Available online at http://scik.org
Commun. Math. Biol. Neurosci. 2016, 2016:10
ISSN: 2052-2541

MODELLING THE DYNAMICS OF BUBONIC PLAGUE WITH YERSINIA PESTIS IN THE ENVIRONMENT

RIGOBERT C. NGELEJA[1,*], LIVINGSTONE S. LUBOOBI[2], YAW NKANSAH-GYEKYE[1]

[1]Department of Applied Mathematics and Computational Science, Nelson Mandela African Institution of Science and Technology (NM-AIST), Arusha,Tanzania

[2]Department of Mathematics, Makerere University, Kampala, Uganda

Abstract. Bubonic plague is an infectious disease that is caused by the bacteria *Yersinia pestis* when it affect a part of circulatory system namely lymphatic system. It is mainly transferred between populations through flea bites. In this paper we develop a deterministic model that includes four compartments namely Human, Rodent, Flea and pathogens in the environment to study the dynamics and spread of bubonic plague. The model is analyzed to determine the role and magnitude of the involvement of the four sub-populations in the transmission and spread of the disease. We use the next generation method to find the disease threshold R_0 which is then used to examine the local stability of the equilibrium points. A sensitivity analysis is carried out to determine the most, medium and least sensitive model parameters that affect negatively or positively the basic reproduction number. The result call for attention to most sensitive parameter which is the progression rate of flea from susceptible state to infected state (β). Other significant parameters are adequate contact rates (Γ_{fh}), (Γ_{hf}), (Γ_{fr}), (Γ_{fr}) and (Γ_{rf}); progression rates (α_1), (α_2), (γ_1) and (γ_2); and the pathogens in the environment under the condition that the their survival is favored by the environment. The numerical simulation also support the analytical solution which then cement the argument that the fruitful strategy to combat bubonic plague disease will be the one that will consider the factors that have shown to have a significant contribution to the increase of the basic reproduction number.

Keywords: Bubonic Plague; Pathogens in the environment; Yersinia Pestis; Sensitivity analysis.

2010 AMS Subject Classification: 91B76, 92B05.

*Corresponding author

E-mail addresses: rigobertn@nm-aist.ac.tz (Rigobert C. Ngeleja)

Received November 23, 2015

1. Introduction

Tanzania is one of the countries that has been and it is still heavly affected by plague disease for over 127 years. In most parts of Tanzania the disease is still endemic and some tangible efforts need to be made to be able to eradicate this historical threat. Plague was introduced to Tanzania and countries in Eastern, Central and Southern Africa from the Middle East or India by various medieval traders together with slavery and through pilgrims to and from Egypt and Saudi Arabia. This happened many yeas ago even before the first documented epidemic in the region [1, 2]. There are three basic forms of plague: Bubonic plague which is when the bacteria (Yersinia pestis) infects lymphatic system (immune system), causing inflammation of lymphoid organs such as spleen and the thymus; Pneumonic Plague is when the bacteria multiply in the lungs and Septicemic Plague is when the bacteria multiply in the bloodstream.The symptoms and sign of plague differ with the kind of plague a person has. In this study we only consider the dynamics of bubonic plague [3, 4].

It is severe infectious feverish disease characterized by chills, prostration, delirium, and formation of buboes. It is transmitted to humans mainly by the bite of a flea that has bitten an infected rodent or human and very rare when infected rodent bite human being [5]. Bubonic plague is the most common form of plague disease. Although in many cases it is contracted when an infected flea bites a Human being or rodent, in some few cases, one can get the bacteria from the environment/soil by touching and/or eating the infected material and contaminated undercooked food or animals that has come into contact with an infected individual [6]. It infects lymphatic system (immune system), causing inflammation of lymphoid organs such as spleen and the thymus. If not treated bubonic plague, can move into the blood and cause septicemic plague, or to the lungs, causing pneumonic plague [7, 8].

Symptoms of bubonic plague generally appear within two to seven days and include: Fever and chills, headache, muscle pain, general weakness and seizures. You may also experience painful swollen lymph glands called buboes, these typically appear in the groin, armpits, neck, or site of the insect bite or scratch. The buboes are what give bubonic plague its name [9].

1.1. Transmission and infection

When the *Yersinia pestis* are in flea's stomach, they multiply themselves making millions of copies, which in due course blocks the flea's digestive system. This makes it incapable of swallowing the blood it feeds on, as a result it gradually cause the hungry flea becomes a ravenous biter. Due to this the flea will attempts to feed on any warm-blooded animal it can possibly reach, it switches hosts frequently as it searches for a blood meal. Every time it bites, it swallows some blood, but since the flea's stomach is so full of Yersinia pestis, it vomits up the blood along with some Yersinia cells as a result cells gets inserted right into the new host [10]. During plague epizootics, many rodents die, causing hungry fleas to seek other sources of blood due to this people and other animals like Mice, rats, rabbits, squirrels, chipmunks, and prairie dogs that visit places where rodents have recently died from plague are at risk of being infected from flea bites [11, 12, 13, 14].

Without medical intervention, about 50 percent of people who have bubonic plague die, but treatment reduces the death rate to 50 percent for both varieties [15]. Bubonic plague can lead to gangrene if blood vessels in your fingers and toes disrupt blood flow and cause death to tissue. In rare cases, any form of plague may cause meningitis, an inflammation of membranes that surround your spinal cord and brain.

Although bubonic plague is historical, but the disease still occurs in different communities around the world. This plague persistance makes it different from many historical disease and thus arouse the need for different studies of the same. [16] developed a model of bubonic plague using the inbred Brown Norway strain of *Rattus norvegicus* to characterize the development and kinetics of infection and the host immune response after intradermal inoculation of Yersinia pestis. The model was also used to characterize the temporal development of histopathology and cellular immune response in the spleen and lymph nodes, and thus evaluate hypothesized mechanisms of Y. pestis pathogenesis and immune evasion during infection. The study made a milestone for studies that relates to microbial pathogenesis, host response, and the efficacy of new medical countermeasures against plague.

[17] also developed a stochastic, spatial metapopulation model to study the dynamic of plague disease by proposing that bubonic plague is driven by the disease kinetics in the rat population. The study further postulate that bubonic plague can continue in relatively small rodent populations from which rare human epidemics arise, which is why historically the plague persisted despite long disease-free periods and how the disease reappear in cities even to those with tight quarantine control. The study based its findings in the rodent population and specifically the metapopulation behavior of rodent population.

[18] developed model for bubonic plague that includes the disease dynamics in rat, flea and human populations. The dynamics of the disease is based in the force of infection to humans, variation in the flea searching efficiency and the movement rates of rats and flea. The study also discussed the stochastic behaviour of the corresponding metapopulation model. It intend to study the dynamics of rats and the force of infection at the local spatial scale and identify the criteria for the spread to human populations in terms of the rat density. The study found that Short-lived local epidemics in rats govern the transmission and spread and the endemic behavior in a few rat sub-populations allows the disease to persist for many years.

