# The 2017 plague outbreak in Madagascar: data descriptions and epidemic modelling

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**Abstract**

Since August 1, 2017, Madagascar has endured an outbreak of plague. A total of 2119 cases of plague has been confirmed, causing until now a death toll of 195. Public health interventions have been introduced, preventing new cases and deaths. However, it is likely that the outbreak could reappear as plague is endemic in the region and typically only last until April annually. We collected real-time data from various official reports. We described the outbreak's characteristics and reported estimates of the key transmission parameters using statistical and mathematical modelling approaches. Plague's epidemic curve depicts a propagated outbreak with multiple peaks, caused by continuing exposure. Plague's reproduction number is at least 1.22, with the effective estimate reaches 6.67. Optimal climate conditions for rat flea to flourish were observed during the epidemic. The main mode of transmission is human-human with a high transmission rate compared to flea-human. With a potential of continuing exposure to infected rat fleas until April 2018, current public health efforts should be maintained at the same level. While efforts in controlling vector to prevent the appearance of new index cases can be critical, maintaining interventions targeting reduce human-human transmission is key to prevent large-scale outbreaks.

*Keywords:* `plague`, `outbreak`, `modelling`, `stochastic`, `climate`, `seasonal`, `Madagascar`

## 1. Introduction

One of the deadliest natural disasters in human history was reported as the Black Death - attributed to the bacterium Yersinia pestis - killing about 50 to 200 million people in the 14th century [1]. Although plague was naturally widespread in ancient times, plague outbreaks occurred following the deliberate use and propagation of this disease, serving as a bioweapon [2]. This lethal bacterium can derive in several forms of plague maintaining its existence in a cycle involving rodents and their fleas [3]. While sanitation and public health surveillance have greatly reduced the likelihood of a plague pandemic, isolated plague outbreaks are lethal threats to humankind.

This gram negative can derive different clinical forms of plague: bubonic, pneumonic and septicemic [1]. Human infection is primary driven by bubonic plague, as a result of being bitten by infected fleas. Additionally, direct contamination with infective material can be an alternative transmission route [1]. Patients with bubonic plague can develop sudden onset of fever, headache, chills, tender and painful lymph nodes [4]. While plague can be successfully treated with antibiotics, if untreated, the bacteria can disseminate from the lymph nodes into the bloodstream causing secondary septicemic plague. In addition to the symptoms presented in the bubonic plague, patients with septicemic plague undergo abdominal pain and possibly bleeding into the skin and other organs, and the same time skin and other tissues may turn black and die, especially on fingers, toes, and the nose [3]. However, the most fulminant form of the disease is driven by pneumonic plague that turns out to be the only form of plague that can be spread from person to person by infectious droplets. The incubation period of pneumonic plague is shorter than in the other forms of the disease, usually 1 to 2 days, leading a high fatality rate despite immediate treatment with antibiotics [4].

Plague epidemics of infectious diseases continue to pose a threat to humans, reporting continuous annual occurrence of plague cases in five countries: Madagascar, Tanzania, Vietnam, China, and the USA [1, 5]. On 13 September 2017,

the Madagascar Ministry of Public Health notified WHO of an outbreak of pneumonic plague [4]. Since then, a total of 2119 cases of plague has been confirmed, causing until now a death toll of 171. Public health interventions have been introduced in Madagascar, preventing new cases and deaths. However, it is likely that the outbreak could reappear as plague is endemic in the region and could last until April 2018. Descriptive and numerical analyses of the plague outbreak could facilitate studies in evaluating the spread of diseases as well as targets for disease control and prevention.

## 2. Materials and Methods

*Outbreak Data - Cumulative Cases.* Data were manually inputted from separate reports of WHO [6], including the cumulative total numbers of clinical cases (confirmed, probable, and suspected). The data can be found at the following link systemsmedicine/plague2017/Cumulative

*Outbreak Data - by Disease Forms.* Data were digitised from the figure reported from WHO [6], including the incidences classified by the three forms of the plague disease: pneumonic, bubonic, and septicemic. The data can be found at the following link systemsmedicine/plague2017/Classification and the digitized figure can also be found at the same repository.

