Leptospirosis models: vaccination of cattle and early detection in humans

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I dedicate this dissertation to my beloved parents, Fadile Aslan and Abdulkadir Aslan whose words of cheer and push for tenacity ring in my ears. My advisor Dr. Suzanne Lenhart, my uncle Muslum Aslan, my sister-in-low Gungor Aslan, and the all teachers in my education life. They always motivated and supported me no matter what and how I have done. In this journey, I have had a lot of challenges but I overcome these challenges thanks to the solid support of these people.

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Abstract

In this dissertation we discuss two mathematical models for leptospirosis. The first project is a mathematical model of leptospirosis with impulse actions in cattle. The project is to understand the propagation of leptospirosis and find a schedule for control programs to eradicate the disease in a cattle ranch. An epidemiological model has been built with ordinary differential equations (ODEs) and included some vaccination and recruitment control programs in the form of impulse actions to prevent the propagation of leptospirosis in the ranch. This system of ODEs with impulse actions determines a schedule of control actions in order to eradicate leptospirosis in the ranch. Parameter estimation and sensitivity analysis were completed as a part of this study. The second project is a stochastic optimization model for cost effectiveness analysis in early detection of leptospirosis in humans. To seek an optimal treatment strategy for the patients coming into a hospital with the symptoms similar to those of leptospirosis, a stochastic processing model with a computational algorithm was developed to compare treatment strategies and determine an optimal management strategy maximizing the number of early detected leptospirosis cases and minimizing the corresponding costs.

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Chapter 1

Introduction

Mathematical modeling has been widely used in many disciplines such as physics, biology and economics to understand and interpret natural phenomena due to their reliability and broad applicability. There are various types of mathematical modeling and each of them can be useful depending on the objective of problem and available data. For instance, modeling with differential equations might be useful to simulate deterministic systems in physics or biology, and Markov chain modeling might be useful to determine strategies for the systems with stochastic events.

Several areas of mathematical modeling have emerged according to biological problems such as infectious diseases, interacting population, etc [33, 27]. In this dissertation, we have developed two mathematical models for an infectious disease, leptospirosis, by using differential equations and scientific computations with a Markov chain.

1.1 Mathematical modeling of epidemiological diseases with differential equations

Infectious diseases are still a growing public health threat across the globe. More than 30 new infectious diseases have been identified for past 30 years [42]. The main challenge is having the opportunity of preventing and controlling them [42]. Mathematical modeling can

be used as a tool to understand the spread of disease, estimate population risk, predict the effects of interventions, and reduce the damage [13].

Mathematical modeling of infectious diseases describe interactions between individuals or populations and other biological structures or environment. While defining these interactions with mathematical equations, complex systems can be broken down into simple pieces to explore deeply and analyze the consequences of different events in the systems [13]. Several methods have been developed using mathematical tools to define these interactions. Differential equations (DEs) have been used in physics since the end of 16th century by Newton and Leibniz, but they do not have that long history in biology and particularly in epidemiological models. One of the first epidemiological models with differential equations which consists of susceptible, infectious, and recovered individual compartments was introduced by Kermack and McKendrick in 1927 [39, 27]. Susceptible individuals are healthy, but they have potential to get infected later, infected individuals may transmit the diseases to others, and recovered individuals were infected previously, but become recovered later.

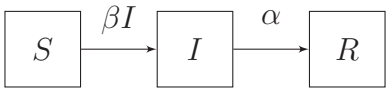


Figure 1.1: SIR model

Kermack and McKendrick's model was constructed based on the rate of change in each compartment. Susceptible individuals move into the infected compartment with a certain rate in a unit of time when they contact with infected individuals. Similarly infected individuals move into recovered compartment with a certain rate in a unit of time when they recover. The mathematical formulation of the model represented in Figure 1.1, is the following:

$$S' = -\beta IS$$
$$I' = \beta IS - \alpha I$$
$$R' = \alpha I$$

where S, I, and R respectively represent the number of susceptible, infected and recovered individuals and β, α represent the transmission rate of disease and the recovery rate of infected individuals. Therefore, the right hand side of system represents the rate of change in the quantity of individuals among the compartments with respect to the unit of time. Many other versions of epidemiological models have been developed according to various scenarios and disease types with features such as age-structure, transmission by vectors and space.

1.2 Disease modeling with control programs and free-living pathogens in environment

Control programs are essential components in modeling of epidemiological diseases, for instance, quarantine, vaccination and culling [39, 27]. These programs usually refer to the actions to prevent the propagation of the disease and reduce the number of new infectious. Vaccination is one of the most common control programs, and depending on its implementation and consequences there are several different ways to formulate an epidemiological model with vaccination [27]. For instance, the vaccination might be applied to the entire population or to a certain compartment, and it might be applied continuously or instantaneously. One version of a vaccine implementation with pulse actions was examined by Shulgin at al. [56] as the following:

$$\begin{aligned}
\frac{dS}{dt} &= \mu - \beta SI - \mu S - pv \sum_{n=0}^{\infty} S(nT^{-})\delta(t - nT), \\
\frac{dI}{dt} &= \beta SI - \gamma I - \mu I,
\end{aligned}$$

where S and I donate the number of susceptible and infected individuals, T is the interval between pulse actions, $S(nT^{-})$ represents the number of susceptible individuals in the instant immediately prior to the n^{th} vaccination pulse ($n = 0, 1, ...$). Dirac delta function, $\delta(t)$ is zero unless $t = 0$. The parameters μ, β, γ are respectively birth, transmission and recovery rates. Biological interpretation of the model is that the susceptible population continuously

gets infected with transmission rate β, infected population continuously become recovered with rate γ and also birth, death occurs with rate of μ during the time interval $[nT, (n+1)T]$, and then susceptible population gets vaccinated instantaneously with a fraction pv at time T. Another study with SIS (susceptible infected susceptible) compartments in a DEs model with pulse vaccination was proposed by F. Cordova-Lepe and coworkers [45]. They modified a function determining pulse vaccination time depending on the current incidence.

Another important component in modeling infectious diseases is the method of the transmission. The transmission may be direct from one host to another as in Figure 1.1, but could also be from indirect contact with pathogens in the environment. R. Breban et al. in [9] built a SI general model with DEs by including the pathogens in the environment as a compartment which causes indirect transmission of the diseases with a function $f(V)$,

$$\begin{aligned}
\frac{dS}{dt} &= \pi - \mu S - \rho S f(V) \\
\frac{dI}{dt} &= \rho S f(V) - (\mu + \gamma) I \\
\frac{dV}{dt} &= \omega I - \eta V
\end{aligned}$$

where S and I denoted the number of susceptible and infected individuals and V represented the pathogens in the environment. The parameter γ is the recovery rate of infected individuals, η is the decay rate of the pathogen from the environment, ω is the shedding rate of infected individuals, π is the susceptible inflow, μ is the natural death rate of individuals and ρ is the contact rate of susceptible individuals with the environment. For pathogen surviving in the environment for a long time, including indirect transmission is important. The model shows the approximation of direct transmission is not sufficient to model influenza accurately. As a result, it is essential to formulate the epidemiological model according to the reality of corresponding transmission roots.

1.3 Leptospirosis in humans and cattle

Leptospirosis is zoonotic disease and has higher prevalence in tropical regions such as Central and South America since the tropical conditions provide favorable conditions to the pathogen

and increase the contact rate between pathogen and host [36, 40]. Infection occurs through direct contact with infected individuals or indirect contact with free-living pathogens in the environment [52, 36]. While the main reservoirs are small mammals such as rodents and rats, domestic animals and humans are hosts as well. Particularly leptospirosis is one of the well known diseases causing reproductive failure in cattle [52, 36].

In humans, the diagnosis of leptospirosis is challenging because most leptospirosis patients do not have specific signs and symptoms, and the clinical manifestation varies from sub-clinical infection to severe potentially lethal multi-system illness with jaundice and renal failure [60, 47]. There are several laboratory tests available for diagnosis of leptospirosis, but their sensitivity and specificity values are low and their usefulness are still under discussion [20, 60]. Therefore, managing patients suspected of leptospirosis is a difficult and important problem for the physicians. In addition, early diagnosis of leptospirosis is essential because antibiotic therapy provides greatest benefit in early and severe stage of leptospirosis. Potentially, doxycycline is the best option of antibiotic in initial treatment while data of its efficacy against leptospirosis is limited [14, 47].

In cattle, control programs are usually more common than treatments. Three possible control programs are available: antibiotic therapy, environmental management, and vaccination. Since antibiotic therapy is relatively expensive, it is not a commonly used program. Even though environmental management could be an effective method to eliminate the pathogen in the environment and prevent the propagation of leptospirosis, it is not applicable for many cattle ranches due to their sizes. Vaccination is the cheapest and the most common control method reducing the incidence of leptospirosis. However, its efficacy varies across countries [40, 37, 52]. It has been reported some certain types of vaccines reduce the incidence of infection and the duration and intensity of urine shedding in some countries [7, 10, 52]. Implementation of vaccine strategies may vary depending on the size of farm and the management strategy. For instance, some ranch managers gather all their cattle once or twice a year in order to apply vaccination to all of their cattle at the same time. These kinds of applications are called impulse actions and since they are practical they are commonly used programs.

1.4 Modeling leptospirosis

We have formulated two projects for leptospirosis. The first part involves age structured models of leptospirosis with impulse actions in cattle. While cattle are one of the most sensitive species for leptospirosis, which creates drastic economical loss for the livestock industries, there is not a mathematical model representing the dynamics of leptospirosis in a cattle ranch. Two studies [46, 53] include livestock in their models using a continuous vaccination policy, but most ranch managers apply vaccination with impulse actions. Thus, we have built mathematical models illustrating the epidemiological dynamics of leptospirosis in a cattle ranch with and without control programs.

We have built the models according to a typical ranch where the managers gather all their cattle to apply vaccination and recruit some cattle at a specific time. We aim to understand the behavior of leptospirosis and determine preventative actions in the cattle ranch. We start with a preliminary age structure SIR model with DEs by excluding preventative actions against leptospirosis to explore the propagation of leptospirosis. We have analyzed the stability of the Disease Free equilibrium (DFE) by using the threshold quantities, basic reproduction and target reproduction numbers, and found the effort required to control leptospirosis. Then, we modified the preliminary model to represent the typical ranch to see the effect of actions of the ranch managers to control leptospirosis. Therefore, we improved the preliminary model with some vaccination and recruitment control programs in the form of impulse actions to prevent the propagation of the disease. This system of ordinary differential equations with impulse actions determines a schedule of control programs to eradicate leptospirosis in the ranch.

The preliminary model indicates that leptospirosis spreads in the ranch without control programs, and thus a control program is required to prevent the propagation of leptospirosis in the ranch. The model with impulse actions suggests the application of control programs once a year drastically reduces the number of infected cattle and corresponding deaths, however, leptospirosis cannot be eradicated from the ranch and death due to the disease always occurs when having impulse actions once a year. On the other hand, the application

of control programs twice a year eradicates leptospirosis from the ranch after a sufficiently long time.

The second part is a mathematical model for cost-effectiveness analysis and early detection of leptospirosis in humans. Antibiotic treatment is supposed to be effective in the course of manifestations towards lower mortality and morbidity when treatment is started in the early acute phase, so diagnosis of leptospirosis in the early stage is essential. However, there is not a mathematical model focusing on early detection of leptospirosis. Suputtamongkol and his co-workers et at. [60] presented a study investigating the benefits of diagnostic tests versus empirical treatment with a broad spectrum antibiotic for the patients presenting at the hospital with complaints compatible with leptospirosis, but early detection of leptospirosis is not included in their study. Thus, we developed a mathematical model to compare treatment strategies and determine an optimal strategy that maximizes the number of early detected patients and minimizes the corresponding costs for the patients suspected of leptospirosis with some symptoms.

Imagine that the patients show up at a hospital with some symptoms, we know whether these symptoms are severe or mild symptoms and how long they have these symptoms. However, we do not know whether the cases are leptospirosis or non-leptospirosis and the patients with mild symptoms will developed severe symptoms or not. The goal is to choose one of six treatment strategies to minimize the corresponding costs and also to maximize the number of early detected leptospirosis case.

We have developed a stochastic processing model with a computational algorithm to achieve the goal. We start with identifying the patients according to their features. There are four features of each patient: late/early case, severe/mild symptoms, leptospirosis /non-leptospirosis and severe/mild pathway. Two of these features are known for each patient, whether they are a late or early case and they have severe or mild symptoms. The other two features are unknown, whether they have leptospirosis or not and they are on severe or mild pathway. We have classified the patients according to their known features and found treatment strategies for each of these classes separately. To identify the other features of the patients we use the random numbers drawn from an uniform distribution, the probability of being leptospirosis and the conditional probability of leptospirosis /non-leptospirosis patients

developing severe symptoms. Eventually we generate tables consisting of the patients with their features and we calculate the corresponding costs with these tables for each choice of the physician for each class separately.

Chapter 2

Leptospirosis in a cattle ranch

2.1 Introduction

Leptospirosis is a worldwide zoonotic disease. In tropical regions having favorable conditions, such as temperature and higher humidity level, for the pathogen to survive for long time periods, leptospirosis became endemic. Large outbreaks of leptospirosis happened in Nicaragua, India Brazil, southeast Asia and the United States. The outbreaks of leptospirosis occur with severe flooding due to increasing contact with contaminated water as in Central and South America [36, 40]. Humans and a wide range of animals, such as domestic animals, and rodents, are at risk. One estimate indicated that the overall prevalence of leptospirosis in U.S. cattle is 35-50% [22]. Another study showed 42% of beef and 57% of dairy herds in the United States are carrying the pathogen causing infection in 2003 and 2007 [50].

The pathogen causing the infection is Leptospira which is a pathogenic spirochaete bacteria. The genus Leptospira involves pathogenic and non-pathogenic species. Nearly 250 serovars were recognized among the pathogenic Leptospira species. Antigenically, serovars are categorized into serogroups, of which twenty-six have been described as pathogenic strains. Leptospires colonize in the proximal renal tubules of various mammals, and eventually they are excreted in the urine of carrier animals [37, 36].

Transmission of leptospirosis can occur through direct contact with infected animals or through indirect contact with water and soil which has been contaminated by infected animals. There are many factors playing a role in the transmission, for instance, climate,

temperature and contact rate with reservoir hosts. While the main reservoirs are small mammals such as rodents and rats, domestic animals such as dairy cattle are also well hosts [52, 36].

Leptospirosis is one of the most serious diseases in cattle for the livestock industry. Cattle can get infected at any age and the consequences of infection vary with age. The main consequences of leptospirosis in juvenile cattle are a lower growth rate and higher disease mortality rate than normal rates. However, the increased rate of abortion is the biggest issue in adult cattle since one of the most common Leptospira serovar, hardjo, can remain and reproduce in the reproductive tract of infected cattle for a long time. The bacteria remaining in the reproductive tract cause vertical transmission of the disease to newborn calves and increased rate of abortion. In addition, the infected cattle colonize the bacteria in their kidneys which leads to bacterial shedding and increases the transmission of disease [22, 50].

Leptospirosis has been reported as one of major causes of reproductive failure in cattle. In Northern Ireland, the hardjo strain was recognized as the reason for nearly half of all bovine abortions. Moreover, leptospirosis causes weak or apparently healthy, but infected newborns [22]. Leptospirosis is also one of causes of milk reduction in cows [50]. In addition, the infected cattle are a source of infection for humans due to Leptospira in their urine. All these create significant economic loss for the livestock industry and society. Nevertheless, in spite of its importance, leptospirosis is neglected due to challenges like the lack of the epidemiological knowledge and prophylaxis, especially in tropical regions [37, 10, 40].

However, there are some control methods currently available. Three feasible control programs available are: antibiotic therapy, environmental management, and vaccination. The programs may not eradicate the causative agent in a herd, but they can significantly reduce economic loss. Antibiotic therapy reduces reproductive problems, bacterial shedding and the transmission of leptospirosis, but its application in the livestock is relatively expensive. Environmental management programs can be effective as well in reducing the incidence of leptospirosis in the herd especially during rainy periods. The implementation of crucial environmental measures for long-term eradication of leptospirosis are hygiene programs, reducing co-grazing, quarantine and isolation of infected animals [40]. Vaccination

is the cheapest control method reducing the incidence of leptospirosis, however, its efficacy varies across countries [40, 37, 52]. Variation in efficacy of hardjo vaccines may be related to several factors, such as the formulation of vaccine, the challenge strain, and the climate of the region. Vaccines containing the hardjo serovar or in combination with serovar pomona have been reported to reduce the incidence of infection and the duration and intensity of urine shedding in some countries [7, 10, 52]. Since vaccination provides temporary immunity [68, 67], vaccinations should be repeated as needed. But, the desired vaccination schedule and its efficacy are still under discussion. In general, vaccination reduces the incidence of infection and the rates of abortion in healthy animals.

There are different types of environments in the livestock industry, e.g., stables, pastures farms, and ranches. Some of them have facilities in which the managers can monitor their livestock and control the outbreak of a possible disease by periodically cleaning the environment. However, most livestock operations cannot control their facilities through cleaning. In most cattle ranches, juvenile and adult cattle live together in pastures, thus it is quite hard monitor the cattle in order to control the outbreak of a possible disease and to prevent the propagation of infection. In general, the ranch managers gather all cattle at certain times to give them necessary care, such as vaccination and anti-tick and anti-lice baths. If the number of cattle is below a desirable size, the ranch managers bring new adult cattle into the ranch for business purposes. These sort of ranches serve dairy and meat production.

Many studies have discussed the severity of leptospirosis and possible intervention methods in human and animals, however, not many mathematical models have been proposed to analyze the epidemiology of leptospirosis and determine strategies to eradicate this disease. In two studies, Khan et al. [31, 29] built models with system of ordinary differential equations (ODEs) by considering the transmission of leptospirosis between human and vector populations and analyzed the local and global stability of the endemic equilibrium and the disease free-equilibrium. In a system of ODEs, Baca et al.[12] studied the stability and intervention techniques for leptospirosis in human and animal populations. His model is one of few models taking into account Leptospira living in the environment and the transmission of disease through the bacteria. However, his model does not have a control method.

Similarly, some other work developed models with ODEs by considering the transmission of leptospirosis between human and rodent populations [66, 28, 49, 26]. Several studies of ODEs used optimal control theory to choose management strategies in human and general vector populations [46, 53, 30, 32]. In two of these [46, 53] the vector population is specified to be livestock and their controls are hygiene, vaccination and some treatment programs. Their models use a continuous vaccination policy, however, most ranch managers apply vaccination at a specific time. Another recently released study developed ODEs for leptospirosis for rotating populations of lambs [3]. The model consists of susceptible and infected lambs with one population rotating out and another population coming in once a year, and includes bacteria living in the environment. Their model predicts the conditions in which the infection persists. Consequently, there is not a mathematical model that analyzes the epidemiology of leptospirosis specifically focusing on cattle, even though cattle are one of the most sensitive species for leptospirosis, which creates drastic economical loss for the livestock industries. Therefore there is a need for a mathematical model representing the events in a cattle ranch and illustrating the epidemiological dynamics of leptospirosis.

The purpose of our study is to understand the epidemiological behavior of leptospirosis and offer some possible intervention strategies to reduce the loss for cattle ranchers. Therefore, two mathematical models of leptospirosis with system of ODEs are proposed to achieve the goal. Initially, a preliminary model is developed in the next section for a ranch scenario, without vaccination. Our intention with this model is to illustrate the main factors of the propagation of leptospirosis and observe the consequences without vaccination in the system. Thus, the stability analysis is studied using the basic reproduction number $\mathcal{R}_0$. In addition, some possible control measures are discussed by using target reproduction numbers. Then, another model with impulse actions is introduced representing the actions on a typical ranch. Vaccination and cattle replacement are implemented as the impulse actions to examine their effect and to compare schedules of impulse actions. The numerical results of models are shown for the model without vaccination and the model with impulse actions. Some sensitivity analysis will be shown in Section 2.5. Finally our conclusions will be discussed in Section 2.6.

