# Modeling plague transmission in Medieval European cities

by

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## Abstract

The Black Death pandemic swept through Europe during the Middle Ages leading to high mortality from plague, caused by the bacterium Yersinia pestis. How it spread, the transmission of the disease within and between cities, remains a subject of controversy among scientists and historians. Prior to the identification of the bacterium in medieval tooth samples, the nature of the pandemic led to speculation that the Black Death was not the same disease as current-day plague. In the classical mode of transmission to humans, black rats act as an intermediate host and the disease spreads by infected rat fleas. But in the case of Black Death, alternate modes have been proposed in which the disease spreads either through pneumonic transmission of plague or through an intermediate human ectoparasite vector, such as the human body louse. To understand the transmission dynamics within cities, we used a spatial metapopulation model with SIR-dynamics for three transmission scenarios and compared how the epidemic curve, epidemic duration, and total mortality differ between each mode and historical data. Here we show that 1) a model of louse-borne transmission of bubonic plague fits the pattern of plague transmission within cities during the Black Death with regards to epidemic duration and the distribution of deaths during an epidemic, and that 2) primary pneumonic plague can produce large scale epidemics, but only under conditions highly favorable for this mode of transmission. These results demonstrate that the louse-borne transmission of bubonic plague is a viable alternative to resolve the inconsistencies between plague during the Black Death and plague with rats. We anticipate that the models and parameters we have presented can be used in future work for more complex models that combine multiple transmission routes. For example, a model with both primary pneumonic and bubonic plague transmission during the same epidemic. Furthermore, the models can be adapted to explore the impact of immunity, public health measures, and seasonality on the disease dynamics.

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## Introduction

Plague is an infectious zoonotic disease, caused by the bacterium Yersinia pestis, which can be transferred between animals and humans by an arthropod vector, direct contact, inhalation, or ingestion (World Health Organization et al. 1999). Plague primarily infects wild rodents and circulates through the rodent community via their commensal fleas. Plague has a global distribution determined by the rodents that it infects and is presently endemic to countries in Africa, the Americas, Asia, and the former Soviet Union (World Health Organization et al. 1999). Infections within the rodent community occasionally lead to human outbreaks, which can be a very severe and often fatal disease in people unless treated by antibiotics.

There are three common forms of plague infections that depend on the transmission route: bubonic, pneumonic, and septicemic. The most common form of plague in humans is bubonic plague, which occurs when bacteria enter the skin through the bite of an infected flea or louse. Y. pestis then travels to the lymph nodes via the lymphatics, causing swelling or buboes (World Health Organization et al. 1999). Untreated bubonic plague has a fatality rate of 66% based on data from the pre-antibiotic age in the United States (Kugeler et al. 2015). In primary pneumonic plague, bacteria enter the lungs in aerosolized droplets and, in secondary pneumonic plague, bacteria enter the lungs from the bloodstream during a bubonic or septicemic infection (World Health Organization et al. 1999). Individuals with a secondary pneumonic plague infection cause primary infections by transmitting plague through the respiratory route. Pneumonic plague is highly virulent and the infectious droplets from primary pneumonic plague can sustain the spread of the disease from person-to-person independent of an arthropod vector (Kool 2005). Untreated pneumonic plague has a mortality rate of almost 100%. Septicemic plague occurs when Y. pestis enters and replicates in the bloodstream from a bubonic or primary pneumonic infection and it is almost always fatal.

Plague is a disease of modern and historical significance. Historically, plague has caused multiple pandemics in human populations. Plague is recognized as the disease that caused three major pandemics spanning Europe, Africa, and Asia: the First Pandemic beginning with the Justinian Plague (6th-8th century CE), the Second Pandemic beginning with the 'Black Death' (13th-18th centuries), and the Third Pandemic (beginning in the 19th century). The most famous pandemic, known as the Black Death (1346-1353), devastated Europe during the Middle Ages with an estimated population loss between 30-60% (Benedictow 2004; Kelly 2005). While plague may seem like a disease of the past, natural plague foci around the world pose a recurrent threat to nearby human populations (Stenseth et al. 2008). The World Health Organization (2004), reported that between 1989 and 2003 there were 38,310 reported plague cases worldwide. Furthermore, the potential for plague to be used as a biological weapon has fostered a continued interest in the disease (Inglesby et al. 2000).

Modern bubonic plague outbreaks in Hong Kong and India in the late-nineteenth century propelled research on the disease leading to the discovery of the bacterium and a proposed mode of transmission from black rats (*Rattus rattus*) to humans via the Oriental rat flea (Xenopsylla cheopis) (Butler 2014; Simond, Godley, and Mouriquand 1998). The discovery of Yersinia pestis, the bacterium that causes plague, is credited to French physician Alexandre Yersin (1863-1943), who traveled to Hong Kong during an epidemic in June of 1894 (Zietz and Dunkelberg 2004; Solomon 1997). Yersin continued his investigations of plague in Hong Kong and noted the same bacillus was present in the lymph nodes of dead rats, which he hypothesized had contracted the disease from the soil (Butler 2014). The work of Yersin was continued in India by his successor, Paul-Louis Simond (1858-1947), who also questioned how the disease could be transmitted to people and rats (Butler 2014; Simond, Godley, and Mouriquand 1998). Simond observed that a large percentage of patients had a primary skin lesion during the early stages of infection, which he related to an insect bite with the insect as the vector for the disease (Simond, Godley, and Mouriquand 1998). Simond came to focus his attention on the rat flea and he captured fleas from dead rats, observed them under the microscope, and found them laden with bacilli (Simond, Godley, and Mouriquand 1998). In 1987, Simond prepared an experimental protocol to test if fleas could transfer bacilli from an infected rat to a healthy rat in separate cages (Crawford Jr. 1996). When he performed the experiment in June of 1989 in Karachi, the healthy rat died of plague and Simond wrote he had, "uncovered a secret that had tortured man since the appearance of plague in the world" (translation in Crawford Jr. 1996). Simond had indeed uncovered the primary way in which plague spread in Asia during the Third Pandemic, however, in the process he also created a narrative of transmission that would be applied to all plague epidemics, including the Black Death, without regard to scientific or historical accounts. The retroactive investigation of the Black Death is often clouded by conclusions that late modern researchers, like Simond, made during their investigation of the Third Pandemic in Asia.

The Black Death and other epidemics during the Second Pandemic have similarities and

differences to modern plague outbreaks. These were outlined in detail in Walløe (2008) with regard to symptoms, mortality, and transmission. The symptoms of the disease taken from descriptions in medieval historical records, include fever, buboes in the armpit and groin, and coughing, which resemble the symptoms of untreated bubonic and pneumonic plague today (Walle 2008). Mortality from the disease was high during the Black Death and low in India, although it is impossible to calculate the exact case mortality rates without knowing the number of people infected (Wallee 2008). Another difference between the Second and Third pandemics is the transmission rate. The rate of transmission of the disease during the Black Death was much higher, an estimated 1070-1480 km/year, compared to the plague in India, which spread about 12-15 km/year (Christakos, Olea, et al. 2005; Indian Plague Commission 1906). Lastly, but most importantly, there is little evidence of the rat-flea-human transmission pathway described by Simond during the Black Death. Certainly this transmission mode of plague requires a rat population, presumably either the black rat (*Rattus rattus*) or the brown rat (*Rattus norvegicus*). We can immediately exclude R. norvegicus as a plague host because they were not present in Europe until after 1700 (D. E. Davis 1986). Evidence for the presence of black rats is similarly tenuous; ecologists argue that they are not suited for the climate of northern Europe, Scandinavia, and Iceland, and historians and archaeologists have noted an absence of rats in records from medieval times (Hufthammer and Walløe 2013; Cohn Jr. 2002; Karlsson 1996; D. E. Davis 1986). The large differences between the manifestation of plague in the Second and Third pandemics ultimately led researchers to speculate if the Black Death was caused by another disease entirely, one that was transmitted directly between people (Cohn Jr. 2002; Welford and Bossak 2010). However, the analysis of ancient DNA from individuals buried in 'plague pits' removes any doubt that the Black Death was indeed caused by Y. pestis (Haensch et al. 2010; Bos et al. 2011).

With the causation of the Black Death defined as plague, we can now look at how the disease could have spread in the human population differently in Europe during the Second pandemic. We have already established that the hallmarks of plague during this time were high mortality and a high speed of transmission, probably without evidence of an intermediate rat host harboring the disease. The idea that an alternate mode of transmission directly between humans was more likely to explain the speed at which plague spread was first proposed by Blanc and Baltazard (1942). Supporters of this hypothesis argue that, in the absence of rats, bubonic plague can spread between people by human ectoparasites, like human fleas (*Pulex irritans*) or body lice (*Pediculus humanus humanus*) (Blanc and Baltazard 1942; Hufthammer and Walløe 2013; Drancourt, Houhamdi, and Raoult 2006). A review by Drancourt, Houhamdi, and Raoult (2006) summarizes the research that supports plague as a human ectoparasite-borne disease including: archaeological evidence for the presence of both fleas and lice in Europe for

thousands of years, historical accounts of plague spreading with clothes, and the collection of plague infected human ectoparasites during modern outbreaks in Africa. However, there is debate over whether or not human fleas P. *irritans* are effective vectors for Y. *pestis* as compared to the rat flea (X. *cheopis*) (Eisen and Gage 2012; Wheeler and Douglas 1945). Recent studies do implicate the body louse (*Pediculus humanus*) as a good candidate for plague transmission. Unlike the human flea, body lice exhibit a high level of host specificity (Raoult and Roux 1999). A study by Houhamdi, Lepidi, et al. (2006) experimentally evaluated the louse as a vector for plague using rabbits and showed the bacteria can be efficiently transmitted through feeding and feces. Lastly, Tran et al. (2011) analyzed ancient DNA from plague victims and found both Yersinia pestis and Bartonella quintana, the causative agent of trench fever, which is transmitted by body lice.