*Temperature and Precpitation Data.* Data were requested from the National Centers for Environmental Information (Order #1133340 Custom GHCN-Daily CSV). The data can be found at systemsmedicine/plague2017/Climate.

*Descriptive analyses.* With the aim to facilitate modelling works, we described dynamics and patterns of variables that have previously shown to be relevant to plague outbreaks, including temperature and precipitation [7]. We described potential cross-correlation of the time series.

*Statistical estimate of the reproduction number.* We estimated the reproduction number (R0) of Yersina pestitis using data of pneumonic cases during the second wave of the epidemic, i.e., visually defined from 22/09/17 onwards. The serial interval of plague was assumed gamma distributed with shape and scale parameters are 5.4 and 0.9, respectively [8]. Visualisation of this generation time distribution can be found in Appendix 1. We reported the R0 estimates using following methods: exponential growth (EG) [9], maximum likelihood (ML) [10], and the sequential bayesian estimation (SB) [11].

*Plague transmission model (PTM).* We conducted an epidemic simulation using a modified SEIR (Susceptible-Exposed-Infectious-Removed) model with two incorporated components reflecting the infection from infected rat fleas and the effects of public health interventions. A schematic illustration of the PTM is shown in Figure 1. Assuming only a small proportion ($p$) of the population

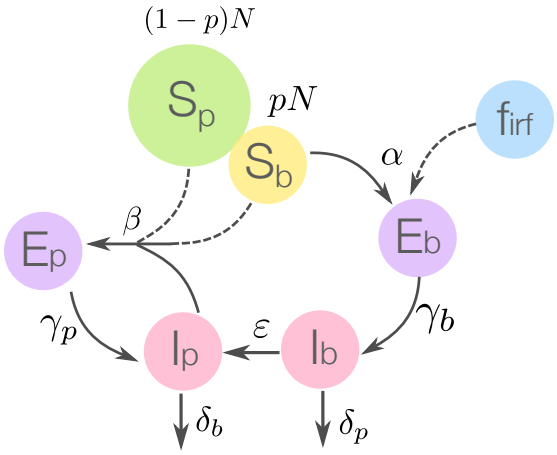


Figure 1: **Schematic of plague transmission model (PTM).** Assuming only a proportion (p) of the population is exposed to the risk of getting bitten with infected rat fleas. The flea density (firf) is approximated with a sinusoidal function fitted on Madagascar temperature (see more details in the text of Materials and Methods section). Dashed lines indicate where public health interventions would presumably take place, i.e., animals control and reducing contact with infected cases.

will expose to the risk of getting bitten with infected rat fleas. The flea density

is approximated with the sinusoidal function fitted on Madagascar temperature. Dashed lines indicate where public health intervention would affect the most, i.e., animals control and reducing contact with infected cases. The model equations are as follows:

$$dS_b/dt = -(S_b \alpha f_{\mathrm{irf}} + \beta S_b I_p/N) f_{\mathrm{itv}} \tag{1}$$

$$dS_p/dt = -\beta S_p I_p/N f_{\mathrm{itv}} \tag{2}$$

$$dE_b/dt = S_b \alpha f_{\mathrm{irf}} f_{\mathrm{itv}} - \gamma_b E_b \tag{3}$$

