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A mathematical model for Lassa fever

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Abstract

A mathematical model for the dynamics of Lassa fever is presented. Contributions from regular contact with the species of rats that carry the virus that cause Lassa fever and infectious contact with those suffering from the disease is seen as significant in the spread of the disease. Steady states of the model are examined for epidemic and endemic situations. A second model that incorporates the effect of vaccination on a subset of the target population is proposed, although at the moment there is no vaccine against the disease. However our model shows that in the interim, control of the rodents carrying the virus and some isolation policy for infected individuals are the best strategies against the spread of the disease.

Keywords: Mathematical model, steady state, Lassa fever, epidemic, endemic

1.0 Introduction

Lassa fever is a viral haemorrhagic fever transmitted by rats. It has been known since the 1950s, but the virus was not identified until 1969, when two missionary nurses died from it in the town of Lassa in Nigeria. Found predominantly in West Africa [12] it has the potential to cause tens of thousands of deaths. Even after recovery, the virus remains in body fluids, including semen [11, 12].

The rat species *Mastomys*, in particular, *M. natalensis* serves as the vectors for the virus. This is a consistent host reservoir for the Lassa virus because of congenital neonatal infection, which results in rats with long-lasting and/or lifelong infection. Because of the mechanism of infection, there is no break in the natural chain from virus to host species [6]. The rats themselves might show no symptoms of the disease, but they shed the virus freely in urine and droppings, and secrete the virus in their saliva.

Because certain varieties of *Mastomys* often live in human homes, the virus is easily transmitted to humans. Transmission of the virus occurs via direct contact with rat urine, faeces, and saliva; via contact with excretion- or secretion-infected materials; or via ingestion of excretion-contaminated food. In some areas, the rodents are used as a food source, thus providing additional exposure to the infected rat blood, as well as allowing ingestion of potentially contaminated meat [8].

Unlike other arenaviruses, Lassa virus can be fairly easily transmitted from human to human. Humans can contract the disease from other humans via aerosol transmission (coughing), or from direct contact with infected human blood, urine, or semen.

The first symptoms of the disease typically occur 1-3 weeks after the patient comes into contact with the virus and can include increasingly high fever, sore throat, cough, eye inflammation (conjunctivitis), facial swelling, retrosternal pain (behind the breastbone), back pain, abdominal pain, vomiting, diarrhea and general weakness lasting for several days. Neurological symptoms have also been described, including hearing loss, tremors, and encephalitis (brain inflammation). The most common long-term complication of Lassa fever is deafness [13].

The mortality rates for Lassa virus are typically estimated at 15% to 20%. Some studies estimate mortality as high as 45%. One survey of Lassa infection vs. mortality rates indicates that less than 1% of all Lassa-virus infections in West Africa will eventually result in fatal disease. The mortality rates for Lassa appear to be much higher in people of non-African stock [6].

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Lassa virus also causes high fetal mortality and high mortality in pregnant women. The mortality rate is 92% for fetuses in early pregnancy, 75% for fetuses in the third trimester, and 100% in the neonatal period for full-term babies. High concentrations of the virus have been found in both fetal tissue and in the placenta [6].

Currently, there is no effective prophylactic treatment for Lassa fever. However, some sources recommend prophylactic doses of Ribavirin for people coming in high-risk contact with viremic patients [6].

There are data evidences to show that Lassa fever activity is rife in the northern part of Edo State [10] and in other parts of Nigeria.

In this paper, we present a mathematical model for the dynamics of the disease. We take a critical look at the link between the rodent population as well as the human population. Steady states are examined and a threshold condition is obtained. We also examined situations that could allow for endemicity. Probable control strategies against the disease are then proposed at the end of the work.

2.0 The mathematical model

The model will be basically a SIS model coupled to a population of the rat species *M.natalensis*. The rationale for using a SIS type is because recovered individuals could become susceptible to the disease again.