This study is underway to study the dynamics of bubonic plague and the effect of survival of bacteria in the environment, the study uses deterministic mathematical modeling approach, in which the bubonic plague disease model is formulated and analyzed for the ultimate goal of understanding the dynamic of bubonic disease and its force of infection to Human, Animal(Rodent), flea and environment.

2. Material and methods

The basic SEIR (Susceptible-Exposed-Infectious-Recovered) model is used with modification depending on the characteristics of the considered population and transmission network of bubonic plague disease. The model has four general settings; the human population, Flea population, Rodent population and pathogens in the soil/environment. In all four settings of the model assumes that all individuals from each population are born susceptible, and there is no

recovery for non-human host, the recovered individuals confer temporary immunity and return to be susceptible again, the infectious are all individuals with bubonic plague.

2.1. Model development

2.1.1. Description of the dynamics of bubonic plague in interactive population

In the model we consider four populations which are Human, Flea, Rodent and the pathogens within the environment. Within Human the population is divided into four subgroups: the group of people who have not contracted the disease but may get it if they get in contact with infectious agent (susceptible) S_H, People who have the disease but haven't shown any symptom and incapable of transmitting the disease(Exposed) denoted by E_H, people who are infected and are capable of transmitting the disease (Infective) denoted by I_H and people who are removed from population I_H through recovery denoted R_H. Flea are divided into two sub-groups: those who have not contracted the disease but may get it if they get in contact with infectious rodent or human (susceptible) S_F and those who are infected and are capable of transmitting the disease (Infective) denoted by I_F. The rodent population is also divided into three sub-groups: those who have not contracted the disease but may get it if they get in contact with infectious agent (susceptible) S_R, those who have the disease but haven't shown any symptom and incapable of transmitting the disease(Exposed) denoted by E_R and those who are infected and are capable of transmitting the disease (Infective) denoted by I_R.

The infection begin when Flea in sub-group S_F gets *Yersinia pestis* bacteria by either biting the infected rodent who are the primary reservoir of the bacteria at a rate Γ_{rf} or biting the infected human being at the rate Γ_{hf} with the proportional of ρ and $(1-\rho)$ respectively and become infected I_F, then I_F may cause the disease through biting the susceptible human being S_H and the susceptible rodent S_R at the rate Γ_{fh} and Γ_{fr} respectively and become latent to the disease thus progress to be exposed human E_H and exposed rodent E_R at the rate α_1 and γ_1 respectively. After two to seven days the sub-groups E_H and E_R become infected and capable of transmitting

the disease and thus progress to sub- group I_H and I_R at the rate α_2 and γ_2 respectively. The fraction of infected human being I_H may recover and attain temporary immunity at a rate α_3 and thus progress to a sub-group R_H which thereafter return to a sub-group S_H at the rate ϖ. The recovery may be through strong immunity and the rest will die either for natural death at the rate μ_1 and due to the disease at the rate δ_1.

After the infection all the infected rodent I_R die out due to disease at the rate δ_3 and naturally at a rate μ_3. The pathogen within the environment when interact with S_H and S_R causes infections at the rate ω_1 and ω_2 respectively. However they are recruited through birth at the rate λ_4 and they suffer natural mortality at a rate μ_4. The human population in sub-groups S_H and E_H , flea population in sub-group S_F and rodent population in sub-groups S_R and E_R both suffer natural mortality at a rate μ_1, μ_2 and μ_3 respectively. The compartments I_H, I_F and I_R suffer both natural death at the rate μ_1, μ_2 and μ_3 and disease induced mortality at rates δ_1, δ_2 and δ_3 respectively. The Human are recruited through immigration at the rate ψ_1, immigration may be to Susceptible, Latent and Recovery classes in proportionals π_1, π_2 and $\pi_3$respectively.

In flea migration differs when the flea is in susceptible or infectious classes, Yersinia pestis causes the flea to become increasingly hungry for blood which makes it feed on any warm-blooded animal it can reach, this situation makes the the infected flea to have a higher rate of migration ψ_{2i} compared to susceptible flea which also migrate at the rate ψ_{2s} which is to say $\psi_{2s} < \psi_{2i}$. Rodent are recruited through immigration at the rate ψ_3, the immigration may be to susceptible, Latent and infectious classes in proportionals k_1,k_2 and k_3 respectively.

The variables and the parameters are summarised in Tables 1 and Table 2 respectively.

TABLE 2. Variables and their description.

Parameters	**Description**
Γ_{rf}	Adequate contact rate: rodent to flea
Γ_{fh}	Adequate contact rate: flea to human
Γ_{fr}	Adequate contact rate: flea to rodent
α_1	Progression rate of susceptible human to exposed

Continued on next page

Table 2 – *Continued from previous page*

Parameters	**Description**
γ_1	Progression rate of susceptible rodent to exposed
Γ_{hf}	Adequate contact rate: human to flea
λ_4	Recruitment rate of pathogens
α_2	Progression rate of exposed human to infected
γ_2	Progression rate of exposed rodent to infected
α_3	Human recovery rate
ϖ	Progression rate of recovered human to susceptible
μ_1	Natural death rate for Human
δ_1	Disease induced death rate for Human
δ_3	Disease induced death rate for rodent
μ_3	Natural death rate for rodent
ω_1	Adequate contact rate: Pathogens to human
ω_2	Adequate contact rate: Pathogens to rodent
μ_4	Natural death rate for Pathogens
μ_2	Natural death rate for flea
δ_2	Disease induced death rate for flea
ψ_1	Immigration rate of human
ψ_{2s}	Immigration rate of Susceptible flea
ψ_{2i}	Immigration rate of Infected flea
ψ_3	Immigration rate of rodent
π_1	The proportional that migrant human are Susceptible
π_2	The proportional that migrant human are Exposed
π_3	The proportional that migrant human are Recovered
κ_1	The proportional that migrant rodent are Susceptible
κ_2	The proportional that migrant rodent are Exposed
κ_3	The proportional that migrant rodent are Infected

Continued on next page

Table 2 – *Continued from previous page*

Parameters	**Description**
β	The rate at which fleas become infected

According to the description of the dynamics of bubonic plague we construct the compartmental diagram for the dynamics of the plague as in Figure 1.