Primary pneumonic plague can also spread without the presence of rats, although it is typically regarded as a byproduct of a bubonic outbreak. The risk of developing secondary pneumonic plague in the pre-antibiotic era is difficult to determine, although one study reviewed radiographic data from 42 confirmed plague cases and found secondary pneumonic plague had developed in 21% (Alsofrom, Mettler, and Mann 1981). With a short infectious period of only 2.5 days, pneumonic plague usually spreads rapidly resulting in small localized outbreaks that are easily contained (Gani and Leach 2004). Pneumonic plague outbreaks reported since 2000 have ranged in size between 1 and 117 cases, with the largest number of cases reported in the Congo and Madagascar (Butler 2013; Bertherat et al. 2011; Vincent et al. 2015). The largest outbreaks attributed chiefly to primary pneumonic plague transmission occurred in Manchuria in 1910-11, 1917-18, and 1920-21, with 60,000, 16,000, and 9,000 deaths, respectively (Teh 1922).

To better understand the complex dynamics of the disease, several studies have modeled plague transmission between animals and humans in different foci around the world. The first mathematical model of a plague outbreak was developed by Kermack and McKendrick (1991) using data from the 1906 outbreak in Bombay, which reduced a population to susceptible, infectious, and recovered compartments and formed the basic susceptible-infected-recovered (SIR) model. Since then, SIR models have been used to model the spread plague by different transmission routes for localized outbreaks in humans, persistence and endemicity in wildlife, and the threat of disease to humans from rodent reservoirs (e.g., Webb et al. 2006; Gascuel et al. 2013; Schmid et al. 2012). A study by S. Monecke, H. Monecke, and J. Monecke (2009) modeled the spread of bubonic plague with rats for the epidemic in Freiberg (1613-1614). Studies by Raggett (1982) and Massad et al. (2004) modeled bubonic and pneumonic transmission combined for an epidemic in Eyam (1665-1666), a closed population created by a self-imposed quarantine. Additionally, a study by Massin et al. (2007) modeled the risk of pneumonic plague transmission in present-day Paris. Finally, a study by Keeling and Gilligan (2000a) and Keeling and Gilligan (2000b) modeled the interplay of plague transmission between rats, fleas, and humans, including the persistence of plague in the rodent population and the force of infection to humans from fleas searching for alternate hosts.

Unfortunately, the studies that model the spread of plague in human populations continue to focus on the spread of bubonic plague with rats, which is only one of the possible routes of transmission during the Black Death. To investigate the spread of plague within medieval towns and cities, we modeled plague epidemics for three routes of transmission: 1) pneumonic plague through the human-human respiratory route, 2) bubonic plague transmitted via a human-lice route, and 3) bubonic plague transmitted through a rat-flea-human route. We compared how the epidemic curves, epidemic duration, and total mortality differ between each mode of transmission and how these fit into the context of historical data for plague outbreaks during the Black Death.

## Methods

We studied the spread of plague in an urban environment by three separate transmission routes using a spatial metapopulation model. The metapopulation consists of contiguous subpopulations arranged in a closed square matrix. The framework of our model is similar to that in a study by Schmid et al. (2012), which modeled the spread of plague in a rodent burrow system. At the start of an epidemic, each subpopulation has a set number of hosts and vectors with internal disease dynamics based on a set of differential equations tailored to each transmission scenario. Larger cities are built by adding more subpopulations, such that the smallest city contains 36 subpopulations arranged in a  $6 \ge 6$  square and the largest city contains 2,401 subpopulations in a 49 x 49 square. For disease to spread across the city, each subpopulation is connected to 4 adjacent suppopulations (in a north-south-east-west configuration) or fewer if it is located on an edge or a corner. For a given amount of time, q, individuals interact with neighboring subpopulations. The force of infection from connecting squares is averaged over the total number of individuals in adjacent subpopulations, regardless of whether it is 4 for a middle square or 2 for a corner. We started all epidemics the same way, regardless of city size, by introducing one infected host and any accompanying ectoparasites into a randomly selected subpopulation.

Within the metapopulation framework, the dynamics of plague in each subpopulation are governed by a set of deterministic equations. The deterministic equations form the basis of the stochastic models that we used to simulate three transmission routes for plague in a medieval city. We describe below the deterministic SIR models, each based on a system of differential equations, for three plague transmission scenarios in order of complexity: pneumonic human-human transmission, bubonic human-lice-human transmission, and bubonic rat-flea-human transmission.

The models were implemented in Python 2.7.6 (https://www.python.org) and released under the name MedPlagSIRS. The programs can be obtained from Bitbucket (https://bitbucket.org/krdean/medplagsirs.git).

### Pneumonic plague model

The pneumonic plague model of human-to-human transmission is based on the SEIR model with births and deaths in Keeling and Rohani (2007). The addition of an exposed class to the standard SIR model takes into account a latent period, during which an individual has contracted the disease but is not yet infectious. We included an exposed class in this model because the duration of the infectious period is short and without the latent period the transition between the susceptible and dead classes would be underestimated. The recovered class is not modeled explicitly because the probability of recovery from pneumonic plague without antibiotic treatment is < 1% (Gani and Leach 2004). The following equations [1-3], describe the number of susceptible, exposed, and infectious humans:

#### Human host submodel

$$\frac{dS_h}{dt} = b_h S_h - (1 - q_h) \frac{\beta_p S_h I_h}{N_h} - d_h S_h \tag{1}$$

$$\frac{dE_h}{dt} = (1 - q_h)\frac{\beta_p S_h I_h}{N_h} - \sigma_p E_h - d_h E_h \tag{2}$$

$$\frac{dI_h}{dt} = \sigma_p E_h - \gamma_p I_h - d_h I_h \tag{3}$$

The total number of individuals in a subpopulation is given by,  $N_h = S_h + E_h + I_h$ . Susceptible individuals reproduce at an intrinsic, density-independent, birth rate  $(b_h)$  and all individuals die at an intrinsic death rate  $(d_h)$ . We regarded the births from exposed and infectious individuals as negligible given the short time between infection and death. The transmission of infection occurs at rate  $(\beta_p)$ , which combines both the encounter rate and probability of transmission. Individuals leave the exposed class based on the average latent period  $(\frac{1}{\sigma_p})$ . Since we assumed that individuals will not recover from a pneumonic infection, the death rate due to plague is equal to  $\gamma_p$ , where the inverse  $(\frac{1}{\gamma_p})$  is the average infectious period. Individuals in the human susceptible class can also become exposed from neighboring subpopulations (denoted by subscript j) shown in the following equation [4], where  $q_h$  is the proportion of time spent with neighboring subpopulations:

$$\frac{dE_h}{dt} = q_h \frac{\beta_p S_h I_{hj}}{N_{hj}} \tag{4}$$

The basic reproduction number,  $R_0$ , is defined as the expected number of secondary infections arising from a single infectious individual during the duration of their infectious period given a population that is entirely susceptible (Van Den Driessche and Watmough 2008). Since the value of  $R_0$  is used as a measure of how well a disease will spread, we calculated it for our models.  $R_0$  for a SEIR model functionally equivalent to ours, was calculated by Heffernan, R. J. Smith, and Wahl (2005) using the next-generation matrix method:

$$R_0 = \frac{\sigma_p \beta_p b_h}{(d_h + \sigma_p)(d_h + \gamma_p)d_h}$$
(5)

The calculation of  $R_0$  is based on the deterministic equations of the model and assumes no population structure, but still provides good approximation for the model. It is difficult to determine the actual value of  $R_0$  from each stochastic simulation, which includes added heterogeneity from population structuring.

### Bubonic model with louse vector

In the first model of bubonic plague transmission, plague is transmitted from human to human with a louse vector (*P. humanus*). The ecology of lice is an important component of their ability to transmit disease, and we considered how other louse borne diseases, like *Rickettsia prowazekii, Bartonella quintana*, and *Borrelia recurrentis*, are transmitted. Body lice are highly host specific and live mostly in clothing, but will venture onto skin to feed five times a day (Badiaga and P. Brouqui 2012; Raoult and Roux 1999). The transfer of lice between hosts occurs with close body-to-body contact, sharing of unwashed clothes, and communal sleeping arrangements (Badiaga and P. Brouqui 2012). Consequently, louse infestation, or pediculosis, is associated with crowded and unhygienic environments like homeless shelters, prisons, and refugee camps (Philippe Brouqui 2011). Several different pathogens have been found in the feces of lice and this supports the mechanical transmission of the disease to people through contact between excreted bacteria and open skin wounds (Houhamdi and Raoult 2005; Fang, Houhamdi, and Raoult 2002; La Scola et al. 2001).

Studies have shown that body lice can contract plague, both from observations of bacteremic rabbits and septic plague patients in Morocco during World War II, verifying the first step of the transmission process (Houhamdi, Lepidi, et al. 2006; Blanc and Baltazard 1942; Ayyadurai et al. 2010). However, the transmission of *Y. pestis* from lice

to people has never been confirmed. One study found that body lice were capable of transmitting plague to naive rabbits shortly after becoming infected, suggesting that body lice are capable vectors for the disease (Houhamdi, Lepidi, et al. 2006).

