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

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Abbreviations: CI, confidence interval; PEM, prior-based expectation maximization; R_e, effective reporduction number

Abstract

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

Plague is a zoonotic disease, caused by the bacterium *Yersinia pestis*, which is well-known as the cause of at least three pandemics in human history: the First Pandemic (6th-8th centuries), the Second Pandemic (14th-19th centuries), and the Third Pandemic (beginning in the 19th century). At the beginning of the Third Pandemic, *Y. pestis* spread from Asia to Europe, Africa, Australia, and the Americas, along maritime transport networks (1). These introductions led to the establishment of plague reservoirs in rodent populations around the world, which today pose a recurrent threat to nearby human populations (2).

The most common form of plague infection in humans is bubonic plague, caused by the bite of an infected flea vector (3, 4). Today, cases of bubonic plague typically arise through contact with sylvatic or commensal animals and their fleas (3, 4). In the past, large epidemics of plague in Asia c. 1900 were caused by epizootics in the susceptible urban rat population, which led infected rat-flea vectors to seek alternate mammalian hosts (5). However, there is some evidence that bubonic plague may also spread between people through human ectoparasite vectors such as body lice (*Pediculus humanus humanus*) or human fleas (*Pulex irritans*). This is supported by experimental and epidemiological studies that have shown that human ectoparasites are potential vectors for plague and they have been found infected during modern outbreaks in Africa (6-9).

In general, the epidemiology of plague outbreaks in Europe is poorly understood. Even though there were hundreds of plague notifications during the Third Pandemic, research on the disease in Europe has largely focused on the time period of the Second Pandemic, for which there is limited information about outbreaks. The investigation of outbreaks in India at the end of the 19th century created an increased scientific awareness of the bacterium and its transmission. Consequently, there are more detailed accounts of plague from the Third Pandemic, which can be used to better understand the epidemiology of the disease in the pre-antibiotic era.

Here we use an official government report of plague in Glasgow, Scotland in 1900 to study the epidemiology of plague in Europe (10). During this remarkably well-documented outbreak, investigators observed that many cases of plague could be linked by contact with a previous case and they found no evidence of a rat epizootic. The information in the report can be used to partially reconstruct the transmission tree, however, some transmission events are not known. To address this problem, we applied a robust likelihood-based method to reconstruct probable transmission trees, from which we estimated several disease transmission parameters (11).

These disease parameters are important for understanding and modeling the spread of plague. For disease spread at an individual level, we estimated the serial interval, also referred to as the generation interval, which is defined as the time between the symptom onset of a case and the symptom onset of their infector (12). To understand how the disease spreads on a scale of disease generations, we calculated the effective reproduction number R_e defined as the average number of secondary cases produced by a primary case (12). We compared R_e before and after notification of the disease to assess the impact of intervention measures on controlling the outbreak. Finally, we discuss different aspects of transmission, including the number of secondary cases arising within the same household and those arising from individuals who ultimately recovered from the disease (non-septicemic transmission).

Methods

Description of the outbreak

On August 25, 1900, the sanitary authorities of Glasgow were notified of several suspected cases of bubonic plague, despite no known cases of plague in Britain (13). By the following day, they confirmed their initial diagnosis of *Y. pestis* infection from cultures taken on glycerin agar, and later in the week by animal experiments at the University of Glasgow

(13). Upon the identification of plague, the Medical Officer of Health in Glasgow opened an immediate investigation into the spread of the disease. The investigation led to the identification of the index cases, known as Mrs. B., a fish hawker, who sickened along with her granddaughter, on August 3 (Day 0 of the outbreak) (13). The sanitary authorities searched for contacts associated with Mrs. B. or who had attended her wake, leading to the examination and quarantine of more than one hundred people in a 'reception house' for observation (13).

In addition to contact tracing and quarantining, the sanitary authorities implemented several other measures to control the spread of plague including 1) removal of cases to the hospital, 2) cessation of wakes for deaths attributed to plague, 3) fumigation of infected homes with liquid sulfur dioxide and disinfection with a formalin solution, 4) removal and treatment of clothing and sheets, 5) disinfection of all homes and communal areas in infected tenements with chloride of lime (chlorine powder) solution, 6) emptying of ashpits, and 7) dissemination of information about the disease to the public and health professionals (14).