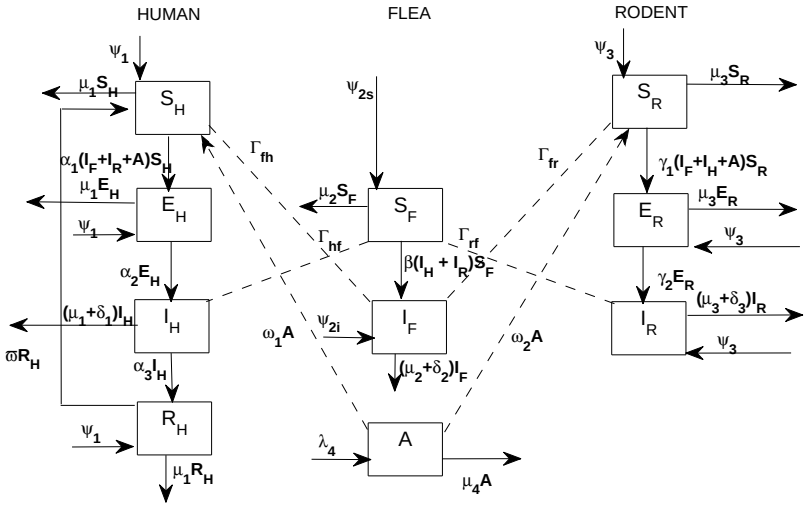


FIGURE 1. Compartment model for bubonic plague

TABLE 1. Variables and their description.

Variable	Description
S_H	Susceptible individuals
E_H	Exposed individuals
I_H	Infected individuals
R_H	Recovered individuals
S_R	Susceptible rodents
E_R	Exposed rodents
I_R	Infected rodents
S_F	Susceptible fleas
I_F	Infected fleas
A	Pathogens in the soil/environment

2.1.2. Model equations for bubonic plague

From the compartmental diagram in Figure 1 we derive the following equations;

Human

$$\frac{dS_H}{dt} = \pi_1\psi_1 + \varpi R_H - \alpha_1(\Gamma_{fh}\frac{I_F}{N_2} + \omega_1 A)S_H - \mu_1 S_H, \tag{1a}$$

$$\frac{dE_H}{dt} = \pi_2\psi_1 + \alpha_1(\Gamma_{fh}\frac{I_F}{N_2} + \omega_1 A)S_H - \alpha_2 E_H - \mu_1 E_H, \tag{1b}$$

$$\frac{dI_H}{dt} = \alpha_2 E_H - \alpha_3 I_H - (\mu_1 + \delta_1)I_H, \tag{1c}$$

$$\frac{dR_H}{dt} = \pi_3\psi_1 + \alpha_3 I_H - \varpi R_H - \mu_1 R_H. \tag{1d}$$

Rodent

$$\frac{dS_R}{dt} = \kappa_1\psi_3 - \gamma_1(\Gamma_{fr}\frac{I_F}{N_2} + \omega_2 A)S_R - \mu_3 S_R \tag{2a}$$

$$\frac{dE_R}{dt} = \kappa_2\psi_3 + \gamma_1(\Gamma_{fr}\frac{I_F}{N_2} + \omega_2 A)S_R - \gamma_2 E_R - \mu_3 E_R \tag{2b}$$

$$\frac{dI_R}{dt} = \kappa_3\psi_3 + \gamma_2 E_R - (\mu_3 + \delta_3)I_R \tag{2c}$$

Flea

$$\frac{dS_F}{dt} = \psi_{2s} - \beta(\rho\Gamma_{hf}\frac{I_H}{N_1} + (1-\rho)\Gamma_{rf}\frac{I_R}{N_3})S_F - \mu_2 S_F \tag{3a}$$

$$\frac{dI_F}{dt} = \psi_{2i} + \beta(\rho\Gamma_{hf}\frac{I_H}{N_1} + (1-\rho)\Gamma_{rf}\frac{I_R}{N_3})S_F - (\mu_2+\delta_2)I_F \tag{3b}$$

where $\psi_{2s} < \psi_{2i}$

Pathogens

$$\frac{dA}{dt} = \lambda_4 - \omega_1 A S_H - \omega_2 A S_R - \mu_4 A \tag{4}$$

3. Basic properties of the model

3.1. Positivity of the solution and invariant regions

Solving the equations of the system in their patches for testing the positivity, we found that by letting the initial values of the system $(1,2,3 and 4)$ be: $(S_H(0),\ S_R(0), S_F(0),\ A(0)) > 0$ and $(E_H(0), I_H(0), R_H(0), E_R(0),\ I_R(0), I_F(0)) \geq 0$ then the solution set $S_H(t)$, $S_R(t), S_F(t), A(t)$, $E_H(t), I_H(t), R_H(t),\ E_R(t), I_R(t)$ and $I_F(t)$ are non-negative $\forall$ t≥ 0.

Since the system is modeling Human, Rodent, Vector(flea) and pathogens populations, we assume that all state variables and parameters of the model are non-negative $\forall t \geq 0$. The bubonic plague disease model has four compartments which are analyzed separately. The model system is analyzed in suitable feasible region. It is proved that all forward solutions in R_+^{10} of the system are feasible $\forall t \geq 0$ if they enter the invariant region Φ for $\Phi = \Omega_H \times \Omega_R \times \Omega_F \times \Omega_A$ where

$$\Omega_H = (S_H, E_H, I_H, R_H) \in R_+^4 : S_H + E_H + I_H + R_H \leq N_1$$

$$\Omega_R = (S_R, E_R, I_R) \in R_+^3 : S_R + E_R + I_R \leq N_3$$

$$\Omega_F = (S_F, I_F) \in R_+^2 : S_F + I_F \leq N_2$$

$$\Omega_A = A \in R_+^1$$

and Φ is the positive invariant region of the whole system.

4. Model analysis

In this section we consider existence of equilibrium states, reproduction number and stability of the equilibrium states.

4.1. Disease free equilibrium

The model has disease free equilibrium which is obtained by setting $I_H = E_H = R_H = 0$, $I_R = E_R = 0$,$I_F = 0$ and $A = 0$ for human , Rodent, Flea and pathogen system respectively. We then substitute the above into the new system obtained by setting the derivatives of (1) - (4) equal to zero.

Then we have the disease free-equilibrium point given as $E_H^0 = \left(\frac{\pi_1\psi_1}{\mu_1}, 0, 0, 0\right)$, $E_R^0 = \left(\frac{\kappa_1\psi_3}{\mu_3}, 0, 0\right)$, $E_F^0 = \left(\frac{\psi_{2s}}{\mu_2}, 0\right)$ and $E_A^0 = 0$ for human, Rodent, Flea and pathogen respectively.

Then the disease free equilibrium of the entire system

$$E^0(S_H^0, E_H^0, I_H^0, R_H^0, S_R^0, E_R^0, I_R^0, S_F^0, I_F^0, A^0) = \left(\frac{\pi_1\psi_1}{\mu_1}, 0, 0, 0, \frac{\kappa_1\psi_3}{\mu_3}, 0, 0, \frac{\psi_{2s}}{\mu_2}, 0, 0\right)$$

4.2. Basic reproduction number R_0

Basic reproduction number is the expected number of secondary cases produced by a single infected individual during the entire infectious period of that particular individual in a completely susceptible population. The epidemiological criterion of R_0 is that if $R_0 < 1$, then the single infected individual in entirely susceptible population infects less than one individual. Hence the disease may be eradicated from the population and the disease-free equilibrium point is asymptotically stable.That is the disease cannot invade the population. If $R_0 > 1$ it means that a single infected individual in entirely susceptible population infects more than one individuals. Hence the disease may persist in the population, and the disease free equilibrium point is unstable. In this case the disease can invade the population and persist for a long time [19].