In our model, humans only become infected from the bite of an infected louse and lice only become infected by feeding on an infected human. This is similar to SIR models with mosquito vectors (Keeling and Rohani 2007). We used the following SIR equations for humans [6-8] and SI equations for lice [10-11], which do not recover once infected:

#### Human host submodel

$$\frac{dS_h}{dt} = b_h (S_h + R_h) - (1 - q_h) \frac{\beta_{lh} S_h I_l}{N_h} - d_h S_h \tag{6}$$

$$\frac{dI_h}{dt} = (1 - q_h)\frac{\beta_{lh}S_hI_l}{N_h} - \gamma_hI_h - d_hI_h \tag{7}$$

$$\frac{dR_h}{dt} = m_h \gamma_h I_h - d_h R_h \tag{8}$$

The equations for the human dynamics of the disease are similar to those we used for pneumonic plague. Both susceptible and recovered humans reproduce at the natural birth rate  $(b_h)$  and all individuals die at the natural death rate  $(d_h)$ . The transmission of plague from lice to humans  $(\beta_{lh})$  depends on the bite rate and the probability of transmission. Untreated bubonic plague has a mortality rate of 66%, therefore we incorporated a recovered class that depends on the likelihood of recovery  $(m_h)$  (Kugeler et al. 2015). Susceptible individuals can become infected from lice in neighboring subpopulations described in the following equation [9]:

$$\frac{dI_h}{dt} = q_h \frac{\beta_{lh} S_h I_{lj}}{N_{hj}} \tag{9}$$

### Lice vector submodel

$$\frac{dS_l}{dt} = r_l S_l (1 - \frac{N_l}{K_l}) - \frac{\beta_{hl} S_l I_h}{N_h}$$
(10)

$$\frac{dI_l}{dt} = \frac{\beta_{hl}S_lI_h}{N_h} - \gamma_l I_l \tag{11}$$

To model lice within a subpopulation, we used susceptible and infected classes. Infected lice do not recover from plague as shown in experiments in Houhamdi, Lepidi, et al. (2006) and Ayyadurai et al. (2010). The intrinsic growth rate of lice is limited by the carrying capacity  $(K_l)$ , which is the product of the lice index and the total number of hosts  $(N_h)$ . The transmission of plague from humans to lice occurs at rate  $\beta_{hl}$ , which depends on the bite rate and the probability of transmission. We did not include an incubation or latent period for humans infected with bubonic plague, and in our model humans are capable of transmitting bacteria to lice only one day post infection. In order for lice or fleas to become infected, they must consume a blood meal from a person that is bacteremic, meaning they have bacteria in their bloodstream. As the disease progresses, the amount of bacteria in the blood increases and may eventually lead to sepsis, during which time the transmission potential increases until eventual death. The average amount of time it takes for an infected person to become capable of transmitting Y. pestis to a vector is not known. However, a recent study found Y. pestis in the spleen of rats only 1 hour after blocked fleas fed on the ear, suggesting that fleas could deposit bacteria directly into the blood during feeding (Shannon, Bosio, and Hinnebusch 2015). Whether lice and fleas can elicit a similar result in humans is not known, but would support the assumption of this model.

The basic reproductive ratio for this model was calculated using the next-generation matrix method described in Diekmann and Heesterbeek (2000) and Heffernan, R. J. Smith, and Wahl (2005). The next-generation matrix intuitively describes the disease transmission routes from the deterministic equations and assumes no population structuring. Following the conventional notation, the next-generation matrix for this system equals:

$$K = \begin{bmatrix} 0 & \frac{\beta_{hl} \frac{N_l}{N_h}}{(d_h + \gamma_h)} \\ \frac{\beta_{lh}}{\gamma_l} & 0 \end{bmatrix}$$

Element  $k_{21}$  describes the number of humans infected by one infectious louse, which depends on the transmission probability from lice to humans  $(\beta_{lh})$  and the likelihood that the vector survives the infectious period  $(\gamma_l)$ . Element  $k_{12}$  is the number of lice infected by one infectious human, which depends on the probability of transmission and survival as well as vector density  $(\frac{N_l}{N_h})$ . From the next-generation matrix, we calculated the basic reproductive ratio for the model [12]:

$$R_0 = \sqrt{\frac{\beta_{hl}\beta_{lh}\frac{N_l}{N_h}}{(d_h + \gamma_h)\gamma_l}} \tag{12}$$

In this case,  $R_0$  is calculated from  $K^2$  because it takes two generations for the disease to go from one person to another (Van Den Driessche and Watmough 2008). However,  $R_0$ would be the same with the square root left off, if written from just K.

## Bubonic model with rat intermediate host and rat flea vector

The bubonic plague model for rat-flea-human transmission is based on the model described in Keeling and Gilligan (2000a) and Keeling and Gilligan (2000b). In this model, fleas transmit plague to their preferred rat hosts, however, as the rat population is reduced from disease the fleas search for new hosts and will infect humans. In the following equations [13-21], the rat and human submodels have a SIR structure, and the fleas are modeled using the average number per rat  $(H_f)$  and the number of free infectious fleas  $(I_f)$ :

### Rat host submodel

$$\frac{dS_r}{dt} = b_r (S_r + R_r (1 - p_r))(1 - \frac{N_r}{K_r}) - (1 - q_r) \frac{\beta_r S_r I_f}{N_r} (1 - e^{-aN_r}) - d_r S_r$$
(13)

$$\frac{dI_r}{dt} = (1 - q_r)\frac{\beta_r S_r I_f}{N_r} (1 - e^{-aN_r}) - \gamma_r I_r - d_r I_r$$
(14)

$$\frac{dR_r}{dt} = p_r b_r R_r \left(1 - \frac{N_r}{K_r}\right) + m_r \gamma_r I_r - d_r R_r \tag{15}$$

In this model, susceptible and resistant rats have a natural birth rate  $(b_r)$  and carrying capacity  $(K_r)$ . Resistance can be passed to offspring with probability  $p_r$ . The carrying capacity  $(K_r)$  is dependent on the area of each subpopulation. The disease is transmitted to rats at rate  $(\beta_r)$  by infectious free fleas  $(I_f)$  searching for a host with searching efficiency (a). Several mechanisms have been proposed for the transmission of plague by fleas, including the introduction of bacteria through the skin by flea mouth parts, feces, or regurgitation (Eisen, Bearden, et al. 2006). Our model assumes the early-phase transmission of plague by unblocked X. cheopis, which was shown to be faster and at least as effective as transmission by blocked fleas (Eisen, Bearden, et al. 2006; Eisen, Wilder, et al. 2007). The probability that rats will recover from plague  $(m_r)$  is supported by field studies of wild black rats in Madagascar, both within and outside of plague foci (Tollenaere et al. 2010).

In this model, plague is a rodent disease and human cases are a consequence of mortality in the rat population. Rat fleas, X. cheopis, are host-specific meaning they will only feed on humans if they do not find a rat host (Guo et al. 1999). This means that plague spreads through the rat community first and we modeled interactions between rats, instead of humans, in neighboring subpopulations. The following equation [16] describes the transmission of plague between rats in different subpopulations:

$$\frac{dI_r}{dt} = q_r \frac{\beta_r S_r I_{fj}}{N_{rj}} (1 - e^{-aN_{rj}})$$
(16)

Flea vector submodel

$$\frac{dH_f}{dt} = r_f H_f (1 - \frac{H_f}{K_f}) + \frac{I_f}{N_r} (1 - e^{-aN_r})$$
(17)

$$\frac{dI_f}{dt} = (d_r + \gamma_r (1 - m_r))I_r H - d_f I_f$$
(18)

Equation [17] describes the average number of fleas living on a host  $(H_f)$ , also called the flea index. The flea population is moderated by the growth rate  $(r_f)$  and the carrying capacity  $(K_f)$ . We assumed that the flea population is limited by the number of rat hosts, which is consistent with research showing that X. cheopis does not reproduce on human hosts (Seal and Bhatacharji 1961). Equation [18] models the number of free infectious fleas  $(I_f)$  that will transmit plague to humans and rats. Free infectious fleas are released into the environment when an infected rat dies and the number released is based on the average number of fleas  $(H_f)$  per rat. Free fleas die when they are away from a host, either from starvation or temperature changes, at rate  $d_f$ .

#### Human host submodel

$$\frac{dS_h}{dt} = b_h(S_h + R_h) - \frac{\beta_h S_h I_f}{N_h} (e^{-aN_r}) - d_h S_h$$
(19)

$$\frac{dI_h}{dt} = \frac{\beta_h S_h I_f}{N_h} (e^{-aN_r}) - \gamma_h I_h - d_h I_h \tag{20}$$

$$\frac{dR_h}{dt} = m_h \gamma_h I_h - d_h R_h \tag{21}$$

As with rats, the transmission of plague to humans occurs through free infectious fleas  $(I_f)$  that fail to find a rat host. As in Keeling and Gilligan (2000a) and Keeling and Gilligan (2000b), rather than modeling the flea population explicitly, transmission is based on the force of infection to rats and humans:

$$\lambda_r = \frac{I_f}{N_r} (1 - e^{-aN_r})$$
$$\lambda_h = \frac{I_f}{N_h} (e^{-aN_r})$$

It should be noted that the equation for  $\lambda_h$  represents the maximum force of infection to humans, as they receive the entire force of infection when the rat population is low. However, it would be much more realistic to consider that, in the absence of rats, fleas would search for any other possible host, not exclusively humans, and the resulting force of infection to humans would be reduced.