In the formulation of our model, we simply invoked the principle of *Occam's razor* [1], which expressed in modern terms by Einstein, is "Everything should be made as simple as possible, but not simpler". Though the model is simple, we strive to ensure that the basic variables involved in the disease dynamics are captured.

The mathematical model is:

$$\begin{aligned}
\frac{dS}{dt} &= \mu N - mS - \beta VS - \alpha IS + \gamma I \\
\frac{dI}{dt} &= \beta VS + \alpha IS - \gamma I - mI \\
\frac{dV}{dt} &= rV(1-\frac{V}{K}) - \phi V \\
S(0) &= N, I(0) > 0, V(0) = 0
\end{aligned} \tag{2.1}$$

The symbols used in the model are listed in Table 1 and a diagrammatic representation of the model is given in Figure 1.

S	Number of susceptibles
I	Number of those who are infected with Lassa fever
V	Population of rodents carrying the virus
μ	Human birth rates (/day)
m	Human death rates (/day)
β	Pairwise infectious contact rate with rodents (/day)
α	Pairwise infectious rate with infected individuals (/day)
γ	Rate at which infected recover from lassa fever (/day)
r	Growth rate of the rodents (/day)
K	Carrying capacity of the environment for the rodents
ϕ	Death rate of the rodents (/day)
N	Total population of humans

Table 1. Symbols used in the mathematical model.

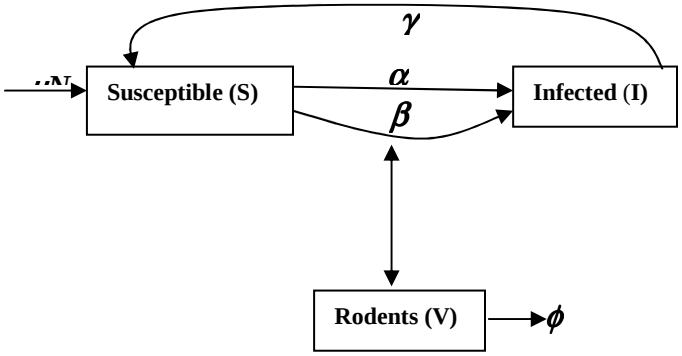

Figure 1: Diagrammatic representation of the Model

The equations in (1) describe the dynamics of susceptible and infected individuals as well as the rodent population. The first equation in (1) describes the dynamics of the susceptibles. The population is of constant size *N*. Susceptibles in the community are renewed at a rate μ and die at the rate m. The susceptibles become infected with the disease due to contacts with the rodents (this will refer to eating the rodents, contact with their faeces e.t.c.) at rate β and also due to infectious contacts with individuals suffering from Lassa fever at rate α. Since it is a SIS model we are using, recovered individuals get back to the susceptible pool at rate γ (recovery rate).

The second equation in (1) describes the dynamics of the infected people in the community; those suffering from Lassa fever. The equation states that the infected population increases as susceptibles become infected (first two terms in the second equation) and decreases as they recover from the disease and the rate at which they die.

The third equation in (1) describes the dynamics of the rodents. We have simply used a logistic growth equation to describe the population of the rodents, with K being the environmental carrying capacity for the rodents and r the growth rate. The rodents die (either naturally or by outright killing) at the rate ϕ.

All individuals in both human classes die at the same rate m. For the sake of the model, we assume that the birth rate is equal to the death rate.

3.0 Equilibrium Analysis

When modelling infectious diseases, the most important issue that arise is whether the disease will invade the community or not. To have a better understanding of the dynamics of the disease, equilibrium and stability analyses are performed.

We set each of the three derivatives in (1) equal to zero and solve for S, I and V. This gives the fixed points, or equilibrium solutions; that is, it gives values of S, I, and V for which the system will no longer change (since all of the derivatives, or rates of change, will be zero).

3.1 Stability Analysis

To determine the behaviour of the different populations near the equilibrium solutions, we need to compute the linearization of the system, which is obtained from the Jacobian matrix of the system.