$$dE_p/dt = \beta I_p/N f_{\mathrm{itv}}(S_b + S_p) - \gamma_p E_p \tag{4}$$

$$dI_b/dt = \gamma_b E_b - \epsilon I_b - \delta_b I_b \tag{5}$$

$$dI_p/dt = \gamma_p E_p - \delta_p I_p + \epsilon I_b \tag{6}$$

where $S$, $E$, $I$ describe Susceptible, Exposed, and Infectious and the subscripts $b$ and $p$ denote bubonic and pneumonic form, respectively. The model assumes in a population size $S_0$, only a small part $S_b = (1-p)S_0$ is exposed to infected rat fleas. The flea-human and human-human transmission rate is denoted as $\alpha$ and $\beta$, respectively. The infected bubonic cases become infectious with a proportion $\varepsilon$ progresses to pneumonic stage. We followed the approach of Aron and May [12], approximating the density of infected rat fleas density as a sinusoidal function of the form $f_{irf} = A + B\sin(2\pi/12t) + C\cos(2\pi/12t)$ which was fitted to the average temperature of Madagascar in the period 1960–2008 as shown in Kreppel et al. [7]. Public health interventions function are assumed reducing both human-human and flea-human transmission that has a logistic form $f_{itv} = 1 - 1/[1 + \exp(-(t-\tau))]$, where $\tau$ denotes the time when the intervention effect reaches half their potential. The infected cases are assumed recovered and died with the total rate of removal from infected pool are $\delta_b$ and $\delta_b$ for pneumonic and bubonic cases, respectively.

Similar to the statistical approach, we fitted the PTM to the daily data of pneumonic and bubonic cases (Outbreak data - by disease forms) during the second wave of the epidemic which was visuallly defined from the epidemic curve, i.e., from 22/09/17 onwards. All the parameters were estimated using

the global optimisation algorithm Differential Evolution [13]. Simulations and estimations were done in R using packages base [14], deSolve [15], and R0 [16] and in Python. Stochastic simulations were performed using a tau-leaping algorithm with a fixed time-step of ca. 15 minutes; code and data can be visited at systemsmedicine/plague2017/Stochastic.

## 3. Results

*Descriptive analyses*

During August, bubonic cases appeared sporadically with almost no records of pneumonic form (fig. 2). An increase in number of pneumonic cases was not necessarily led by a surge in the number of bubonic cases (fig. 2). Cross-correlation between the bubonic and pneumonic were above .8 for lags from -4 to 1 day (fig. S2). It seemed to be the pneumonic curve had three peaks. Figure 3 shows that cases appear throughout the weeks. No visible time lag

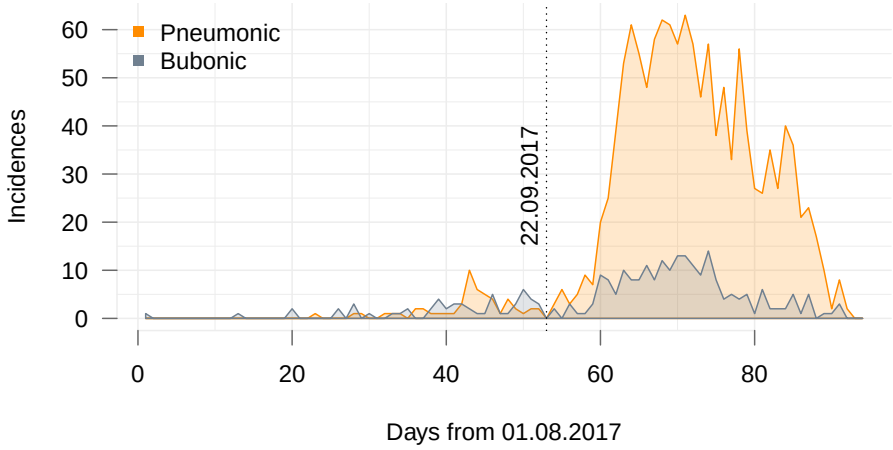


Figure 2: **Plague dynamics August-October 2017**. Reported incidences of the three-forms of plague diseases during the 2017 outbreak. The data were digitized from WHO report's figure [4]. Data can be assessed and updated by sending merge requests at smidgroup/plague2017.

is observed between the appearances of bubonic and pneumonic cases. The

incidences were negligible during the period when Famadihana tradition was presumably practiced. Precipitation measure exhibited no pattern before or during the outbreak but generally showed a dry climatic condition. Average temperature appeared increasing and reached a higher level (above 23 degree Celsius) around the same time as the outbreak. Cross-correlation between average temperature and bubonic cases was measured above 0.7 for lags from 8 to 13 days (but notice that the temperature lag behind the bubonic incidences - Figure S2). Figure S3 shows that the temperature would typically remain at