Human infections are only a byproduct of plague transmission in the rat community, they do not contribute to the propagation of the disease. This is reflected in our calculation of the basic reproduction number. We made the following next-generation matrix from the deterministic equations for the rat and flea submodels:

$$K = \begin{bmatrix} 0 & K_f(1-m_r) \\ \frac{\beta_r(1-e^{-aK_r})}{d_f} & 0 \end{bmatrix}$$

The number of rats infected by a free infectious flea, represented by element  $k_{21}$ , depends on the transmission rate  $(\beta_r)$  and the probability that the flea will survive  $(d_f)$  to find a rat host  $(1 - e^{-aK_r})$ . Element  $k_{12}$  shows the average number of fleas released from an infected rat, equal to the product of the flea index per rat at carrying capacity  $(K_f)$  and the likelihood that the rat dies to release those fleas  $(1 - m_r)$ . From the next-generation matrix we calculated the basic reproduction number [22]:

$$R_0 = \sqrt{\frac{\beta_r K_f (1 - e^{-aK_r})(1 - m_r)}{d_f}}$$
(22)

Our model was constructed with several changes to the one presented by Keeling and Gilligan to more accurately depict the dynamics of plague transmission in Europe (Keeling and Gilligan 2000a; Keeling and Gilligan 2000b). We incorporated modifications made in Gascuel et al. (2013) that applied a carrying capacity to resistant rat births so they do not grow exponentially. Additionally, we made the transmission of plague to humans a frequency-dependent process as it was with rats in the Keeling and Gilligan model (Keeling and Gilligan 2000a; Keeling and Gilligan 2000b). Finally, our calculation of the basic reproduction number is adjusted to include the recovery of infected rats, which do not contribute free fleas to the environment. We also used parameters specific to black rats (*Rattus rattus*), rather than brown rats (*Rattus norvegicus*) used in Keeling and Gilligan 2000a; Keeling and Gilligan 2000b; D. E. Davis 1986).

### Parameter values and estimation

The parameter values used in the models are listed in Table 1 and are taken from field and laboratory experiments when available. The remaining values are set to biologically reasonable estimates. When possible, we maintained consistencies in the parameters shared by more than one model and all three models have a time-step of one day. The parameters used in the models are determined stochastically by Poisson distributions to simulate variation in individuals and the environment. To fit the output of the models to the observed historical data, we tested a range of values for parameters that were estimated or had multiple values from different studies.

We estimated the initial size of each subpopulation for an area of 2,500 sq. m. Notably, this area is a reasonable home range estimate for a rat (David E. Davis, Emlen, and Stokes 1948). To estimate the number of people in an area of this size within a medieval city, we used the population density of the walled City of London, which was an estimated 60,000 in 1600 for an area of 2.90 sq. km. (Harding 1990). The result was approximately 52 people for each subpopulation. We modeled a rat population equal to the human population (Keeling and Gilligan 2000a; Keeling and Gilligan 2000b).

Parameter	Value	Definition	Reference
Pneumonic	plague		
$b_h$	0.04	Reproductive rate of humans (yearly)	$^{1,2}$
$d_h$	0.04	Death rate of humans (yearly)	$^{1,2}$
$\beta_p$	$0.5^{*}$	Transmission rate	$^{3,\ddagger}$
$\sigma_p^{-1}$	4.3	Average latent period of pneumonic plague	4
$\gamma_p^{r-1}$	2.5	Average infectious period of pneumonic plague	4
$q_h$	0.2 - 0.4	Mixing parameter	†,‡
Bubonic pla	igue with	lice (Pediculus humanus humanus)	
$b_h$	0.04	Reproductive rate of humans (yearly)	$^{1,2}$
$d_h$	0.04	Death rate of humans (yearly)	$1,\!2$
$\gamma_h^{-1}$	26.0	Average human infectious period of bubonic plague	1,2,5,6
$\beta_{lh}$	$0.05^{*}$	Transmission rate from lice to humans	$7,8,\ddagger$
$eta_{hl}$	$0.05^{*}$	Transmission rate from humans to lice	$7,8,\ddagger$
$r_l$	0.11	Natural lice growth rate	9
$K_l$	$10.0^{*}$	Lice index at carrying capacity	$10,\ddagger$
$\gamma_l^{-1}$	3.0	Average louse infectious period of bubonic plague	7,8
$m_h$	0.33	Probability of recovery for humans	11
$q_h$	0.2 - 0.4	Mixing parameter	†,‡
Bubonic pla	igue with	rats (Rattus rattus) and fleas (Xenopsylla cheopis)	
$b_r$	3.57	Reproductive rate of rats (yearly)	12
$d_r$	1	Death rate of rats (yearly)	13
$K_r$	52	Carrying capacity of rats $(.0025 \text{ km}^{-2})$	†
$eta_r$	0.0641	Transmission rate from fleas to rats	14
$\gamma_r^{-1}$	5.15	Average rat infectious period of bubonic plague	15
$p_r$	0.5	Probability of rat inherited resistance	16
$m_r$	0.10	Probability of recovery for rats	15
$r_{f}$	0.0084	Natural flea growth rate	1,2
$d_f$	0.20	Death rate of fleas off host	17
$K_{f}$	$4.0^{*}$	Flea index at carrying capacity	$18,\!19,\!\ddagger$
a	$0.038^{*}$	Flea searching efficiency $(.0025 \text{ km}^{-2})$	†,‡
$b_h$	0.04	Reproductive rate of humans (yearly)	1,2
$d_h$	0.04	Death rate of humans (yearly)	1,2
$eta_h$	0.0641	Transmission rate from fleas to humans	14
$\gamma_h^{-1}$	26.0	Average human infectious period of bubonic plague	$1,\!2,\!5,\!6$
$m_h$	0.33	Probability of recovery for humans	11
$q_r$	0.2 - 0.4	Mixing parameter	$^{\dagger,\ddagger}$

Table 1: Parameter values for three models of plague transmission

All rates are measured per day or otherwise specified. \* Example of values when  $R_0 = 1$ . † Estimated. ‡ Fitted to historical data. 1. Keeling and Gilligan 2000a, 2. Keeling and Gilligan 2000b, 3. See Table 2, 4. Gani and Leach 2004, 5. Benedictow 2004, 6. Scott and C. J. Duncan 2001, 7. Houhamdi, Lepidi, et al. 2006, 8. Ayyadurai et al. 2010, 9. Evans and F. E. Smith 1952, 10. See Table 3, 11. Kugeler et al. 2015, 12. Hone, R. P. Duncan, and Forsyth 2010, 13. Morand and Harvey 2000, 14. Eisen, Wilder, et al. 2007, 15. Tollenaere et al. 2010, 16. Gascuel et al. 2013, 17. Bacot and Martin 1924, 18. Guernier et al. 2014, 19. Carrión 1932

Outbreak dataset	$R_0$	$\beta_p$	Reference
8 outbreaks, worldwide (1907-1997)	1.3	0.67	Gani and Leach 2004
From Gani and Leach 2004	1.37	0.70	Lloyd-Smith et al. 2005
Madagascar (1957) and Mukden (1946)	2.4 - 3.5	1.2 - 1.8	H. Nishiura et al. 2006
US Public Health Service (1900-2009)	1.18	0.61	Hinckley et al. $2012$
19 outbreaks, worldwide (1906-2006)	1.13	0.58	H. Nishiura et al. $2012$

Table 2: Summary of studies of primary pneumonic plague outbreaks and the basic reproduction number  $(R_0)$ 

Table 3: Summary of studies on body louse infestation and abundance

Participants	Infected $(\%)$	Abundance	Reference
146 soldiers (Western front)	95%	$mean \ 10.5$	Peacock 1916
112 school children (Ethiopia)	7.9%	-	Figueroa et al. 1996
300 homeless males (Russia)	19%	$range \ 3-25$	Rydkina et al. 1999
930 homeless people (Marseilles)	22%	-	P. Brouqui et al. 2005
151 homeless people (Tokyo)	11%	-	Seki et al. 2006
33 homeless people (Marseilles)	84.9%	mean~67.7	Foucault et al. $2006$
138 homeless people (San Fran)	23.9%	$mean \ 18.9$	Bonilla et al. $2009$

## Historical data

There is an abundance of historical records pertaining to the Black Death, and later epidemics during the Second Pandemic, which vary greatly with regards to reliability, quality, language, and accessibility. With this in mind, we relied heavily on published studies by historians and scientists for information that has already been collected and interpreted. A study by Olea and Christakos (2005) found a linear relationship between pre-plague city size and the duration of plague epidemics during the Black Death. They began their study with a dataset of plague outbreaks in 531 places, which they later reduced to 53 cities that had reliable information for the initial population size and the duration of the epidemic (Olea and Christakos 2005). The linear regression obtained in their study formed the basis with which to compare the models we made to historical data from the Black Death.

Weekly and monthly mortality information for historical epidemics can often be obtained from gravestones, burial records, or registered wills. The distribution of deaths is sometimes the only way to understand the dynamics within a past epidemic, without rapid diagnoses and contact tracing. Even the first SIR-model developed by Kermack and McKendrick was fitted to the number of deaths per week for the 1905-6 plague epidemic in Bombay (Kermack and McKendrick 1991). To study the dynamics of single epidemics, we searched for the monthly mortality of plague outbreaks that would represent diversity in location, size, and time. We included the monthly mortality graphs for epidemics in Givry in 1348, London in 1563-64, Florence in 1630-31, and Manchuria 1910-11. Background information and sources of monthly mortality data are included in the Case Studies section.

## Analysis

We compared the output of the models to historical data with regards to epidemic duration, epidemic curve, and total mortality. We defined epidemic duration as the time when the last person was exposed, and we stopped the simulation if twice the average infectious period had passed without a new infection. We removed outbreaks where the initial exposed or infected individuals failed to spread the disease because we assumed these would not be recorded in historical records.

## Results

## Model fit and parameter sensitivity

### Pneumonic plague model

We investigated the effects of varying parameters on simulation output with regards to pre-plague city size and epidemic duration for the model of pneumonic plague transmission. In this model, nearly all of the parameter values were taken from published studies that used datasets from pneumonic plague outbreaks (see Table 1). However, several studies, summarized in Table 2, reported different values for the basic reproduction number,  $R_0$ , which we used to calculate the transmission rate,  $\beta_p$ . In order to consider all of the results of these studies, we tested the model using a range numbers for  $\beta_p$ , corresponding to the published estimates for  $R_0$ . In addition to varying  $\beta_p$  ( $R_0$ ) we also considered the effect of different amounts of interaction between subpopulations by changing the mixing parameter,  $q_h$ .