2.2 The preliminary model

In order to analyze the spread of leptospirosis in a cattle ranch, a preliminary epidemiological model of leptospirosis without vaccination is proposed. Using a system of ODEs, the model is based on a cattle ranch in which adult and juvenile cattle live in the same environment.

2.2.1 Formulation of preliminary model

As discussed in the introduction, the transmission rates of leptospirosis and its consequences differs between adult and juvenile cattle, therefore the cattle are classified into two main age classes, juvenile and adult, in the model. Each age class is split into three compartments according to their infection status; susceptible juveniles S_J, infected juveniles I_J, and recovered juveniles R_J, susceptible adults S_A, infected adults I_A, and recovered adults R_A. The unit of these cattle compartments is the number of cattle. In addition to the cattle compartments, due to bacterial shedding from infected cattle, there is a compartment of bacteria B living free in the environment. The unit of this bacteria compartment is 10^{10} Leptospires [12]. The cattle move from one compartment to another according to their age and disease progression. Figure 2.1 depicts the compartments and the transitions among them.

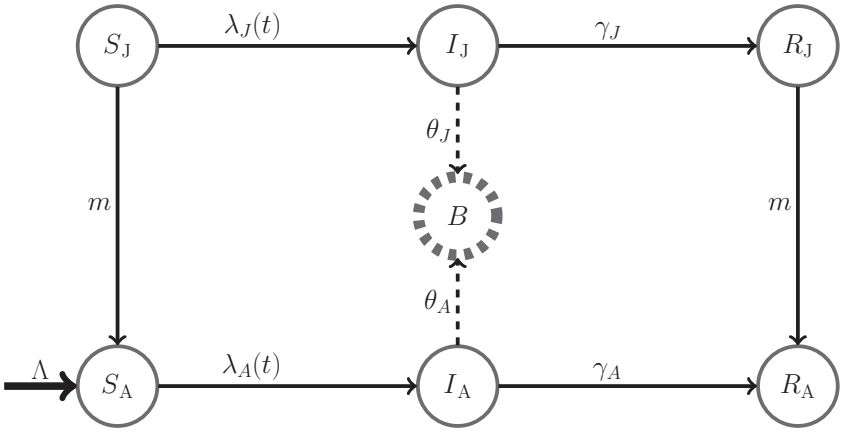


Figure 2.1: Flow diagram of the transition of leptospirosis among the compartments for the preliminary model.

Regarding the ranch scenario and transition of cattle among the compartments, a mathematical model is formulated by DEs as following.

$$
\begin{aligned}
\frac{dS_J}{dt} &= b(S_A + (1-q)I_A + R_A) - S_J(m+\mu_J) - S_J\left(\beta_{JJ}I_J + \beta_{JA}I_A + \frac{\beta_J B}{K+B}\right) \\
\frac{dI_J}{dt} &= (1-\sigma)qbI_A + S_J\left(\beta_{JJ}I_J + \beta_{JA}I_A + \frac{\beta_J B}{K+B}\right) - I_J(\gamma_J + \mu_{I_J} + \mu_J) \\
\frac{dR_J}{dt} &= \gamma_J I_J - R_J(m+\mu_J) \\
\frac{dS_A}{dt} &= \Lambda + mS_J - \mu_A S_A - S_A\left(\beta_{AA}I_A + \beta_{AJ}I_J + \frac{\beta_A B}{K+B}\right) \\
\frac{dI_A}{dt} &= S_A\left(\beta_{AA}I_A + \beta_{AJ}I_J + \frac{\beta_A B}{K+B}\right) - I_A(\gamma_A + \mu_{I_A} + \mu_A) \\
\frac{dR_A}{dt} &= \gamma_A I_A + mR_J - \mu_A R_A \\
\frac{dB}{dt} &= \theta_J I_J + \theta_A I_A - kB
\end{aligned}
\tag{2.1}
$$

The time unit in the differential equations is one day, therefore, the right hand side of the system (2.1) represents the rate of change per day. As shown in Figure 2.1, the cattle move from the susceptible compartments to the corresponding infected compartments due to transmission from infected cattle or the bacteria in the environment. The cattle move from the infected compartments to the recovered compartments due to their natural recovery. The cattle make a transition from the juvenile class to the adult class due to age progression. However, since the duration of the disease is short the infected juvenile cattle does not make transition to the adult class. The infected cattle shed the bacteria into the environment, therefore the amount of bacteria in the environment increases as the infected cattle population increases. The amount of bacteria decays over time in the environment at a rate k. The ranch managers bring some susceptible cattle into the ranch regularly to keep the population constant, and this is approximated by a constant rate Λ. The rate of juvenile and adult cattle leaving the ranch μ_J, μ_A, and birth rate adult cattle b are taken into account in the model, in addition to that, the death rates due to the disease μ_{I_A}, μ_{I_J} are considered because leptospirosis has a severe mortality rate. Since the reproductive failure is one of the main results of leptospirosis, abortion and vertical transmission of the disease in newborn

calves from the infected cattle are taken into account by putting some weight factors on the birth rate of infected cattle. The parameters in this model are described below.

The force of infection from the susceptible juvenile compartment to the infected juvenile compartment given by

$$\lambda_J(t) = \beta_{JJ} I_J + \beta_{JA} I_A + \frac{\beta_J B}{K + B}.$$

This λ_J represents the rate of susceptible juvenile cattle getting infected by contacting infected cattle or the bacteria in one day.

β_{JJ} := Transmission rate of the disease among juvenile cattle, with units of $\frac{1}{\text{day}\cdot\text{cattle}}$

β_{JA} := Transmission rate of the disease from adult cattle to juvenile cattle, with units of $\frac{1}{\text{day}\cdot\text{cattle}}$

β_J := Infection rate of juvenile cattle due to contact with the bacteria, with units of $\frac{1}{\text{day}}$

The force of infection from the susceptible adult compartment to the infected adult compartment given by

$$\lambda_A(t) = \beta_{AA} I_A + \beta_{AJ} I_J + \frac{\beta_A B}{K + B}.$$

This λ_A represents the rate of susceptible adult cattle getting infected by contacting infected cattle or the bacteria in one day.

β_{AA} := Transmission rate of the disease among adult cattle, with units of $\frac{1}{\text{day}\cdot\text{cattle}}$

β_{AJ} := Transmission rate of the disease from juvenile cattle to adult cattle, with units of $\frac{1}{\text{day}\cdot\text{cattle}}$

β_A := Infection rate of adult cattle due to contact with the bacteria, with units of $\frac{1}{\text{day}}$

The rest of the parameters are described below

- K := Half saturation constant on the infection rate of the bacteria with unit of bacteria.

- $\Lambda :=$ Recruitment rate of susceptible adult cattle with units of $\frac{\text{cattle}}{\text{day}}$. The value of Λ represents the number of susceptible cattle added into system in one day.

- $m :=$ Age transit rate of juvenile cattle, with units of $\frac{1}{\text{day}}$.

- $\gamma_J :=$ Recovery rate due to natural immune response in juvenile cattle with units of $\frac{1}{\text{day}}$. The value of γ_J represents the rate of infected juvenile cattle becoming recovered by their natural immune response in one day.

- $\gamma_A :=$ Recovery rate due to natural immune response in adult cattle with units of $\frac{1}{\text{day}}$. The value of γ_A represents the rate of infected adult cattle becoming recovered by their natural immune response in one day.

- $\theta_J :=$ Amount of the bacterial shedding from an infected juvenile cattle with units of $\frac{\text{bacteria}}{\text{day}\cdot\text{cattle}}$. The value of θ_J represents the unit of bacteria shedded into the environment by an infected juvenile cattle in one day.

- $\theta_A :=$ Amount of the bacterial shedding from an infected adult cattle with units of $\frac{\text{bacteria}}{\text{day}\cdot\text{cattle}}$. The value of θ_A represents the unit of bacteria shedded into the environment by an infected adult cattle in one day.

- $b :=$ Birth rate of healthy adult cows with units of $\frac{1}{\text{day}}$. The value of b represents the rate of healthy cow giving birth in one day.

- $\mu_J :=$ Rate of juvenile cattle leaving the ranch with units of $\frac{1}{\text{day}}$. The value of μ_J represents the rate of juvenile cattle leaving the ranch due to the natural death or some other reason in one day.

- $\mu_A :=$ Rate of adult cattle leaving the ranch with units of $\frac{1}{\text{day}}$. The value of μ_A represents the rate of adult cattle leaving the ranch due to the natural death or some other reason in one day.

- $q :=$ Disease vertical transmission rate, which is unitless. The value of q represents the rate of calves born with infection from an infected adult cow.

- σ := Abortion rate of an infected adult cattle, which is unitless. The value of σ represents the rate of calves born dead from an infected adult cow.

- μ_{I_J} := Death rate due to the disease in infected juvenile cattle with units of $\frac{1}{\text{day}}$. The value of μ_{I_J} represents the rate of infected juvenile cattle dying due to the disease in one day.

- μ_{I_A} := Death rate due to the disease in infected adult cattle, with units of $\frac{1}{\text{day}}$. The value of μ_{I_A} represents the rate of infected adult cattle dying due to the disease in one day.

- k := Decay rate of the bacteria with units of $\frac{1}{\text{day}}$.

2.2.2 Stability analysis of the disease free equilibirum

One of the main concept of mathematical modelling for epidemiological study is to investigate the disease free equilibrium (DFE) and the stability of DFE. [27, 8, 17]. This subsection concentrates on the existence of a DFE and necessary conditions for the stability of DFE.

The disease free is an equilibrium point where disease does not exist and the entire population is susceptible. Therefore,

$$X^* = (I_J^*, I_A^*, B^*, S_J^*, S_A^*, R_J^*, R_A^*) = (0, 0, 0, S_J^*, S_A^*, 0, 0) \tag{2.2}$$

is the form of the DFE for the system (2.1). The first step is to examine the existence of a DFE. In order to find a DFE, the right hand side of system (2.1) is set to zero at the

equilibrium point given in (2.2):

$$\begin{aligned}
\frac{dS_J}{dt} &= bS_A^* - S_J^*(m+\mu_J) = 0\\
\frac{dI_J}{dt} &= 0\\
\frac{dR_J}{dt} &= 0\\
\frac{dS_A}{dt} &= \Lambda + mS_J^* - \mu_A S_A^* = 0\\
\frac{dI_A}{dt} &= 0\\
\frac{R_A}{dt} &= 0\\
\frac{dB}{dt} &= 0.
\end{aligned}$$

By doing some algebra, an equilibrium

$$\begin{aligned}
S_J^* &= \frac{\Lambda b}{(m+\mu_J)\mu_A - bm}\\
I_J^* &= 0\\
R_J^* &= 0\\
S_A^* &= \frac{\Lambda(m+\mu_J)}{(m+\mu_J)\mu_A - bm}\\
I_A^* &= 0\\
R_A^* &= 0\\
B^* &= 0
\end{aligned}$$

is obtained. Therefore

$$(I_J^*, I_A^*, B^*, S_J^*, S_A^*, R_J^*, R_A^*) = (0,0,0,\frac{\Lambda b}{(m+\mu_J)\mu_A - bm}, \frac{\Lambda(m+\mu_J)}{(m+\mu_J)\mu_A - bm}, 0, 0) \qquad (2.3)$$

is an equilibrium point. However, a DFE must be biological feasible, which means $S_J, S_A > 0$. If we assume that $\Lambda, b, m+\mu_J$ are positive and $(m+\mu_J)\mu_A - bm > 0$, then the equilibrium point in (2.3) is the DFE for the system (2.1). Notice that the DFE is uniquely identified for

a given set of parameter values. The biological interpretation of those assumptions are that the ranch managers must import some susceptible cattle and there must be the following relationship among the positive death, birth and maturation rates

$$\frac{\mu_A}{m} > \frac{b}{m+\mu_J}.$$

After ensuring that the DFE exists for the system (2.1) under the assumptions, the stability of DFE has to be checked. To check the stability of (2.3), the Next Generation Matrix (NGM) method is used. The method provides simplicity by considering only the infected classes in the calculation [5, 18, 63, 64]. The procedure of NGM method is described as following:

$$\vec{x'} = \mathscr{F} - \mathscr{V}$$
$$x_i' = f_i(x) = \mathscr{F}_i(x) - \mathscr{V}_i(x) = \mathscr{F}_i(x) - (\mathscr{V}_i^-(x) - \mathscr{V}_i^+(x)), \quad i = 1, ..., 7$$

where $\vec{x} = (I_J, I_A, B, S_J, S_A, R_J, R_A)$ and

- $\mathscr{F}_i(x)$:= Rate of appearance of new infections in compartment i

- $\mathscr{V}_i^+(x)$:=Rate of transfer of individuals into compartment i by all other means

- $\mathscr{V}_i^-(x)$:= Rate of transfer of individuals out of compartment i by all other means.

Hence, $\mathscr{F}$ and $\mathscr{V}$ are calculated for the system of (2.1):

$$\mathscr{F} = \begin{bmatrix} (1-\sigma)qbI_A + S_J\lambda_J(t) \\ S_A\lambda_A(t) \\ \theta_J I_J + \theta_A I_A \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}.$$

and

$$\mathscr{V} = \begin{bmatrix} I_J(\gamma_J + \mu_{I_J} + \mu_J) \\ I_A(\gamma_A + \mu_A + \mu_{I_A}) \\ kB \\ -b(S_A + (1-q)I_A + R_A) + S_J(m + \mu_J) + S_J\lambda_J(t) \\ -\Lambda - mS_J + \mu_A S_A + S_A\lambda_A(t) \\ -\gamma_J I_J + R_J(m + \mu_J) \\ -\gamma_A I_A - mR_J + \mu_A R_A \end{bmatrix}.$$

Notice that we assume the bacteria is an infected class and the shedding term is a new infection and recall

$$\lambda_J(t) = \beta_{JJ}I_J + \beta_{JA}I_A + \frac{\beta_J B}{K+B}$$
$$\lambda_A(t) = \beta_{AA}I_A + \beta_{AJ}I_J + \frac{\beta_A B}{K+B}$$

We denote

$$\mathbf{F_{ij}}(\mathbf{X}^*) = \frac{\partial \mathscr{V}_i}{\partial x_j}(X^*) \quad \text{and} \quad \mathbf{V_{ij}}(\mathbf{X}^*) = \frac{\partial \mathscr{V}_i}{\partial x_j}(X^*)$$

where x_j are corresponding the infected classes and $i, j = 1, 2, 3$. Then $\mathbf{F}$ and $\mathbf{V}$ are obtained as

$$\mathbf{F}(\mathbf{X}^*) = \begin{bmatrix} \beta_{JJ}S_J^* & (1-\sigma)qb + \beta_{JA}S_J^* & \frac{\beta_J S_J^*}{K} \\ \beta_{AJ}S_A^* & \beta_{AA}S_A^* & \frac{\beta_A S_A^*}{K} \\ \theta_J & \theta_A & 0 \end{bmatrix}$$

and

$$\mathbf{V}(\mathbf{X}^*) = \begin{bmatrix} \gamma_J + \mu_{I_J} + \mu_J & 0 & 0 \\ 0 & \gamma_A + \mu_{I_A} + \mu_A & 0 \\ 0 & 0 & k \end{bmatrix}$$

Next by taking the inverse of $\mathbf{V}(\mathbf{X}^*)$,

$$\mathbf{V^{-1}}(\mathbf{X}^*) = \begin{bmatrix} \frac{1}{\gamma_J + \mu_{I_J} + \mu_J} & 0 & 0 \\ 0 & \frac{1}{\gamma_A + \mu_{I_A} + \mu_A} & 0 \\ 0 & 0 & \frac{1}{k} \end{bmatrix}$$

then, the product of $\mathbf{F}$ and $\mathbf{V}^{-1}$ at X^* gives us the Next Generation Matrix

$$\mathbf{F}\mathbf{V}^{-1}(X^*) = \begin{bmatrix} \frac{\beta_{JJ}S_J^*}{\gamma_J + \mu_{I_J} + \mu_J} & \frac{(1-\sigma)qb + \beta_{JA}S_J^*}{\gamma_A + \mu_{I_A} + \mu_A} & \frac{\beta_J S_J^*}{Kk} \\ \frac{\beta_{AJ}S_A^*}{\gamma_J + \mu_{I_J} + \mu_J} & \frac{\beta_{AA}S_A^*}{\gamma_A + \mu_{I_A} + \mu_A} & \frac{\beta_A S_A^*}{Kk} \\ \frac{\theta_J}{\gamma_J + \mu_{I_J} + \mu_J} & \frac{\theta_A}{\gamma_A + \mu_{I_A} + \mu_A} & 0 \end{bmatrix} \tag{2.4}$$

The each entry of NGM k_{ij} represents the expected number of new cases arise in a fully susceptible population by an infected individual of type j among the susceptible individuals of type i [55]. The spectral radius of NGM is called the basic reproduction number $\mathcal{R}_0$ which is the average number of secondary cases arising in the the entirely susceptible population [18], i.e. ,

$$\rho(\mathbf{F}\mathbf{V}^{-1}) = \max\{\lambda_1, \lambda_2, \lambda_3\} = \mathcal{R}_0$$

where λ_i are the eigenvalues of NGM given in (2.4). The value of $\mathcal{R}_0$ determines the stability of DFE. The DFE in (2.3) is locally stable if and only if $\mathcal{R}_0 < 1$ [63, 18]. The quantity of $\mathcal{R}_0$ is a measure of the disease propagation, and the explicit format of $\mathcal{R}_0$ gives intuition to know the potential impact of various parameters. However, the explicit format of $\mathcal{R}_0$ is very complicated and hard to interpret for the NGM given in (2.4), but the numerical value of $\mathcal{R}_0$ can be calculated with a given set of parameter values.

2.2.3 Repoduction numbers of the preliminary model

Although the basic reproduction number $\mathcal{R}_0$ can be interpreted as a control measurement to prevent the propagation of a disease for a homogeneous host population, this interpretation may not be valid for a heterogeneous host population [25]. Therefore, some other definitions of control measurements are needed to be used for heterogeneous host types. One definition of control measurements for the heterogeneous host types is the type-reproduction number. This definition can play the role of $\mathcal{R}_0$ when the propagation of the disease can be prevented by targeting a subset of the population, instead of the whole population [25]. For instance, a disease control strategy might be an application of vaccination to reduce the susceptibility of a particular host type rather than the whole population, then the type-reproduction number can inform us whether the propagation of the disease can be controlled with this vaccination strategy. If so, how much effort is required to eradicate the disease. The definition of type-reproduction number is only useful when the control strategy is the reduction of susceptibility of a particular host type or the reduction of infectiousness of a particular host type. Thus, another analogous definition of the type-reproduction number, the target reproduction number $\mathcal{T}_S$, is to be used for the control measurement to prevent the propagation of a disease by targeting multiple host types or vectors causing the disease propagation for the heterogeneous host populations [55]. The definition of target reproduction number is more general than the type-reproduction number. For instance, we may want to control the propagation of the disease by reducing the infectiousness of multiple vector types rather than the susceptibility of a particular host type.