For the system of equations in (2.1), the Jacobian, J, is the following matrix:

$$\begin{pmatrix} -m-\beta V-\alpha I & -\alpha S+\gamma & -\beta S \\ \beta V+\alpha I & \alpha S-\gamma-m & \beta S \\ 0 & 0 & r(1-\frac{V}{K})-\frac{rV}{K}-\phi \end{pmatrix} \qquad (3.1)$$

Now we compute the equilibrium points for the epidemic and endemic situations (if they exist) and do their stability analysis using the Jacobian matrix in (3.1) above.

3.2 Lassa free population.

There is a disease free equilibrium point, where the point is $(S^*, I^*, V^*) = (N, 0, 0)$. The superscript indicates equilibrium quantities. The important question here is: assume a small number of infectives come into a community, what will happen to the community? Will the disease free state be achieved? To answer that question, we carry out the stability analysis for the steady state.

For the point $(S^*, I^*, B^*) = (N, 0, 0)$, the Jacobian of the system is the following matrix:

$$\begin{pmatrix} -m & -\alpha N + \gamma & -\beta N \\ 0 & \alpha N - \gamma - m & \beta N \\ 0 & 0 & r - \phi \end{pmatrix} \qquad (3.2)$$

The eigenvalues of the Jacobian was found to be $\lambda_1 = -m,\ \lambda_2 = \alpha N - (\gamma + m),\ \lambda_3 = r - \phi$.

For the disease free state to be stable, all eigenvalues of (3.2) must be negative. This is possible if and only if

$$\gamma + m > \alpha N \qquad (3.3)$$

$$\phi > r \qquad (3.4)$$

So if (3.3) and (3.4) are achieved, then the disease dies out and there will be no invasion of the population by the disease. The inequality in (3.4) tells us that there should be a bound on the growth (population) of the rodents in the community. Once the inequalities in (3.3) and (3.4) are satisfied, then the disease dies out after enough time has passed and then we achieve a disease free situation i.e. the disease free state is asymptotically stable. From (3.3) we can obtain a threshold condition. From the equation, we see that $N < \frac{\gamma + m}{\alpha}$ (3.5)

Hence the critical susceptible pool is $S_c = \frac{\gamma + m}{\alpha}$ (3.6))

If the initial susceptible, $S_o > S_c$ then the disease will spread and there will be an epidemic. From (3.6), the basic reproduction number for the infection is given by $R_o = \frac{\alpha}{\gamma + m} S_c$ (3.7)

If $R_o > 1$, a disease outbreak will occur (the equilibrium point under consideration becomes unstable and the infection spreads), otherwise the diseases dies out and an introduction of infectives into a wholly susceptible population will not be enough to start an outbreak of the disease. In other words, the number of Lassa cases will reduce and will in fact return to zero if $R_o < 1$.

The S_c threshold (3.7) increases proportionally to the recovery and death rates of the infected. It decreases, on the other hand, when infectious contact rate with infected individuals increase. Hence, **reduce the contact rate with infected persons** (by say an isolation policy); the greater must be the number of susceptibles in order to trigger an outbreak of Lassa fever.

Interestingly, the threshold condition does not depend on contact rate with the rodents. This is obviously because the human population has nothing to do with the population of the rodents. However, as far as condition (3.3) is satisfied, then the threshold condition holds i.e. condition (3.6) and (3.7). Figure 4 shows a situation where the rate of killing the rats is less than their population growth rate, yet the disease free state was not achieved even though the initial susceptible pool did not exceed S_c. Hence **all** conditions ((3.3), (3.4), (3.6) and (3.7)) must be taking 'simultaneously' to achieve a disease free state.

We note though that contacts with infected humans is also very crucial to the overall dynamics of the disease, when considering the disease free state, since it is a major factor in determining S_c.