We use next generation method as described by [20] to find the basic reproductive number. Consider a heterogeneous population whose individuals are distinguishable by stage of the disease, and hence identifiable and put into epidemiological compartments $S_H, E_H, I_H, R_H, S_R, E_R, I_R$, S_F, I_F and A. By first re-arranging the system to have the infection classes come first we sort the compartments so that the first m compartments correspond to infected individuals.

We now let $F_i(x)$ be the rate of appearance of new infections in compartment i, $V_i^+(x)$ be the rate of transfer of individuals into compartment i by all other means other than the epidemic and $V_i^-(x)$ be the rate of transfer of individuals out of compartment i.

The disease transmission model consists of the system of equations $x_i^{'} = F_i(x) - V_i(x)$
where $V_i(x) = V_i^-(x) - V_i^+(x)$
Since we already have the disease free equilibrium x_0 we then compute matrices F and V which are $m \times m$ matrices defined by:

$$F = \left(\frac{\partial F_i}{\partial x_j}(x_0)\right), V = \left(\frac{\partial V_i}{\partial x_j}(x_0)\right)$$

With $1 \leq i, j \leq m$ Since F is non-negative and V is a non-singular matrix then V^{-1} is non-negative and also FV^{-1} is non-negative. Matrix FV^{-1}, is defined as next generation matrix [21]. Therefore the basic reproductive number is defined as $R_0 = \rho(FV^{-1})$, the maximum modulus of the eigenvalues of the non-negative matrix FV^{-1}.

F and V are the Jacobian matrices of F_i and V_i respectively at x_0. From FV^{-1} after the computation we can now obtain the basic reproduction number R_0 which is computed by finding the spectral radius $\rho(FV^{-1})$ of the next generation matrix in which the dominant eigenvalue of matrix FV^{-1} will be the required R_0.

The basic reproduction number is now:

$$R_0 = \sqrt{\frac{\beta}{(\mu_2+\delta_2)}\left(\frac{\gamma_2\gamma_1\Gamma_{rf}\Gamma_{fr}(1-\rho)}{(\mu_3+\gamma_2)(\mu_3+\delta_3)} + \frac{\rho\alpha_2\alpha_1\Gamma_{hf}\Gamma_{fh}}{(\alpha_2+\mu_1)(\alpha_3+\mu_1+\delta_1)}\right)}$$

This dimensionless quantity measuring the average number of secondary infection produced when a typical infectious individual enters an entirely susceptible population but since our model has multiple transmission cycle which are flea to rodent , flea to human , pathogens in the environment to rodent and human, rodent to flea and human to flea transmissions then the basic

reproductive number obtained via next-generation method does not give the number of host infected by a single individual (as there are more than one agents for transmission), but rather the geometric mean of the number of infections per generation [22]. It depend on the rate at which fleas gets infected β, fleas infective period $\frac{1}{\mu_2+\delta_2}$, probability that rodent survive the infected class $\frac{\gamma_2}{\mu_3+\gamma_2}$, rodent's infective period $\frac{1}{\mu_3+\delta_3}$, the proportion that flea gets the disease from the rodent or human which are $(1-\rho)\Gamma_{rf}$ or $\rho\Gamma_{hf}$ respectively, human's infective period $\frac{1}{\mu_1+\delta_1+\alpha_3}$, probability that human survive the infected class $\frac{\alpha_2}{\mu_1+\alpha_2}$, the adequate contact rate flea to human Γ_{fh}, the adequate contact rate flea to rodent Γ_{fr} and the rate at which human and rodent become exposed to the the disease which are α_1 and γ_1 respectively.

5. Sensitivity analysis, simulation and discussion

Sensitivity analysis is normally used to determine the strength of model predictions to parameter values. In this section we use sensitivity analysis to determine the impact of parameters on R_0. In order to determine an outstanding way that can reduce human and rodent (domestic animals) mortality and morbidity due to bubonic plague disease, it is very important to deeply understand the comparative importance of factors that are responsible for the transmission and prevalence of the disease [23].

Parameter values; Table 3 shows the values of the parameters of bubonic plague disease model. The parameters are taken from the previous studies that relate to this study, existing information and through estimation.

TABLE 3. Parameters values for plague disease model..

Parameters	**Value/Range**	**Reference/Source**
Γ_{rf}	0.6	Estimated
Γ_{fh}	0.09	[24]
Γ_{fr}	4.7	[25]
α_1	0.9	Estimated
γ_1	0.9	Estimated

Continued on next page

Table 3 – *Continued from previous page*

Parameters	**Value/Range**	**Reference/Source**
Γ_{hf}	0.28	[24]
λ_4	0.89	Estimated
α_2	0.04	[18]
γ_2	0.05	[18]
α_3	0.1	[18]
ϖ	0.1	[18]
μ_1	0.04	[18]
δ_1	0.04	[18]
δ_3	0.05	[17]
μ_3	0.2	[26]
ω_1	0.01	[18]
ω_2	0.073	[24]
μ_4	0.1	Estimated
μ_2	0.07	[24]
δ_2	0.03	[24]
ψ_1	0.09	Estimated
ψ_{2S}	0.008	[17]
ψ_{2i}	0.08	Estimated
ψ_3	0.03	[18]
β	0.99	Estimated

Figure 2a, Figure 2b, Figure 2c and Figure 2d shows the dynamics of the compartments in Human, Rodent, Flea and Pathogens population respectively. In Human population it can be seen that there is an increase in susceptible and infected human for a short period of time, then

it decreases to the endemic equilibrium point. Compartments Exposed and Recovered human shows the exponential decay to the endemic points.

In Rodent population we also note that there is a fast increase of infected rodent it then undergo exponential decay together with susceptible and Exposed rodent classes to the endemic point. The sub population Flea also experience an increase of infected flea for the short time before it decays together with susceptible flea class to the endemic point. The Pathogens in the environment experience a rapid decay to the endemic point. The features displayed by all groups is realistic and biologically relevant as there is no any intervention to combat the disease, the little recovery rate that is seen in human group is based on the individual's immunity only. Thus it is fact that the compartment in all groups will eventually decrease to the endemic points and if there is no intervention then the whole population (Human, Rodent and flea) become infected and ultimately go to extinct.

