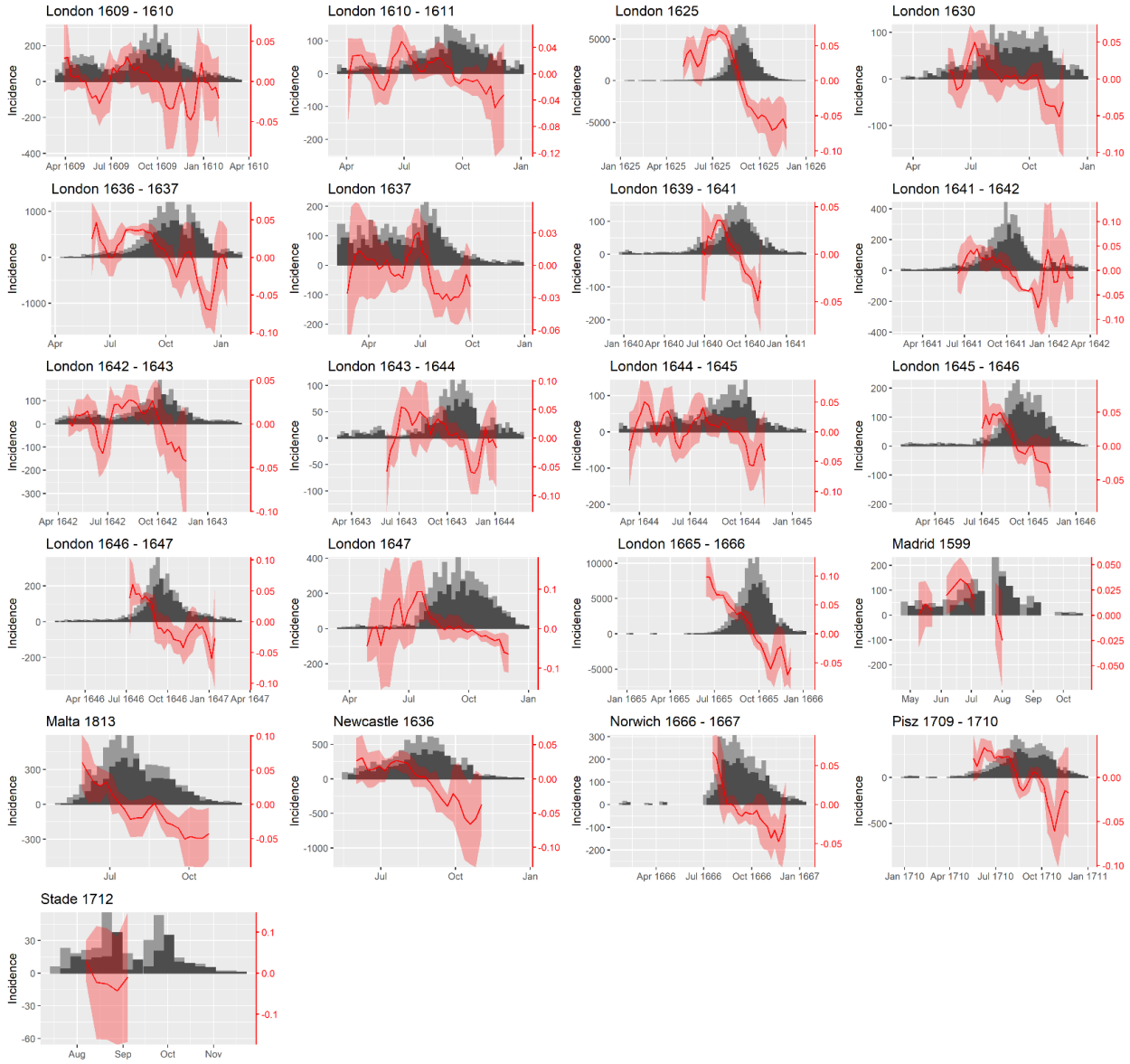


Figure S6. Results from the sensitivity analysis for the association of the time-varying growth rates and temperature. The red line and pink ribbon is the mean and 95% CI of the GAMM model prediction. (A) Prediction based on a subset of large outbreaks (at least 500 cases at peak), (B) prediction based on dataset omitting observations from London.