3.3 Endemic Lassa fever.

Again setting the derivatives in (2.1) to zero and solving algebraically, we obtain the endemic equilibrium:

$$S^* = N - I^* \qquad (3.8)$$

$$B^* = \frac{K(r-\phi)}{r} \tag{3.9}$$

$$\alpha I^{*2} + I^*\left(\frac{\beta K(r-\phi)}{r} - \alpha N + \gamma + m\right) - \frac{\beta K(r-\phi)}{r} N = 0 \tag{3.10}$$

where (3.10) needs to be solved as a quadratic equation to give the positive value(s) for I^*.
For the point (S^*, I^*, B^*), the Jacobian is:

$$\begin{pmatrix} -m-\beta V^*-\alpha I^* & -\alpha S^*+\gamma & -\beta S^* \\ \beta V^*+\alpha I^* & \alpha S^*-\gamma-m & \beta S^* \\ 0 & 0 & r(1-\frac{V^*}{K})-\frac{rV^*}{K}-\phi \end{pmatrix} \tag{3.11}$$

After carrying out some algebra and applying the second-order Routh-Houwitz criteria (calculations are omitted here as they are a little lengthy), all three eigenvalues of (3.11) are negative if and only if

$$V^* > \frac{K(r-\phi)}{2r} \tag{3.12}$$

$$N > 2S^* + \frac{1}{\alpha}\left(\frac{\beta K(\phi-r)}{r} - (\gamma+2m)\right) \tag{3.13}$$

$$N > 2S^* + \frac{1}{\alpha}\left(\frac{\beta K(\phi-r)}{r} - (\gamma+m)\right) \tag{3.14}$$

Hence the endemic steady state will be stable if and only if the inequalities in (3.12), (3.13) and (3.14) are all satisfied; otherwise the equilibrium point will remain unstable.

Condition (3.12) will always be satisfied for endemicity but condition (3.14) is a little stronger than (3.13) on the total population size. Once this size satisfies the inequality in (3.14) and condition (3.12) is also satisfied, then Lassa fever becomes endemic in the community.

We give numerical solutions to the model (2.1) for a hypothetical community with the following parameters given in Table 2:

Parameters	**Community**
N	500
μ	0.00054
m	0.00054
β	0.005
α	0.0002
γ	0.2
r	0.02
K	300
ϕ	0.045

Table 2: Data for numerical simulation of the model.

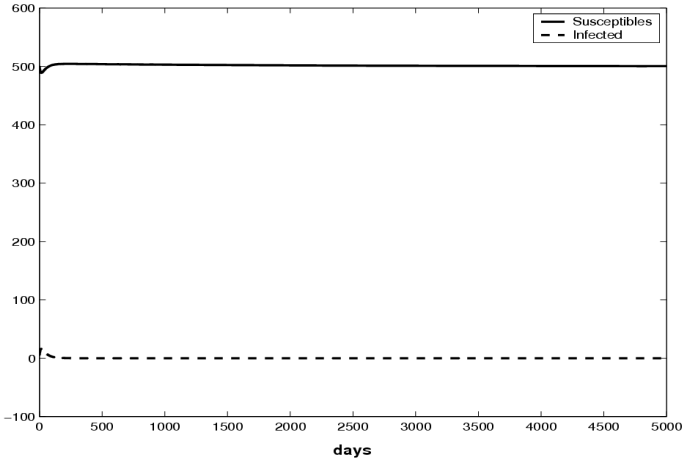

Figure 2: Population size of susceptibles and infected

We are interested in what happens to the community when striving to achieve a disease free state. That is our priority; to eradicate the disease if possible.

Figure 2 and figure 3 gives the population size of the community as well as the rat population. From figure 2, we clearly observe that the community gets to a disease free state, since the population of the rodents (figure 3) returned to zero as well as the population of the infected (figure 2). Worthy of note is that S_c = 1003. The initial susceptible pool is far less than S_c and the other conditions for achieving a disease free state were met; hence the disease could not invade the population but died out after enough time has passed.