Before giving the definition of target reproduction number, we want to give a motivation. Recall that each entry of a NGM represents the transmission of the disease from one

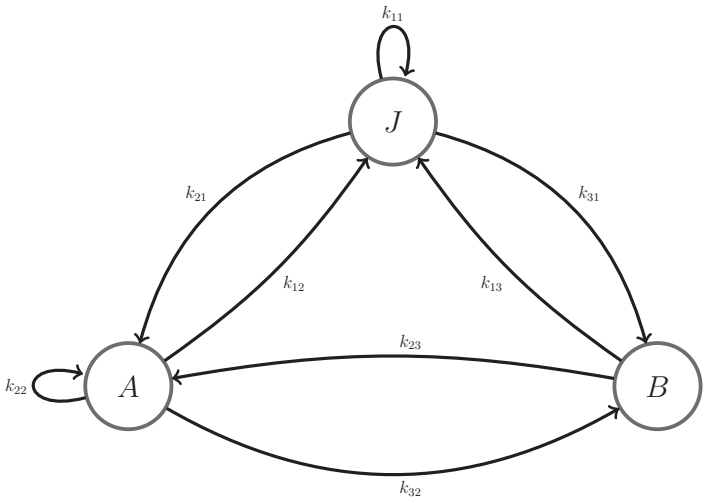
generation to the next generation. If we revisit the NGM given in (2.4)

$$K = \begin{bmatrix} k_{11} & k_{12} & k_{13} \\ k_{21} & k_{22} & k_{23} \\ k_{31} & k_{32} & 0 \end{bmatrix},$$

an entry k_{ij} of K is the expected number of new cases due to an infected individual of type j causing the infection of type i among fully susceptible individuals of type i [55, 25]. Thereby, the entries of NGM in (2.4) can be interpreted

- $k_{11} = \frac{\beta_{JJ} S_J^*}{\gamma_J + \mu_{I_J} + \mu_J}$: The expected number of new cases arise in the susceptible juvenile compartment due to one individual in the infected juvenile compartment.
- $k_{12} = \frac{(1-\sigma)qb + \beta_{JA} S_J^*}{\gamma_A + \mu_{I_A} + \mu_A}$: The expected number of new cases arise in the susceptible juvenile compartment due to one individual in the infected adult compartment.
- $k_{13} = \frac{\beta_J S_J^*}{Kk}$: The expected number of new cases arise from the susceptible juvenile compartment due to the bacteria compartment.
- $k_{21} = \frac{\beta_{AJ} S_A^*}{\gamma_J + \mu_{I_J} + \mu_J}$: The expected number of new cases arise in the susceptible adult compartment due to one individual in the infected juvenile compartment.
- $k_{22} = \frac{\beta_{AA} S_A^*}{\gamma_A + \mu_{I_A} + \mu_A}$: The expected number of new cases arise in the susceptible adult compartment due to one individual in the infected adult compartment.
- $k_{23} = \frac{\beta_A S_A^*}{Kk}$: The expected number of new cases arise in the susceptible adult compartment due to the bacteria compartment.
- $k_{31} = \frac{\theta_J}{\gamma_J + \mu_{I_J} + \mu_J}$: The expected amount of the bacteria contributed by one individual in the infected juvenile compartment.
- $k_{32} = \frac{\theta_A}{\gamma_A + \mu_{I_A} + \mu_A}$: The expected amount of the bacteria contributed by one individual in the infected adult compartment.

The following figure shows how the transmission of the disease moves among the juvenile and adult cattle and the bacteria compartments



The transmission of the disease occurs from a generation to the next generation by k_{ij}. If one can reduce the infectiousness of a infected compartment, then the transmission of the diseases between this infected compartment and all other susceptible compartments will diminish. Thus, the all entries of a column of K will diminish. Similarly, if one can reduce the susceptibility of a susceptible compartment meaning that reducing the possibility of a susceptible individual getting infected, then the transmission of the disease between this susceptible compartment and the infected compartments will decrease. Thus, the all entries of a row of K will decrease. According to this intuition, the target reproduction number is defined by,

$$\mathcal{T}_S = \rho(K_S(I - K + K_S)^{-1})$$

where K is the corresponding Next Generation Matrix, I is the identity matrix and K_S is the matrix consist of targeted entries in the NGM [55]. For instance, If the propagation of the disease can be controlled by reducing a set of entries in the NGM, then K_S is the matrix of this set of entries and zeros. To define the target reproduction number, an inequality of $\rho(K - K_S) < 1$ is required. If the inequality of $\rho(K - K_S) < 1$ fails, then the propagation of disease cannot be controlled by targeting these entries of the NGM. There are two useful results for the target reproduction number: First, $\mathcal{T}_S < 1$ if and only if $\mathcal{R}_0 < 1$ [55]. The

other is the quantity of effort required to eradicate the disease given by

$$1 - \frac{1}{\mathcal{T}_S}, \tag{2.5}$$

meaning that each entry of the targeted set is multiplied by quantity $\frac{1}{\mathcal{T}_S}$, then the disease free equilibrium is locally stable. Note that quantity will always between 0 and 1 as long as $\mathcal{T}_S > 1$ which means the DFE is not stable and effort is required to eradicate the disease. We say the disease can be controlled as long as the quantity of effort given in (2.5) is implemented [55]. If the set of targeted entries is all the entries of a row of the NGM, then the target reproduction number turns out to be the type-reproduction number which is given

$$\mathcal{T}_i = e_i^T K (I - K + K_S)^{-1} e_i \tag{2.6}$$

where i the index of targeted row and e_i represents i the unit vector. Note that we show that $\mathcal{T}_i$ is a positive number in the appendix.

A target reproduction number can be defined for the NGM given in (2.4) in order to find the effort required to eradicate the disease and the control measurement $\mathcal{T}_S$ for the stability of DFE. Imagine that the propagation of the disease can be controlled by reducing the susceptibility of adult cattle compartment, such as applying vaccination to the adult cattle population. Therefore the second row of the NGM given in (2.4) is targeted,

$$K_S = \begin{bmatrix} 0 & 0 & 0 \\ k_{21} & k_{22} & k_{23} \\ 0 & 0 & 0 \end{bmatrix}$$

Using $e_2 = (0, 1, 0)$,

$$K - K_S = \begin{bmatrix} k_{11} & k_{12} & k_{13} \\ 0 & 0 & 0 \\ k_{31} & k_{32} & 0 \end{bmatrix}.$$

The condition to define the target reproduction number is

$$\rho(K - K_S) = \frac{k_{11} + \sqrt{k_{11}^2 + 4k_{31}k_{13}}}{2} < 1. \tag{2.7}$$

If we assume (2.7) holds, the target reproduction number can be defined. By using the formula given in (2.6),

$$\mathcal{T}_S = \frac{(k_{11} - 1)(k_{23}k_{32} + k_{22}) + k_{13}(k_{22}k_{31} - k_{21}k_{32}) - k_{12}(k_{23}k_{31} + k_{21})}{k_{31}k_{13} + k_{11} - 1}.$$

Note that $\mathcal{T}_S$ is the measure of the disease propagation with same threshold as $\mathcal{R}_0$. Therefore, if $\mathcal{T}_S < 1$ then the DFE is locally stable. Note finding an explicit form of the target reproduction number is easier than $\mathcal{R}_0$.

Another consequence of the target reproduction number is that if the susceptibility of adult cattle compartment which means the second row entries of NGM given in (2.4) can be reduced by a factor of

$$1 - \frac{1}{\mathcal{T}_S} = \frac{(k_{11} - 1)(k_{23}k_{32} + k_{22}) + k_{13}(k_{22}k_{31} - k_{21}k_{32}) - k_{12}(k_{23}k_{31} + k_{21}) - k_{31}k_{13} - k_{11} + 1}{(k_{11} - 1)(k_{23}k_{32} + k_{22}) + k_{13}(k_{22}k_{31} - k_{21}k_{32}) - k_{12}(k_{23}k_{31} + k_{21})}$$

then the DFE is stable and the disease dies out.

2.2.4 Parameter selection

In this section, the parameters used in the model (2.1) are chosen according to the events happening in the ranch and some biological facts. We assume that 300 cattle can occupy the ranch, and 70 of those are juvenile. The ranch managers aim to maintain the distribution of population while they approximately sell 70 adult cattle every year for their business purposes. They adjust the birth rate of healthy cattle b and the rate of adult cattle leaving the ranch μ_A to achieve their goal. We constructed a model with ODEs to find the best estimation of b and μ_A that serves the rancher goals while ignoring all other external factors

that affect the population structure such as disease,

$$\frac{dN_J(t)}{dt} = bN_A(t) - N_J(t)(m + \mu_J)$$
$$\frac{dN_A(t)}{dt} = mN_J(t) - \mu_A N_A(t)$$

where N_J, N_A are total number of juvenile and adult cattle. We assume the rate of juvenile cattle leaving the ranch is $\mu_J = \frac{1}{43\times365}$ as in Silva et al. [58]. The duration of newborns staying in the juvenile class is 14 months, so the age transition rate of juvenile cattle is approximately $m = \frac{1}{420}$. We run this model for one year with values and estimate μ_A, b that best serve the rancher goals which is to get 70 newborns every year and let 70 adult cattle out of the ranch. So the b, μ_A that

- $b = \frac{1}{3.5\times365}$
- $\mu_A = \frac{1}{3.5\times365}$

There are approximately 65 newborns and 70 adult cattle leaving the ranch at the end of year with this set of parameters. This is a bit below the rancher goal, however, there are some other facts preventing us to change the parameters more such as maturation rate. Figure 2.2 shows the dynamic of juvenile and adult populations.

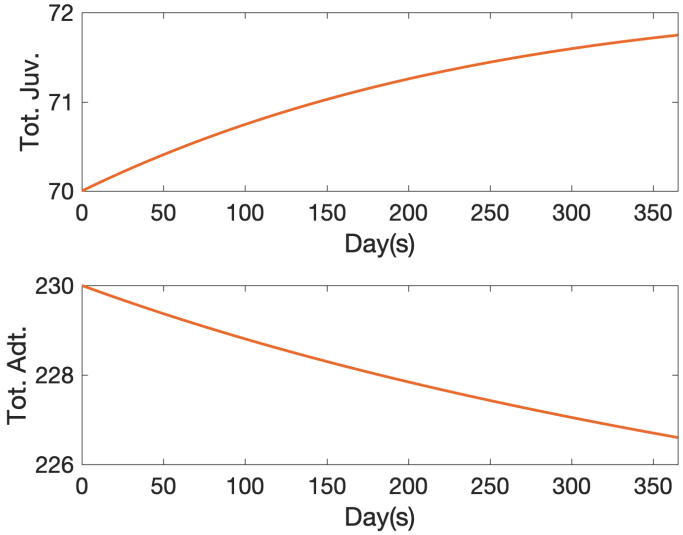


Figure 2.2: Total number of juvenile and adult cattle during one year with initial condition $N_J(0) = 70, N_A(0) = 230$

Some parameters used in the model (2.1) can be chosen based on biological facts.

- θ_J : If a unit of bacteria is 10^{10} Leptospires, there are 10 units of bacteria in one liter cattle urine [12]. Most bacteria cannot survive or be effective in the transmission of disease after being shed [3]. If we assume 0.01% of these bacteria survive, the bacteria contributing to the transmission of the disease when an infected cattle urinate one litter is 0.001 units of bacteria. If we assume each juvenile cattle produces 7 liters of urine in a day, then $\theta_J = 0.007$ [65].

- θ_A : Similarly, if we assume each adult cattle produces 14 liters of urine in a day, then $\theta_A = 0.014$ [65].

- k : The bacteria can survive in the environment from two weeks to several months depending on the climate conditions [52, 3]. In this study we choose $k = \frac{1}{90}$ as in Baca et al.[12].

- σ : There are not many resources discussing the value of an abortion rate of leptospirosis which is the proportion of pregnant leptospirosis cows making abortion due to leptospirosis. Some agricultural extension publications state that the abortion rate of leptospirosis can be up to 30 percent [1]. Silva et al. [57] mentions 3 cases of abortion in 38 infected cattle by leptospirosis. We assume $\sigma = 0.0789$ by dividing 3 by 38.

- q : We have not found any resources about the vertical transmission rate. An experiment by Zimmerman at al. [67] indicates 5 of 18 infected cattle had positive results of bacteriologic culture of reproductive reproductive system tissue. By relying on some expert opinions, we assume $q = 0.27$.

- γ_J : The duration in the infected compartments equals the duration of bacterial shedding. An experiment by Leonard et al. [35] indicates a group of naturally infected heifers, juvenile cattle, shed Leptospires for between 28 and 40 weeks, and a group of experimentally infected heifers shed Leptospires for between 8 to 60 weeks [35]. We choose a point close to the mean of the numbers between 8 and 60. Therefore we assume 26 weeks duration, and so $\gamma_J = \frac{2}{365}$.

- γ_A : We assume the duration of bacterial shedding in adult cattle is twice as long as in juvenile cattle. Using [46], the recovery rate of adult cattle to be $\frac{1}{365}$. Therefore, we assume $\gamma_A = \frac{1}{365}$.

- μ_{I_A} : We use the rate from a mathematical model for leptospirosis in cattle by Sadiq et al. [53] in which the death rate of adult cattle due to leptospirosis was $\mu_{I_A} = \frac{1}{150}$.

- μ_{I_J} : We have not found any resources about disease death rate for juvenile. Since juveniles are known to die more frequently due to leptospirosis, we assume $\mu_{I_J} = \frac{1}{30}$.

- Λ : We assume the recruitment rate is $\frac{2}{365}$ to make $\mathcal{R}_0$ reasonable.

Next we estimate the transmission rates, $\beta_{JJ}, \beta_{JA}, \beta_{AA}, \beta_{AJ}, \beta_J, \beta_A$ and K, the half saturation constant. They are the most challenging parameters to estimate since many factors impact their values such as the disease type, environmental condition, and contact rates. Before starting their estimations we assume a relationship among the transmission rates because of some disease background such as adult cattle get infected and transmit the disease at a higher rate than juvenile cattle [23]

$$\beta_{AJ} = \beta_{AA} = \beta_{JA} = 2 \times \beta_{JJ} \quad \text{and} \quad \beta_A = 2 \times \beta_J \tag{2.8}$$

With the relationship given in (2.8), we estimate the transmission rates and half saturation constant by assuming the prevalence of leptospirosis being 35% in the preliminary model between 200 and 365 days. We have run the preliminary model for one year and found the best fit of transmission rates and half saturation constant for 35% prevalence between 200 and 365 days. The best fit of the transmission rates and half saturation constant are

- $\beta_{JJ} = 5 \times 10^{-5}$
- $\beta_{JA} = 10^{-4}$
- $\beta_J = 6 \times 10^{-4}$
- $\beta_{AA} = 10^{-4}$
- $\beta_{AJ} = 10^{-4}$

- $\beta_A = 12 \times 10^{-4}$
- $K = 34$

The entire list of parameters used this study given in Table 2.1

2.3 Model with impulse actions

The next model that serves our main goal is built according to real events happening in a ranch. We assume that juvenile and adult cattle live in a ranch and the ranch managers gather their cattle at a certain time to give them necessary care such as vaccination. In addition, the ranch managers want to keep a certain amount of cattle in the ranch for their business purposes if possible. Thus, they bring some adult cattle into the ranch at the time of gathering if the current number of cattle is below the desirable size. All these events happen at once, therefore a mathematical model consist of DEs and impulse actions of vaccination and replacement is developed to imitate the dynamic in the ranch. The purpose of this model is to see whether the number of application of vaccination in a year is enough to eradicate the disease or reduce the loss for the ranchers.

Table 2.1: The parameters with their description

Parameter	Description	Value
b	Birth rate of newborns from healthy adult cattle	7.8278×10^{-4}
μ_J	Rate of juvenile cattle leaving ranch	6.3715×10^{-5}
μ_A	Rate of adult cattle leaving ranch	7.8278×10^{-4}
m	Age transition rate of juvenile cattle	2.4×10^{-3}
θ_J	Amount of bacterial shedding from an infected juvenile cattle	7×10^{-3}
θ_A	Amount of bacterial shedding from an infected adult cattle	1.4×10^{-2}
K	Half saturation constant on transmission rate due to contact with bacteria	34
k	Decay rate of the bacteria	1.1×10^{-2}
σ	Abortion rate of infected adult cattle	0.0789
q	Vertical transmission rate from infected cattle	0.27
γ_J	Recovery rate due to natural immune response in juvenile cattle	5.5×10^{-3}
γ_A	Recovery rate due to natural immune response in adult cattle	2.7×10^{-3}
μ_{I_J}	Death rate due to disease in infected juvenile class	3.3×10^{-2}
μ_{I_A}	Death rate due to disease in infected adult class	6.7×10^{-3}
β_{JJ}	Transmission rate of disease among juvenile cattle	5×10^{-5}
β_{JA}	Transmission rate of disease from adult cattle to juvenile cattle	10^{-4}
β_J	Infection rate of juvenile cattle due to contact with bacteria	6×10^{-4}
β_{AA}	Transmission rate of disease among adult cattle	10^{-4}
β_{AJ}	Transmission rate of disease from juvenile cattle to adult cattle	10^{-4}
β_A	Infection rate of adult cattle due to contact with bacteria	12×10^{-4}
Λ	Recruitment rate of susceptible adult cattle	5.5×10^{-3}

2.3.1 Formulation of model with impulse actions

Before introducing the model with impulse actions, we want to point some facts about vaccination on which the model is based. Vaccination reduces the incidence of infection, the reproductive failure, the duration and intensity of urine shedding, however, its efficacy is temporary [68, 67, 7, 1]. Therefore, we assume that the level of immunity from vaccination increases gradually right after the application of vaccination until it reaches a maximum level, then it stays at that level for a while and then it gradually decreases until it hits the minimum level. The vaccination only provides the immunity to the susceptible cattle [23]. The susceptible cattle that are vaccinated are called "vaccinated susceptible cattle". However, the vaccination is not perfectly protective, so some of the vaccinated susceptible cattle can get infected while they are in a vaccinated [52, 7, 67, 54, 23]. These infected cattle are called "vaccinated infected cattle", and they are not same as the cattle that were infected before the application of vaccination. We assume these vaccinated infected cattle shed less bacteria compared to the infected cattle that were infected before the application of vaccination and they colonize less bacteria in their kidney and reproductive track [67, 50]. Thus, they do not have an serious issue of reproductive failure. Therefore, their abortion and vertical transmission rate are lower than the infected adult cattle that are infected before the application of vaccination. Since the vaccination does not affect the cattle that were infected before the application of vaccination, we assume the application of vaccination does not make any change in the bacterial shedding and the reproductive failure of these infected cattle [23]. The recovered cattle can get infected with a different strain of leptospirosis. Since we only consider serovar hardjo strain, we assume that the recovered cattle will not get infected again and the application of vaccination does not offer any advantage or disadvantage to them. With all these assumptions, we construct the mathematical model with impulse actions using the situation in the ranch. The model consist of two main parts. The first part is the impulse actions that happen at the gathering time where all the cattle instantaneously get vaccinated and replacement happens as discussed in the subsection 2.3.2. The second part is the system of ODEs where the cattle make transitions among the compartments until next gathering time as discussed in the subsection 2.3.3. Figure 2.3 illustrates the impulse

actions and the system of ODEs. As Figure 2.3 shows the cattle make transition among the compartments similar to the preliminary model discussed in the section 2.2. However, there are four additional compartments: V_{SJ} vaccinated susceptible juvenile cattle, V_{SA} vaccinated susceptible adult cattle, V_{IJ} vaccinated infected juvenile cattle and V_{IA} vaccinated infected adult cattle compartments. The vaccinated susceptible cattle are less likely to be infected compared to the susceptible cattle being infected. Therefore, there are additional r_{SJ}, r_{SA} reduction factors on their transmission rate. The vaccinated infected cattle shed less bacteria in their urine compared to the infected cattle, therefore there are r_{IJ}, r_{IA} reduction factors on their bacterial shedding. All these reduction factors are $0 < r_{SJ}, r_{SA}, r_{IJ}, r_{IA} < 1$. Note that there are no vaccinated recovered cattle compartments because we assume the application of vaccination does not make any change in their situation. Additional parts in Figure 2.3 are the bold V arrows into the vaccinated compartments. These bold arrows stand for impulse actions of vaccination.