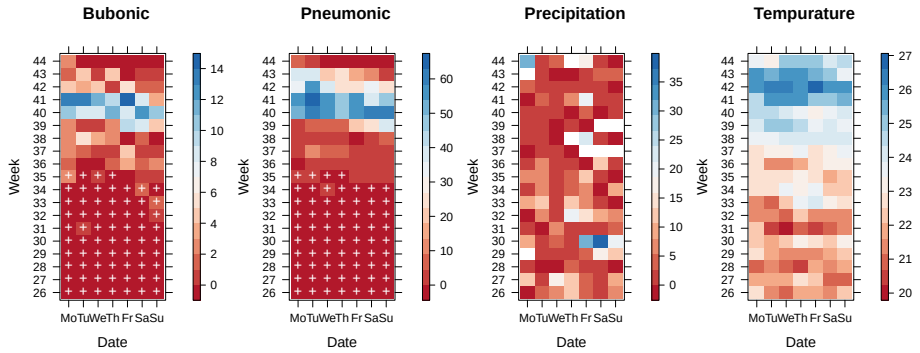


Figure 3: **Incidences and climate variables**. Reported incidences and average temperature and precipitation classifying by week and day of the weeks. The "+" signs indicate a supposed time period when the Famadihana tradition is practiced.

the level favoring the rat fleas (20–25°C [17]) in the upcoming months and until May in the next year.

*Estimates of the reproduction number using pneumonic cases*

Figure 4 shows that the plague's basic reproduction number was at least 1.22. The effective reproduction number, however, could be as high as $6.67[4.01-8.80]$ at the early growing phase of the epidemic. From the 27.10.2017, the effective reproduction number had plunged below unity.

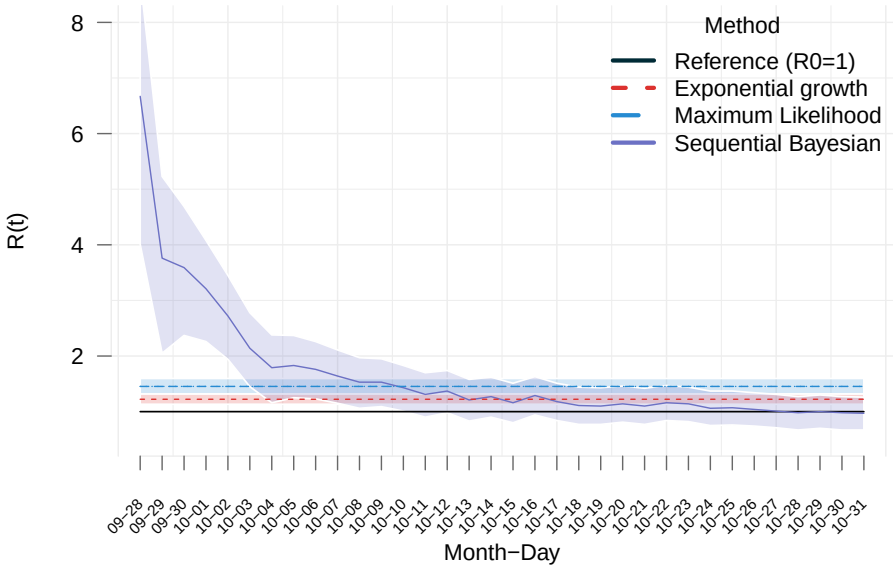


Figure 4: **Estimates of the 2017 plague outbreak reproduction number**. Lines are means; polygons of the same colour are the corresponding 95% Confidence Interval. The Exponential Growth and Maximum Likelihood method used only data from 28.09-15.10 when the number of cases increased quickly to the peak of the epidemic curve; their corresponding estimates are $1.22[1.13 - 1.32]$ and $1.45[1.32 - 1.59]$.

*Mathematical model of plague epidemics*

Table 1 shows the estimated values of the deterministic PTM model. Figure 5 shows that the model and the parameters capture well the dynamics of both pneumonic and bubonic data. Stochastic transition could lead to larger or smaller wave of the dynamics. The parameters suggest that approximately 5% of total population would expose to the infected rat flea. The human-human transmission rate was much higher than the flea-human transmission rate. The average time spending in the exposed state before infectious was 5.96 and 1.74 days for bubonic and pneumonic cases, respectively.

