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

Van Kinh Nguyen*, Cesar Parra-Rojas, Esteban A. Hernandez-Vargas**

Frankfurt Institute for Advanced Studies, Ruth-Moufang-Str. 1, 60438, Frankfurt am Main, Germany

Abstract

From August to November 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. Optimal climate conditions for rat flea to flourish were observed during the epidemic. Estimate of the Plague's reproduction number based on pneumonic data was 6.9. The main mode of transmission is human-to-human with a much higher transmission rate than that of flea-to-human mode. With a potential of continuing exposure to infected rat fleas until April 2018, current public health efforts should be maintained at the high level. While efforts in controlling vector to prevent the appearance of new index cases can be critical, maintaining interventions targeting reduce human-to-human transmission is key to prevent large-scale outbreaks.

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

*Corresponding authors: knguyen@fias.uni-frankfurt.de, vargas@fias.uni-frankfurt.de

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 result in 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, at 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 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 to 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: Mada-

gascar, 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 2417 cases of plague has been confirmed, causing until now a death toll of 209 [6]. 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 [4]. 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 digitized 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 Precipitation 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 of facilitating modelling works, we described dynamics and patterns of variables that have previously shown to be relevant to plague outbreaks, including temperature and precipitation [7].

Statistical estimate of the reproduction number. We estimated the reproduction number (R0) of Yersina pestitis using data of pneumonic cases during the second

(large) 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]. We reported the R0 estimates using the 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

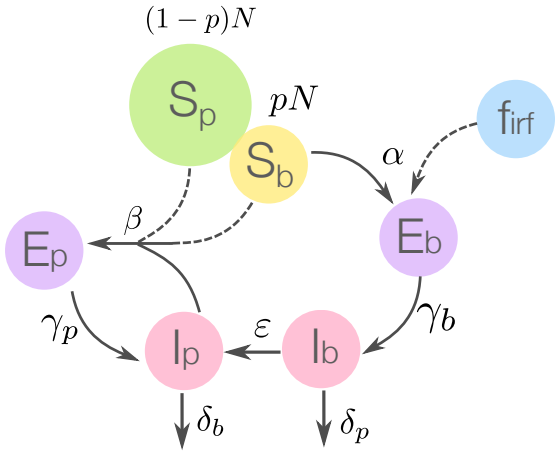

Figure 1: **Schematic of plague transmission model (PTM).** Assuming only a proportion (p) of the population is exposed to the risk of being bitten with infected rat fleas. The flea density (f_{irf}) is approximated with a sinusoidal function fitted on Madagascar temperature (see more details in the 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 be exposed to the risk of being bitten by infected rat fleas. The flea density is approximated by a sinusoidal function fitted to Madagascar temperature. Dashed lines indicate where public health intervention would have the strongest effect, i.e., animals control and reducing contact with infected cases. The model

equations are as follows:

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

$$dS_p/dt = -\beta S_p I_p/N f_{\text{itv}} \quad (2)$$

$$dE_b/dt = S_b \alpha f_{\text{irf}} f_{\text{itv}} - \gamma_b E_b \quad (3)$$

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

$$dI_b/dt = \gamma_b E_b - \epsilon I_b - \delta_b I_b \quad (5)$$

$$dI_p/dt = \gamma_p E_p - \delta_p I_p + \epsilon I_b \quad (6)$$

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

We fitted the PTM to the daily data of pneumonic and bubonic cases during the large wave of the epidemic curve which was visually defined from 22/09/17 onwards. Model 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 are publicly available 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 an increase in the number of bubonic cases (fig. 2). It seemed to be the epidemic curves include several waves of incidence overlapping each others.