5.1. Sensitivity analysis of R_0

The sensitivity analysis of R_0 for plague disease model helps to determine the impact of various parameters in R_0 and thus parameters effect on the prevalence of bubonic plague disease. In this section we analyze a bubonic plague model by evaluating the sensitivity indices of the basic reproductive number, R_0, to model parameters using the baseline values given in Table 3. Since R_0 is a measure of initial disease transmission, these sensitivity indices allow us to determine the relative importance of different parameters in bubonic plague transmission and prevalence [27]. The basic reproduction number R_0 of bubonic plague depends on seventeen parameters, we derive an analytical expression for its sensitivity to each parameter using the normalized forward sensitivity indices of R_0 with respect to parameters n_i involved in R_0 as given below:

$$\Upsilon_{n_i}^{R_0} = \frac{\partial R_0}{\partial n_i} \times \frac{n_i}{R_0}$$

For example the sensitivity indices of R_0 with respect to β and δ_2 are given respectively by:

$$\Upsilon_{\beta}^{R_0} = \frac{\partial R_0}{\partial \beta} \times \frac{\beta}{R_0} = \frac{1}{2} \quad \text{and } \Upsilon_{\delta_2}^{R_0} = \frac{\partial R_0}{\partial \delta_2} \times \frac{\delta_2}{R_0} = \frac{-\beta}{2(\mu_2 + \delta_2)}$$

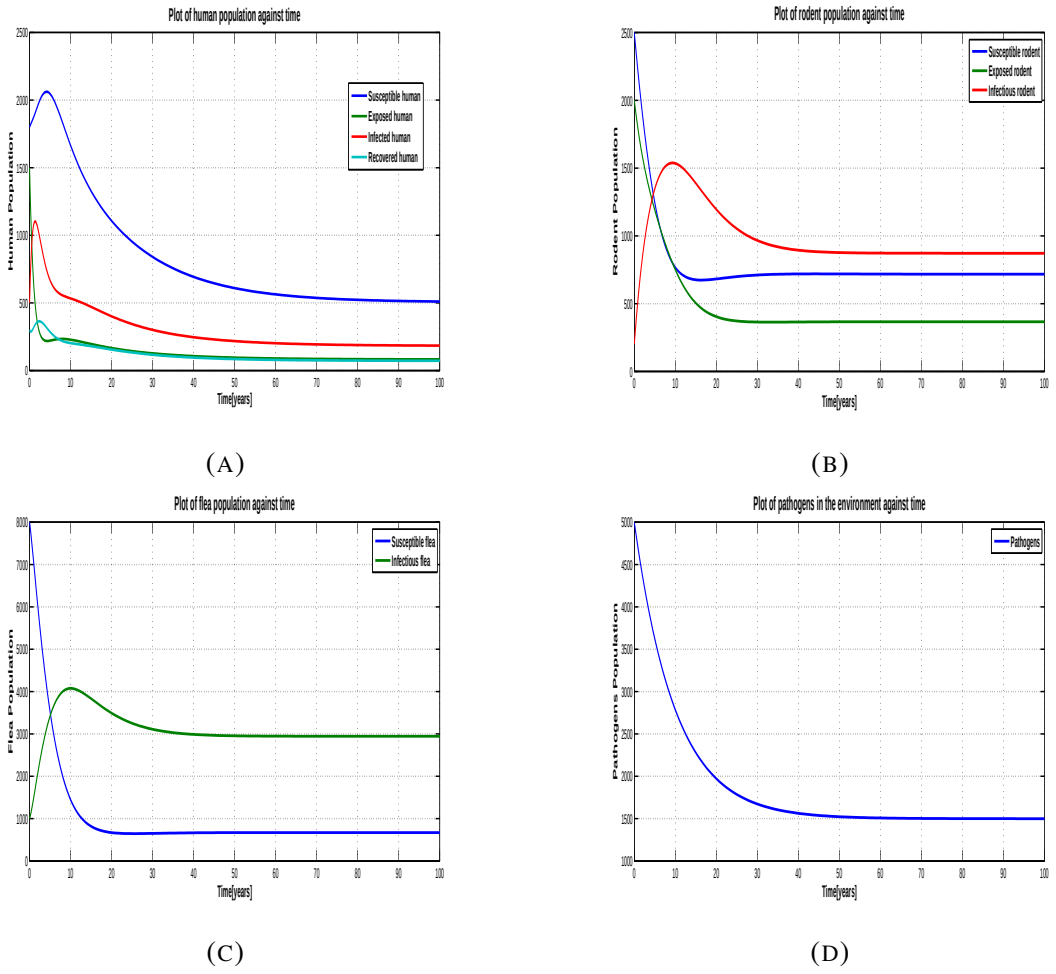


FIGURE 2. The dynamics of all compartments from Human, Rodent, Flea and Pathogens in the environment with baseline parameter values given in Table 3. These parameters correspond to $R_0 = 3.2$.

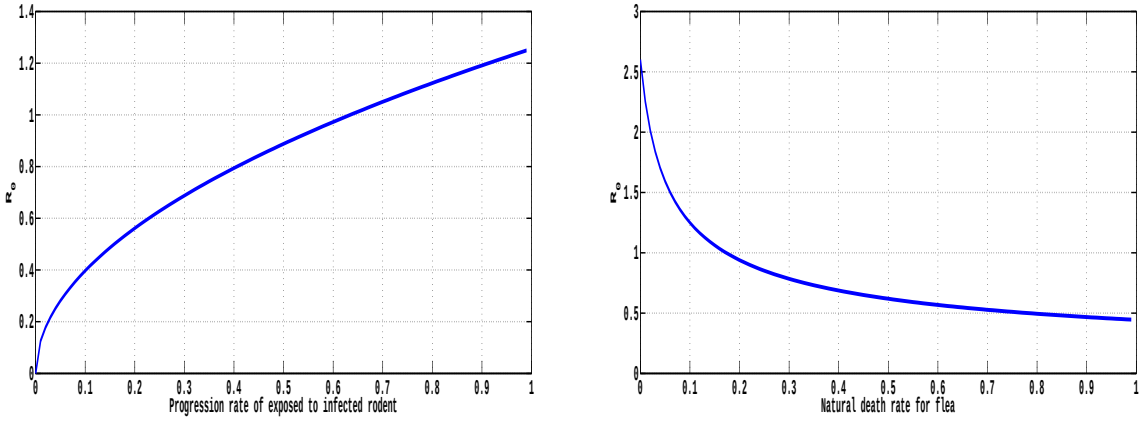
Now using the same procedure we can find the indices for $\Upsilon^{R_0}_{\Gamma_{fh}}$, $\Upsilon^{R_0}_{\Gamma_{hf}}$, $\Upsilon^{R_0}_{\Gamma_{fr}}$, $\Upsilon^{R_0}_{\Gamma_{rf}}$, $\Upsilon^{R_0}_{\alpha_1}$, $\Upsilon^{R_0}_{\alpha_2}$, $\Upsilon^{R_0}_{\alpha_3}$, $\Upsilon^{R_0}_{\delta_1}$, $\Upsilon^{R_0}_{\delta_3}$, $\Upsilon^{R_0}_{\gamma_1}$, $\Upsilon^{R_0}_{\gamma_2}$, $\Upsilon^{R_0}_{\mu_1}$, $\Upsilon^{R_0}_{\mu_2}$ and $\Upsilon^{R_0}_{\mu_3}$ as tabulated in Table 4;