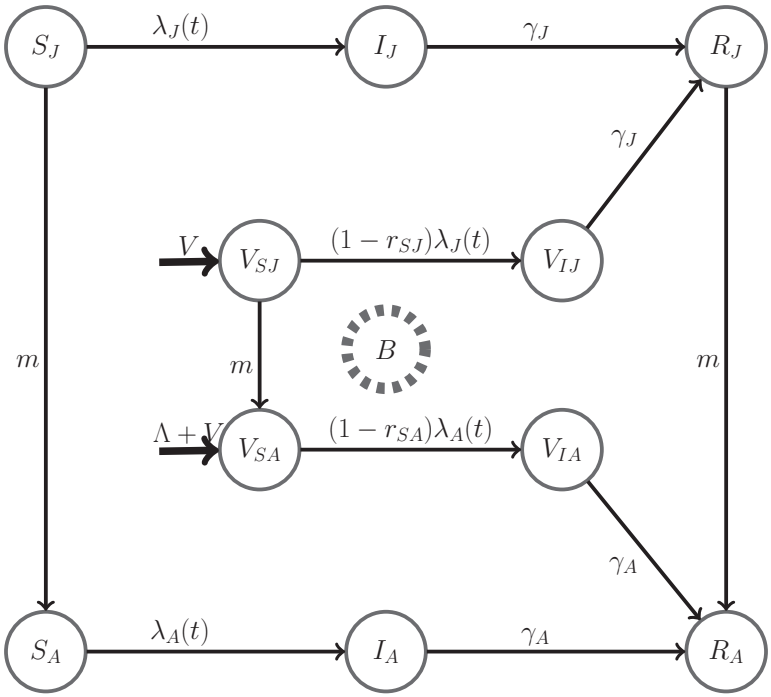


Figure 2.3: Flow diagram of the transition of cattle among the compartments with impulse actions and ODEs

2.3.2 The impulse actions

The first procedure of the model are the impulse actions. We assume that the ranch managers apply instantaneously the vaccination to all the cattle in the ranch at the gathering time. They want to keep N cattle in the ranch. If the number of cattle is dropped below N, they bring new susceptible cattle into the ranch at the time of gathering. Therefore a mathematical representation of these impulse actions is as follows

$$
\begin{aligned}
N = N(0) &= V_{SJ}(0) + V_{IJ}(0) + R_J(0) + V_{SA}(0) + V_{IA}(0) + R_A(0) \\
S_J(kT^+) &= 0 \\
V_{SJ}(kT^+) &= V_{SJ}(kT^-) + S_J(kT^-) \\
I_J(kT^+) &= I_J(kT^-) \\
V_{IJ}(kT^+) &= V_{IJ}(kT^-) \\
R_J(kT^+) &= R_J(kT^-) \\
S_A(kT^+) &= 0 \\
V_{SA}(kT^+) &= V_{SA}(kT^-) + S_A(kT^-) + \underbrace{N - N(kT^-)}_{\text{Imported new cattle}} \\
I_A(kT^+) &= I_A(kT^-) \\
V_{IA}(kT^+) &= V_{IA}(kT^-) \\
R_A(kT^+) &= R_A(kT^-) \\
\Rightarrow N(kT^+) &= N
\end{aligned}
\tag{2.9}
$$

we assume that N cattle are in the ranch at the beginning. T represents the length of time between two gatherings time. Therefore T^- is the time before impulse actions and T^+ is the time that after impulse actions. Since the impulse actions repeats over time, k represents the index of impulse actions. The consequence of this impulse action is the susceptible cattle move into vaccinated susceptible cattle compartment, the infected and recovered cattle stay in their compartments at the end of gathering time. Since the ranchers want to keep N cattle in the ranch, an additional term $N - N(kT^-)$ is added to the vaccinated susceptible adult compartment. The consequence of the impulse actions is that there are N cattle in the

ranch and all of them are vaccinated at T^+ except that the infected, I and the recovered, R cattle are not affected.

2.3.3 The system of ODEs

The second part of the model is a system of ODEs. Right after the impulse actions, a system of DEs continue until the next impulse action. This system is a modification of the preliminary model discussed in the section 2.2. There are four additional compartments $V_{SJ}, V_{SA}, V_{IJ}, V_{IA}$ and some reduction factors due to application of vaccination in the system as discussed in the subsection 2.3.1. The description of the model is similar to the description of the preliminary model given in (2.1), however, there are several additional parameters and differences. Since vaccinated infected cattle colonize less bacteria in their reproductive track, we assume the vertical transmission rate of the disease and abortion rate are smaller in vaccinated infected adult cattle than in infected adult cattle. Therefore, there are additional terms q_V and σ_V in the model (2.10). Vaccinated susceptible juvenile cattle, V_{SJ}, make transition to vaccinated infected juvenile cattle, V_{IJ}, compartment with a smaller rate than the transmission rate between susceptible juvenile cattle and infected juvenile cattle. Therefore, a reduction factor r_{SJ} is multiply with the force of infection in order to reduce the transmission rate between vaccinated susceptible juvenile cattle and vaccinated infected juvenile cattle. Similarly, vaccinated susceptible adult cattle, V_{SA}, make transition to vaccinated infected adult cattle ,V_{IA}, compartment with a smaller transmission rate than the transmission rate between susceptible adult cattle and infected adult cattle. Therefore, a reduction factor r_{SA} is multiply the force of infection.

Note that r_{SJ}, r_{SA} are functions of time due to change in the vaccine efficacy. In addition, vaccinated infected juvenile and adult cattle shed bacteria into the environment, but they shed less bacteria compare to the infected juvenile and adult cattle. Therefore, some additional reduction factors, as r_{IJ}, r_{IA} functions of time are multiply the bacterial shedding of vaccinated infected juvenile and adult cattle. There are a few parameters and functions needed to be chosen in the model (2.10).

- q_V : Disease vertical transmission rate. The value of q_V represents the rate of calves born with infection from vaccinated infected adult cows. We assume that the vertical transmission rate of vaccinated infected cows is half of vertical transmission rate of infected cows, therefore $q_V = 0.135$.

- σ_V : Abortion rate of vaccinated infected adult cows. The value of σ represents the rate of calves born dead from vaccinated infected adult cows. We assume that the abortion rate of vaccinated infected cows is half of infected cows, therefore $\sigma_V = 0.0394$.

$$
\begin{aligned}
\frac{dS_J}{dt} &= b(S_A + (1-q)I_A + (1-q_V)V_{IA} + R_A + V_{SA}) - S_J(m+\mu_J) \\
&\quad - S_J\left(\beta_{JJ}(I_J + V_{IJ}) + \beta_{JA}(I_A + V_{IA}) + \frac{\beta_J B}{K+B}\right) \\
\frac{dV_{SJ}}{dt} &= -V_{SJ}(1-r_{SJ})\left(\beta_{JJ}(I_J + V_{IJ}) + \beta_{JA}(I_A + V_{IA}) + \frac{\beta_J B}{K+B}\right) - V_{SJ}(m+\mu_J) \\
\frac{dI_J}{dt} &= (1-\sigma)qbI_A + (1-\sigma_V)q_V bV_{IA} + S_J\left(\beta_{JJ}(I_J + V_{IJ}) + \beta_{JA}(I_A + V_{IA}) + \frac{\beta_J B}{K+B}\right) \\
&\quad - I_J(\gamma_J + \mu_{I_J} + \mu_J) \\
\frac{dV_{IJ}}{dt} &= V_{SJ}(1-r_{SJ})\left(\beta_{JJ}(I_J + V_{IJ}) + \beta_{JA}(I_A + V_{IA}) + \frac{\beta_J B}{K+B}\right) - V_{IJ}(\mu_J + \mu_{I_J} + \gamma_J) \\
\frac{dR_J}{dt} &= \gamma_J(I_J + V_{IJ}) - R_J(m+\mu_J) \qquad (2.10) \\
\frac{dS_A}{dt} &= mS_J - \mu_A S_A - S_A\left(\beta_{AA}(I_A + V_{IA}) + \beta_{AJ}(I_J + V_{IJ}) + \frac{\beta_A B}{K+B}\right) \\
\frac{dV_{SA}}{dt} &= mV_{SJ} - \mu_A V_{SA} - V_{SA}(1-r_{SA})\left(\beta_{AA}(I_A + V_{IA}) + \beta_{AJ}(I_J + V_{IJ}) + \frac{\beta_A B}{K+B}\right) \\
\frac{dI_A}{dt} &= S_A\left(\beta_{AA}(I_A + V_{IA}) + \beta_{AJ}(I_J + V_{IJ}) + \frac{\beta_A B}{K+B}\right) - I_A(\gamma_A + \mu_A + \mu_{I_A}) \\
\frac{dV_{IA}}{dt} &= V_{SA}(1-r_{SA})\left(\beta_{AA}(I_A + V_{IA}) + \beta_{AJ}(I_J + V_{IJ}) + \frac{\beta_A B}{K+B}\right) - V_{IA}(\mu_A + \mu_{I_A} + \gamma_A) \\
\frac{dR_A}{dt} &= \gamma_A(I_A + V_{IA}) - \mu_A R_A + mR_J \\
\frac{dB}{dt} &= \theta_J I_J + \theta_J(1-r_{IJ})V_{IJ} + \theta_A I_A + \theta_A(1-r_{IA})V_{IA} - kB
\end{aligned}
$$

2.3.4 Reduction functions on the bacterial shedding and force of infection

We assume the reduction factors $r_{SJ}(t), r_{SA}(t), r_{IJ}(t), r_{IA}(t)$ are functions of time and their values range over [0, 1]. The efficacy of vaccination is not at the maximum level right after the application of vaccination, therefore, we assume the reduction functions are at a minimum level at the time of the application of vaccination and increase until they reach the maximum level. In addition, the efficacy of vaccination does not stay at the maximum level for forever, therefore the reduction functions decrease after staying at the maximum level for a while. In this study, we assume the reduction functions are piecewise linear. A representation of reduction functions for once a year vaccination is

$$r(t) = \begin{cases} \frac{r_{\max} - r_{\min}}{t_H} t + r_{\min} & t \in [0, t_H] \\ r_{\max} & t \in [t_H, t_M] \\ \frac{r_{\max} - r_{\min}}{t_M - 365} t - \frac{r_{\max} 365 - r_{\min} t_M}{t_M - 365} & t \in [t_M, 365] \end{cases}$$

with

- $r_{\max}$:= The maximum level of reduction rate. This represents the highest rate of reduction on the transmission rates due to vaccination.
- $r_{\min}$:= The minimum level of reduction rate. This represents the lowest rate of reduction on the transmission rates due to vaccination.
- t_H := The time that the reduction rate achieves the maximum level
- t_M := The time that the reduction rate starts to decrease

In order for find reduction functions in the model (2.10), we need to estimate $r_{\max}, r_{\min}, t_H, t_M$ for each $r_{SJ}, r_{SA}, r_{IJ}, r_{IA}$. That means we need to know $r_{\max}, r_{\min}, t_H, t_M$ in the reduction of bacterial shedding and disease transmission for adult and juvenile cattle separately. Several studies agree that the application of vaccination reduces the bacterial shedding and the disease incidence [54, 7, 15, 52]. However there is not significant information for the reduction

rate of the disease transmission and bacterial shedding in vaccinated cattle. We assume that A study points out the efficacy of vaccination is higher in young cattle [54]. Another study supports that vaccinated young cattle are less likely to become infected compare to vaccinated adult cattle [23]. Based on these two studies [54, 23], we assume that the vaccination is 15% less effective in the adult cattle than the juvenile cattle.

$$r_{IA} = .85 \times r_{IJ} \quad \text{and} \quad r_{SA} = .85 \times r_{SJ} \tag{2.11}$$

A study concludes that the efficacy of vaccination is approximately 88.7% [54]. Therefore, we choose $r_{\max} = 88.7$ and assume $r_{\min} = .1$ in the reduction functions on the transmission rate of the disease for vaccinated susceptible juvenile cattle. With the assumption in (2.11) $r_{\max} = 0.754$ and $r_{\min} = 0.085$ in the reduction function on the transmission rate of disease for vaccinated susceptible adult cattle.

A study mentions Leptospires were detected in the urine of one vaccinated infected heifer via Immunofluorescence assay at 3 time points, compare with infected heifer that were Immunofluorescence assay positive for up to 5 time points [67]. Therefore, we assume that the bacterial shedding rate is 40% less, $r_{\max} = 0.4$ and the efficacy of vaccination drop to 0, $r_{\min} = 0$ in vaccinated infected juvenile cattle. With the assumption in (2.11) $r_{\max} = 0.34$ and $r_{\min} = 0$ on the bacterial shedding rate of vaccinated infected adult cattle. Next we need to adjust the time points t_H, t_M. For the sake of simplicity, we assume t_H, t_M values are same in the reduction functions $r_{SJ}, r_{SA}, r_{IJ}, r_{IA}$. We have not found any resource informing us about the durations that vaccination reaches the maximum level and stays at the maximum level. However, there are some studies indicating vaccination provides a protection against leptospirosis up to one year [7, 1]. Therefore, we assume the effectiveness of vaccination is one year and we adjust t_H, t_M values according to the procedure of experiments. In three experiments [7, 15, 52] two doses of vaccination are applied 3 or 16 weeks apart and heifers were challenged 0 or 16 weeks after the application of vaccination. According to this we assume the efficacy of vaccination reaches the maximum level in 30 days, $t_H = 30$, and stays at the maximum level during 240 days, $t_M = 240$. Figure 2.4 shows the graphs of the

reduction function on the bacterial shedding and the disease transmission of juvenile cattle for impulse actions once a year.

The reduction function can be modified for twice a year vaccination as following

$$r(t) = \begin{cases} \frac{r_{\max} - r_{\min}}{t_H} t + r_{\min} & t \in [0, t_H] \\ r_{\max} & t \in [t_H, 180] \\ \frac{r_{\max} - r^*_{\min}}{t_H} t - 180 \frac{r_{\max} - r^*_{\min}}{t_H} + r^*_{\min} & t \in (180, 180 + t_H] \\ r_{\max} & t \in [180 + t_H, 365]. \end{cases}$$

Note that a few animals will be newly vaccinated and those few animals will bring the reduction down a little at that time. This change at a vaccination time is approximated by $r^*_{\min}$, which is the proportion of newly vaccinated animals (out of the total number of animals at time of vaccination) multiplied by $r_{\max}$. Figure 2.5 shows the graphs of the reduction functions on the bacterial shedding and on the disease transmission of juvenile cattle for impulse actions twice a year.

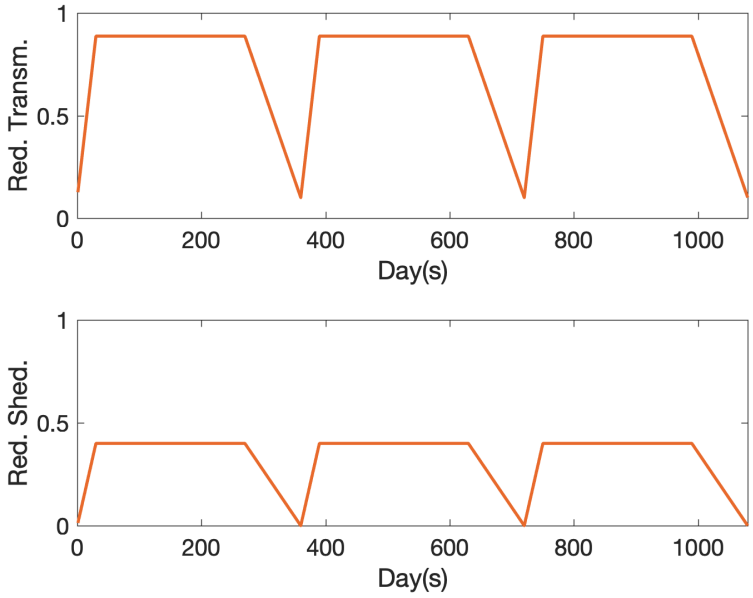


Figure 2.4: The reduction functions on the bacterial shedding and the disease transmission due to once a year vaccination

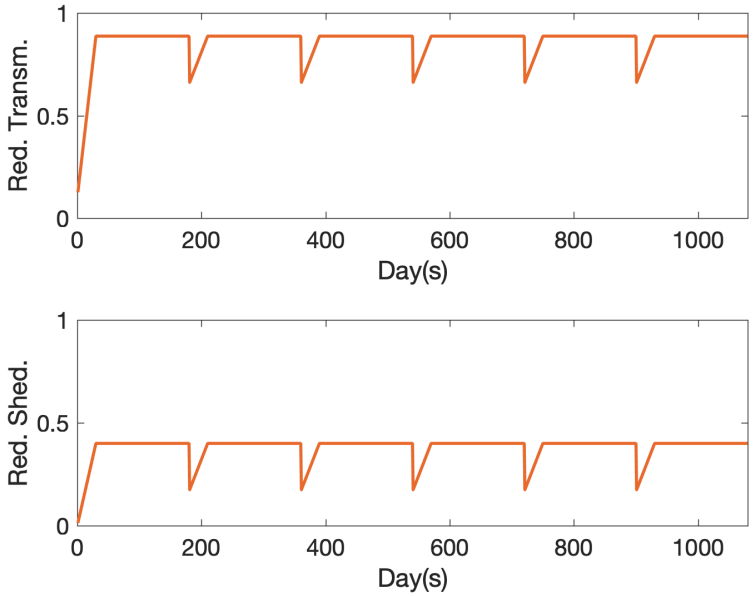


Figure 2.5: The reduction functions on the bacterial shedding and the disease transmission due to twice a year vaccination

2.4 Numerical results

2.4.1 The numerical results of preliminary model

The numerical simulations of the models are shown in this section to see the dynamical behavior of the models with application of impulse actions and without application of impulse actions. We start with simulating the preliminary model (2.1) for four years with the parameters listed in Table 2.1 and the initial conditions given in Table 2.2. Figure 2.6 shows the number of infected cattle during four years for the preliminary model. The number of infected cattle increases fast in the first 250 days. This indicates the outbreak of the disease occurs in the first two hundred fifty days. Note that the number of infected cattle in the ranch reaches seventy in two hundred fifty days. This is a high number relative to a ranch with 300 cattle. The number of new case decays to zero at the end of three years, however, the total number of cattle is around 100 at the end of three years. To understand the severity of the disease comprehensively, the number of death due to disease is calculated during four years.