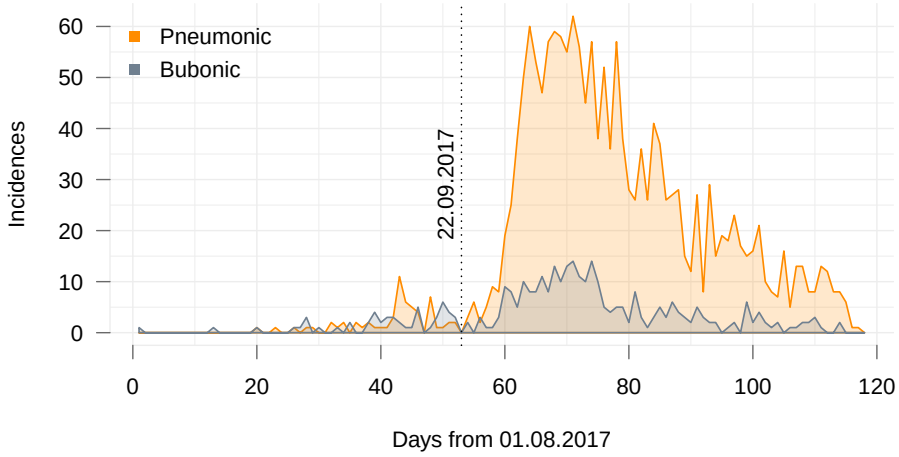

Figure 2: **Plague dynamics August-October 2017**. Reported incidences of the three forms of plague diseases during the 2017 outbreak. The data were digitized from WHO report's figure [4]. Data can be accessed and updated by sending merge requests at smidgroup/plague2017.

Figure 3 shows that plague incidences emerged everyday in the weeks although in some weeks a smaller number of cases were reported in the weekends. No distinctive time lag was observed between the appearances of bubonic and pneumonic cases (fig. 3). The incidences were negligible during the period when Famadihana tradition was presumably practised. 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.

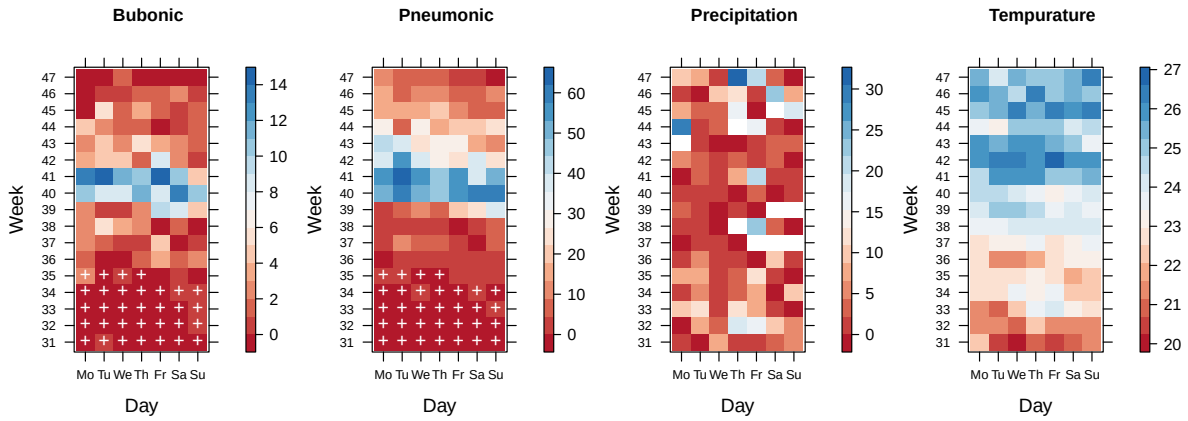

Figure 3: **Incidences and climate variables**. Reported incidences and average temperature and precipitation classifying by week and day of the weeks. The "+" signs indicate a supposed time period when the Famadihana tradition is practised.

Figure 4 shows that the temperature would typically remain at the level favoring the rat fleas (20–25°C [17]) in the upcoming months and until May in the next year.

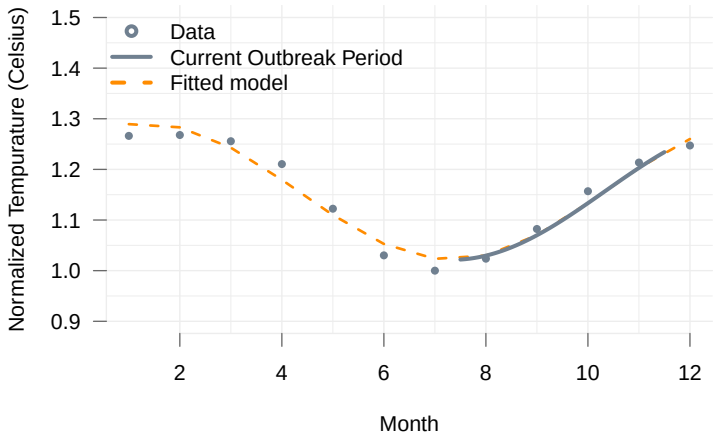

Figure 4: **Fitted sinusoidal of Madagascar temperature.**. Fitted sinusoidal of Madagascar temperature (see Materials and Methods) with $A = 1.15$, $B = 0.08$, $C = 0.1$. The temperature is normalised by the lowest value of July.