Table 1: **Parameter estimates from the PTM model.** Differential Evolution algorithm was run minimizing the least absolute difference. The total population used for simulations is $N = 25570895$ [18]. Upper bound and lower bound are boundary constrains used for parameter estimation.

| | $p$ | $\tau$ | $\alpha$ | $\beta$ | $\gamma_b$ | $\gamma_p$ | $\delta_b$ | $\delta_p$ | $\varepsilon$ |
|---|---|---|---|---|---|---|---|---|---|
| Estimate | 48 | 7.993 | 2.73E-06 | 1.294 | 116 | 399 | 120 | 72 | 3 |
| Upper | 0.5 | 20 | 10 | 10 | 6 (day) | 3 (day) | 15 (day) | 15 (day) | 0.5 |
| Lower | 1E-05 | 1E-03 | 1E-08 | 1E-08 | 2 (day) | 1 (day) | 1 day | 1 day | 1E-03 |

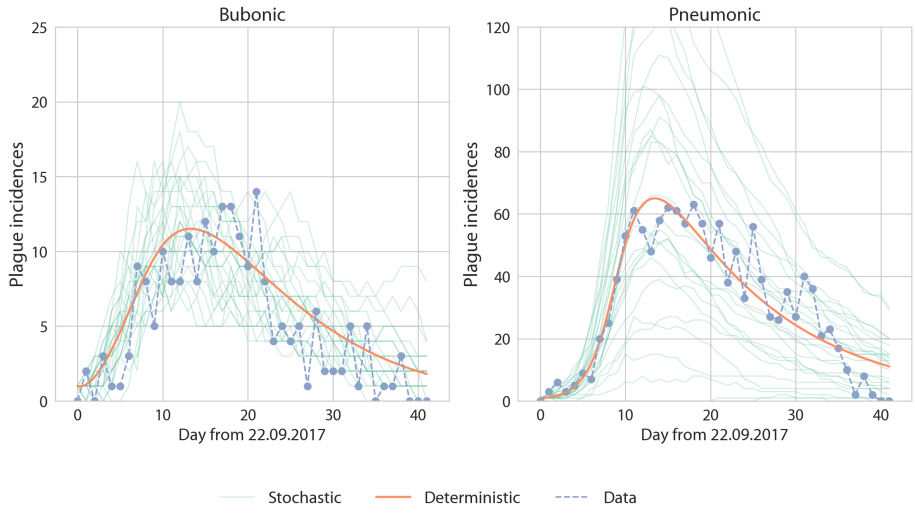


Figure 5: **Deterministic and stochastic simulations of plague epidemics**. The parameters were estimated with the global optimisation algorithm Differential Evolution. Stochastic simulations were done with tau-leaping algorithm. Python code can be viewed at systemsmedicine/plague2017/Fitting.

## 4. Discussion

Mathematical models of infectious diseases have played a central role in understanding epidemics, providing an effective way of assessing disease transmission as well as evaluating disease control and prevention strategies [19]. Mathematical modeling has proposed new vaccination strategies against influenza infection [20]; supported public health strategies for containing emerging influenza pandemics [21, 22] and for the use of antiretroviral treatment for HIV-infected

patients as a preventive measure [23], reported real-time estimates of Ebola's R0 to inform the outbreak situation [24], among others.

However, while it has been noted for the last Ebola outbreak [24], data sharing are still poor and WHO practices of reporting (separate PDF files) are putting constraints on modelling works. In the 2014 Ebola outbreak, most of the modelling studies were also done rather late in the process [25]. The solution can be as simple as putting a unique Excel file and update it, or better establishing a central website for all WHO outbreak reports, or alternatively, a data hub to encourage user contributed reports.