Two years prior to the outbreak in Glasgow, Paul-Louis Simond had discovered that rats and their fleas could transmit plague to humans (15). Consequently, the sanitary authorities in Glasgow were particularly interested in the role of rats in spreading the disease. They noted that rats were numerous in the infected tenements, however, there was no evidence that the mortality among rats was abnormal (14). The authorities undertook an extensive trapping and extermination campaign, which included the examination of 300 rats (10). Despite their efforts, they found no evidence of plague in the rat population at any time during the outbreak, leading them to conclude that plague may have spread directly between humans through clothing among other means, and possibly by 'the suctorial parasites of mankind' (10).

In the official report of the outbreak published in 1901, the local authorities identified 37 cases of plague in and around Glasgow between August 3rd and September 24th, 1900 (10). Thirty-six of the cases were identified as primary bubonic or septicemic plague by the presence

of external buboes (10). However, we excluded one of these confirmed cases, called 'Govan boy', for whom there was no case information (10). The additional suspected case presented with primary pneumonia, but it was noted that the survival of the patient and failure to retrieve the bacteria discredited the assumption of plague pneumonia (10). Thus, our analysis included 35 cases with information about their date of symptom onset and possibly their contacts with previous cases. We broadly defined a contact to be any individual that lived at the same address as the case; any individual who visited the house of a case; or any individual who provided formal or informal care to the case.

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

Using the notation in Hens et. al. (2012), we assigned each case a unique case identifier (i). We numbered the cases by the symptom onset date (t_i) and if the symptom onset dates were equal we used the original order from the case reports (11). For each case i, except the index cases, we denoted the unique infector as $\boldsymbol{v}(i)$ or contacts as $\boldsymbol{w}(i)$, if known. With no missing information for $\boldsymbol{v}(i)$, the serial interval can be calculated as a positive number for each case i as $t_i - t_{v(i)}$, which is the difference between the symptom onset of case i and the symptom onset of the infector $\boldsymbol{v}(i)$. The observed serial intervals can be used to describe the serial interval distribution $g(t_i - t_{v(i)}|\boldsymbol{\theta})$ and the effective reproduction number, R_e. However, for the outbreak in Glasgow the transmission tree is not fully resolved, and information about the infectors is often missing.

To find the missing transmission pairs, we used the method in Hens et. al. (2012), which finds the probability $p_{ij}(\boldsymbol{v}, \boldsymbol{w})$ that case i was infected by case j, given the serial interval, and given information on the possible infector $\boldsymbol{v}$ and the known contacts $\boldsymbol{w}$. The total log-likelihood of the data is then given by the total log-likelihood of all cases, excluding the index cases:

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

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

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

$$p_{ij}\big(\boldsymbol{v},\boldsymbol{w},\widehat{\boldsymbol{\theta}}\big) = \frac{g(t_i - t_j|\widehat{\boldsymbol{\theta}}) \times \pi_{ij}(\boldsymbol{v},\boldsymbol{w})}{\sum_{k\neq i} g\,(t_i - t_k|\widehat{\boldsymbol{\theta}}) \times \pi_{ik}(\boldsymbol{v},\boldsymbol{w})}. \quad (2)$$

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

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

We used the prior-based expectation maximization (PEM) algorithm described by Hens et. al. (2012) to obtain the maximum expected log-likelihood value (11). By this process, the probability of infectious contacts based on information collected during the outbreak is evaluated first (P-step), then the probability of transmission is evaluated given the current estimate of the serial interval parameters $\boldsymbol{\theta}$ (E-step), and then the parameters of $\boldsymbol{\theta}$ are found that maximize the likelihood given the probabilities of transmission (M-step), repeating the E-step and M-step until the results converge to the maximum log-likelihood estimate (11).

To examine the effect of potentially false information for the known pairs on the estimated serial interval distribution, we repeated the analysis for each pair in turn with missing information for the infector $\boldsymbol{v}(i)$. The resulting change in the expected log-likelihood estimate for the parameter set θ for case i is called the 'global influence measure' and can be written as: $GI_i = E\{\ell(\widehat{\boldsymbol{\theta}}_{[-i]})\} - E\{\ell(\widehat{\boldsymbol{\theta}})\}$ (11). Additionally, we considered the extreme case that all recorded contact information was unreliable and repeated the PEM algorithm using only the symptom onsets.