Estimates of the reproduction number using pneumonic cases

Figure 5 shows that three estimation methods gave the same estimate for plague's basic reproduction number during the epidemic growing phase, approximating 7. The effective reproduction number, however, could be seen quickly

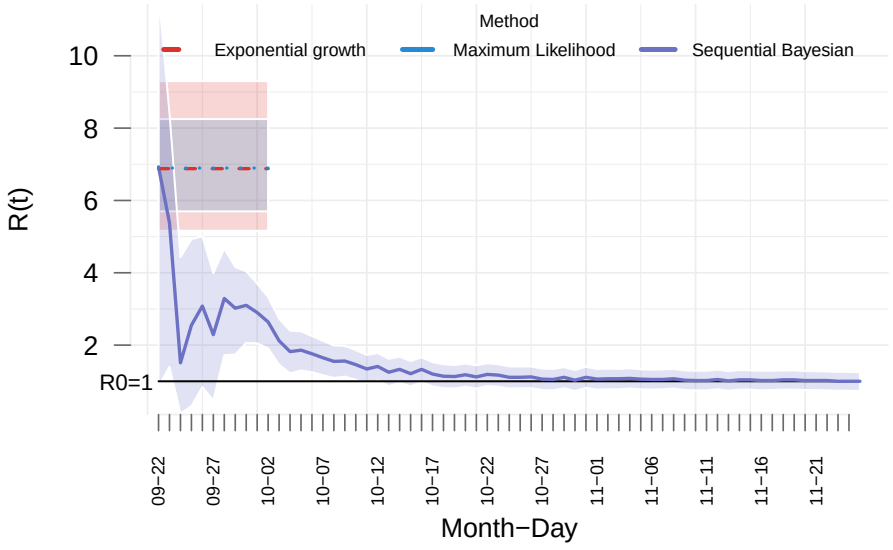

Figure 5: **Estimates of the 2017 plague outbreak reproduction number**. Lines are means; shaded regions of the same colour are the corresponding 95% Confidence Interval. Noting that the Exponential Growth and Maximum Likelihood method used only data from 22.09-02.10 when the number of cases increased quickly to the peak of the epidemic curve; their corresponding estimates are $6.9[5.2, 9.3]$, $6.9[5.7, 8.3]$.

plunge toward unity.

Mathematical model of plague epidemics

Figure 6 shows that the model and the estimated parameters (table 1) capture well the dynamics of both pneumonic and bubonic data. Stochastic transitions could lead to larger or smaller waves of the dynamics. The parameters suggest that only a small fraction (1 per 10000) exposed to infected rat fleas is enough to generate the observed epidemic. The human-to-human transmission

rate was much higher than the flea-to-human transmission rate. The average time spent in the exposed state before infectious was 5.614 and 1.537 days for bubonic and pneumonic cases, respectively.

Table 1: **Parameter estimates from the PTM model.** Differential Evolution algorithm was run minimizing the least absolute differences of both the bubonic and pneumonic data weighted by their range. The total population used for simulations is $N = 25570895$ [18]. Note that the upper and lower bounds indicate boundary constrains used for parameter estimation.

	p	τ	α	β	γ_b	γ_p	δ_b	δ_p	ε
Estimate	0.0001	7.7926	0.0012	1.1363	0.1235	0.4509	0.0059	0.0779	0.0470
Upper	1	20	30	10	6 (day) [3, 19]	3 (day) [3]	15 (day)	15 (day)	1
Lower	1E-05	1E-08	1E-08	1E-08	2 (day) [3, 19]	1 (day) [3]	1 (day) [3]	1 (day) [3]	1E-08