From modelling aspects, plague outbreak can be more challenging because: (1) there is a continuous input of flea-human transmission (fig. 2); this implies the observed epidemic curve can be a mixed of multiple waves of infected cases generated from different index cases. Thus, epidemic evaluations could risk to over- or under-estimate the consequences; (2) there are a known seasonal pattern of the plague epidemic [7] in which a directly measure of the rat flea population does not exist; (3) The flea-human transmission as well as the transition from bubonic cases to pneumonic cases appeared stochastically driven (fig. 2) and could be highly affected by interventions.

Here, the epidemic curves showed plague incidences appear sporadically during August (fig. 2). The pneumonic epidemic curve suggests that superspearders were likely to exist in order to generate the larger number of cases observed in the later periods. Figure 2 shows that a large increase in pneumonic cases was preceded with only a few bubonic cases. Estimates of the effective reproduction number also showed a high estimate is needed to capture the early growing phase of the epidemic (fig. 4).

Figure 2 also shows that bubonic cases appear regularly, making a continuous input of index cases to the human-human transmission network. This can also be observed via the pneumonic epidemic curve which seems exhibiting multiple peaks. This suggests that vector control interventions is key to avoid potential next waves of the epidemic.

Experiments have shown that an optimal climate for rat fleas to flourish

is a dry climatic with temperature of 20–25°C [17]. These conditions were observed during the current outbreak: a generally dry weather with the optimal temperature coincided with the period of high epidemic activities. As further shown in fig. S3, these conditions would typically remain the same until the next May, see further in Kreppel et al. [7]. This again stresses the role of vector control in preventing the next waves.

Nevertheless, the estimate of the human-human transmission rate is much higher than flea-human. This prompts that interventions aim at human-human transmission route need to remain at high level. Figure 6 shows simulations of the model assuming these speculations. The result shows that efforts, in cases of

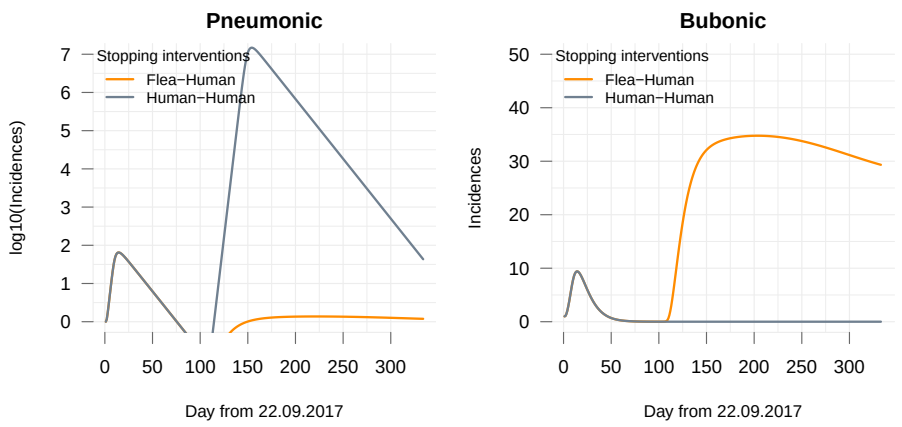


Figure 6: **Simulating epidemic curves for the next 6 months assuming interventions are dropped.**. Assuming the interventions are gradually dropped after 02.11.2017 (the intervention function $f_{itv}$ is changed to $1/(1+\exp(-(t-\tau-100)))$) in one of the two modes of transmission. The time point 100 is approximately to the date 01.01.2018 in the model time scale.

exhaustive of resources, should prioritise stopping human-human transmission route. In this case, while the bubonic cases would continue to appear they would not generate large size outbreaks. The usual approach of early detection the incidences would not only stop the human-human transmission but also give chances for new bubonic cases to be treated.

In this paper, we collected and described real-time relevant data for the 2017 plague epidemic. We proposed a working mathematical model for evaluating and predicting potential epidemic consequences and what-if scenarios. We hope that the results would provide informative insights for public health officers who are doing their bests to stop the epidemic.

### Authors contributions

VKN, EAHV: conceptualization and data curation. VKN, CPR: methodology, formal analysis, investigation, and visualization. EAHV: funding acquisition, supervision. All authors: review & editing.