Table 2.2: Initial conditions of the preliminary model

	Susceptible	Infected	Recovered
Juvenile	70	0	0
Adult	225	5	0

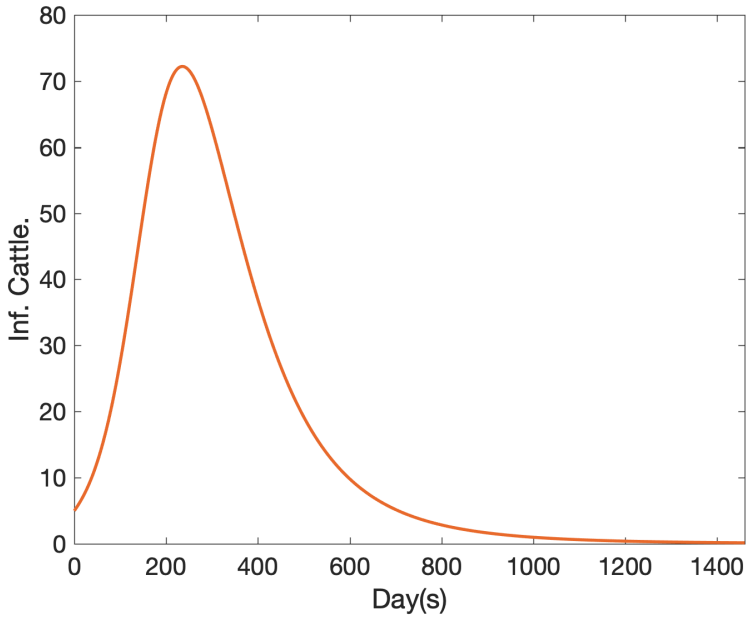


Figure 2.6: The number of infected cattle in the ranch during four years for the preliminary model

Table 2.3 shows the total number of death due to disease for each year. As shown, the total number of death due to disease is 150 four in the first year which is high for a ranch occupying three hundred cattle. After three years, the number of death due to disease drop to one. However, there are less than 100 cattle in the ranch after three years. To know whether the ranch manager can maintain the structure of population without any actions taking against leptospirosis, we plot the structure of population.

Figure 2.7 shows number of juvenile and adult cattle in the ranch during four years. The number of adult cattle drop seventy and the number of juvenile cattle drop below twenty in the middle of second year. The system reaches an equilibrium point, but with a low number of cattle. There are approximately one hundred cattle in total in the ranch at that equilibrium point. Therefore, the ranch manager cannot maintain the desirable structure of population in the ranch without any preventative action. Recall that we discussed DFE, $\mathcal{R}_0$ and $\mathcal{T}_S$ in section 2.2 for model (2.1). The numerical value of these quantities are calculated with parameters given in Table (2.1)

- Disease Free Equilibrium

$$(I_J^*, I_A^*, B^*, S_J^*, S_A^*, R_J^*, R_A^*) = (0, 0, 0, 86, 268, 0, 0)$$

- $\mathcal{R}_0 = 3.2195$
- $\mathcal{T}_S = 4.8343$

As seen in the simulations the DFE is not stable and the control measurements $\mathcal{R}_0$ and $\mathcal{T}_S$ also confirms that the DFE is not stable since both quantities are greater than one. The other conclusion of target reproduction number $\mathcal{T}_S$ is the required effort to control the outbreak of disease.

Table 2.3: The total number of deaths due to the disease during four years for the preliminary model

Year(s)	First	Second	Third	Fourth
Deaths	154	54	6	1

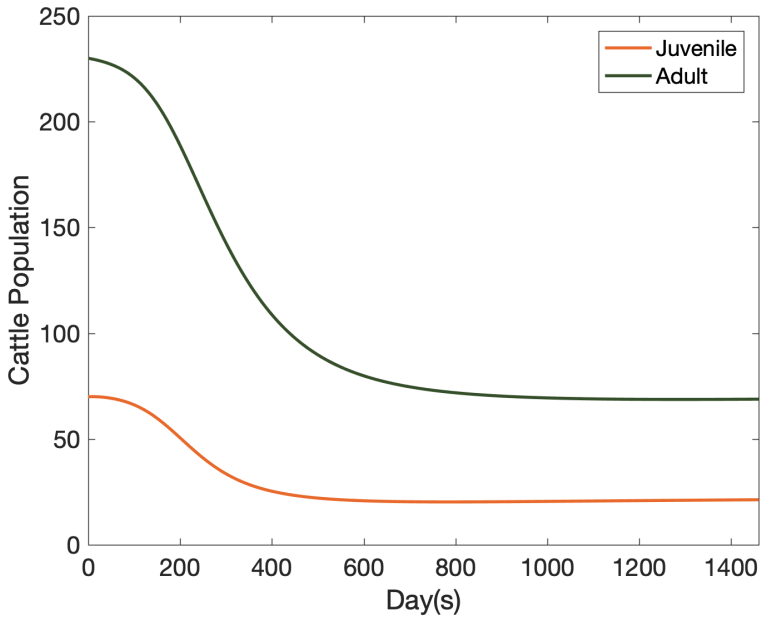


Figure 2.7: The number of juvenile and adult cattle in the ranch during four years for the prelimary model

Recall that we said if the transmission of disease can be reduced by

$$1 - \frac{1}{\mathcal{T}_S}$$

then the DFE will be locally stable. Therefore, with the value of target reproduction number found, the required effort is $1 - \frac{1}{\mathcal{T}_S} = 0.79$ to eradicate the disease in the ranch. If a such control program can reduce the rate of adult cattle getting infected by 79% then the disease free equilibrium will be stable.

2.4.2 The numerical results of model with impulse actions once a year

Next, we want to observe the numerical simulations of the model with impulse actions once a year. The model has been run for four years with parameters listed in Table 2.1 and the initial conditions given in Table 2.4.

Table 2.4: Initial conditions of the model with impulse actions

	Susceptible	Vaccinated Susceptible	Infected	Vaccinated Infected	Recovered
Juvenile	0	70	0	0	0
Adult	0	225	5	0	0

Figure 2.8 shows the number of infected cattle in the ranch during four years. As shown, the number of infected cattle fluctuates between 5 and 12 during four years. However, the number of infected cattle increases gradually in the long run. The application of impulse actions reduces the number of infected cattle in the ranch, however, the applications once a year cannot eradicate the disease in the ranch. The disease exists in the ranch and deaths due to the disease occurs for long time.

Table 2.5 shows the number of death due to disease during four years. As seen, the application of impulse actions does not only reduce the number of infected cattle, but also the number of deaths due to disease. However, the number of deaths due to disease increases gradually during four years. We also want to see the structure of population in the ranch for the model with impulse actions once a year.

Figure 2.9 shows the number of juvenile and adult cattle in the ranch during four years for the model with impulse actions once a year. The ranch managers may maintain the desirable structure of populations with a lower juvenile size, however, they lose over twenty cattle every year and the lost increases each year because the vertical gaps between impulse actions shown in Figure 2.8 extends. Therefore, more impulse actions is required to save the cattle.

2.4.3 The numerical results of model with impulse actions twice a year

Finally, the model with impulse actions twice a year has been run for four years with parameters listed in Table 2.1 and the initial conditions given in Table 2.4.

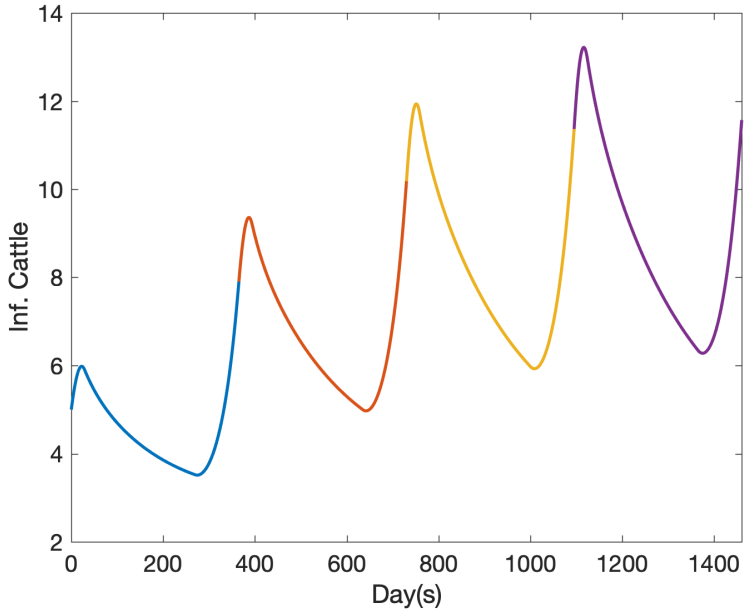


Figure 2.8: The number of infected cattle in the rach during four years for the model with impulse actions once a year

Table 2.5: The number of deaths due to the disease during four years for the model with impulse actions once a year

Year(s)	First	Second	Third	Fourth
Deaths	14	22	28	29

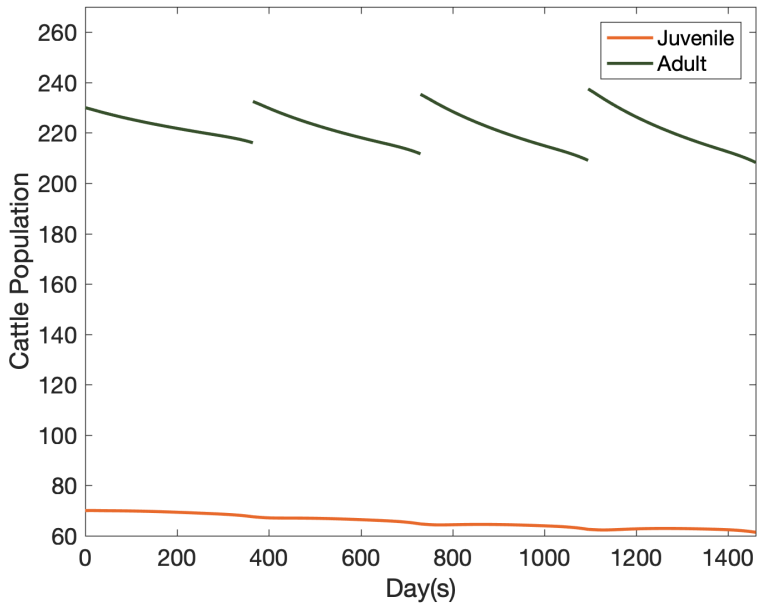


Figure 2.9: The number of juvenile and adult cattle in the ranch during four years for the model with impulse actions once a year

Figure 2.10 shows the number of infected cattle in the ranch during four years with model impulse actions twice a year. The number of infected cattle in the ranch decays gradually with the application of impulse actions twice a year. Therefore, the disease can be controlled with the applications twice a year.

Table 2.6 shows the number of death due to disease during four years. We observe that none of the cattle die due to disease by the end of four years. In addition, the application of impulse actions twice a year preserves the structure of population.

Figure 2.11 shows the number of juvenile and adult cattle in the ranch during four years. As shown, the ranchers can maintain the structure of ranch as they want with the application of impulse actions twice a year. They do not need to bring new cattle into ranch at the end of four years because the vertical gaps between impulse actions shown in Figure 2.11 narrows. Finally, Figure 2.12 shows the simulations of three models with respect to number of new cases for 4 years.

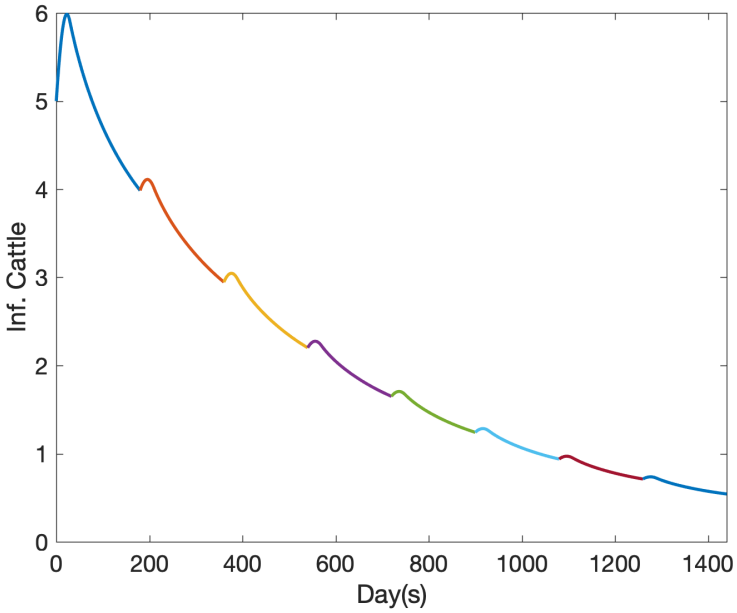


Figure 2.10: The number of infected cattle in the ranch during four years in the model with impulse actions twice a year

Table 2.6: The number of deaths due to the disease during four years for the model with impulse actions twice a year

Year(s)	First	Second	Third	Fourth
Deaths	10	7	3	2

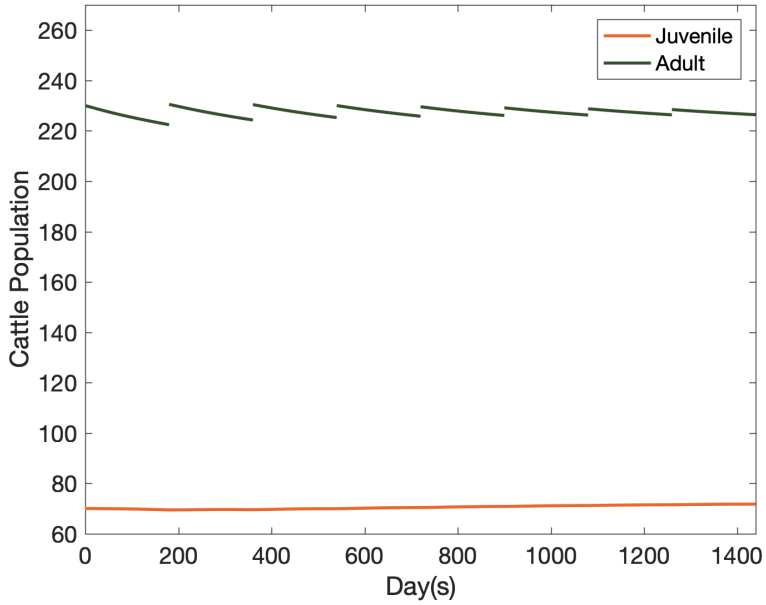


Figure 2.11: The number of juvenile and adult cattle in the ranch for the model with impulse actions twice a year

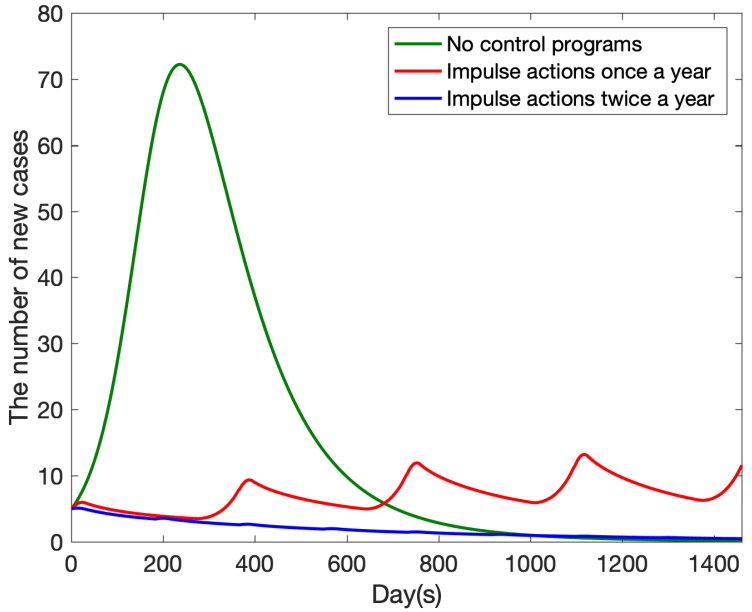


Figure 2.12: The results of each model with respect to the number of infected cattle in the ranch during four years

2.5 Sensitivity analysis

A method of global sensitivity analysis, Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficients (PRCC), is performed to investigate the impact of the parameters used in the model 2.10 on the total number of new infected cattle in the ranch. The input variables are the parameters used in the model (2.10) and the output variable is total number of new infected cattle during four years in the procedure of sensitivity analysis.

The input variables are sampled through LHS method which belongs to Monte Carlo (MC) sampling method and achieves same accuracy with fewer samples compare to the other sampling methods [38]. The method generates N by p LHS-matrix consisting of N samples of each parameter drawn from a probability distribution function (pdf). Then the model (2.10) is run with LHS-matrix to calculate N output variables.

To measure the correlation between input and output variables, PRCC is performed which is a measure of correlation between residuals obtained from a regression of ranked input and output variables. PRCC provides reliable results as long as a monotonic relationship exists between input and output variables, not necessary linear relationsip [38].

To examine a monotonic relationship between input and output variables, a corresponding input variable is sampled on a certain range N times and all other input variables are fixed on some base line values, then the model is run with these input variables N times to get N output variable, and then the relationship between each corresponding input variable and output variable is observed. This process is repeated for each input variable.

To examine the monotonic relationship between the parameters and output variables of the model (2.10), a sample of size 300 is generated for each parameter to run the model (2.10) and total number of new infected cattle calculated in the model (2.10) during four years as an output variables. Figures 2.13-2.15 show the monotonicity results of input versus output variables for each parameter value. As shown a monotonic relationship holds between input and output variables for each parameters, therefore, we can rely on LHS-PRCC method to conclude a possible correlation between input and output variables.