Reconstruction and analysis of possible transmission trees

From the likelihood procedure, we obtained probabilities that any case i was infected by any case j. Using these probabilities to specify a multinomial distribution, we sampled a single infector $\boldsymbol{v}(i)$ for each case i (excluding the index cases) to produce a fully reconstructed transmission tree. We repeated this process to produce 1000 possible transmission trees. For each simulated tree, we calculated the average serial interval and counted the number of secondary cases produced by each case. We calculated the effective reproduction number as the average secondary infections for cases with symptom onsets on day t: $R_e(t) = \sum_j \sum_{i=3} p_{ij}(\boldsymbol{v}, \boldsymbol{w}, \widehat{\boldsymbol{\theta}})$. Additionally, we counted the number of cases with infectors in the same household and the number of cases with infectors that ultimately survived their infections (i.e., that spread the disease without being terminally septicemic).

Results

All 35 (100%) suspected cases of plague in Glasgow were diagnosed by the presence of external buboes; and 17 (48.5%) of these cases were confirmed by bacteriological examination (10). The median patient age was 20 years (range <1-60 years): 21 (60%) of the cases were female and 14 (40%) were male. The overall case-fatality rate for the outbreak was 42.8%. From the 15 fatal cases, we found that the median symptomatic period was six days

(range 2-44 days). There was not enough information in the patient histories to calculate the symptomatic periods for non-fatal cases.

The observed transmission tree for the outbreak is shown in Figure 1. The report included contact information for 24 (69%) of the cases; and for eight of these, they identified a single known infector. From the eight observed pairs, we found that the mean serial interval was 11.5 days (95% CI: 9.0, 20.6).

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

To estimate the serial interval and the time course reproduction numbers for the outbreak, we used the probabilities from the likelihood-based approach to simulate transmission trees. The mean serial interval estimated from the simulated trees was 7.4 days (95% CI: 6.5, 8.6) (Figure 2A). We found that the effective reproduction number declined throughout the duration of the outbreak, shown in Figure 2B. Before notification of the outbreak on day 22, the average reproduction number was 1.6 (95% CI: 0.9, 2.9). Following notification and implementation of control measures, the average reproduction number was 0.6 (95% CI: 0.0, 2.5).

Using the simulated trees, we also estimated the proportion of secondary household transmissions and the proportion of transmissions from non-septicemic infections (Figure 3). From the observed data, we found from that 62.5% of infections occurred between household contacts. Using the simulated trees, we found that the proportion of secondary household infections was 51.5% (95% CI: 51.5, 51.5). When simulating trees using only the symptom

onset data and ignoring known contact information, we estimated that 24.4% (95% CI: 18.1, 34.6) of the transmission pairs occurred within a household (Figure 3A). Next, we identified transmission pairs where the infector had a non-lethal infection. Based on the eight known pairs in the data, 37.5% of cases were infected by persons who survived their infection (non-septicemic transmission). The proportions of non-septicemic transmission were 51.7% (95% CI: 39.3, 66.6) and 38.9% (95% CI: 27.3, 48.6), using the trees with and without contact information, respectively (Figure 3B).

Discussion

Our study reports on the epidemiological characteristics of an outbreak of bubonic plague in Glasgow in 1900. From the information in the report, we found that the symptomatic period for bubonic plague in fatal cases was six days, which agrees well with the estimate of 5.5 days reported for 100 fatal cases in India (16). The case fatality rate of around 40% was consistent with bubonic plague from the pre-antibiotic era (4). These estimates support the diagnosis of bubonic plague made by the sanitary officials.

We used the contact-tracing information from the official report and applied a likelihood-based method to infer plausible transmission trees. With the reconstructed trees, we directly inferred the serial interval and the effective reproduction number for the outbreak. We estimated that the mean serial interval was 7.4 days, which was shorter than the mean observed serial interval of 11.5 days. The difference in the means could be attributed to the small number of observed serial intervals or a bias towards observing longer intervals. To our knowledge, there are no other estimates of serial intervals for bubonic plague, thus the reliability of either estimate is difficult to assess. Given that *Y. pestis* can be cultivated from the serum on average five days post-infection, and as early as two days, an estimate of one week seems biologically plausible (17).