Changes to the basic reproductive number  $(R_0)$  impacted the transmission rate and, consequently, the duration of epidemics simulated by the model. The calculation of  $R_0$ [Eq. 5], was based on the deterministic model, rather than the stochastic one used in the simulations, however, it still gives an indication of the expected output. When the value of  $R_0$  was less than 1, epidemics failed to persist as shown in Figure 1 (a)-(c). This is in agreement with the basic definition of  $R_0$ , or the average number of secondary infections for a primary infection, where  $R_0$  must be greater than 1 to sustain an epidemic (e.g., Keeling and Rohani 2007). When the value of  $R_0$  was greater than 1, shown in Figure 1 (d)-(i), transmission continued until there were few susceptible individuals left in the population. Further increasing this value led to an overall decrease in the average duration of the simulated epidemics.

The spatial spread of disease through a metapopulation is governed by contacts and mobility between individuals in local and neighboring subpopulations. In our models, the amount of connectivity between spatially distinct subpopulations depends on the value of q for the primary host, referred to as the mixing parameter. We tested a range of quantities for  $q_h$ , because this parameter was estimated and would otherwise be unique to each city depending on structure and social patterns. The value for  $q_h$  can be thought of as the percentage of the day people spend in neighboring subpopulations, thus 0.2 is 4.8 hours and 0.4 is 9.6 hours. Today, city-dwelling Americans spend an average of 12 hours at home and the remainder of time divided into work, school, and recreational activities, among others (Del Valle et al. 2007). We assumed that number of hours outside of a localized area in medieval cities would not exceed 10 hours. We found that increasing  $q_h$  reduced the duration and variation of epidemics for different values of  $R_0$  shown in Figure 1. However, given the limited reasonable range for  $q_h$ , the effect on the simulation output was less than we observed when changing  $R_0$ .

We used different combinations of values for  $R_0$  and  $q_h$  to fit the pneumonic plague model to the linear regression of pre-plague city size and epidemic duration from plague outbreaks in 53 cities between 1347-1351 in Olea and Christakos (2005). We used a threshold of 5% as a minimum mortality threshold, assuming that outbreaks below this threshold would not have resulted in a recorded plague outbreak. Moreover, many of the cases that failed to make the 5% threshold were those where plague dies out within the first few transmissions. We used the average distance of the simulated results to the expected result, based on the historical data for a city of equal size, as an indication of overall fit. Several combinations of parameters resulted in simulated data that fit well to the historical epidemics, shown in Figure 2. The parameter combination with the best fit was  $\beta_p = 1.0$  ( $R_0 = 1.9$ ) and  $q_h = 0.4$ . These parameters produced simulations with an average duration within 1.5 months of the historical regression.

Since model fit is not only a question of epidemic duration with respect to Black Death epidemics in Olea and Christakos (2005), we compared the epidemic curves and total mortality for simulations of single epidemics shown in Figure 3. We considered two sets of parameters, one from the closest fitting model in terms of epidemic duration and the other for a low  $R_0$ . In the closet fitting parameter set ( $R_0 = 1.9$ ,  $q_h = 0.4$ ) shown in Figure 3 (a) and (c), the spread of plague was limited by the number of susceptible people with the vast majority of plague introductions developing into epidemics. For a city size of 20,800 residents, the number of infectious individuals at any given time peaks around 700 and the average mortality was 90%. For the set of parameters that had a low  $R_0$ ,  $R_0 = 0.8$ ,  $q_h = 0.3$ , epidemics failed to persist, resulting in a low average mortality of 2%. In the few epidemics with higher mortality, the disease moved slowly through the population, with a maximum of around only 20 infectious individuals at any time for a city of 20,800.



Figure 1: Duration of primary pneumonic plague outbreaks as a function of pre-plague city size for metapopulations ranging in size from  $6 \times 6$  to  $49 \times 49$  subpopulations, blue dots; linear regression, blue dashed line. The black line shows the linear regression for outbreaks in 53 cities from 1347-1351 Black Death published by Olea and Christakos (2005). Simulations for each city size were repeated 5 times, restarting epidemics that did not spread beyond the initial number of infected individuals. The epidemics stopped when t = 1000 days if they had not ended earlier. (a)-(i) Each row of subfigures has different values of  $\beta_p$  ( $R_0$ ), and columns have different values of  $q_h$ .



Figure 2: Heatmap of the pneumonic plague model simulations for  $\beta_p = 0.6 - 1.4$ ( $R_0 = 1.16 - 2.7$ ) and  $q_h = 0.2 - 0.4$ . The grayscale shows the average distance between the simulation output and linear regression from historical data in Olea and Christakos (2005). The simulations had metapopulations ranging in size from  $6 \times 6$  to  $49 \times 49$  subpopulations and were repeated 5 times. Only epidemics that resulted in a > 5% mortality were included, otherwise they were restarted.



(c) City size = 20800,  $\beta_p = 1.0$  ( $R_0 = 1.9$ ),  $q_h = 0.4$ , Epidemic duration = 5.2 months

(d) City size = 20800,  $\beta_p = 0.40$  ( $R_0 = 0.8$ ),  $q_h = 0.3$ , Epidemic duration = 10.6 months

Figure 3: (a)-(b) Duration of a primary pneumonic plague outbreaks as a function of pre-plague city size for metapopulations ranging in size from  $6 \times 6$  to  $49 \times 49$  subpopulations, blue dots; linear regression, blue dashed line. The black line shows the linear regression for outbreaks in 53 cities from 1347-1351 Black Death published by Olea and Christakos (2005). Simulations for each city size were repeated 5 times, restarting epidemics that did not spread beyond the initial number of infected individuals. The epidemics stopped when t = 1000 days if they had not ended earlier. (c)-(d) Example of epidemic curves for a single outbreak of pneumonic plague for a metapopulation composed of  $20 \times 20$  subpopulations, for a total city size of 20,800 residents. Note the difference in axes between the two figures.

#### Bubonic model with louse vector

Disparities between the plague epidemics in India during the Third Pandemic and those in Europe during the Second Pandemic led researchers to question the etiology of the disease. The central arguments against the spread of plague with rats during the Black Death can be reduced to: 1) the lack of evidence for a rat population in Europe, particularly in northern climes, and 2) the high speed of transmission of plague through Europe (Hufthammer and Walløe 2013). The direct transmission of plague by a human ectoparasite vector has been suggested as a more plausible mechanism for plague dissemination in Europe (Blanc and Baltazard 1942; Walløe 2008; Houhamdi, Lepidi, et al. 2006). In order to test this suggestion, we modeled the transmission of bubonic plague from human to human using human body lice (*P. humanus*) as vectors.

The direct transmission of Y. pestis by body lice has never been verified during a plague epidemic but there is evidence that supports this assertion. The transmission of plague from humans to lice was observed in Morocco by Blanc and Baltazard (1942), who found lice infected with plague on septicemic patients. Another study has found Y. pestis in body lice collected from the homes of bubonic plague patients in a plague endemic region of the Democratic Republic of Congo (Piarroux et al. 2013). The full transmission cycle has been demonstrated experimentally in rabbits, showing that lice are also capable of transmitting plague (Houhamdi, Lepidi, et al. 2006). A study by Tran et al. (2011) found Y. pestis and B. quintana, a louse-borne disease, in bodies excavated from an 11-15th century burial site in France. Furthermore, the first record of endemic typhus (R. prowazekii), another louse-borne disease, comes from Spain in 1489, which killed 17,000 soldiers during a siege in Granada (Smallman-Raynor and Cliff 2004).

In this model, transmission of plague between humans is a two-step process, where lice contract the bacteria from infected humans and become vectors for the disease. Changes to the basic reproduction number  $(R_0)$  and the mixing parameter  $(q_h)$  altered the model output and the fit to historical data from the Black Death. In our model, we varied  $R_0$ rather than the individual transmission rates between lice and humans to efficiently search the parameter space. We found that the basic reproduction number for this model [Eq. 12] is directly proportional to the transmission rate from humans to lice  $(\beta_{hl})$ , the transmission rate from lice to humans  $(\beta_{lh})$ , and the number of lice per human  $(\frac{N_l}{N_h})$ . The sensitivity of the model to these three parameters is comparable, however, the elasticity of the parameters is very different. Reasonable values for both of the transmission rates,  $\beta_{hl}$ and  $\beta_{lh}$ , range between 0 and 1, thus the impact of changing the value of these parameters on  $R_0$  is low. The number of body lice per person had a higher impact on  $R_0$ , because of the large possible range of lice per person, on average from 3 to 68 (see Table 3). As previously reported with the model of pneumonic plague, varying  $R_0$  and  $q_h$  changed the output of this model with respect to city size and duration of epidemics shown in Figure 4. We observed the same behavior when  $R_0$  was less than 1, shown in Figure 4 (a), where epidemics failed to persist. In the simulations where  $R_0$  is greater than 1, shown in Figure 4 (b)-(f), plague spreads faster with increasing values of  $R_0$ . As with the pneumonic plague model, different values for mixing between subpopulations changed the duration and variation in the simulated output, shown in Figure 5. Once again, the effect of changing  $q_h$  on the model output was low compared with different values for  $R_0$ . We found that a wide range of values for  $R_0$ , from 2.4 to 6.3, fit within three months of the historical data. The heatmap, shown in Figure 6, has two combinations of  $R_0$  and  $q_h$  that fit best. The first set,  $R_0 = 3.9$  and  $q_h = 0.3$ , fit on average within 2.41 months of the Black Death epidemics. The second set,  $R_0 = 5.5$  and  $q_h = 0.2$ , had a higher  $R_0$  and lower mixing, fit within 2.38 months.