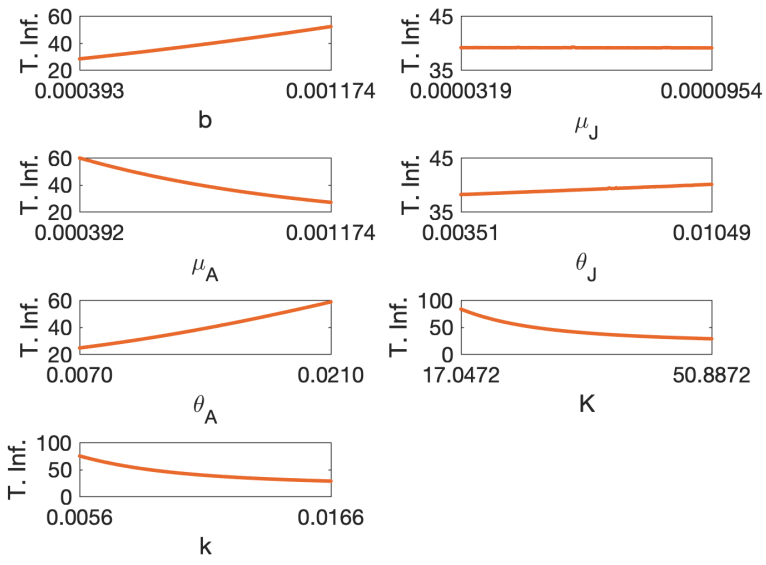


Figure 2.13: X-axis is the range of parameters $b, \mu_J, \mu_A, \theta_J, \theta_A, K, k$ and Y-axis is total number of new infected cattle in the ranch

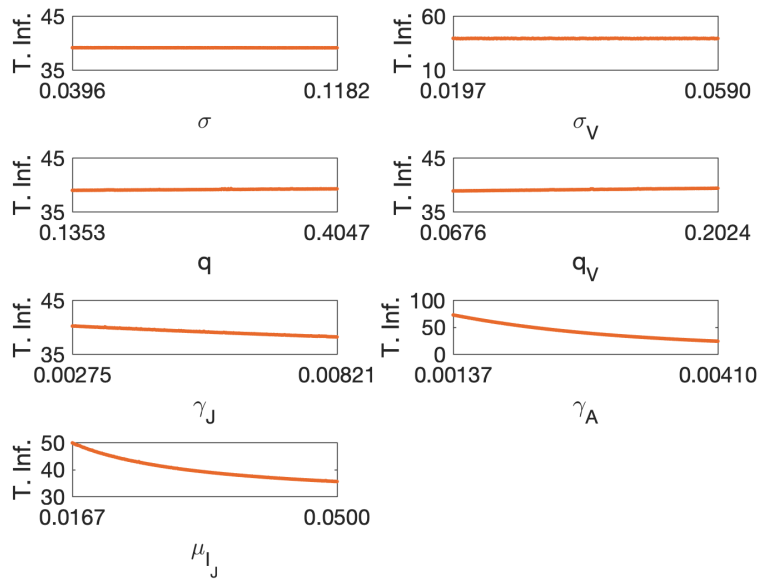


Figure 2.14: X-axis is the range of parameters $\sigma, \sigma_V, q, q_V, \gamma_J, \gamma_A, \mu_{I_J}$ and Y-axis is total number of new infected cattle in the ranch

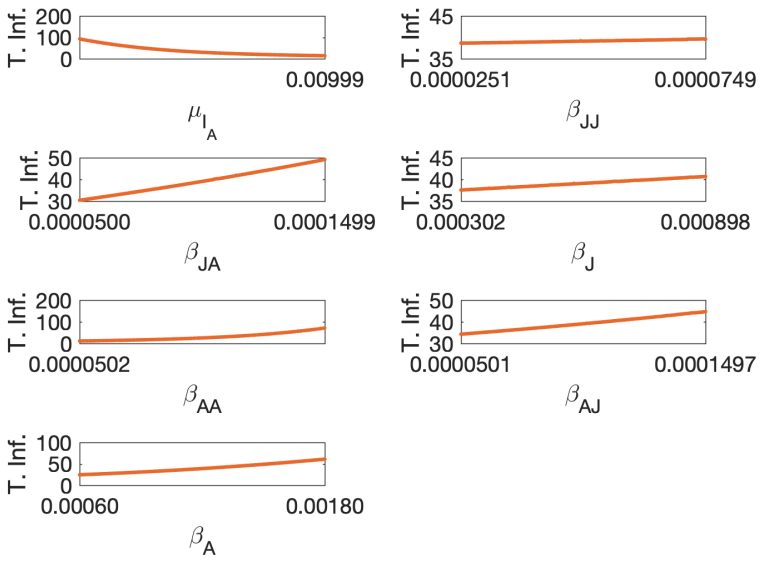


Figure 2.15: X-axis is the range of parameters $\mu_{I_A}, \beta_{JJ}, \beta_{JA}, \beta_J, \beta_{AA}, \beta_{AJ}, \beta_A$ and Y-axis is total number of new infected cattle in the ranch

The value of parameters in the Table 2.1 are used as baseline values and the range of %50 above and below these baseline values are defined to sample the input variables. The input variables are sampled 300 times in these ranges from a uniform pdf to form the LHS matrix. The LHS matrix is used to run the model 2.10 for four years with once and twice a year impulse actions and total number of new infected cattle is calculated as an output variable. PRCC values between these input and output variables, and corresponding p-values are calculated under a null hypothesis assuming PRCC value is zero. Table 2.7 shows statistical results of parameter in the model with impulse actions twice a year.

If we assume that the significant level of $\alpha = 0.05$, then there are significant evidence to conclude that the highlighted parameters have some impact on the total number of new infected cattle in the model with impulse actions once a year. We also perform LHS-PRCC with the model with impulse actions twice a year, we observed same list of parameters that are statistically significant. These results intuitively make sense for instance, we have more adult cattle in the ranch than juvenile and transmission rates are the main factors that impacts the number of new infected cattle, therefore we expect the transmission rate β_{AA} to be statistically significant.

Table 2.7: The result of PRCC and p-values in sensitivity analysis for the model with impulse actions once a year

PRM.	PRCC	p-value	Baseline V.	Lower B.	Upper B.
b	0.36	1.9e-10	0.00078	0.00039	0.0012
μ_J	-0.01	0.86	6.4e-05	3.2e-05	9.6e-05
μ_A	-0.54	1.7e-24	0.00078	0.00039	0.0012
θ_J	0.033	0.57	0.007	0.0035	0.011
θ_A	0.4	8.6e-13	0.014	0.007	0.021
K	-0.5	5.1e-20	34	17	51
k	-0.44	1.2e-15	0.011	0.0056	0.017
σ	-0.022	0.71	0.079	0.039	0.12
σ_v	0.023	0.69	0.039	0.02	0.059
q	-0.13	0.022	0.27	0.14	0.41
q_v	-0.0012	0.98	0.14	0.068	0.2
γ_J	-0.18	0.0023	0.0055	0.0027	0.0082
γ_A	-0.63	4e-34	0.0027	0.0014	0.0041
μ_{I_J}	-0.16	0.0058	0.033	0.017	0.05
μ_{I_A}	-0.87	7.3e-94	0.0067	0.0033	0.01
β_{JJ}	0.011	0.85	5e-05	2.5e-05	7.5e-05
β_{JA}	0.39	1.5e-12	0.0001	5e-05	0.00015
β_J	0.1	0.085	0.0006	0.0003	0.0009
β_{AA}	0.93	2.5e-129	0.0001	5e-05	0.00015
β_{AJ}	0.2	0.00064	0.0001	5e-05	0.00015
β_A	0.58	1.8e-28	0.0012	0.0006	0.0018

,

2.6 Conclusions

We have studied two mathematical models of leptospirosis to analyze the behavior of leptospirosis and the consequences of control programs in the cattle ranch. The preliminary model 2.1 suggests the ranch managers need to apply some control programs to eradicate leptospirosis or reduce the damage due to leptospirosis in the ranch. As shown in Figure 2.12, leptospirosis spreads out fast and causes significant number of deaths in the ranch in a few months. The model with impulse actions (2.10) shows the application of impulse actions reduce the number of deaths and the number of infected cattle in the ranch as shown in Figure 2.12. However, the application of impulse actions once a year is not sufficient in order for eradicate leptospirosis in the ranch. The number of new infected cattle increases gradually with the application of impulse actions twice a year. Therefore, the application of impulse actions need to be done more frequently. The application of impulse actions twice a year eliminates leptospirosis in the ranch after their applications for sufficiently long time.

These results are coincide with the ideal treatment suggested in the literature, in which vaccines are applied twice a year. This practice can eradicate the disease, and even more through the target reproduction number analysis in section 2.2.3 it is possible to control the disease only by applying vaccination to the adult cattle.

This chapter is collaboration with Prof. Suzanne Lenhart, University of Tennessee, Knoxville, Prof. Jorge X. Velasco-Hernandez, Instituto de Matematicas UNAM and Prof. David Baca Carrasco, Instituto Tecnológico de Sonora.

Chapter 3

A mathematical model for cost-effectiveness analysis and early detection of leptospirosis in human

3.1 Introduction

Leptospirosis is a neglected zoonotic diseases caused by various types of pathogenic Leptospira including more than 9 genospecies and over 200 serovars. While leptospirosis has been an increasing health problem in urban regions in developing countries due to hygiene and overcrowding issues, and it is also a life-threatening disease in developed countries due to climate conditions [4, 51, 21]. This life-threatening disease is recognized as one of main causes of pulmonary haemorrhage syndrome, however, there are not a lot of studies estimating mortality and morbidity of leptospirosis for the global burden [16]. One study estimates 1.03 million cases with 58,900 deaths annually, resulting in a total of approximately 2.9 million Disability Adjusted Life Years (DALY) (a health metric used by the World Health Organization (WHO)). This is more than 70% of the global DALY level of cholera estimated in 2010, and the DALY levels are higher in tropical regions such as South East Asia, Central and South America [62].

Transmission of leptospirosis occurs in humans through contact with infected animals or soil and water contaminated by infected animals' urine. Therefore, the transmission rate of leptospirosis varies depending on the climate, rainfall and occupations (change contact rate of susceptible humans to the bacteria). Since the transmission rate increases in flood seasons outbreak happens during flood seasons. While rodents are the main reservoir hosts, humans are accidental hosts that are less likely to cause infection [19, 4]. Clinical presentation of leptospirosis varies from self-limited anicteric febrile illness with or without meningitis to severe and potentially lethal multisystem illness with jaundice and renal failure, and even death [61, 60, 21]. The average incubation period is 1 or 2 weeks, with a range of 2 days to 30 days. The most common symptoms are chills, headache myalgia, and abdominal pain. Due to common symptoms with other diseases such as dengue and malaria, misdiagnosis of leptospirosis is very common in many endemic countries [44, 4].

In humans, antibiotic therapy is the most common and effective method as compared with vaccination to provide immunity against leptospirosis. However, early and correct diagnosis of leptospirosis is crucial for antibiotics to provide benefit. There are several laboratory tests available for diagnosis of leptospirosis, but their sensitivity and specificity values are low and their usefulness are still under discussion [20, 60]. Antibiotic treatment is suggested as soon as leptospirosis is suspected, and physician should not wait for the test result [44]. While a diverse range of antibiotics is available in some countries, doxycycline is potentially the best option for initial antimicrobial treatment [47, 61]. Doxycycline is effective against most of Leptospira, bacteria causing infection, so it is extensively recommended and used in many countries. It has been shown that doxycycline decreased the duration of illness by 2 days and also affected fever, malaise, headache, and myalgias without any side effects [14, 41].

There were several studies discussing the effectiveness of doxycycline and other antibiotics in treatment of leptospirosis [20, 14, 47]. In addition, there has been some work about accuracy and usefulness of the diagnostic tests for leptospirosis, and the comparison of their performances [61, 48]. Several papers pointed out the global burden of leptospirosis in terms of DALYs [21, 62, 16]. There is a study discussing the strategies for treatment of suspected leptospirosis by a Thailand group [60]. This study compared treatment strategies with and without tests confirmation by using a framework of cost-benefit analysis conducted at 5

hospitals in Thailand between July 2003 and January 2005 and accounted for all direct medical costs in diagnosing and treating patients. The outcomes are measured respect to length of fever after treatment and then converted to productivity losses for the full economic costs. They found that empirical doxycycline treatment to be the most effective way without waiting for a test confirmation due to their low sensitivity and performance time. However, they did not focus on early detection of leptospirosis while doxycycline provides greatest benefit in early stage of disease.

In this study, our goal is to determine a treatment strategy for patients coming into a hospital and being suspected of leptospirosis. We developed a computational algorithm under stochasticity by using Markov-cycle tree and Monte Carlo simulations similar to the study by Sonnenberg and Beck in [59]. Our mathematical model finds an optimal treatment strategy for the patients depending on whether they have severe or mild symptoms and whether they are late case patients who are coming to the hospital after seven days of onset of their symptoms or early case patients who are coming to the hospital within seven days of onset of their symptoms. The model is a useful tool to determine the treatment strategies during flood session for a large group of patients. Due to the lack of data related to our problem, some of the parameter values are chosen according to some expert opinions [43, 24].

Imagine that a group of patients shows up at a hospital, the physicians know whether their symptoms are severe or mild and whether the patients are late or early case. The physicians do not know whether those symptoms are caused by leptospirosis or some other disease and whether the mild symptom patients will develop severe symptoms or stay with their mild symptoms. Under these circumstances, the physicians have six different treatment strategies as described in Figure 3.1 and they have to choose one of these six options to minimize DALYs, number of deaths and monetary costs and indirectly maximize the number of early detected leptospirosis cases.

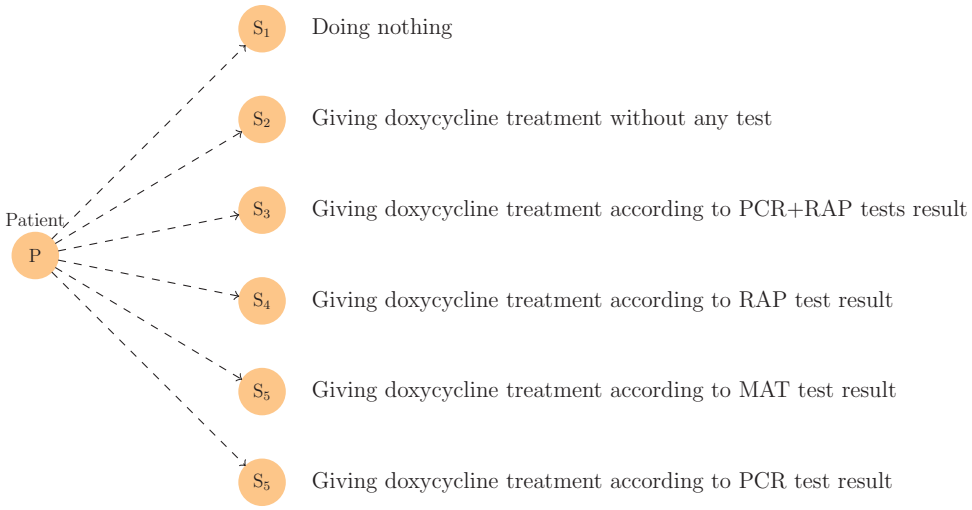


Figure 3.1: The choice of physicians

3.2 Model formulation

A cost-effectiveness analysis model with various scenarios is proposed to compare six treatment strategies regarding to the corresponding costs for leptospirosis and non-leptospirosis patients and indirectly maximize the number of early detected leptospirosis patients. Before introducing the model formulation we give some background about three diagnostic tests and assumptions that are used in this study.

Polymerase Chain Reaction based assay (PCR): They are classified as Conventional (including nested) and Real-time PCRs. As a molecular diagnosis test PCRs detect genes, which is present in the bacteria, such as *gyrB*, *rrs* (16S rRNA gene), *secY* or genes restricted to pathogenic Leptospira supplement such as *lipL32*, *lfb1*, *ligA*, *ligB2*. PCRs are effective diagnosis tests within first 5 to 15 days after the disease onset. A positive PCR result usually refers to presence of a pathogenic Leptospira species in the sample, however, the serovar type is not specifed [44]. These tests commonly used because of their higher sensitivity and early diagnosis in acute stages of diseases. However, performing PCR requires highly skilled personel and a laboratory with special equipments. Specimen collection can be from blood, urine, CSF or tissues. The processing time takes from couple hours to a day

depending on the type of PCR used and they are recommended to be used with one of rapid tests such as IgM ELISA to increase sensitivity in the first phase of the disease[11, 48, 44].

Microscopic Agglutination Test (MAT): As a serological test, MAT detects both immunoglobulin M (IgM) and immunoglobulin G (IgG) class agglutinating antibodies. MAT starts to give positive results from 10 to 12 days after the disease onset, so a positive result is considered a confirmed case. While the sensitivity is 41% during first week, it becomes 82% to 96% during second and third weeks. Performing MAT is very complicated and requires reference laboratories, such as the maintenance of a large panel of live pathogenic Leptospira standard cultures. Incomplete procedure while performing the test causes false negative results. Specimen collection must be from the blood and the processing time takes several weeks [44, 45].

Rapid screening tests: These tests just provide quick results which are not necessarily accurate, so the diagnosis is not necessarily to be early. They are easy to use and do not require an expert to perform. While their reading and interpretation are simple, they still require some training to perform accurately. They are mostly IgM detection tests. Since IgM cannot be detectable before second week of disease onset, these tests have very low sensitivity in the early acute stage of the illness. There are several rapid tests available, and lateral flow assays (LFA) is one of them, which is used in the decision process of this work. LFA can be applied to the patient at the bedside, as whole blood can be used for testing. While LFA results are available in 10 minutes, it does not confirm a case. In addition, it cannot detect antibodies against serovars belonging to the serogroup *Icterohaemorrhagiae*, so its result cannot be generalizable [48, 44].

Assumptions:

- The patients showing up at the hospital have similar symptoms to leptospirosis, such as fever, headache, chills, muscle aches, vomiting, etc.
- The effect of doxycycline is known respect to DALYs for leptospirosis and non-leptospirosis diseases such as influenza and dengue fevers.
- The tests diagnose only leptospirosis patients. The physicians believe that if the test result of a patient is positive, then the patient has leptospirosis and they give

doxycycline. If the test result of a patient is negative, then the patient does not have leptospirosis and they do not give doxycycline.

3.2.1 Patients classification

Regarding the assumptions we developed a computational algorithm and we start with classifying the patients according to their features. Recall that the physicians know the severity of symptoms and the duration of symptoms, however, they do not know whether these symptoms are caused by leptospirosis or some other diseases and whether the patients with mild symptoms will develop severe symptoms or stay with their mild symptoms. Therefore, each patient has four features: 1) Late or early case, 2) Severe or mild symptoms, 3) Severe or mild pathway, 4) leptospirosis or non-leptospirosis. Two of these four features are known by the physicians. We classified the patients according to their known features. Based on the known features, there are four different classes

- Late case, severe symptoms patients
- Late case, mild symptoms patients
- Early case, severe symptoms patients
- Early case, mild symptoms patients.

Each class has different transmission probabilities, so we should find a treatment strategy for each class separately.

3.2.2 Patients identification

We assigned the patients' unknown features by using the probability of having leptospirosis and the conditional probability of leptospirosis or non-leptospirosis patients moving to a severe pathway. To assign whether a patient has leptospirosis or not, a random number is drawn for the patient from an uniform distribution defined on the interval $[0, 1]$, if the random number is less than the probability of having leptospirosis then the patient is assigned to have leptospirosis, otherwise, non-leptospirosis.

To assign whether the patient is on the mild or severe pathway, another random number is drawn for the patient from an uniform distribution defined on the interval $[0, 1]$, if the random number is less than the conditional probability of leptospirosis or non-leptospirosis patients moving to severe pathway then the patient is assigned to be on severe pathway, otherwise, on mild pathway. Figure 3.2 shows the diagram of patient identification for late case, severe symptoms patient, where p_1 is the probability of having leptospirosis when a patient is in late case, severe symptoms class. Since the patients in this class have already had severe symptoms, they are severe pathway patients.

Late case mild symptoms class patients have a slightly different diagram since they can stay in mild pathway or they can make a transition to severe pathway depending on the conditional probability of leptospirosis or non-leptospirosis patients moving to severe pathway. Figure 3.3 shows the diagram of patient identification for late case, mild symptoms patients, where p_2 is the probability of having leptospirosis for late case, mild symptoms class patients, p_3 is the conditional probability of leptospirosis patients in late case, mild symptoms class moving to severe pathway, and p_4 is the conditional probability of non-leptospirosis patients in late case, severe symptoms class moving to severe pathway.

This process is same for early case, severe symptoms class and early case, mild symptoms class. Hereby a table can be generated for large number of patients for each class such that each row represents the patients' identification as shown in Table 3.1, for instance the first patient has leptospirosis and is on severe pathway.