The reproduction numbers were significantly different before and after notification of the disease. Our estimate of 1.6 before disease notification is within the range reported for nine outbreaks of plague in Europe during the Second Pandemic with suspected human ectoparasite transmission (18). The later drop in R_e below 1 after the implementation of control measures suggests that quarantining and sanitation were effective in stopping the spread of plague.

Many studies have reported household clustering of cases during historical plague outbreaks in Europe (19-24). For Glasgow, we estimated that more than half of the secondary cases arose from infectors in the same household. Household clustering of plague cases in historical outbreaks may be attributed to pneumonic plague, which spreads directly between people (21). However, our results show that a high rate of secondary transmission within households can also occur during bubonic outbreaks. A similar finding was reported for a plague outbreak in Nepal in 1967, with suspected human ectoparasite transmission (25). In contrast, household clustering was not a feature of plague epidemics spread by rats, as observed in Bombay, Syndey, and New Orleans (26-28).

For many vector-borne diseases, like plague spread by rats, it may be difficult or impossible to trace successive cases and establish transmission chains. However, human ectoparasites are tightly associated with their hosts or host environment, and switching hosts may require close and prolonged contact, such as staying in the home or sharing clothes (29, 30). Under these conditions the transmission of bubonic plague through a human ectoparasite vector would in theory exhibit a household clustering. Given the absence of evidence for plague in the rat population and the observed case pattern, the bubonic plague outbreak in Glasgow is likely to be the result of human-to-human transmission, possibly by a human ectoparasite vector, as already noted by the original investigators of the outbreak.

Human ectoparasite transmission is controversial because there is very limited information about the levels of bacteremia required for humans to transmit plague to fleas (31).

Experimental studies suggest that high levels of bacteremia, consistent with terminal septicemia, are necessary for hosts to reliably infect certain flea vectors (32). However, we observed from the eight known pairs that three secondary transmissions occurred from two individuals who ultimately recovered; this agrees with observations that mild bacteremia may be exhibited by individuals that are resistant to the disease or those that eventually recover (17, 32, 33). Based on the above, we allowed recovered individuals to be potential infectors in the simulated trees. Even with this assumption, we found that the majority of secondary infections in the reconstructed trees occurred from moribund individuals, as expected. Nonetheless, the limited information from this study suggests that recovered individuals may contribute meaningfully plague epidemics, despite having a low probability of disease transmission.

The likelihood-based method we used makes three assumptions about the outbreak to fully resolve the transmission trees (11). The first assumption is that all cases during the outbreak are observed. During this outbreak, underreporting of cases is unlikely given both the thorough nature of the outbreak investigation and the overt and unequivocal course of the disease in humans. At the time of the outbreak, the symptoms for bubonic plague in humans were known, easily recognizable, and cases could be confirmed with early bacteriological methods. Moreover, plague was an extremely rare disease in Scotland at the beginning of the 20th century, yet officials were acutely aware of the plague pandemic spreading in India (10). The second assumption is that that all cases, excluding the index cases, are infected by another case. Humans were the only known source of the infection during the outbreak; there were no known local reservoirs for plague in Scotland and there was no evidence of plague in the rat population (10). The third condition, that the distribution of the serial interval remains stable over the course of an outbreak, is more difficult to evaluate. To our knowledge, there are no studies reporting on the temporal heterogeneity of the serial interval distribution for plague. Thus, we consider our approach valid for the given outbreak. As shown in the sensitivity

analysis, our estimates of the serial interval distribution are unchanged when the contact information is reduced, and this method is thus robust enough to deal with potential contact misclassifications.

In conclusion, our study provides an in-depth review of the bubonic plague outbreak in Glasgow in 1900 and yields estimates for several epidemiological characteristics of bubonic plague in the pre-antibiotic era. We show that transmission tree reconstruction can be applied to historical outbreaks to better understand disease processes in the past. The information from this study can be applied to models for current plague outbreaks, where parameters for untreated cases may be particularly relevant for areas where there is limited access to healthcare.