We used these two parameter sets to investigate the behavior of the model within a single epidemic, since the values for  $R_0$  are quite different. To get an idea of how each fit, Figure 7 (a) and (b) shows the pre-plague city size and epidemic duration for simulations using the two parameter sets. We simulated a single epidemic for a town of 20,800 residents and found that the epidemic curves were similar for both parameter combinations. As shown in Figure 7 (c) and (d), both had a maximum of 7,000 infectious people and 13,000 infectious lice at any given time. Simulations for both parameter sets produced an average mortality of 69%.



Figure 4: Duration of bubonic plague outbreaks with lice as a function of pre-plague city size for metapopulations ranging in size from  $6 \times 6$  to  $49 \times 49$  subpopulations, blue dots; linear regression, blue dashed line. The black line shows the linear regression for outbreaks in 53 cities from 1347-1351 Black Death published by Olea and Christakos (2005). Simulations for each city size were repeated 5 times, restarting epidemics that did not spread beyond the initial number of infected individuals. The epidemics stopped when t = 1000 days if they had not ended earlier. Subfigures (a)-(f) show the outcome of simulations with different values for the basic reproduction number  $(R_0)$ .



(g)  $R_0 = 4.7$ ,  $q_h = 0.2$ , Mean (h)  $R_0 = 4.7$ ,  $q_h = 0.3$ , Mean (i)  $R_0 = 4.7$ ,  $q_h = 0.4$ , Mean dist = 2.34 dist = 2.64 dist = 2.68

Figure 5: Duration of bubonic plague outbreaks with lice as a function of pre-plague city size for metapopulations ranging in size from  $6 \times 6$  to  $49 \times 49$  subpopulations, blue dots; linear regression, blue dashed line. The black line shows the linear regression for outbreaks in 53 cities from 1347-1351 Black Death published by Olea and Christakos (2005). Simulations for each city size were repeated 5 times, restarting epidemics that did not spread beyond the initial number of infected individuals. The epidemics stopped when t = 1000 days if they had not ended earlier. (a)-(i) Each row of subfigures has different values of  $R_0$ , and columns have different values of  $q_h$ .



Figure 6: Heatmap of the bubonic plague model with lice model simulations for  $R_0 = 2.4 - 6.3$  and  $q_h = 0.2 - 0.4$ . The grayscale shows the average distance between the simulation output and linear regression from historical data in Olea and Christakos (2005). The simulations had metapopulations ranging in size from  $6 \times 6$  to  $49 \times 49$  subpopulations and were repeated 5 times. Only epidemics that resulted in a > 5% mortality were included, otherwise they were restarted.



 $q_h = 0.3$ , Epidemic duration = 7.0 months

(d) City size = 20800,  $R_0 = 5.5$ ,  $q_h = 0.2$ , Epidemic duration = 7.6 months

Figure 7: (a)-(b) Duration of bubonic plague outbreaks with lice as a function of pre-plague city size for metapopulations ranging in size from  $6 \times 6$  to  $49 \times 49$  subpopulations, blue dots; linear regression, blue dashed line. The black line shows the linear regression for outbreaks in 53 cities from 1347-1351 Black Death published by Olea and Christakos (2005). (c)-(d) Example of epidemic curves for a single outbreak of bubonic plague with lice for a metapopulation composed of  $20 \times 20$  subpopulations, for a total city size of 20,800 residents.

#### Bubonic model with rat intermediate host and rat flea vector

To model the classical mode of plague transmission, we used an SIR-model where black rats (*R. rattus*) and their fleas (*X. cheopis*) transmit plague to humans. Transmission between rats is a multi-step process, where an infected rat must die to release infected fleas into the population, and then the fleas search for a new host. Human plague infections are dependent on the progression of the disease in the rat population. As free infected fleas fail to find rat hosts the force of infection to humans increases. Owing to the uncertainty of several parameters which contributed to the transmission of disease, we fit the simulations using the basic reproduction number ( $R_0$ ) and the mixing parameter ( $q_r$ ) as with the previous model of bubonic transmission with lice.

Using the calculation of  $R_0$  from the deterministic model [Eq. 22], we were able to numerically explore some of the estimated parameters values important for disease transmission. The model is sensitive to both the carrying capacity of rats  $(K_r)$  and the flea searching efficiency (a) as these are components of both the basic reproduction number and the force of infection (Keeling and Gilligan 2000a; Keeling and Gilligan 2000b; Buzby et al. 2008; Gascuel et al. 2013). By setting  $R_0$  equal to 1, we estimated the minimum value of aKr required for an epidemic in the rat population. The result was  $aK_r > 2.02$  for an epizoonic to occur. The dense rat population (20,800  $km^{-2}$ ) of our model provided optimal conditions for plague to spread, and from this density we estimated the minimum value for the flea searching efficiency to be a = .038 (.0025  $km^{-2}$ ).

The parameters in this model were based on the assumption that the rat population was not only dense, but that the black rats in the city were not descendants from black rats from plague foci, and therefore less resistant to plague. Experimental studies by Tollenaere et al. (2010) showed that black rats from a plague focus had a mortality rate of 5.8-18.3% depending on bacterial dose, much less than the mortality rate of 90% for rats from a plague-free zone. If we replaced the rat population with descendants from plague foci, with inherited resistance to plague, the basic reproduction number would be 5-16 times less than in the rat population we modeled. This means a plague epidemic severe enough to reach the human population is much less likely to occur.

As with the previous two models, we compared how different values for  $R_0$  and  $q_r$  changed the duration of epidemics with respect to those during the Black Death. We tested  $R_0$ values between 0.8 and 3.0, shown in Figure 8, and found once again that changing  $R_0$ had a high effect on the model output, with many epidemics failing to persist when  $R_0$ was less than 1. As previously noted, changes to  $q_r$  had only a minimal effect on the output. Epidemics where  $q_r = 0.4$  were shorter and less varied than when we used lower  $q_r$  inputs, shown in Figure 9. We tested how well the simulations from different combinations of  $R_0$  and  $q_r$  fit the duration of Black Death epidemics shown in Figure 10 and found the closest fitting set ( $R_0 = 3.15, q_r = 0.2$ ) had epidemics within 1.21 months of the historical regression. The average total human mortality in these simulations was 66%. The epidemics in this model began in the rat population, consequently there was always a delay between the first rat infection and the first human infection. This delay varied greatly depending on the value for  $R_0$ , from an average of 17 days when  $R_0 = 0.8$ , to 4 days when  $R_0 = 3.0$ . In simulations with the closest fitting value of  $R_0$ , the average delay between the first rat infection and the first human infection was 3 days. Given that our rat population was highly susceptible to plague, outbreaks typically resulted in a total rat mortality of around 90%.

As with the previous models, we looked at the behavior of the model within a single epidemic in a city of 20,800 residents. Figure 11 (c) shows the epidemic curve for people and rats for a city when  $R_0 = 1$ , where the disease spreads slowly and the number of infected humans reaches a maximum of around 900 at any given time. In contrast, Figure 11 (d) shows the same epidemic curve for  $R_0 = 3.15$ , it is clear the disease spreads much faster and the number of infected humans reaches a maximum of around 900.



Figure 8: Duration of bubonic plague outbreaks with rats as a function of pre-plague city size for metapopulations ranging in size from  $6 \times 6$  to  $49 \times 49$  subpopulations, blue dots; linear regression, blue dashed line. The black line shows the linear regression for outbreaks in 53 cities from 1347-1351 Black Death published by Olea and Christakos (2005). Simulations for each city size were repeated 5 times, restarting epidemics that did not spread beyond the initial number of infected individuals. The epidemics stopped when t = 1000 days if they had not ended earlier. Subfigures (a)-(f) show the outcome of simulations with different values for the basic reproduction number  $(R_0)$ .



(g)  $R_0 = 3.3$ ,  $q_r = 0.2$ , Mean (h)  $R_0 = 3.3$ ,  $q_r = 0.3$ , Mean (i)  $R_0 = 3.3$ ,  $q_r = 0.4$ , Mean dist = 1.51 dist = 2.18 dist = 2.69

Figure 9: Duration of bubonic plague outbreaks with rats as a function of pre-plague city size for metapopulations ranging in size from  $6 \times 6$  to  $49 \times 49$  subpopulations, blue dots; linear regression, blue dashed line. The black line shows the linear regression for outbreaks in 53 cities from 1347-1351 Black Death published by Olea and Christakos (2005). Simulations for each city size were repeated 5 times, restarting epidemics that did not spread beyond the initial number of infected individuals. The epidemics stopped when t = 1000 days if they had not ended earlier. (a)-(i) Each row of subfigures has different values of  $R_0$ , and columns have different values of  $q_r$ .



Figure 10: Heatmap of the bubonic plague with rats model simulations for  $R_0 = 1.99 - 3.99$ and  $q_r = 0.2 - 0.4$ . The grayscale shows the average distance between the simulation output and linear regression from historical data in Olea and Christakos (2005). The simulations had metapopulations ranging in size from  $6 \times 6$  to  $49 \times 49$  subpopulations and were repeated 5 times. Only epidemics that resulted in a > 5% mortality were included, otherwise they were restarted.



(c) City size = 20800,  $R_0 = 1.0$ ,  $q_r = 0.3$ , Epidemic duration = 37.5 months

(d) City size = 20800,  $R_0 = 3.15$ ,  $q_r = 0.2$ , Epidemic duration = 6.0 months

Figure 11: (a)-(b) Duration of bubonic plague outbreaks with rats as a function of preplague city size for metapopulations ranging in size from  $6 \times 6$  to  $49 \times 49$  subpopulations, blue dots; linear regression, blue dashed line. The black line shows the linear regression for outbreaks in 53 cities from 1347-1351 Black Death published by Olea and Christakos (2005). (c)-(d) Example of epidemic curves for a single outbreak of bubonic plague with rats for a metapopulation composed of  $20 \times 20$  subpopulations, for a total city size of 20,800 residents.