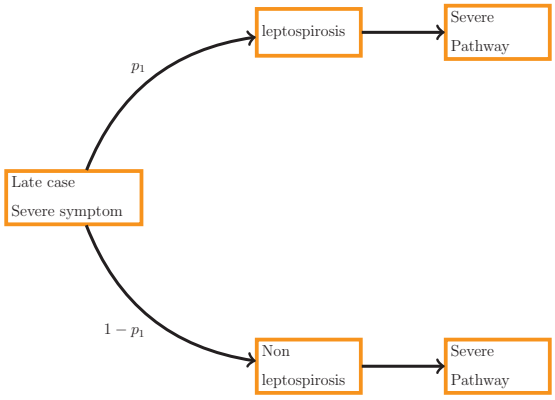


Figure 3.2: The diagram for identifying late case, severe symptoms patients

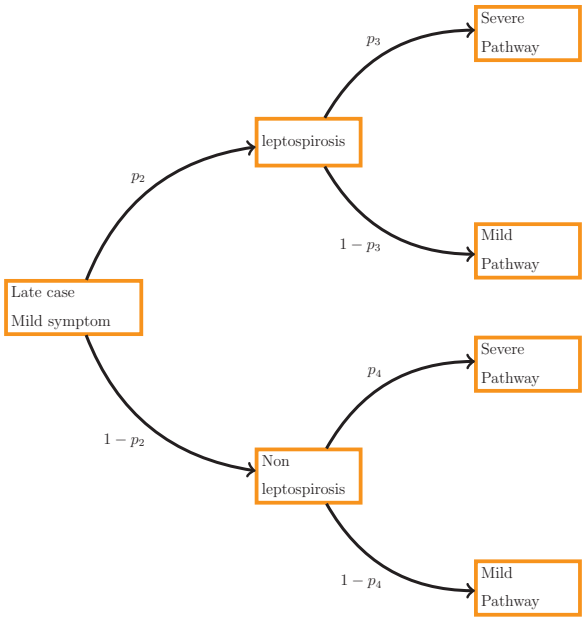


Figure 3.3: The diagram for identifying late case, mild symptoms patients

Table 3.1: Patients' identification beyond the known class

Patient	leptospirosis	Pathway
1	Yes	Severe
2	No	Severe
3	No	Mild
4	No	Severe
5	Yes	Mild
⋮	⋮	⋮
⋮	⋮	⋮
⋮	⋮	⋮

3.2.3 Decision process

There are six choices for the physicians to make a decision. We have assigned each choice with a probability d_i where $i = 1, 2, ..., 6$ and $d_1 + d_2 + d_3 + d_4 + d_5 + d_6 = 1$. Notice that the distribution of $d = (d_1, d_2, d_3, d_4, d_5, d_6)$ is the only choice of the physicians that affects the overall cost in the model. Thus we will get a different set of $d = (d_1, d_2, d_3, d_4, d_5, d_6)$ for the optimal strategies depending on the classes and the goal is to find the best distribution of d for each class by evaluating the costs associated with Table 3.1 at each distribution. Therefore, the cost function depends on the distributions in the model. We are going to tell more about this part in the cost calculation section.

Figure 3.4 shows the choices of physicians corresponding each distribution. There are as many as distributions of d can be generated, however we are going to evaluate the cost function with certain choices of these distributions only. There are six simple distributions, as given below.

- $(1, 0, 0, 0, 0, 0)$ Doing nothing
- $(0, 1, 0, 0, 0, 0)$ Giving doxycycline treatment without any test
- $(0, 0, 1, 0, 0, 0)$ Giving doxycycline treatment according to PCR+RAP tests result
- $(0, 0, 0, 1, 0, 0)$ Giving doxycycline treatment according to RAP test result
- $(0, 0, 0, 0, 1, 0)$ Giving doxycycline treatment according to MAT test result
- $(0, 0, 0, 0, 0, 1)$ Giving doxycycline treatment according to PCR test result

These six distributions are obtained by using $\{0, 1\}$. If we want to use $\{0, 0.5, 1\}$, then we come up with a table with 21 different distributions. Table 3.2 shows a list of twenty-one different distributions by using 0, 1 and 0.5. Each distribution has different meaning, such as $(0.5, 0, 0, 0, 0.5, 0)$ means applying the first strategy with the probability 0.5 and applying the fifth strategy with the probability 0.5.

To decide which strategy to choose for more general distributions, such as $(d_1, d_2, d_3, d_4, d_5, d_6) = (0.1, 0, 0.2, 0.2, 0.4, 0.1)$, we use Monte Carlo method [6] :

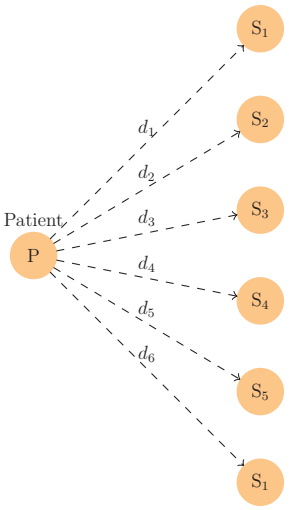


Figure 3.4: The choices of physicians with probabilities

$$l_i = \sum_{k=1}^{i} d_k, \qquad \text{such that} \quad \sum_{k=1}^{6} d_k = 1, \quad i = 1, 2, 3, 4, 5, 6$$

For a given random number r, if $l_j \leq r < l_{j+1}$ then choose path l_{j+1}, where $l_0 = 0$ and $j = 0, 1, 2, 3, 4, 5$

For instance, $(d_1, d_2, d_3, d_4, d_5, d_6) = (0.1, 0, 0.2, 0.2, 0.4, 0.1)$, then $\vec{l} = (l_0, l_1, l_2, l_3, l_4, l_5, l_6) = (0, 0.1, 0.1, 0.3, 0.5, 0.9, 1)$. Assume the chosen random number $r = 0.4$, then the algorithm choose path l_4 which means choosing strategy 4 since the random number is in $[l_3, l_4]$.

3.2.4 Evaluation of each strategy

After the algorithm decides the choice of the strategy, the model uses the sensitivity and specificity of the tests to find out the tests' result. The sensitivity of a test is the performance of detecting the true positives, given as the following

$$\mathbb{P}\{+\text{Test}|\text{Disease}\} = \frac{\text{TP}}{\text{TP} + \text{FN}}$$

Table 3.2: Twenty-one distributions generated by 0, 0.5, 1

Index	d_1	d_2	d_3	d_4	d_5	d_6
1	1	0	0	0	0	0
2	0.5	0.5	0	0	0	0
3	0	1	0	0	0	0
4	0.5	0	0.5	0	0	0
5	0	0.5	0.5	0	0	0
6	0	0	1	0	0	0
7	0.5	0	0	0.5	0	0
8	0	0.5	0	0.5	0	0
9	0	0	0.5	0.5	0	0
10	0	0	0	1	0	0
11	0.5	0	0	0	0.5	0
12	0	0.5	0	0	0.5	0
13	0	0	0.5	0	0.5	0
14	0	0	0	0.5	0.5	0
15	0	0	0	0	1	0
16	0.5	0	0	0	0	0.5
17	0	0.5	0	0	0	0.5
18	0	0	0.5	0	0	0.5
19	0	0	0	0.5	0	0.5
20	0	0	0	0	0.5	0.5
21	0	0	0	0	0	1

where TP is the number of true positives and FN is the number of false negatives. Similarly, the specificity of a test is the performance of detecting the true negatives, given as the following

$$\mathbb{P}\{-\text{Test}|\text{No Disease}\} = \frac{\text{TN}}{\text{TN} + \text{FP}}$$

where TN is the number of true negatives and FP is the number of false positives [34, 2]. One of the physicians choices is to use combination of two tests, PCR+Rapid, and we assume either of these test positive, the physicians consider the tests' results to be positive. Therefore, the sensitivity of this choice is calculated as following

$$\begin{aligned}\mathbb{P}\{(+\text{T}_1) \text{ or } (+\text{T}_2)|\text{Disease}\} =& \mathbb{P}\{+\text{T}_1|\text{Disease}\} + \mathbb{P}\{+\text{T}_2|\text{Disease}\} \\ & - \mathbb{P}\{+\text{T}_1|\text{Disease}\}\,\mathbb{P}\{+\text{T}_2|\text{Disease}\}\end{aligned}$$

and the specificity by

$$\mathbb{P}\{(-\text{T}_1) \text{ and } (-\text{T}_2)|\text{No Disease}\} = \mathbb{P}\{-\text{T}_1|\text{No Disease}\}\,\mathbb{P}\{-\text{T}_2|\text{No Disease}\}$$

.

To decide whether the test result is positive or negative for a patient having leptospirosis in Table 3.1, a random number is drawn for the patient from an uniform distribution defined on the interval $[0, 1]$. If the random number is less than the sensitivity of the test, then we decide the test result is positive, otherwise the test result is negative. To decide whether the test result is positive or negative for a patient not having leptospirosis in Table 3.1, a random number is drawn for the patient from an uniform distribution defined on the interval $[0, 1]$. If the random number is less than the specificity of the test, then we decide the test result is negative, otherwise the test result is positive.

3.2.5 Accurate and inaccurate actions with and without the tests

Notice that the patients are going to be given doxycycline or not after the decision of the test result. Therefore, doxycycline might be given to the patients who do not have leptospirosis if their test result is positive. Similarly, doxycycline might not be given to the patients who have leptospirosis if their test result is negative.

Figure 3.5 shows the diagram of evaluation of each strategy for late case, severe symptoms class. We are illustrating all possible consequences that might happen after a test result in the last green column of Figure 3.5. For instance, the first row of the last column indicates leptospirosis patient getting doxycycline, and the second row of the last column indicates non-leptospirosis patient getting doxycycline.

Late case, mild symptoms class has a slightly different diagram since they have mild symptoms and they may develop severe symptoms as shown in Figure 3.6

The rest of the diagrams follow the same for patients who are not getting doxycycline. Figures 3.5 and 3.6 are same for early case, severe and mild symptoms class.

- **Late case, severe symptoms:**

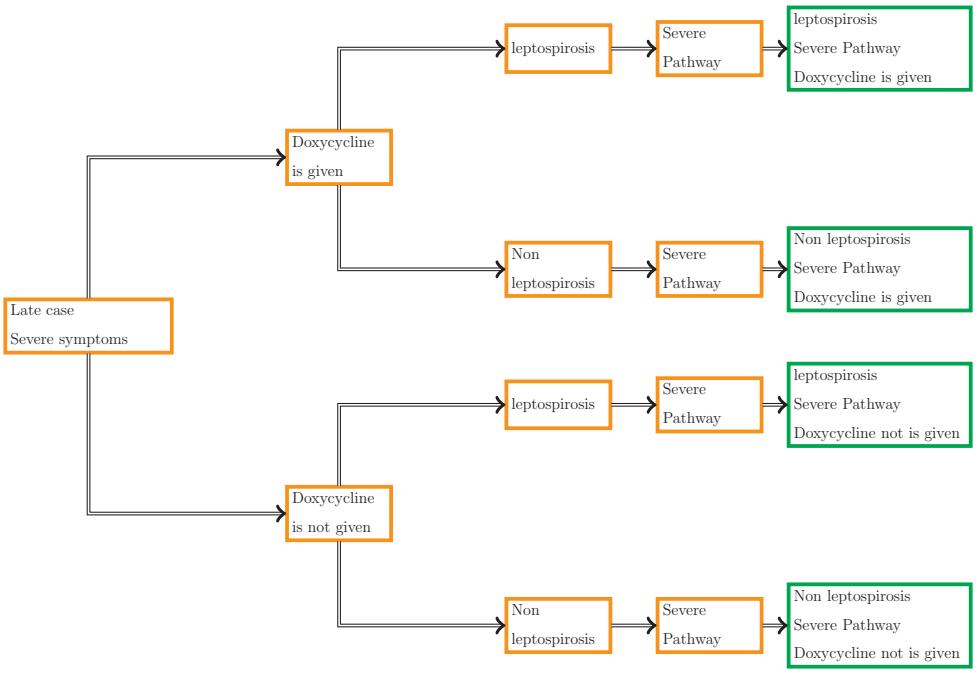


Figure 3.5: After test results, the diagram of each strategy for late case, severe symptoms class

- **Late case, mild symptoms:**

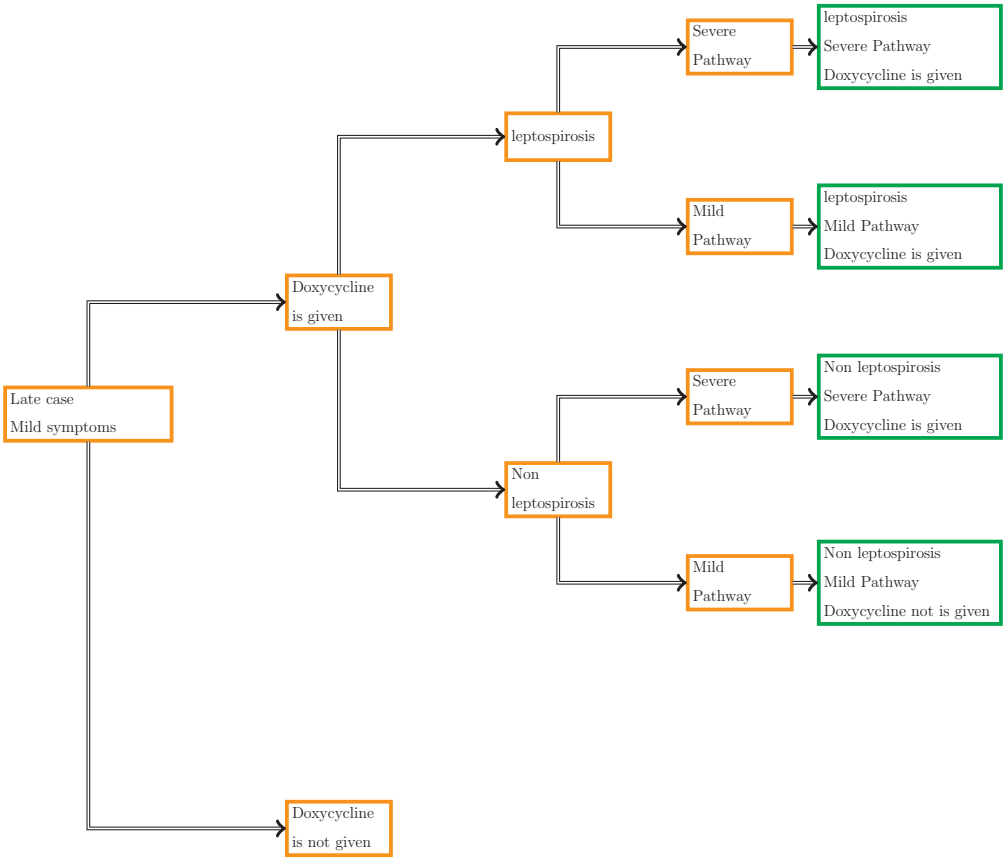


Figure 3.6: After test results, the diagram of each strategy for late case, mild symptoms class

Since the tests are given not only to detect leptospirosis patients but also to prevent inaccurate treatment of non-leptospirosis patients, the accuracy of treatment with test confirmation must be counted. Therefore the accurate test confirmation must reduce overall cost for leptospirosis and non-leptospirosis patients. A leptospirosis patient given doxycycline with a positive test result must have lower cost values with respect to death and DALY than a leptospirosis patient given doxycycline without a test confirmation. Similarly a non-leptospirosis patient not given doxycycline with a negative test result must have lower cost values than a non-leptospirosis patient not given doxycycline without a test confirmation.

Figure 3.7 depicts the all possible cases of test outcomes for a patient. The last column points out accurate and inaccurate actions with and without test confirmation. For instance, the first row of the last column in Figure 3.7 indicates an accurate action with a test confirmation, however the second row indicates an accurate action without a test confirmation.

3.2.6 Cost calculation

Three types of values are counted in the model: i) DALYs which is the years that the patients lose due to disability and death, ii) the number of deaths due to the diseases and iii) the monetary cost during hospital process. These values are going to be calculated separately for each of four classes. The goal is to find the best choice for the physicians in Figure 3.4 that minimizes each of these cost values.

Note that no matter which strategy that the physician uses, the patients in Table 3.1 are going to be in one of four categories: leptospirosis patients receiving doxycycline, leptospirosis patients not receiving doxycycline, non-leptospirosis patients receiving doxycycline, and non-leptospirosis patients not receiving doxycycline. Therefore, the cost values are calculated based on the patients' pathways, whether the patients are receiving doxycycline, and whether the patients have leptospirosis, and the patients can be given any of the tests as shown in Figures 3.5-3.7 and as discussed in subsection 3.2.5. The costs depend also on the known two features of the patients. Hence, if we minimize the following objective function of the distributions for a particular cost value, then we can achieve our goal

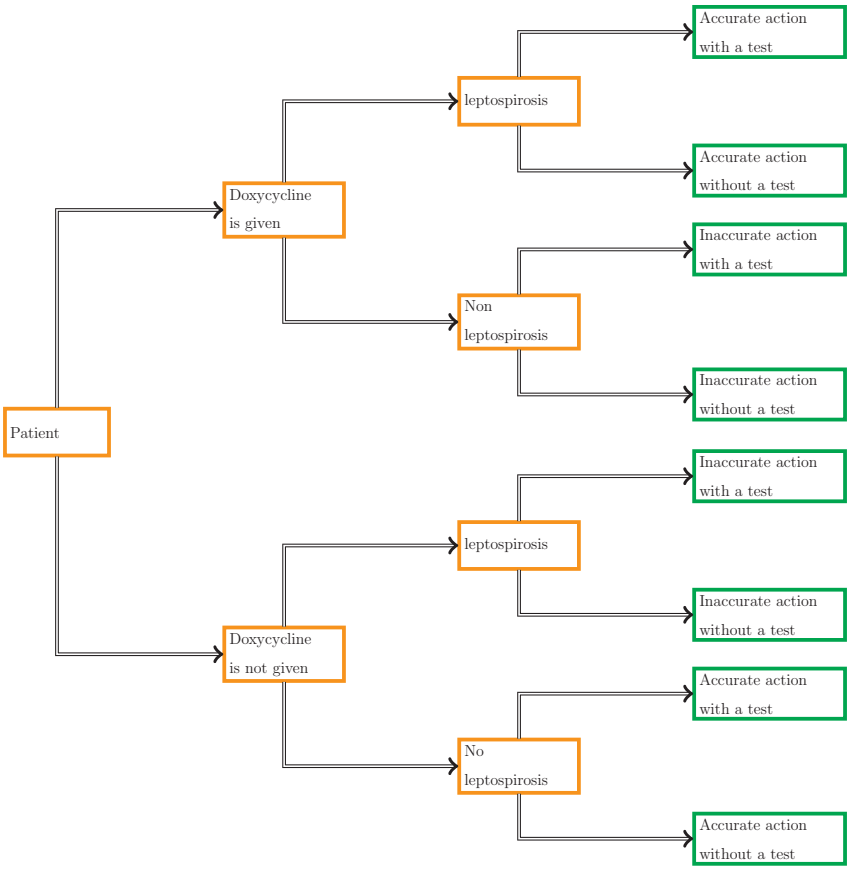


Figure 3.7: Accurate and inaccurate actions with and without test options

$$c(d) = \min_{d} \{c_1(d) + c_2(d) + c_3(d) + c_4(d)\}$$

where

- $d = (d_1, d_2, d_3, d_4, d_5, d_6)$ is the distribution for the choice of the physicians
- $c_1(d)$ is the cost for leptospirosis patients receiving doxycycline
- $c_2(d)$ is the cost for leptospirosis patients not receiving doxycycline
- $c_3(d)$ is the cost for non-leptospirosis patients receiving doxycycline
- $c_4(d)$ is the cost for non-leptospirosis patients not receiving doxycycline.

DALYs: This cost value is calculated by using:

$$\text{DALYs=YLLs+YLDs},$$

where YLLs represents the years lost due to death and YLDs represents the years lost due to disability. Both are measured in years. One can convert this unit to dollar unit by converting one year DALYs loss to monetary cost. We can assume that YLLs is 20 years for death of any patient according to the expert opinions [43, 24]. However YLDs depend on the situations that whether the patient is on severe or mild pathways, the patient receiving doxycycline, the patient has leptospirosis, and the patient takes any of the tests. The values in Tables 3.3 and 3.4 are found based on these situations. The values in these tables are adjusted according to the expert opinions [43, 24]. Table 3.3 represents calculated YLDs costs of patients depending on whether they receive doxycycline, they have leptospirosis, they are on severe or mild pathway.