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Tables

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

Case (i)	Likely infectors j based on symptom onset	Likely infectors j based on symptom onset and contacts
5	v1, v2 (0.274) v3, v4 (0.225)	v1, v2 (0.192) v3, v4 (0.307)
6	v3, v4 (0.273) v5 (0.276)	v3, v4 (0.277) v5 (0.299)
7	v3, v4 (0.220) v5 (0.240) v6 (0.203)	v2 (0.185) v3 (0.818)
8	v3, v4 (0.183) v5 (0.203) v6 (0.224) v7 (0.116)	v2 (0.178) v3 (0.821)
10	v3, v4 (0.144) v5 (0.163) v6 (0.211) v7 (0.167) v8 (0.103)	v3, v4 (0.117) v5 (0.136) v6 (0.210) v7 (0.206) v8 (0.161)
12	v5 (0.107) v6 (0.155) v7 (0.149) v8 (0.124)	v6 (0.133) v7 (0.148) v8 (0.141) v9, v10, v11 (0.110)
13	v5 (0.107) v6 (0.155) v7 (0.149) v8 (0.124)	v7 (0.512) v8 (0.487)
14	v6 (0.115) v7 (0.123) v8 (0.117)	v7 (0.492) v8 (0.507)
15	v6 (0.115) v7 (0.123) v8 (0.117)	v7 (0.492) v8 (0.507)
16	v6 (0.115) v7 (0.123) v8 (0.117)	v7 (0.113) v8 (0.117) v9, v10, v11 (0.111)
17	v6 (0.115) v7 (0.123) v8 (0.117)	v7 (0.113) v8 (0.117) v9, v10, v11 (0.111)
18	(<0.100)	v9, v10 (0.500)
19	(<0.100)	(<0.100)
20	(<0.100)	v7(0.188)

		v8 (0.217) v13 (0.281) v14 (0.312)
21	(<0.100)	v7(0.188) v8 (0.217) v13 (0.281) v14 (0.312)
22	(<0.100)	v7(0.188) v8 (0.217) v13 (0.281) v14 (0.312)
23	(<0.100)	v13 (0.124) v14 (0.142) v20, v21, v22 (0.187)
24	(<0.100)	v14 (0.111) v20, v21, v22 (0.177) v23 (0.131)
25	v23 (0.113) v24 (0.126)	v9, v10 (0.500)
27	v25 (0.212) v26 (0.224)	v25 (0.230) v26 (0.255)
28	v25 (0.212) v26 (0.224)	v25 (0.230) v26 (0.255)
30	v25 (0.161) v26 (0.175)	v29 (0.945)
31	v25 (0.161) v26 (0.175)	v29 (0.945)
32	v25 (0.161) v26 (0.175)	v29 (0.945)
35	v30, v31, v32 (0.101) v33, v34 (0.158)	v29 (0.220) v30, v31, v32 (0.259)
Mean (95% CI)	8.28 (6.81, 9.72)	7.4 (6.48, 8.63)

Table 2. Global influence of the observed serial intervals

Case ($\boldsymbol{i}$)	Infector ($\boldsymbol{v}(\boldsymbol{i})$)	Global influence measure ($\boldsymbol{GI}_i$)
3	1	0.0
4	1	0.0
9	3	0.42
11	4	0.42
26	18	0.46
29	12	2.85
33	26	0.49
34	26	0.49