### Case studies

We fit the models using the relationship between pre-plague city size and the duration of epidemics during the Black Death (Olea and Christakos 2005). From the closest fitting parameters for each model, we made graphs of the monthly mortality during individual epidemics and compared them to epidemics in Givry in 1348, London in 1563-64, Florence in 1630-31, and Manchuria in 1910-11.

### **Givry 1348**

Very few epidemics during the Black Death have reliable monthly mortality information, but the outbreak in Givry, France is an exception. The town of originally 1500-2000 residents lost 30-40% of the population between July and November (Signoli 2012, Christakos and Olea 2005). Figure 12 shows the monthly plague mortality for Givry and the simulated monthly mortality from the three models of transmission in a town of 1,872 residents. A total of 619 residents died in Givry, while the models predicted 1,878 (PPP), 1,263 (BP with lice), and 1,250 (BP with rats) deaths.



Figure 12: Monthly plague mortality in Givry, France from July to November 1348 (bars) and the predicted monthly mortality for three models of plague transmission: primary pneumonic plague (green line), bubonic plague with a louse vector (red line), and bubonic plague with rat intermediate host and rat flea vector (blue line). Monthly data for Givry is from Christakos, Olea, et al. (2005).

#### London 1563-64

After the Black Death, London and surrounding parishes suffered plague epidemics for the next 100 years, beginning in 1563 and ending with the 'Great Plague of London' in 1665 (Creighton 1891). The accounts of weekly plague burials in 1563-64 are the earliest available for London, even though the city was struck by plague during the Black Death (Creighton 1891). We included this epidemic, shown in Figure 13, as a case study because it is the oldest and highest resolution set for plague in a large city during the Second Pandemic. The estimated population size in London in 1560, for 108 parishes, was between 70,000 and 90,000 residents, and the losses to plague in 1563 were around 17,500 (Harding 1990; Creighton 1891). Our models predicted a total mortality of 71,898 (PPP), 49,909 (BP with lice), 50,543 (BP with rats) for different transmission modes for a city of 71,188 people. The model for rat transmission of bubonic plague also predicted 64,000 rat deaths, however, we could not find any contemporary accounts of deceased rats.



Figure 13: Weekly plague mortality in London from June 1563 to January 1564 (bars) and the predicted monthly mortality for three models of plague transmission: primary pneumonic plague (green line), bubonic plague with a louse vector (red line), and bubonic plague with rat intermediate host and rat flea vector (blue line). Weekly data for London is from Creighton (1891).

#### Florence 1630-31

The city of Florence lost an estimated 60% of the population during the Black Death in 1348 (Benedictow 2004). Plague returned to Florence in August of 1630, brought to Italy with invading French and German troops in November of 1629 (Eckstein 2015). The city had a population of roughly 76,000 residents when plague arrived and lost at least 10,000 to 12,000 people to plague over the next year, with the highest mortality in the first five months of the epidemic (Cipolla 1978; Litchfield 2008). Figure 14 shows the monthly deaths in Florence during the first six months of the epidemic combined from three sources: the Misericordia, the Lazaretto, and the Libri dei Morti (Henderson 1990; Litchfield 2008). The total number of deaths was 11,695, however, some historians believe that this figure, and the overall mortality for the epidemic, has been underestimated (Henderson 1990; Litchfield 2008). We simulated plague in a city with 75,088 people, and the three models estimated a total mortality of 75,589 (PPP), 53,312 (BP with lice), and 51,059 (BP with rats), for different transmission routes.



Figure 14: Monthly mortality in Florence from August to November 1630 (bars) and the predicted monthly mortality for three models of plague transmission: primary pneumonic plague (green line), bubonic plague with a louse vector (red line), and bubonic plague with rat intermediate host and rat flea vector (blue line). Monthly data for Florence is from Henderson (1990) and Litchfield (2008).

#### Manchuria 1910-11

The epidemic of primary pneumonic plague in Manchuria in 1910 is the largest confirmed outbreak of the disease in recorded history (H. Nishiura 2006). The epidemic was thought to have been started by Chinese marmot hunters in October 1910, from which time it was spread by people to many areas along the Chinese Eastern Railway (Summers 2012). By January of 1911, primary pneumonic plague was spreading in Kantoshu, where public health officials were convened to record and quarantine suspected cases (H. Nishiura 2006). Despite efforts to contain the outbreak, the officials recorded 5,009 cases concentrated in the first three months of the epidemic and a case fatality rate of 100% (H. Nishiura 2006; Welford and Bossak 2009). Figure 15 shows the number of plague deaths each month in Kantoshu and the number of deaths simulated by each transmission mode were 5,007 (PPP), 3,639 (BP with lice), and 3,576 (BP with rats). We could not find an estimate of the population size of the area in Kantoshu that was affected by plague so we used a starting population size of 5,200 people, which was the number cases.



Figure 15: Monthly primary pneumonic plague mortality in Kantoshu from January to March 1911 (bars) and the predicted monthly mortality for three models of plague transmission: primary pneumonic plague (green line), bubonic plague with a louse vector (red line), and bubonic plague with rat intermediate host and rat flea vector (blue line). Monthly data for Kantoshu is from H. Nishiura (2006) and Welford and Bossak (2009).

## Discussion

We presented a spatial metapopulation model with different SIR dynamics to investigate the transmission of plague in an urban environment during the Black Death. We modeled the following plague transmission routes: 1) pneumonic plague through the human-human respiratory route, 2) bubonic plague transmitted via a human-lice route, and 3) bubonic plague transmitted through a rat-flea-human route. Of the three models, our results show that the model of louse-borne transmission of bubonic plague fits most closely to the pattern of plague transmission within cities during the Black Death. For the remaining two models, we found that primary pneumonic plague transmission can cause large epidemics like those during the Black Death, but only under highly favorable conditions, and that the model of bubonic plague with rats did not fit the mortality curves in the case studies because of the slow onset of human infections.

We used the findings of a study by Olea and Christakos (2005) on the duration of epidemics during the Black Death as a function of pre-plague city size to fit the models. Each of the models had enough flexibility in its parameter space to fit the historical data well, thus, model fit alone was not enough to discriminate between the transmission modes. Therefore, we used other factors to differentiate between the models including:  $R_0$ , total mortality, fit to the case studies, and factors that may increase transmission risk. A summary of the results is presented in Table 4, which shows how the models and Black Death epidemics compare on the basis of several epidemiological features.

For all three models we used  $R_0$ , calculated from the deterministic models, to coalesce multiple parameters, rather than vary them individually.  $R_0$  was the most important parameter we considered for predicting the duration and magnitude of epidemics across all of the models. In general, epidemics failed to spread when the basic reproduction number,  $R_0$ , was less than 1. This is in agreement with the basic definition of  $R_0$ , or the average number of secondary infections for a primary infection, where  $R_0$  must be greater than 1 for an epidemic to persist (e.g., Keeling and Rohani 2007).

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Ships carrying infection, contaminated cloth, contact with infected persons <sup>7</sup>	Givry (1348) <sup>6</sup>	$30-60\%^{5}$	$0.7^{4}$	ı	I	ſ	Black Death
Rat infestation, rat mortality, sharing clothes and bedding	'	66	1.2	0.2	3.2	Rat flea bites, contamination of bite site, flea regurgitation <sup>3</sup>	BP with rats
Sharing clothes and bedding, crowded living	Givry (1348), London (1563), Florence (1630)	69	2.4	$\begin{array}{c} 0.3 \& \\ 0.2 \end{array}$	$\begin{array}{c} 3.9 \ \& 5.5 \end{array}$	Louse bites, contamination of bite site <sup>2</sup>	BP with lice
Coughing, crowded living	Manchuria (1911)	06	1.5	0.3	1.9	Inhalation of infectious droplets <sup>1</sup>	PPP
Factors that signal an increased risk of transmission	Case studies matching this mode of transmission	Mortality	Fit* (months)	q	$R_0$	Transmission mechanism	

Table 4: Summary of the properties of three models of plague transmission and the Black Death

2006, 4. Olea and Christakos 2005, 5. Benedictow 2004, 6. Signoli 2012, 7. e.g., Cohn 2008

The results from the model for primary pneumonic plague showed that to sustain several large scale epidemics that fit the duration of those during the Black Death, the basic reproduction number  $(R_0)$  was 1.9. Multiple studies, shown in Table 2, have estimated a basic reproduction number closer to 1, based on small outbreaks of pneumonic plague that are typical for the disease. It is clear from these studies that the value we found for  $R_0$  is high but still within the reported range from one study (Hiroshi Nishiura et al. 2006). The range of  $R_0$  estimates is an example of how the pattern of disease transmission can change in different environments.

Unlike the model for pneumonic plague, the transmission of plague with body lice has never been verified during an epidemic and there is no basis for comparing  $R_0$ . The results showed that this model fit the historical data across a wide range of values for  $R_0$  and was best when  $R_0$  was 5.5 or 3.9, the highest of the three models. From  $R_0$ , we found that an important part of this model is the contribution of the lice index to the basic reproduction number. A population heavily infested with lice could drive the spread of the disease, even if lice are found to be poor vectors of plague. The lice index is highly variable in different groups of people, studies have reported between 3 and 68 lice per person (see Table 3).