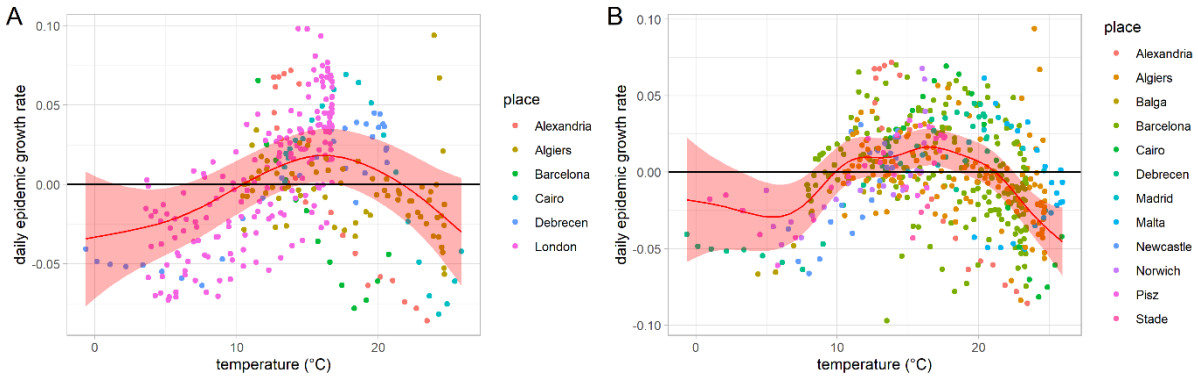


Figure S7. Association of growth rates with precipitation. The red line and pink ribbon is the mean and 95% CI of the GAMM model prediction. (A) Prediction based on the full dataset, (B) prediction based on a dataset omitting observations from London.

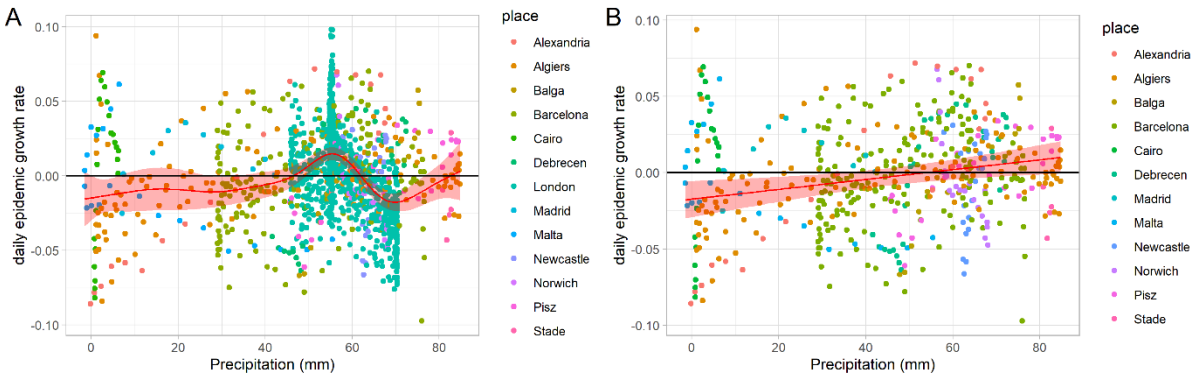
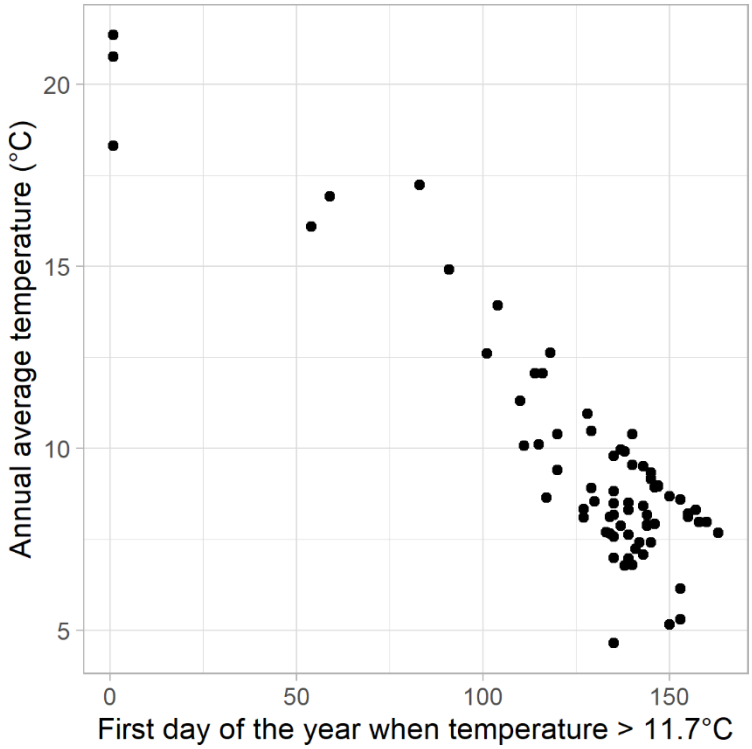