From Table 4 we discover that the most sensitive parameter is the progression rate of flea from susceptible state to infected state (β), the parameters adequate contact rate from infectious flea to susceptible human being (Γ_{fh}), adequate contact rate infectious human being to susceptible flea (Γ_{hf}), progression rate of susceptible human to exposed human (α_1), adequate contact rate infectious flea to susceptible rodent (Γ_{fr}), adequate contact rate infectious rodent to susceptible flea (Γ_{rf}), progression rate of exposed human to infected human (α_2), progression rate of susceptible rodent to exposed rodent (γ_1) and progression rate of exposed rodent to infected

TABLE 4. Sensitivity indices evaluated at baseline parameter values.

Parameter	**Sensitivity Index**	**Parameter**	**Sensitivity Index**
Γ_{rf}	+0.4986	δ_3	-0.0100
Γ_{fh}	+0.0014	μ_3	-0.3144
Γ_{fr}	+0.4986	μ_2	-0.8846
α_1	+0.0014	δ_2	-0.1154
γ_1	+0.4986	α_2	+0.0006
Γ_{hf}	+0.0014	γ_2	+0.4155
α_3	-0.0005	δ_1	-0.0004
μ_1	-0.0011	β	+0.5
ρ	+0.1232		

rodent (γ_2) are positive. The positive sign of the mentioned parameters implies that increasing (decreasing) one of these parameters while keeping others constant increases (decreases) the value of the basic reproduction number. For example the sensitivity indices of R_0 with respect to β is $\frac{1}{2}$, this implies that increasing progression rate of susceptible flea to infectious flea by 10%, increases the value of basic reproduction number by 5% and hence increases the persistence of the disease; the vice versa is also true. Additionally the indices of human recovery rate (α_3), disease induced death rate for Human (δ_1), disease induced death rate for flea (δ_2), disease induced death rate for rodent (δ_3), natural death rate for Human (μ_1), natural death rate for flea (μ_2) and natural death rate for rodent (μ_3) are negative. This entails that increasing (decreasing) one of these parameters while keeping the other constant decreases (increases) the value of basic reproduction number R_0 and hence decreases (increases) the persistence of bubonic plague. Figure 3 illustrates the effect of the most sensitive positive index (progression rate of exposed flea to infected (β)) and the most sensitive negative index (flea's natural death rate (μ_2)) on the basic reproduction number. In Figure 3a we note that the increase of progression rate of exposed flea to infected result to the rapid increase of the basic reproduction number this may be due to the fact that the infected flea is the main transmitter of plague disease. Figure 3b shows quite significant exponential decrease of the basic reproduction number as we increase flea's



(A) (B)

FIGURE 3. The effect of progression rate of exposed flea to infected and flea's natural death rate on the basic reproduction number

natural death rate (μ_2). The behavior that is seen in Figure 3b cement the point we made in Figure 3a that since fleas are the major player in the transmission and spread of plague disease, the increase of flea's death rate will reduce the flea's population and thus automatically reduces the transmission rate of bubonic plague disease in human, rodent and to the environment. [28] postulates that generally as the number of infected flea increases the disease transmission into the rodent and human populations increase as well, this is because, flea plays the vital role in the transmission of bubonic plague as demonstrated in Figure 4. The parameters that increases the basic reproduction number proportionally increase the endemicity of the disease [29]. In the

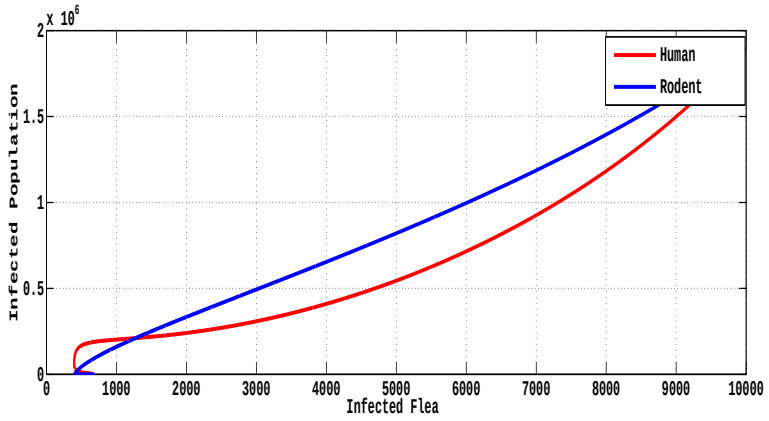
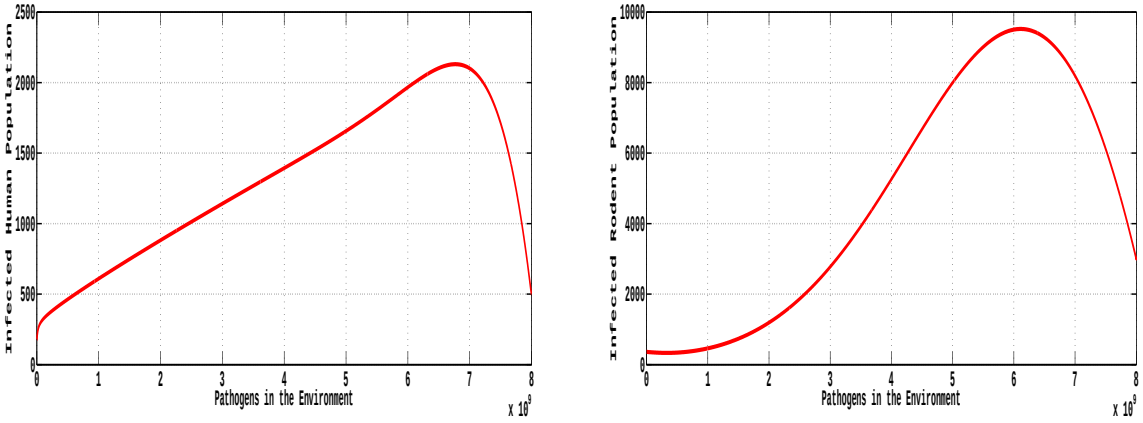