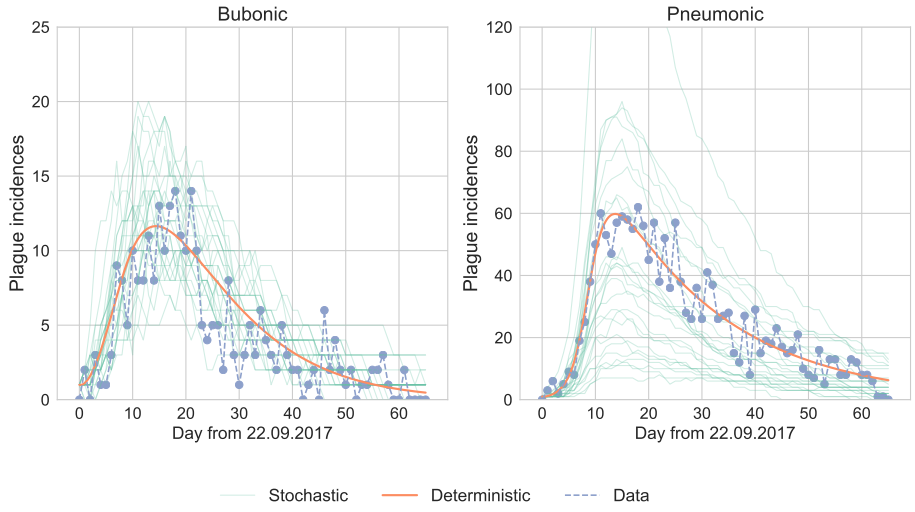

Figure 6: **Deterministic and stochastic simulations of plague epidemics**. The parameters were estimated with the global optimisation algorithm Differential Evolution. Stochastic simulations were done with tau-leaping algorithm. Python code are publicly available at systemsmedicine/plague2017/Fitting.

4. Discussion

Mathematical models of infectious diseases have played a central role in understanding epidemics, providing an effective way of assessing disease transmis-

sion as well as evaluating disease control and prevention strategies [20]. Mathematical modeling has proposed new vaccination strategies against influenza infection [21]; supported public health strategies for containing emerging influenza pandemics [22, 23] and for the use of antiretroviral treatment for HIV-infected patients as a preventive measure [24]; reported real-time estimates of Ebola's R0 to inform the outbreak situation [25], among others.

However, while it has been noted for the last Ebola outbreak [25], 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 [26]. 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-to-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, e.g. the reproduction number or the end time of epidemics; (2) there are a known seasonal pattern of the plague epidemic [7] in which a direct measure of the rat flea population does not exist; (3) The flea-to-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. This can be observed from fig. 2 where the large increase in pneumonic cases was preceded by only a few bubonic cases. Estimates of the effective reproduction number also showed that a high estimate is needed to capture the early growing phase of the epidemic (fig. 5); which is almost double the previous estimates [8]. However, considering the potential mixed of epidemic

waves and outbreak locations in the used data, the reproduction number could be overestimated. Approaches adjusting for the propagated outbreak data are needed to gain further insights in epidemic processes.

In addition, the bubonic cases appeared regularly making a continuous input of index cases to the human-to-human transmission network (fig. 2); as a result, the pneumonic epidemic curve seemed exhibiting multiple peaks. This suggests that vector control interventions are key to avoid potential next waves of the epidemic. Experiments have shown that an optimal climate for rat fleas to flourish is a dry climate with temperatures 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 activity. As further shown in fig. 4, these conditions would typically remain the same until 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-to-human transmission rate is much higher than that of the flea-to-human transmission. This prompts that interventions aim at human-to-human transmission route need to remain at high level. Figure 7 shows extreme scenarios of the model trajectories assuming these speculations. The result shows that efforts, in cases of exhaustive of resources, should prioritise stopping human-to-human transmission route. In this case, while the bubonic cases would continue to appear they would not able to generate large size outbreaks. This is practical as with the usual public health intervention of early detection of the incidences would not only stop the human-to-human transmission but also provide a better chance for new bubonic cases to be treated early.

In this paper, we collected and described relevant data of the 2017 plague epidemic in Madagascar. We proposed a working mathematical model for evaluating and predicting epidemic consequences and what-if scenarios. We discussed potential drawbacks in modelling propagated epidemic data. We hope that the results would contribute informative insights for public health officers and provide a framework for further understanding the dynamics of plague outbreaks.