Figures

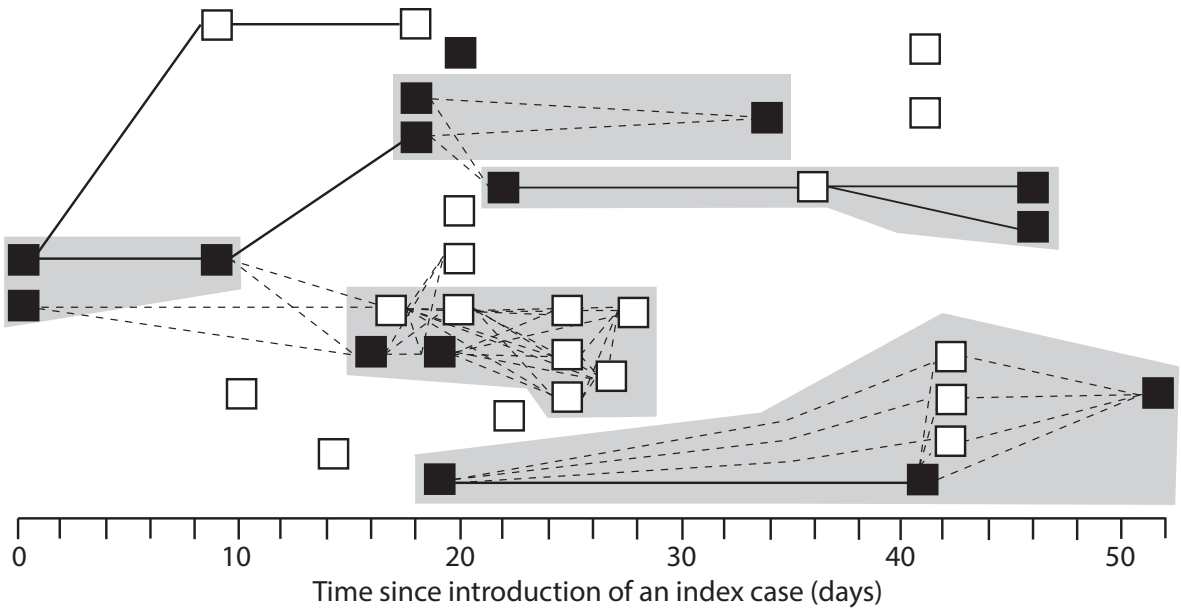

Figure 1. Recorded transmission events during a plague outbreak in Glasgow, Scotland, from 3 August 1900 to 24 September 1900. Cases are represented by squares (solid=dead) and ordered by the date of symptom onset. Solid lines indicate transmission events between cases with a known infector. For cases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