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## Supporting Information

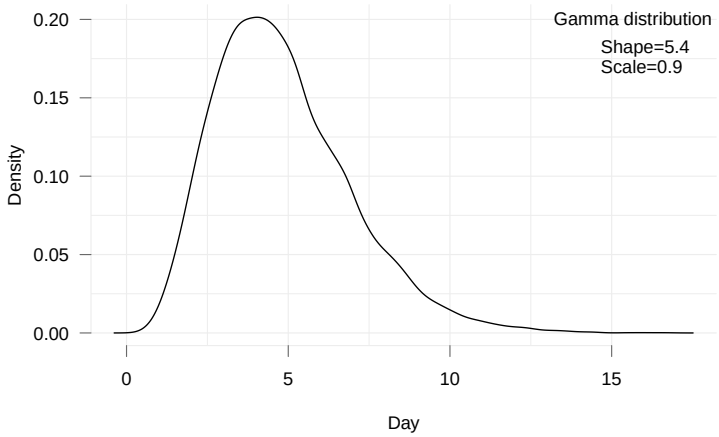


Figure S1: **Visualisation of plague generation time.**. The figure was produced by sampling 10000 samples using rgamma(5.4, scale=0.9) in R, the parameters were estimated in the work of Nishiura et al. [8].

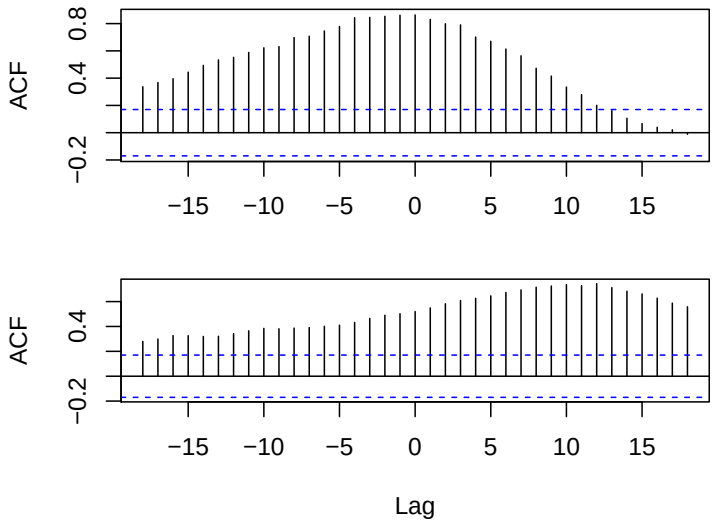


Figure S2: **Potential autocorrelation**. Top: Bubonic versus Pneumonic dynamics. Bottom: Average temperature versus bubonic dynamics.

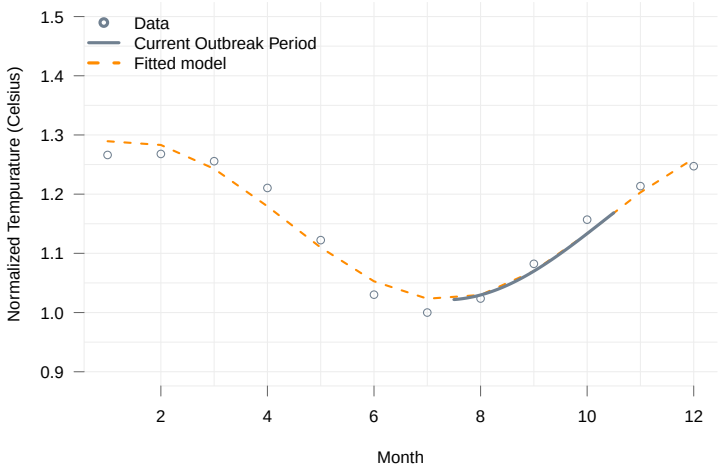


Figure S3: **Fitted sinusoidal of Madagascar temperature.**. Fitted sinusoidal of Madagascar temperature (see Materials and Methods) with $A = 1.15[0.006 - 187]$, $B = 0.08[0.008 - 9.888]$, $C = 0.1[0.008 - 11.854]$. The temperature is normalised by the lowest value of July.

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