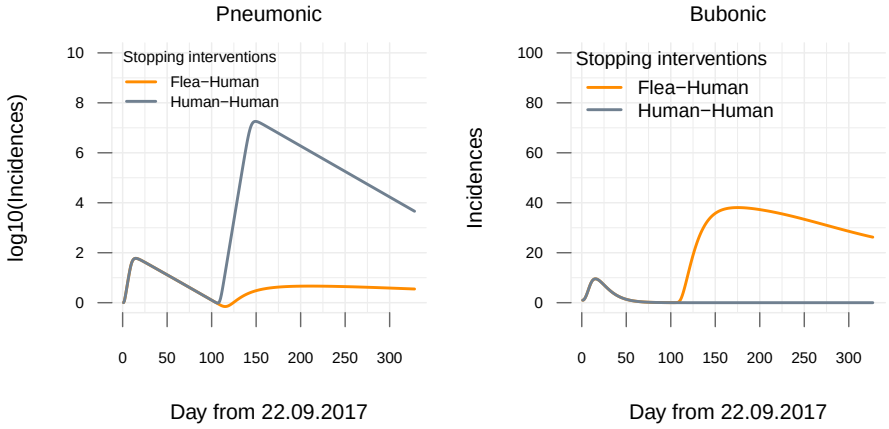

Figure 7: **Simulating epidemic curves for the next 6 months assuming interventions are dropped.**. Assuming the interventions are gradually dropped after 02.11.2017 (the intervention function f_{itv} is changed to $1/(1+\exp(-(t-\tau-100)))$) in one of the two modes of transmission. The time point 100 is approximately to the date 01.01.2018 in the model time scale.

Authors contributions

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

Acknowledgment

This work was supported by the Alfons und Gertrud Kassel-Stiftung.

References

[1] N. A. Boire, V. A. A. Riedel, N. M. Parrish, S. Riedel, Lessons Learned from Historic Plague Epidemics: The Relevance of an Ancient Disease in Modern Times, Journal of Infectious Diseases & Preventive Medicine 2 (2). doi:10.4172/2329-8731.1000114.

[2] S. Riedel, Plague: from natural disease to bioterrorism., Proceedings (Baylor University. Medical Center) 18 (2) (2005) 116–124.

[3] Centers for Disease Control and Prevention. Plague [online] (2005).

[4] World Health Organization, Plague – Madagascar, WHO.
URL http://www.who.int/csr/don/02-november-2017-plague-madagascar/en/

[5] D. T. Dennis, K. L. Gage, N. G. Gratz, J. D. Poland, E. Tikhomirov, World Health Organization. Epidemic Disease Control, Plague manual : epidemiology, distribution, surveillance and control.

[6] World Health Organization, Plague outbreak situation reports.

[7] K. S. Kreppel, C. Caminade, S. Telfer, M. Rajerison, L. Rahalison, A. Morse, M. Baylis, A Non-Stationary Relationship between Global Climate Phenomena and Human Plague Incidence in Madagascar, PLOS Neglected Tropical Diseases 8 (10) (2014) e3155. doi:10.1371/journal.pntd.0003155.
URL http://dx.plos.org/10.1371/journal.pntd.0003155

[8] H. Nishiura, M. Schwehm, M. Kakehashi, M. Eichner, Transmission potential of primary pneumonic plague: time inhomogeneous evaluation based on historical documents of the transmission network, Journal of Epidemiology & Community Health 60 (7) (2006) 640–645. doi:10.1136/jech.2005.042424.

[9] M. L. J Wallinga, How generation intervals shape the relationship between growth rates and reproductive numbers, Proceedings of the Royal Society B: Biological Sciences 274 (1609) (2007) 599–604. doi:10.1098/rspb.2006.3754.

[10] L. F. White, J. Wallinga, L. Finelli, C. Reed, S. Riley, M. Lipsitch, M. Pagano, Estimation of the reproductive number and the serial interval in early phase of the 2009 influenza A/H1N1 pandemic in the USA, Influenza and Other Respiratory Viruses 3 (6) (2009) 267–276. doi:10.1111/j.1750-2659.2009.00106.x.
URL http://doi.wiley.com/10.1111/j.1750-2659.2009.00106.x

[11] L. M. A. Bettencourt, R. M. Ribeiro, Real Time Bayesian Estimation of the Epidemic Potential of Emerging Infectious Diseases, PLoS ONE 3 (5) (2008) e2185. doi:10.1371/journal.pone.0002185.