FIGURE 4. Variation of Infected Human and Rodent with Infected Flea population

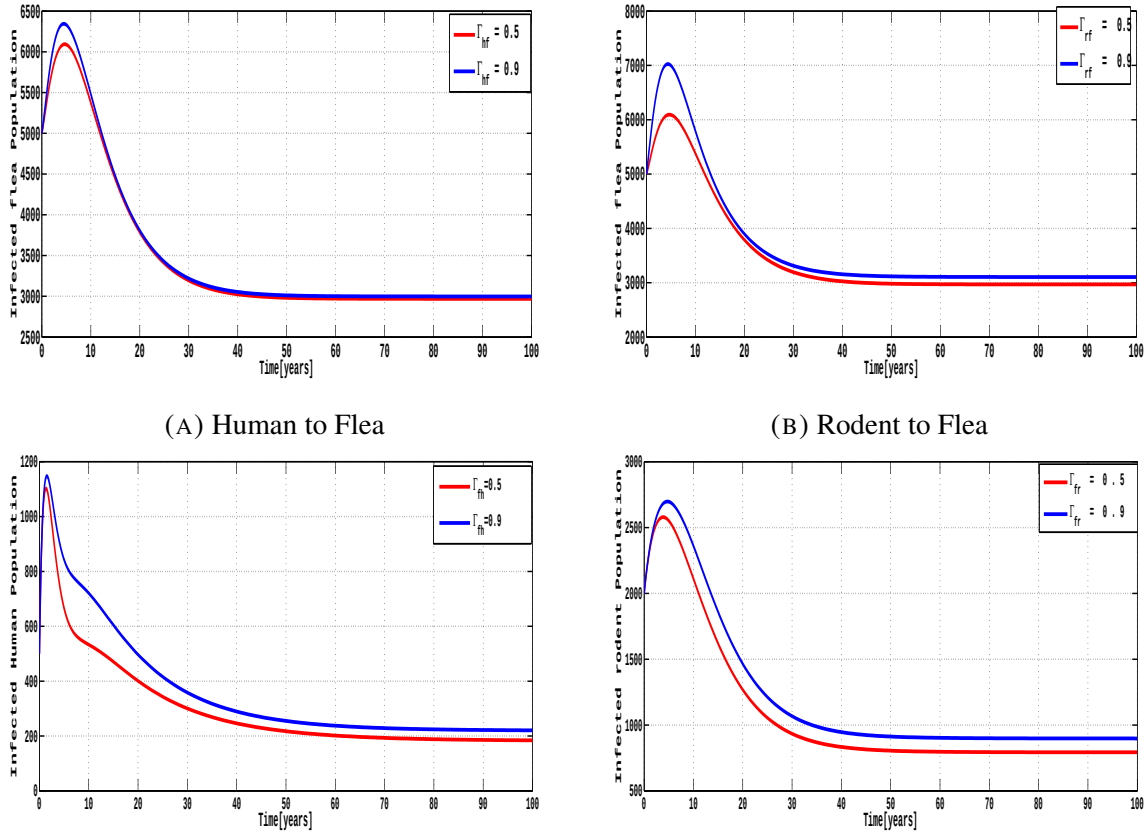


(A) (B)

FIGURE 5. Variation of Infected Human and Rodent with the increased number of Pathogens in the Environment

basic reproduction number the contribution of the pathogens in the environment is negligible, this is due to the fact that due to the nature of bubonic plague (when the Yersinia pestis affect the lymphatic system) the transmission from the environment to the human and rodent population is very rare, which is also confirmed by [30]. [31] who postulate that *Yersinia pestis* survives at the temperature between $4°C$ to $8\ °C$. But under normal circumstances taking Tanzania as an example it is uncommon to find the area with such temperature, the absence of this condition lead to enormous number of death of pathogens in the environment which as a result lead to its poor contribution in the transmission and spread of Bubonic Plague.

Assuming the availability of the favorable condition for pathogen's growth, will result to the enormous increases of pathogens population in the environment. This will increases the possibility of the disease transmission from the pathogens in the environment to the human and rodent. Figure 5a and Figure 5b illustrate the effect of the increasing number of pathogens in the environment to the infected human and rodent respectively. The figures shows the increase number of infected human and rodent with the increase number of pathogens in the environment to their maximum which is the point where all human and rodent become infectious. The populations then decline due to natural and disease induced death. The bubonic plague transmission is initiated after the adequate contact between the infected flea with either the human being or



(A) Human to Flea

(B) Rodent to Flea

(C) Flea to Human

(D) Flea to Rodent

FIGURE 6. The effect of contact rate to the infected Human and Rodent and to the infected Flea

the rodent: and the vise versa. As seen in Table 4 adequate contact rates carries the very significant task in the transmission and spread of bubonic plague disease. Figure 6a, Figure 6b, Figure 6c and 6d shows the effect of contact rate between human to flea, rodent to flea, and flea to human and rodent. We note that in all cases the increase of contact rate between the infected and the susceptible results to the increase of infected class. Therefore any mechanism/strategy of controlling the disease must, take the parameters that have shown a great importance in the transmission and spread of bubonic plague into consideration. Most of the parameters may be reduced by reducing/eradicating the infected fleas and rodent population and treating the contaminated environment by using various ways that will kill the pathogens in the environment. The analysis shows the best control measure of the bubonic plague disease outbreak will be the one that will reduce the value of β which will then reduce the number of infected fleas which

are the major players in the transmission and spread of bubonic plague disease in human and rodent population. The infected flea carries the significant contribution in the transmission and spread of bubonic plague disease, although some susceptible human and rodent may get the disease through their interaction with the environment but in most cases it is fleas that cause the disease to the two groups.

There are also parameters in which their increase reduces the initial diseases transmission, these are natural and disease induced death rate for human, flea and rodent and human recovery rate. The increase of disease induced death rates in human , rodent and flea will reduce the population of infectious classes as a result hinders the occurrence of new infection to susceptible population and thus reduce initial bubonic plague transmission, the natural death rates for human, rodent and flea reduces the general population but most importantly the infectious and exposed classes which in turn reduces the infectious classes which then reduces the transmission force of the disease. The human recovery rate reduces the number of infected human population which in this study we consider it to be through natural recovery, the reduction of I_H also reduces the the transmission force of the disease.

To effectively guide public policy and public health decision making, the mentioned factors that affect the parameter values must be highly considered. Using the values of the parameters used in this study the value of R_0 exceeds one, this tells us that the disease will persist within the community and thus various control measures should be taken to control and/or eliminate the disease.

6. Discussion and conclusion

The SEIR model with modification is developed and analyzed to study the dynamics of bubonic plague disease, the model includes four population which are Human, Rodent who are also the primary reservoir of Yesinia pestis, Flea and pathogens within the environment. The analytical results shows that the Disease Free Equilibrium (DFE) and the Endemic Equilibrium (EE) are locally and globally asymptotically stable, it also shows that bubonic plague

transmission to both human and rodent population depends largely on the infected flea population. Moreover infected rodent and human are the major transmission agent to flea population of which their increase course the severe effect on the transmission and spread of bubonic plague.