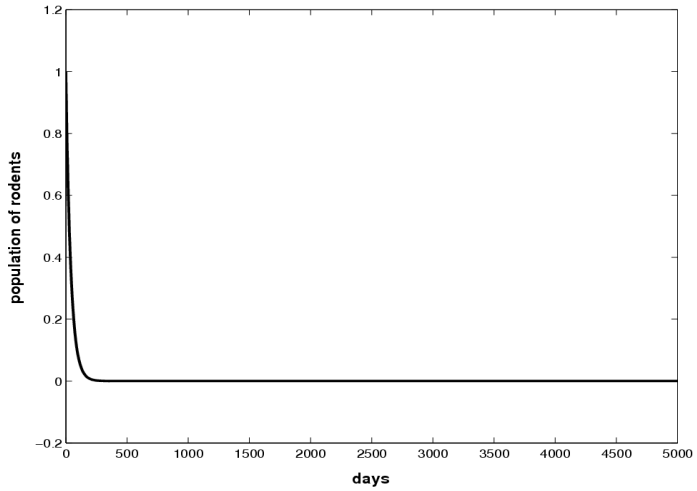

Figure 3: Rodent population

In figure 4, we adjusted the value for ϕ and r in Table 2, where we took the former to be 0.045 and the latter to be 0.2 (population growth rate of rats exceeds the rate at which they are killed). The critical susceptible pool S_c (3.6) remains the same, the initial susceptible number was still less than S_c, yet from figure 4, we see that a disease free state was not achieved. In fact the number of infected is so large to indicate an epidemic in the community. This shows that to achieve a disease free state, we must take into consideration **all** conditions that are needed to achieve such a state i.e. (3.3), (3'4), (3.6) and (3.7).

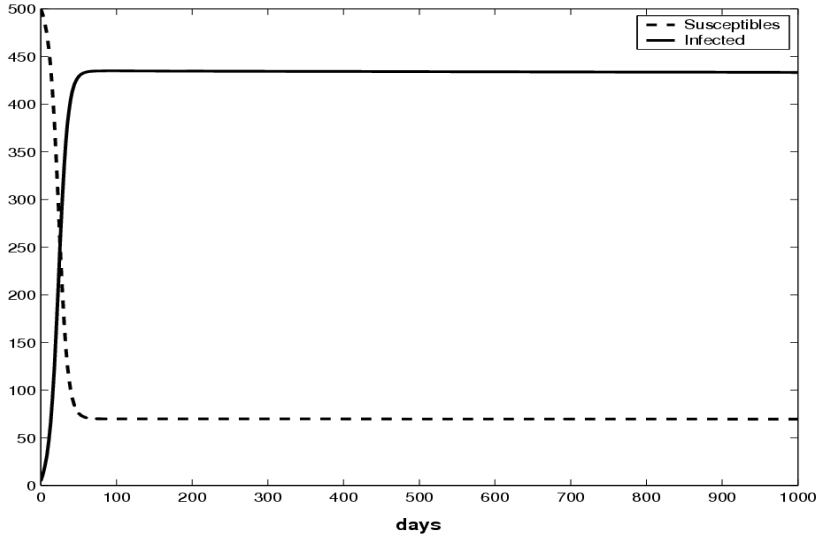

Figure 4: Population of susceptibles and infected where the rate of killing the rodents is less than their growth rate

4.0 The impact of vaccination.

Vaccination remains the only means for controlling many infectious diseases [5]. We are interested in seeing what fraction of the susceptibles should be vaccinated to eliminate the infectious disease from the whole population. The critical vaccination fractions are those fractions of the population that should be vaccinated to just achieve elimination. Knowledge of the critical vaccination fractions provides a starting point for disease elimination. These fractions can provide epidemiologists with information about the best deployment of limited quantities of vaccine to contain the infectious disease.

Unfortunately, at the moment, there is no vaccination against Lassa fever. However recent research has shown that there is a possibility of getting vaccines for humans. This assertion is based on trials of some vaccines on primates [2]. The findings in [2] showed that vaccination is still the most viable control measure. It was discovered that there is no correlation between antibody levels and outcome in human patients, and inactivated vaccines produce high titers of antibodies to all viral proteins but do not prevent virus replication and death in nonhuman primates.