[12] J. L. Aron, R. M. May, The population dynamics of malaria, in: The Population Dynamics of Infectious Diseases: Theory and Applications, Springer US, Boston, MA, 1982, pp. 139–179. doi:10.1007/978-1-4899-2901-3_5.
URL http://link.springer.com/10.1007/978-1-4899-2901-3_5

[13] K. M. Mullen, D. Ardia, D. L. Gil, D. Windover, J. Cline, DEoptim: An R Package for Global Optimization by Differential Evolution, Journal of Statistical Software 40 (1) (2011) 1–26. doi:10.18637/jss.v040.i06.

[14] R Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria (2017).
URL https://www.R-project.org/

[15] K. Soetaert, T. Petzoldt, R. W. Setzer, Solving Differential Equations in R: Package deSolve, Journal of Statistical Software 33 (9). doi:10.18637/jss.v033.i09.
URL http://www.jstatsoft.org/v33/i09/

[16] T. Obadia, R. Haneef, P.-Y. Boëlle, The R0 package: a toolbox to estimate reproduction numbers for epidemic outbreaks, BMC Medical Informatics and Decision Making 12 (1) (2012) 212. doi:10.1186/1472-6947-12-147.
URL http://bmcmedinformdecismak.biomedcentral.com/articles/10.1186/1472-6947-12-147

[17] J. F. D. Shrewsbury, A History of Bubonic Plague in the British Isles, Cambridge University Press, 2005.
URL https://books.google.nl/books?id=ATOlhaEvN3wC

[18] United Nations Department of Economic and Social Affairs. World Population Prospects: The 2017 Revision [online] (2017).

[19] A. J. Dos Santos Grácio, M. A. A. Grácio, Plague in Madagascar, Tropical Doctor 48 (1) (2018) 1–2. doi:10.1177/0049475517749302.
URL http://journals.sagepub.com/doi/10.1177/0049475517749302

[20] H. Heesterbeek, R. M. Anderson, V. Andreasen, S. Bansal, D. De Angelis, C. Dye, K. T. D. Eames, W. J. Edmunds, S. D. W. Frost, S. Funk, T. D. Hollingsworth, T. House, V. Isham, P. Klepac, J. Lessler, J. O. Lloyd-Smith, C. J. E. Metcalf, D. Mollison, L. Pellis, J. R. C. Pulliam, M. G. Roberts, C. Viboud, Isaac Newton Institute IDD Collaboration, Modeling infectious disease dynamics in the complex landscape of global health, Science 347 (6227) (2015) aaa4339–aaa4339. doi:10.1126/science.aaa4339.
URL http://www.sciencemag.org/cgi/doi/10.1126/science.aaa4339

[21] M. A. Rose, O. Damm, W. Greiner, M. Knuf, P. Wutzler, J. G. Liese, H. Krüger, U. Wahn, T. Schaberg, M. Schwehm, T. F. Kochmann, M. Eichner, The epidemiological impact of childhood influenza vaccination using live-attenuated influenza vaccine (LAIV) in Germany: predictions of a simulation study, BMC Infectious Diseases 14 (1) (2014) 379. doi:10.1186/1471-2334-14-40.
URL http://bmcinfectdis.biomedcentral.com/articles/10.1186/1471-2334-14-40

[22] N. M. Ferguson, D. A. T. Cummings, S. Cauchemez, C. Fraser, S. Riley, A. Meeyai, S. Iamsirithaworn, D. S. Burke, Strategies for containing an emerging influenza pandemic

in Southeast Asia. - PubMed - NCBI, Nature 437 (7056) (2005) 209–214. doi:10.1038/nature04017.

[23] I. M. Longini, Containing pandemic influenza at the source. - PubMed - NCBI, Science 309 (5737) (2005) 1083–1087. doi:10.1126/science.1115717.

[24] F. Tanser, T. Barnighausen, E. Grapsa, J. Zaidi, M. L. Newell, High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. - PubMed - NCBI, Science 339 (6122) (2013) 966–971. doi:10.1126/science.1228160.

[25] C. L. Althaus, Estimating the Reproduction Number of Ebola Virus (EBOV) During the 2014 Outbreak in West Africa, PLOS Currents Outbreaksdoi:10.1371/currents.outbreaks.91afb5e0f279e7f29e7056095255b288.
URL http://currents.plos.org/outbreaks/?p=40381

[26] J.-P. Chretien, S. Riley, D. B. George, Mathematical modeling of the West Africa Ebola epidemic, eLife 4 (2015) e09186. doi:10.7554/eLife.09186.