The basic reproduction number R_0 is computed and discussed using the sensitivity analysis, and thus obtain the parameter which are most, medium and least sensitive to the initial transmission of bubonic plague. The rate at which the infected flea are recruited and the contact rate between Flea - Huma and Flea - Rodent have shown to have a significant positive contribution in the transmission and spread of bubonic plague disease as seen in Figure 3a and Figure 6. Other parameters like Fleas, Rodent and Human natural and disease induced death rate contribute negatively on the bubonic plague transmission as in Figure 3b. These parameters are very vital in determining where and how to implement the control strategies for the eradication of the disease

The numerical solutions shows that without the intervention the population vary for some point but ultimately they all go/approach to endemic points and after a long time if there is no any intervention every one will be infected and die naturally and due to the disease. This study recommends that for the sustainable control of bubonic plague any intervention strategy should take into consideration the parameter that have shown to be very sensitive (negatively and positively) to the basic reproduction number in order to reduce the endemicity of the disease or if possible eradicate the disease whenever an outbreak occur.

Conflict of Interests

The authors declare that there is no conflict of interests.

REFERENCES

[1] B. Kilonzo, R. Makundi, and T. Mbise, "A decade of plague epidemiology and control in the western usambara mountains, north-east tanzania," *Acta tropica*, 50(1992), no. 4, 323–329.

[2] M. H. Ziwa, M. I. Matee, B. M. Hang'ombe, E. F. Lyamuya, and B. S. Kilonzo, "Plague in tanzania: an overview," *Tanzania Journal of Health Research*, 15(2014), no. 4, 1–9.

[3] L. D. Crook and B. Tempest, "Plague: a clinical review of 27 cases," *Archives of internal medicine*, 152(1992), no. 6, 1253–1256.

[4] N. C. Stenseth, B. B. Atshabar, M. Begon, S. R. Belmain, E. Bertherat, E. Carniel, K. L. Gage, H. Leirs, and L. Rahalison, "Plague: past, present, and future," *PLoS medicine*, 5(2008), no. 1, p. e3.

[5] R. R. Parmenter, E. P. Yadav, C. A. Parmenter, P. Ettestad, and K. L. Gage, "Incidence of plague associated with increased winter-spring precipitation in new mexico.," *The American journal of tropical medicine and hygiene*, 61(1999), no. 5, 814–821.

[6] S. Scott and C. J. Duncan, *Biology of plagues: evidence from historical populations*. Cambridge University Press, 2001.

[7] D. Emmeluth and I. E. Alcamo, *Plague*. Infobase Publishing, 2009.

[8] C. A. Benedict, *Bubonic plague in nineteenth-century China*. Stanford University Press, 1996.

[9] W. E. Wingfield and S. B. Palmer, *Veterinary disaster response*. John Wiley & Sons, 2009.

[10] P. Moore, *Pandemic: The Terrifying Threat of the New Killer Plagues*. Citadel Press, 2007.

[11] R. J. Eisen and K. L. Gage, "Adaptive strategies of yersinia pestis to persist during inter-epizootic and epizootic periods," *Veterinary research*, 40(2009), no. 2, 6–9.

[12] M. Drancourt, L. Houhamdi, and D. Raoult, "Yersinia pestis as a telluric, human ectoparasite-borne organism," *The Lancet infectious diseases*, 6(2006), no. 4, 234–241.

[13] R. D. Perry and J. D. Fetherston, "Yersinia pestis–etiologic agent of plague.," *Clinical microbiology reviews*, 10(1997), no. 1, 35–66.

[14] M. J. Echenberg, *Plague ports: the global urban impact of bubonic plague, 1894-1901*. NYU Press, 2007.

[15] M. F. Antolin, P. Gober, B. Luce, D. E. Biggins, W. E. Van Pelt, D. B. Seery, M. Lockhart, and M. Ball, "The influence of sylvatic plague on north american wildlife at the landscape level, with special emphasis on black-footed ferret and prairie dog conservation," *US Fish & Wildlife Publications*, p. 57, 2002.

[16] F. Sebbane, D. Gardner, D. Long, B. B. Gowen, and B. J. Hinnebusch, "Kinetics of disease progression and host response in a rat model of bubonic plague," *The American journal of pathology*, 166(2005), no. 5, 1427–1439.

[17] M. Keeling and C. Gilligan, "Metapopulation dynamics of bubonic plague," *Nature*, 407(2000), no. 6806, 903–906.

[18] M. Keeling and C. Gilligan, "Bubonic plague: a metapopulation model of a zoonosis," *Proceedings of the Royal Society of London. Series B: Biological Sciences*, 267(2000), no. 1458, 2219–2230.

[19] L. J. Allen, F. Brauer, P. Van den Driessche, and J. Wu, *Mathematical epidemiology*. Springer, 2008.

[20] P. Van den Driessche and J. Watmough, "Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission," *Mathematical biosciences*, 180(2002), no. 1, 29–48.

[21] O. Diekmann, J. Heesterbeek, and J. A. Metz, "On the definition and the computation of the basic reproduction ratio r 0 in models for infectious diseases in heterogeneous populations," *Journal of mathematical biology*, 28(1990), no. 4, 365–382.

[22] J. Li, D. Blakeley, and R. Smith, "The failure of r0. computational and mathematical methods in medicine, 2011," *Article ID*, vol. 527610, 2011.

[23] T. Cohen and M. Murray, "Modeling epidemics of multidrug-resistant m. tuberculosis of heterogeneous fitness," *Nature medicine*, 10(2004), no. 10, 1117–1121.

[24] S. Benkirane, C. Shankland, R. Norman, and C. McCaig, "Modelling the bubonic plague in a prairie dog burrow, a work in progress," *PASTA 2009*, p. 145, 2009.

[25] W.-H. Li, "Unbiased estimation of the rates of synonymous and nonsynonymous substitution," *Journal of molecular evolution*, 36(1993), no. 1, 96–99.

[26] N. Galtier and D. Mouchiroud, "Isochore evolution in mammals: a human-like ancestral structure," *Genetics*, 150(1998), no. 4, 1577–1584.

[27] N. Chitnis, J. M. Hyman, and J. M. Cushing, "Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model," *Bulletin of mathematical biology*, 70(2008), no. 5, 1272–1296.

[28] W. McNeill, *Plagues and peoples*. Anchor, 2010.

[29] N. Hartemink, S. Randolph, S. Davis, and J. Heesterbeek, "The basic reproduction number for complex disease systems: Defining r0 for tick-borne infections," *The American Naturalist*, 171(2008), no. 6, 743–754.

[30] J. F. D. Shrewsbury, *A history of bubonic plague in the British Isles*. Cambridge University Press, 2005.

[31] R. Armon and U. Cheruti, *Environmental aspects of zoonotic diseases*. IWA Publishing, 2012.