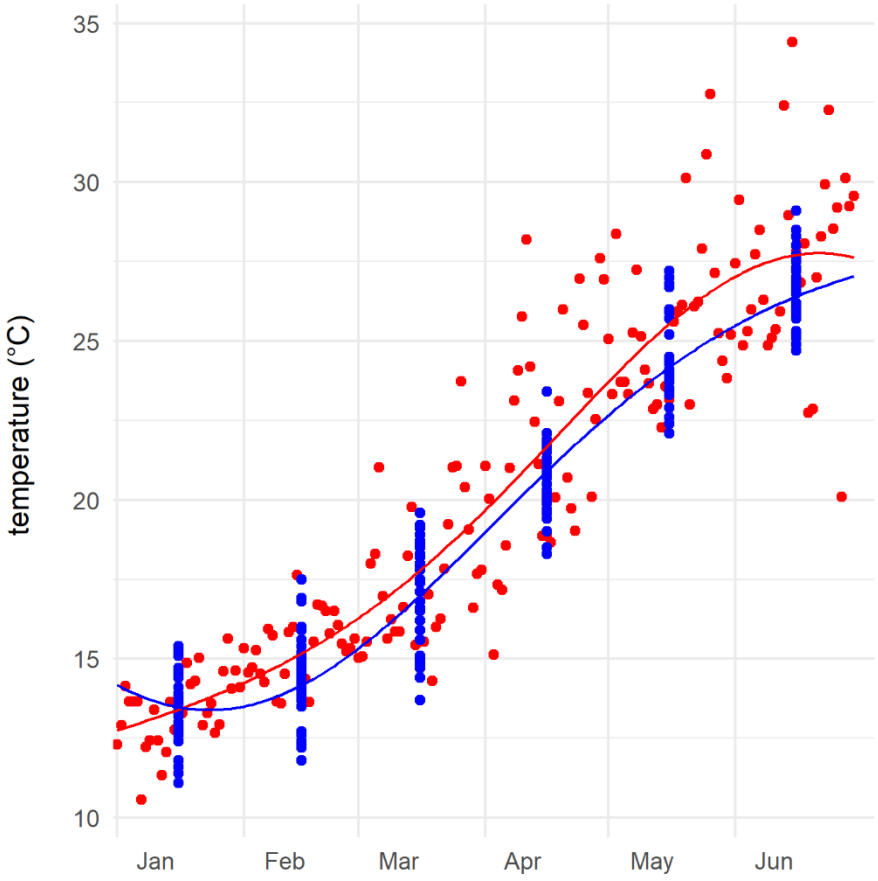
Figure S8. Correlation of the threshold time for epidemic growth and the average, annual temperature.



Text S2. Assessment of discrepancy between historical and modern temperature data

We sought to address the limitation of using modern, averaged temperature data instead of concurrent historical data. Due to the scarcity of historical meteorological data during outbreaks, we were able to find only one set of temperature measurements, which was recorded during the 1835 outbreak in Cairo together with the plague mortality [14]. The data consist of three daily recordings at 6 am, 2 pm and 10 pm made from January to June 1835. We averaged the three measurements for each day and fitted the same Fourier series model (see main text) to the historical data. As shown in Fig. S7, the predicted temperature from the CRU series was lower than the predicted temperature from the historical series (median difference 0.9 °C, range -1.4 to 1.5°C). The difference appeared to be systematic except for the beginning of January, where the historical data temperatures are lower than the modern ones. Of note, the historical measurements lack a recording during the night, when temperature was presumably lowest, which means that the calculated averages and thus the difference to the CRU time series, which are based on modern weather stations with continuous readings, might be slightly lower. This comparison shows that the difference between averaged modern temperatures and averaged historical temperatures may be up to several degrees.

Figure S9: Difference between daily averaged historical temperature (red dots) and the corresponding fit (red line) recorded during the plague outbreak in 1835 and the monthly averaged temperature measurements (blue dots) and the corresponding fit (blue) for the CRU time series data (1901-1939).



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Paper II

Paper III

Paper IV