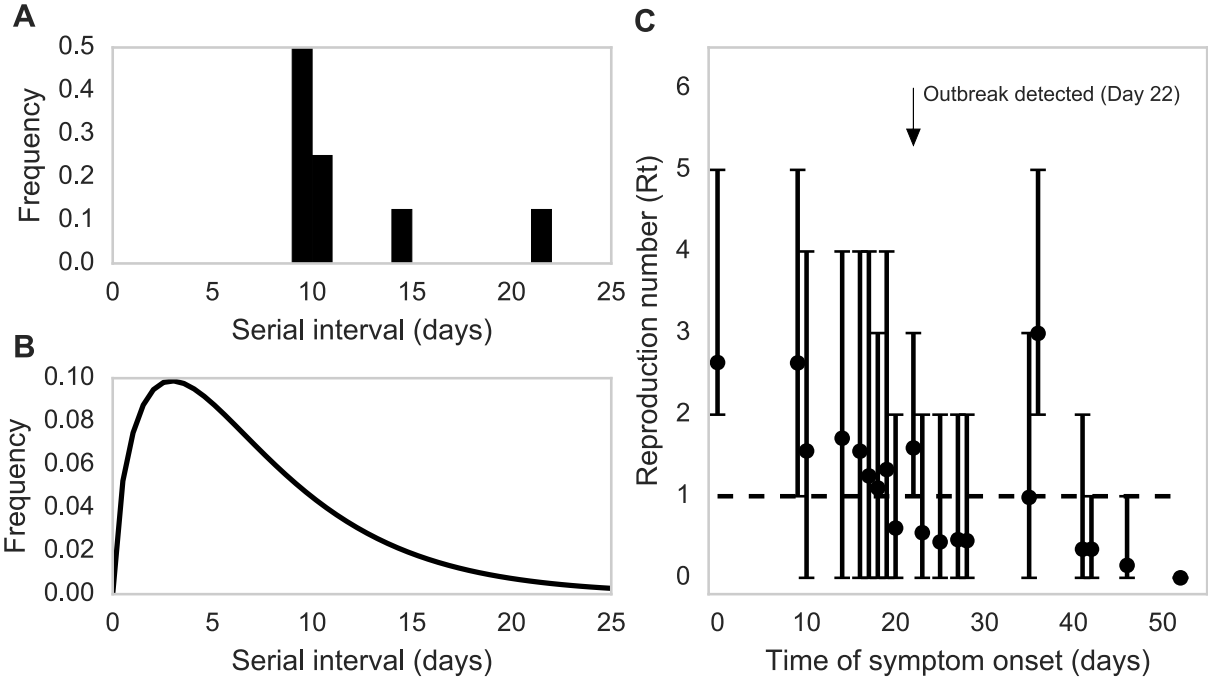

Figure 2. Reconstruction of transmission events for a plague outbreak in Glasgow, Scotland, from 3 August 1900 to 24 September 1900. A) Relative frequency of the serial intervals, based on 8 observed transmission events, B) Relative frequency of the serial intervals, based on 8 observed transmission events and 27 reconstructed transmission events. Mean = 7.4 days [95% CI: 6.5, 8.6], C) Average effective reproduction number ($R_e(t)$) per day (dots) and 95% bootstrap percentile confidence interval (bars).

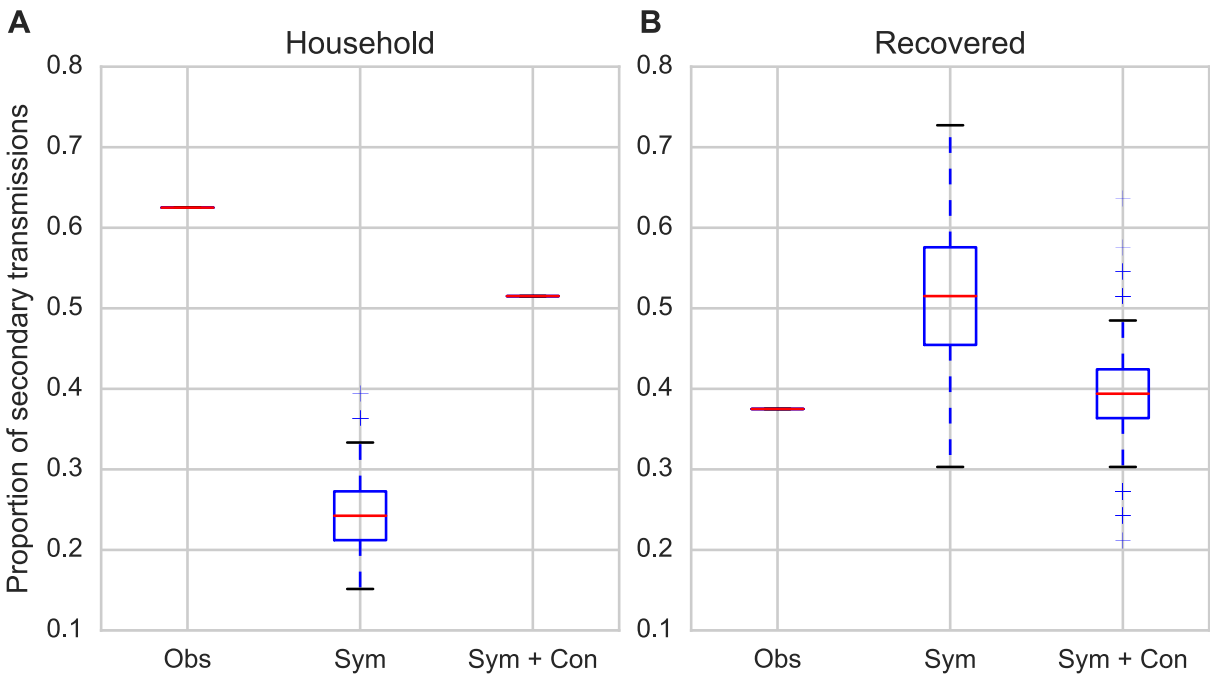

Figure 3. Proportion of secondary cases arising from A) primary cases within the same household for observed pairs (Obs), simulated trees using only symptom onset information (Sym), and simulated trees using symptom onset and contact information (Sym+Con), and B) primary cases that ultimately recovered from their infection for observed pairs (Obs), simulated trees using only symptom onset information (Sym), and simulated trees using symptom onset and contact information (Sym+Con).