Accordingly 44 macaques were vaccinated with vaccinia virus-expressed Lassa virus structural proteins separately and in combination, with the object of inducing a predominantly TH1-type immune response. Following Lassa virus challenge, it was discovered that all unvaccinated animals died (0% survival). Nine of 10 animals vaccinated with all proteins survived (90% survival). Although no animals that received full-length glycoprotein alone had a high titer of antibody, 17 of 19 survived challenge (88%). In contrast, all animals vaccinated with nucleoprotein developed high titers of antibody but 12 of 15 died (20% survival). All animals vaccinated with single glycoproteins, G1 or G2, died, but all those that received both single glycoproteins (G1 plus G2) at separate sites survived, showing that both glycoproteins are independently important in protection. Neither group had demonstrable antibody levels prior to challenge.

It was demonstrate that in primates, immune responses to epitopes on both glycoproteins are required to protect against lethal challenge with Lassa virus without having untoward side effects and that this protection is likely to be primarily cell mediated [2]. This clearly shows that an effective, safe vaccine against Lassa virus can and should be made for the human population.

In this regard, we simply state a mathematical model that incorporates vaccination of those entering the susceptible population and those who recover from the disease. There is no need vaccinating the infected population. The model proposed is:

$$\begin{aligned}
\frac{dS}{dt} &= (1-\nu)\mu N - mS - \beta VS - \alpha IS \\
\frac{dI}{dt} &= \beta VS + \alpha IS - \gamma I - mI \\
\frac{dR}{dt} &= \nu\gamma I + \nu\mu N \\
\frac{dV}{dt} &= rV\left(1-\frac{V}{K}\right) - \phi V
\end{aligned} \tag{4.1}$$

Of course the rodent population remains as there will always be rodents in the community.

In the mathematical model in (16), we vaccinate a proportion $\boldsymbol{\nu}$, of those entering the susceptible population and then also vaccinate those who recover from the disease. The new class $\boldsymbol{R}$ stands for individuals that are vaccinated and have a measure of immunity against the disease. Of course the efficacy of the vaccine used will determine the length of time one has the immunity. We leave analysis of the model for future work.

5.0 Discussion and conclusion

We present a mathematical model for the dynamics of Lassa fever. We observe that to achieve a disease free situation and prevent an epidemic, we strongly need to control the vectors causing the disease, the rodents of the M.natalensis family. Simply stated, this will mean eradicating the rat population. This is totally in agreement with the findings done by the Merlin Institute, London in [8]. However most people will kick against the idea as the rats serve as meat for some people especially in West Africa [8].

Eradication or at least serious control of the rodents is clearly in agreement with our mathematical conditions that will make the disease free state achievable (conditions (3.3) and (3.4)). In addition a serious effort to reduce contacts with infected individuals is suggested. This can be achieved by an isolation policy where the

infected individuals are isolated until they recover from the disease. All of this is needed since human infection is due to contact with rodents or infected patients. However widespread prevention of such contact is presently impractical, so provision of a vaccine for community and hospital use is an imperative public health need and remains the best option to tackle the menace [4, 7, 9].

In addition to the work on vaccination presented in [2], production of a combined, single dose vaccine against yellow fever and Lassa fever has also been proposed in [3]. However, the cost and logistical problems of delivering it would be huge, particularly in developing countries where there is some level of endemicity. In the interim, vector control and isolation of infected persons still remain the best strategy against the spread of Lassa fever.

Further developments on lassa modelling require a better understanding of the rodent vectors. We may incorporate movements of the rodents as well as movements of the infected individuals into virgin territory into the model and see the effect this will have on the overall dynamics of the disease.

The epidemiology of both rat and human populations requires urgent investigation if we are to understand this disease fully. It could be done through developing

- International collaboration over research
- A map of the complete epidemiological and clinical story
- Involvement of the communities affected
- Effective and affordable diagnostic kits and treatment
- Efficient and effective specialist treatment centres
- An effective and affordable vaccine to control the infection in its natural habitat, protect international visitors, and deter the use of the virus as an agent of biological warfare [11]

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