Lastly, the model of bubonic plague with rats fit best with an  $R_0$  of 3.2. We can compare this to a study by Bacaër (2012) that estimated an  $R_0$  of 1.3 from a model of rat transmission using the mortality curves for the 1906 plague epidemic in Bombay. Similarly, other models of plague in rat populations often use an  $R_0$  close to 1 to reflect endemic persistence (Keeling and Gilligan 2000a; Keeling and Gilligan 2000b; Gascuel et al. 2013). This suggests that during the Black Death, there would have needed to be a period of optimal conditions for the spread of plague through rats and fleas in Europe, followed by an endemic phase of plague persistence in Europe (with an  $R_0$  of approximately 1) that lasted for centuries. Such optimal conditions would have involved a combination of high susceptibility, high population density, a high flea index, and ideal climatic conditions.

In addition to  $R_0$ , we fit the models using q, the mixing parameter governing contacts and mobility between subpopulations. We found that the value of q in the range we tested had a relatively low impact on the output, compared to changes in  $R_0$ . Low mixing increased the duration of epidemics and made them more variable, whereas high mixing produced more uniformly distributed epidemics with a shorter duration.

Given that 1) all three models can produce reasonable fits to the data in Olea and Christakos (2005), and 2) there have been no studies that inferred  $R_0$  (or q) for plague epidemics in Europe,  $R_0$  and q cannot be used to distinguish between the transmission modes. We can however, use summary descriptions from historical accounts on how the disease spread through individual towns to get a better idea of how the models fit the total mortality and the shape of the mortality curve.

Plague is estimated to have killed 30-60% of the population in Europe during the Black Death (Benedictow 2004). We found that the average mortality for all three models exceeded the historical range. The morality reflected the likelihood of recovery from the disease, and was 90% for pneumonic transmission and 66-69% for bubonic transmission. We expect that the mortality in the models is overestimated because the underlying assumption of a closed population with stable mixing patterns would not hold true during an epidemic, particularly in a human population. The introduction if plague to cities during the Black Death caused people to flee, especially the wealthy, which lowered the number of susceptible people in the population (Newman 2012). Additionally, public health measures, such as quarantines, if enacted, would lower the encounter rate between susceptible and infectious individuals (Conrad et al. 1995). Increasing immunity to plague also lowers mortality, although this would be a larger factor after the Black Death in areas that experienced multiple plague introductions.

We considered the mortality curves from four historical epidemics, including one epidemic from the Black Death in Givry, France. It was clear from the case studies, that the model of plague transmission with rats failed to predict the pattern of mortality during epidemics in Europe. The additional time for plague to spread through the rat population, meant that there were only a few human cases in the early stages of an epidemic. The low mortality during the burn-in phase of the rat model noticeably delayed the time of peak mortality, causing a poor fit to the case studies. The pneumonic plague model had mortality curves that fit better for the European case studies than the rat model. Disease spread quickly in the pneumonic plague model, and this shows in the curves which stop shortly after a high mortality peak. This pattern of mortality fit well to the Manchurian epidemic, as expected. Finally, the bubonic plague model with lice fit the distribution of deaths and matched the months of peak mortality for epidemics in Givry, London, and Florence. The curve of the lice model has a positive skew, when lice disperse the disease quickly, followed by a long tail. The curves from this model matched the distribution of deaths, but not the magnitude. This highlights again the impact of increased immunity and behavioral adaptations on mortality. The constant presence of plague in Europe for 400 years meant that most large cities were frequently exposed to plague, and that part of their population comprised of recovered individuals with partial immunity to reinfection.

The risk of transmission associated with each model is different based on the underlying mechanisms that spread disease. Crowded living conditions increase the transmission of pneumonic plague and louse-borne diseases, in general (Kool 2005; Philippe Brouqui 2011). This is reflected in our models, where high population density increases the contact rate, which is incorporated in the transmission rate. Contemporaries during the Second

Pandemic believed that the disease could be spread by 'breath' and touch (Cohn 2008). In contrast, the spread of bubonic plague with rats is determined by characteristics of the rat population. The force of infection to humans is a function of rat density and mortality. Yet, there are no accounts of rat infestations or dead rats during Second Pandemic that are a prerequisite for human cases (Hufthammer and Walløe 2013; Karlsson 1996).

The results summarized in Table 4 show that no single model of plague transmission accounted for all of the features of Black Death in Europe. The commonly cited problems with the classical mode of transmission with rats were apparent in both our exploration of  $R_0$  and in the case studies. In order to fit this model to Black Death epidemics, the  $R_0$ was 2.5 times greater than the  $R_0$  for the transmission of plague by rats in India. Furthermore, the mortality curves for this model illustrate the slow transmission of plague to humans at the start of an epidemic with a late peak in mortality, which does not fit the distribution of deaths in the case studies for Givry, London, or Florence. If we exclude rats as a possible transmission mode for plague during the Black Death, we are left with the models for primary pneumonic plague and bubonic plague spread by body lice. For primary pneumonic plague, it is not a question of if plague was transmitted by this route during the Black Death, but rather how often did pulmonary transmission occur. A study has found that secondary pneumonic plague develops in 21% of bubonic cases, creating the potential for primary pneumonic plague to spread even if it is not the dominant mode of transmission for the bacteria (Alsofrom, Mettler, and Mann 1981). Primary pneumonic plague typically has an  $R_0$  around 1.2 to 1.3, from small localized outbreaks that are easily contained (Table 2). We found that a higher  $R_0$  of 1.9 fit the Olea and Christakos (2005) data well, but an  $R_0$  this high is rare as evidenced by the limited number of large pneumonic outbreaks in the past. Finally, this brings us to the lice model, which predicted the distribution of deaths and peak mortality in the Second Pandemic case studies with surprising consistency. This model also had a lower mortality than pneumonic plague, closer to the mortality during the Black Death. We could not rule out the model of bubonic transmission with body lice and this in itself is a significant result. The role of a human ectoparasite vector in the transmission of plague during the Black Death has been alluded to for decades and countless studies have proposed this mechanism to rationalize bubonic plague without rats (Blanc and Baltazard 1942; Ayyadurai et al. 2010; Walløe 2008; Hufthammer and Walløe 2013). With this model of louse-borne transmission we can now show that this mode produces a pattern of transmission in towns and cities that is similar to those from the Black Death.

The lack of reliable parameters from epidemiological and experimental studies remains the greatest challenge of modeling plague, specifically for the models depending on vectors and additional host species. Because of the scarcity of parameters to describe the progression of the disease, we chose not to explicitly model a latent period for bubonic

plague in the primary host and associated vector. We expect that this would not drastically delay transmission that is limited in other ways by the metapopulation structure. We need to improve our understanding of the mechanics of plague transmission, specifically between vectors and humans, in order to elucidate the individual components of  $R_0$ . This would enable us to improve the models of bubonic plague transmission and better test the feasibility of different bubonic transmission routes in Europe.

The use of metapopulation dynamics in disease modeling has been key to understanding the geographic spread of disease (Keeling and Rohani 2007). Therefore, we used a metapopulation structure in the models, in which the amount of connectivity between subpopulations was determined by q. We considered the same values of q for each model, which had a relatively small effect on the simulations. By design, the connectivity in the models focused on the impact of spatial structure, rather than a social network, on the spread of disease. Social networks have been used in disease models and generally take into account demography, travel habits, and mixing behavior, both in neighboring and distant subpopulations (e.g., Eubank et al. 2004; Balcan et al. 2010). Additional heterogeneity in our models would have increased the spread of disease, particularly in large cities, where having infectious individuals moving large distances would introduce the disease to new localities faster. To further complicate modeling networks, human behaviors are likely to change during a large scale epidemic, for example if quarantine and sanitation procedures are enacted. During the Black Death cities in Croatia, Italy, and France enacted coordinated public health measures against plague, such as maritime quarantines, or 'lazzarettos' (Conrad et al. 1995).

Models are always an exercise in simplicity, and one of the effects we did not consider here is the effect of seasonality on transmission within cities. The connection between plague outbreaks and seasonality in Europe remains unclear. In the Mediterranean and England, plague epidemics peaked in the midsummer months, from June to August (Welford and Bossak 2009; Welford and Bossak 2010). Meanwhile, in the Baltic region, plague peaked in autumn, from September to November (Welford and Bossak 2009; Welford and Bossak 2010). Finally, a study of plague epidemics in Switzerland showed that mortality peaked in November (Eckert 1980). This list represents a wide range of climatic conditions when plague transmission was favorable within Europe, which has significance for the mode of transmission. Plague epidemics in Europe appear unaffected by changes in temperature, humidity, and rainfall, the climatic conditions that predicted the onset and duration of outbreaks in India (Rogers 1928; Bacaër 2012). The seasonality of epidemics in India is due to the sensitivity of the rat flea (X. cheopis) to humidity and temperature, which affects both their abundance and plague transmission efficiency (Bacot and Martin 1924; Schotthoefer et al. 2011). Given the variation in the way plague pandemics and transmission modes can be affected by climate, we have not included the effects of

seasonality in our models.

The historical significance of plague in Europe is undeniable and the transmission of the disease within and between cities remains a subject of controversy among scientists and historians (Cohn 2008; Walløe 2008; Scott and C. J. Duncan 2001). To our knowledge, this study is the first comparison of three transmission modes for plague using a modeling approach. We compared the models to epidemics during the Black Death using characteristics like,  $R_0$ , mortality, and the shape of the epidemic curve. From our results, we identified important parameters for each model and the corresponding values to fit the Black Death. Of the three plague transmission modes, the model of bubonic plague transmitted by body lice fit most closely to Black Death epidemics. We propose that transmission of plague in cities during the Black Death was dominated by bubonic plague transmission with a human ectoparasite vector. Additionally, we acknowledge that primary pneumonic plague can contribute to a percentage of cases during bubonic outbreaks, and our results show that this mode of transmission may be particularly important under highly favorable conditions. The transmission of plague using multiple transmission routes remains an interesting problem for future research, as does the impact of seasonality, medieval prevention measures, and conferred immunity.

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