To minimize DALYs value, we minimize the following objective function of the distributions

$$x(d) = \min_{d} \{x_1(d) + x_2(d) + x_3(d) + x_4(d)\}$$

Table 3.3: YLDs values

Parameter	Description	Value
YLDs	YLDs value for leptospirosis patients on severe pathway receiving doxycycline	0.0302
YLDs	YLDs value for non-leptospirosis patients on severe pathway receiving doxycycline	0.05
YLDs	YLDs value for leptospirosis patients on mild pathway receiving doxycycline	0.0102
YLDs	YLDs value for non-leptospirosis patients on mild pathway receiving doxycycline	0.015
YLDs	YLDs value for leptospirosis patients on severe pathway not receiving doxycycline	0.0604
YLDs	YLDs value for non-leptospirosis patients on severe pathway not receiving doxycycline	0.0604
YLDs	YLDs value for leptospirosis patients on mild pathway not receiving doxycycline	0.0205
YLDs	YLDs value for non-leptospirosis patients on mild pathway not receiving doxycycline	0.0205

where

- $x_1(d)$ is the total DALYs cost for leptospirosis patients receiving doxycycline
- $x_2(d)$ is the total DALYs cost for leptospirosis patients not receiving doxycycline
- $x_3(d)$ is the total DALYs cost for non-leptospirosis patients receiving doxycycline
- $x_4(d)$ is the total DALYs cost for non-leptospirosis patients not receiving doxycycline

Recall that an accurate test confirmation reduces the overall cost, as discussed earlier in subsection 3.2.5. Therefore, we need to use the weight factor in Table 3.4 for the values in Table 3.3 to reduce the DALYs values for the patients with accurate test results. The values in Table 3.4 are adjusted according to the expert opinions [43, 24] and the studies in [60, 62].

Table 3.4 represents the weight factors on YLDs costs for the patients accurately detected. For instance, if a leptospirosis patient takes a test and the result of the test is positive, then we multiple YLDs value by half which means we reduce YLDs value by half. However, if a leptospirosis patient takes a test and the result of the test is negative, then we multiple YLDs value by one which means we do not change YLDs value.

Since doxycycline is most effective in the early stage of leptospirosis, a lower YLDs are counted for early case leptospirosis patients. Thus, the model is indirectly forced to maximize the number of early detected leptospirosis cases while finding the treatment strategy minimizing the costs.

DEATHS: The number of deaths are counted only for the patients on the severe pathway. This number of deaths can be converted dollars by converting one death of a patient to monetary cost.

The number of deaths is calculated by using the probability of deaths and the probability of death depends on whether the patients receive doxycycline, the patients have leptospirosis, and the patients take any of the tests. To decide whether a patient dies, we draw a random number from an uniform distribution defined on the interval $[0, 1]$ for patients on severe pathway in Table 3.1, if the random number is less than the probability of deaths for their feature then we assume the patient dies. Table 3.5 represents the probability of deaths for

Table 3.4: Weight factors on YLDs due to accurate test confirmation

Parameter	Description	Value
m_1	Weight factor on YLDs for leptospirosis patient with a positive test result compared to no test options	0.5
m_2	Weight factor on YLDs for leptospirosis patient with a negative test result compared to no test options	1
m_3	Weight factor on YLDs for non-leptospirosis patient with a positive test result compared to no test options	1
m_4	Weight factor on YLDs for non-leptospirosis patient with a negative test result compared to no test options	0.3

Table 3.5: Probability of deaths

Parameter	Description	Value
q_1	Probability of leptospirosis patients receiving doxycycline to die	0.1
q_2	Probability of leptospirosis patients not receiving doxycycline to die	0.5
q_3	Probability of non-leptospirosis patients receiving doxycycline to die	0.05
q_4	Probability of non-leptospirosis patients not receiving doxycycline to die	0.05

patients depending on whether they receive doxycycline or they have leptospirosis and these probabilities are chosen according to the expert opinions [43, 24] and the studies in [60, 62].

To minimize the number of deaths, we minimize the following objective function of the distributions, as before

$$y(d) = \min_{d} \{y_1(d) + y_2(d) + y_3(d) + y_4(d)\}$$

where

- $y_1(d)$ is total number of deaths for leptospirosis patients receiving doxycycline
- $y_2(d)$ is total number of deaths for leptospirosis patients not receiving doxycycline
- $y_3(d)$ is total number of deaths for non-leptospirosis patients receiving doxycycline
- $y_4(d)$ is total number of deaths for non-leptospirosis patients not receiving doxycycline.

Recall that an accurate test confirmation reduces the overall cost, as discussed earlier in subsection 3.2.5. Therefore, we need to use the weight factors in Table 3.6 for the values in Table 3.5 to reduce the number of deaths for the patients with accurate test results. For instance, if a leptospirosis patient takes a test and the result of the test is positive, then we multiply the death probability by half, which means we reduce the death probability by half. However, if a leptospirosis patient is given a test and the result of the test is negative, then we multiply the death probability by one, which means we do not change the death probability. These weight factors are adjusted according to the expert opinions [43, 24] and the studies in [62]. Since doxycycline is most effective in the early stage of leptospirosis, a lower probability of death is counted for early case leptospirosis patients in the algorithm. We consider the probability of deaths for the early stage of leptospirosis patients to be half of the late stage of leptospirosis patients. Thus, the model is indirectly forced to maximize the number of early detected leptospirosis cases.

HOSPITAL: The costs in the hospital for a patient depend on four different values:

Table 3.6: Weight factors on the death probabilities due to accurate test confirmation

Parameter	Description	Value
n_1	Weight factor on the death probability for leptospirosis patient with a positive test result compared to no test option	0.5
n_2	Weight factor on the death probability for non-leptospirosis patient with a positive test result compared to no test option	1
n_3	Weight factor on the death probability for leptospirosis patient with a negative test result compared to no test option	1
n_4	Weight factor on the death probability for non-leptospirosis patient with a negative test result compared to no test option	0.3

- Medicine cost
- Tests cost
- Days staying in the hospital
- Supportive treatments for test confirmed patients.

Medicine, tests and supportive treatment costs depend on the physician's choice, however, the number of days staying in the hospital depends on whether the patients receive doxycycline, the patients have leptospirosis.

We assume only patients on severe pathways stay in the hospital. In order to calculate the hospital costs we use the values in Tables 3.7 and 3.8. Table 3.7 represents the dollar cost of doxycycline and the tests, and Table 3.8 represents the dollar cost of patients daily staying in the hospital depending on whether they receive doxycycline or they have leptospirosis. These values are adjusted according to the expert opinions [43, 24] and the studies in [48, 60].

To minimize the hospital costs, we minimize the following objective function of the distributions, as before

$$z(d) = \min_{d} \{z_1(d) + z_2(d) + z_3(d) + z_4(d)\}$$

where

- $z_1(d)$ is the total hospital cost for leptospirosis patients receiving doxycycline
- $z_2(d)$ is the total hospital cost for leptospirosis patients not receiving doxycycline
- $z_3(d)$ is the total hospital cost for non-leptospirosis patients receiving doxycycline
- $z_4(d)$ is the total hospital cost for non-leptospirosis patients not receiving doxycycline.

In addition, an accurate test confirmation reduces the overall cost, as discussed earlier in subsection 3.2.5. Thus we use the weight factors in Table 3.9 for the values in Table 3.8 to reduce costs of hospital stays for the patients with accurate test results. The values in Table 3.9 are adjusted according to the expert opinions [43, 24]. Table 3.9 represents the weight factors on hospital costs for the patients accurately detected. For instance, if a leptospirosis patient takes a test and the result of the test is positive, then we multiply the hospital cost by half which means we reduce the hospital cost by half. However, if a leptospirosis patient takes a test and the result of the test is negative, then we multiply the hospital cost by one which means we do not change the hospital cost.

Since doxycycline is most effective in the early stage of leptospirosis, lower costs of hospital stays is counted for early case leptospirosis patients.

Table 3.7: The treatment costs

Parameter	Description	Value
Doxycycline	Medicine	\$10
Rapid test	Diagnostic test	\$10
PCR test	Diagnostic test	\$60
MAT test	Diagnostic test	\$100

Table 3.8: Costs of hospital stays

Description	Daily cost
Leptospirosis patients receiving doxycycline	$6000
Non-leptospirosis patients receiving doxycycline	$10000
Leptospirosis patients not receiving doxycycline	$12000
Non-leptospirosis patients not receiving doxycycline	$12000

Table 3.9: Weight factors on hospital cost due to accurate test confirmation

Parameter	Description	Value
r_1	Weight factor on hospital cost for leptospirosis patient with a positive test confirmation compared to no test option	0.5
r_2	Weight factor on hospital cost for leptospirosis patient with a negative test result compared to no test option	1
r_3	Weight factor on hospital cost for non-leptospirosis patient with a negative test confirmation compared to no test option	0.3
r_4	Weight factor on hospital cost for non-leptospirosis patient with a positive test result compared to no test option	1

Thus, the model is indirectly forced to maximize the number of early detected leptospirosis cases. In addition, since supportive treatments, for instance special health care like dialysis, are given to the test confirmed patients, the monetary cost of supportive treatments are counted for patients with confirmed tests. We chose reasonable values in Table 3.10.

3.2.7 Combined cost function

Before we move to the simulations, one can combine the functions of distributions $x(d), y(d), z(d)$ to form the following total cost function of DALYs, deaths, hospital costs in order to make final decisions

$$\mathcal{T}(d) = ax(d) + by(d) + z(d)$$

Table 3.10: Monetary costs for supportive treatment

Parameter	Description	Value
s_1	Supportive treatment cost for leptospirosis patient with a positive test confirmation compared to no test option	\$1000
s_2	Supportive treatment cost for leptospirosis patient with a negative test result compared to no test option	\$500
s_3	Supportive treatment cost for non-leptospirosis patient with a negative test confirmation compared to no test option	\$500
s_4	Supportive treatment cost for non-leptospirosis patient with a positive test result compared to no test option	\$1000

where a, b are corresponding conversion constants for DALYs and deaths, and d is the distribution of strategy. The unit of the total cost function $\mathcal{T}(d)$ is dollars, the unit of a is dollars per DALY and the unit of b is dollars per death.

Recall that we assume the death of a patient costs 20 YLLs, thus we can draw a relationship $b = 20a$. Therefore, we only need to determine the value of a. It is hard to decide the value of a, but we may evaluate the total cost function for some different values of a to see how these different values change the final decision.

3.3 Simulations and results

In this section, we show some of the simulation results with available parameters for six simple distributions and the distribution in Table 3.2. The model is run with 1000 patients for each class. The parameters used in these simulations are given in Table 3.11 and 3.12 and the values in Table 3.12 are adjusted according to the expert opinions [43, 24] and a hospital results in Thailand [60].

3.3.1 Simulations with respect to the number of patients

The following tables 3.13- 3.16 show the results of 1000 patients with corresponding strategy and one single run for each class. We want to see the outcomes of each strategy with respect to the number of positive outcomes, leptospirosis detected cases, and accurate action results. Positive outcome means the number of patients with positive test results out of 1000 patients no matter whether the patients truly have leptospirosis or not. Leptospirosis detected cases means the number of positive tests for the patients truly having leptospirosis out of 1000 patients. Accurate action means the patient has leptospirosis and their test result is positive, or the patient does not have leptospirosis and their test result is negative. For example in Table 3.13 there are 88 leptospirosis cases, 88 leptospirosis on severe pathway, and 912 non-leptospirosis on severe pathways out of 1000 patients in simulation of late case, severe symptoms class. The strategies giving doxycycline according to PCR+Rapid gives 72 positive results, 75 accurately detected leptospirosis cases and 936 accurate actions. One can read the other Tables 3.14 -3.16 for the other classes in a similar way.

Table 3.11: Sensitivity and specificity of tests

Tests	Sensitivity Late case	Sensitivity Early case	Specificity Late case	Specificity Early case	Reference
PCR	34%	86%	99%	100%	[48, 51, 4]
MAT	82%	41%	100%	95.7%	[44, 45, 61]
LFA	81%	34%	96%	88 %	[48, 60]

Table 3.12: Transmission probabilities. L S: Late case, severe symptoms class, L M: Late case, mild symptoms class, E S: Early case, severe symptoms class, E M: Early case, mild symptoms class.

Parameter	Description	Class	Value
p_1	Prevalence leptospirosis	L S	0.1
p_2	Prevalence leptospirosis	L M	0.1
p_3	Transmission probability from mild pathway to severe pathway in leptospirosis patients	L M	0.2
p_4	Transmission probability from mild pathway to severe pathway in Non leptospirosis patients	L M	0.2
p_5	Prevalence leptospirosis	E S	0.1
p_6	Prevalence leptospirosis	E M	0.1
p_7	Transmission probability from mild pathway to severe pathway in leptospirosis patients	E M	0.2
p_8	Transmission probability from mild pathway to severe pathway in Non leptospirosis patients	E M	0.2

Table 3.13: Evaluating each strategy with respect to number of patients for late case, severe symptoms class

Strategy	Positive outcome	Lepto. detected	Accurate action
Doing Nothing	-	-	912
Doxycycline without test	-	-	88
PCR+Rapid	126	75	936
Rapid	113	71	941
MAT	72	72	984
PCR	44	33	934

Table 3.14: Evaluating each strategy with respect to number of patients for late case, mild symptoms class

Strategy	Positive outcome	Lepto. detected	Accurate action
Doing Nothing	-	-	889
Doxycycline without test	-	-	111
PCR+Rapid	135	96	946
Rapid	118	88	947
MAT	90	90	979
PCR	43	35	916

Table 3.15: Evaluating each strategy with respect to number of patients for early case, severe symptoms class

Strategy	Positive outcome	Lepto. detected	Accurate action
Doing Nothing	-	-	891
Doxycycline without test	-	-	109
PCR+Rapid	196	96	887
Rapid	131	31	822
MAT	44	44	935
PCR	92	92	983

Table 3.16: Evaluating each strategy with respect to number of patients for early case, mild symptoms class

Strategy	Positive outcome	Lepto. detected	Accurate action
Doing Nothing	-	-	914
Doxycycline without test	-	-	86
PCR+Rapid	170	78	900
Rapid	120	28	850
MAT	32	32	946
PCR	76	76	990

We observe from Tables 3.13 - 3.16 that choosing the strategy giving doxycycline treatment according to PCR+Rapid tests result gives the maximum number of positive outcomes and also the maximum number of early detected leptospirosis cases. On the other hand, the strategy giving doxycycline treatment according to MAT test gives the maximum number of accurate actions for late case patients and the strategy giving doxycycline treatment according to PCR test gives the maximum number of accurate actions for early case patients. Note that if we use the strategy giving doxycycline treatment without any test, the maximum number of leptospirosis case will receive doxycycline.

3.3.2 Simulations with respect to DALYs, Death and Monetary cost

The model has been run with 1000 patients and six simple distributions. Tables 3.17-3.20 list the results from the four classes. The results show the number of leptospirosis cases, leptospirosis cases on severe pathways and the cost values with respect to each strategy for each class. The first column refers to the strategy, the second column refers to the number of deaths for the strategy, the third column refers the DALYs values for the strategy and the fourth column refers to the dollars hospital cost for the strategy. The values of parameters are used in the simulation are in Tables 3.3 - 3.12

The number of leptospirosis cases is 98, the number of leptospirosis on severe pathway cases is 98 in the simulation of late case, severe symptoms class. For instance,consequence of choosing the strategy giving doxycycline according to PCR+Rapid tests results is 45 deaths out of 1000 patients, 940 DALYs years and $\$11,030,916$ dollars of hospital cost. Similarly, the conclusions from the other tables can be found. From tables 3.17-3.20, we observe that choosing the strategy giving doxycycline treatment according to PCR+Rapid tests result gives the minimum number of deaths and DALYs and the strategy giving doxycycline treatment without any test gives the minimum hospital cost for the all four classes.

Since our model is stochastic we want to find the best strategies on average and to see the uncertainty of the system. Therefore, the model has been run 100 times with 1000 patients and six simple distributions.

Table 3.17: Evaluating each strategy with respect to the number of deaths, DALYs and hospital costs for late case, severe symptoms class

Strategy	Deaths	DALYs	Hospital cost
Doing Nothing	83	1704	$12,000,000
Doxycycline without test	57	1187	$6,344,204
PCR+Rapid	45	940	$11,030,916
Rapid	52	1081	$11,123,160
MAT	50	1041	$11,394,490
PCR	69	1422	$11,708,545

Table 3.18: Evaluating each strategy with respect to the number of deaths, DALYs and hospital costs for late case, mild symptoms class

Strategy	Deaths	DALYs	Hospital cost
Doing Nothing	16	341	$2,364,000
Doxycycline without test	7	160	$1,029,714
PCR+Rapid	6	139	$2,200,334
Rapid	9	199	$2,177,864
MAT	10	219	$2,316,760
PCR	13	280	$2,345,996

Table 3.19: Evaluating each strategy with respect to the number of deaths, DALYs and hospital costs for early case, severe symptoms class

Strategy	Deaths	DALYs	Hospital cost
Doing Nothing	92	1884	$12,000,000
Doxycycline without test	46	966	$6,165,992
PCR+Rapid	46	960	$10,553,702
Rapid	73	1503	$11,096,828
MAT	69	1422	$11,646,565
PCR	48	1000	$11,144,325

Table 3.20: Evaluating each strategy with respect to the number of deaths, DALYs and hospital costs for early case, mild symptoms class

Strategy	Deaths	DALYs	Hospital cost
Doing Nothing	14	301	$2,544,000
Doxycycline without test	5	120	$1,077,800
PCR+Rapid	5	119	$2,212,382
Rapid	10	221	$2,304,368
MAT	11	240	$2,526,745
PCR	6	139	$2,370,825

The results in tables 3.21-3.24 show the average of 100 runs of number for leptospirosis cases, severe pathway and cost values with respect to each distribution for each class. The value of parameters used in the simulation are in Tables 3.3 - 3.12. From Tables 3.21-3.24, we observe that the results of 100 runs are very similar to the results of one run. This shows there is not significant uncertainty in the system.

3.3.3 Simulations with more distributions

We want to see whether the results vary when we run our model with more sets of distributions. Therefore, the model has been run with same number of patients and the parameters values in Tables 3.3-3.12. In addition the number of distributions increases to 21 and the distributions used in these simulations are given in Table 3.2.

In Tables 3.25-3.28, we list the results for the four classes. The tables show the number of deaths, DALYs and the hospital cost for each index of strategies. Note that the index of strategies refer to Table 3.2, for instance the strategy 13 is $(d_1, d_2, d_3, d_4, d_5, d_6) = (0, 0, 0.5, 0, 0.5, 0)$ which means choosing the strategy giving doxycycline treatment according to PCR+Rapid tests result with probability of 0.5 and choosing the strategy giving doxycycline treatment according to MAT test result with probability of 0.5. The results with 21 distributions is same as the results with six-simple distributions, however, some mix-strategies which means applying one strategy with a probability 0.5 and another one with probability 0.5, might change the results. We observe that choosing the strategy giving doxycycline treatment according to PCR+Rapid tests result gives the minimum number of deaths and DALYs, and the strategy giving doxycycline treatment without any test gives the minimum hospital costs for all of the classes. These results are true if we exclude the mixed-strategies such as applying the strategies choosing the strategy giving doxycycline treatment according to PCR+Rapid tests with probability 0.5 and the strategy giving doxycycline treatment without any test with 0.5 probability.

Table 3.21: Evaluating each strategy with respect to the number of deaths, DALYs and hospital costs in average of 100 runs for late case, severe symptoms class

Strategy	Deaths	DALYs	Hospital cost
Doing Nothing	82	1681	$12,000,000
Doxycycline without test	50	1045	$6,330,470
PCR+Rapid	43	893	$11,026,717
Rapid	45	948	$11,077,002
MAT	45	933	$11,345,647
PCR	67	1380	$11,697,764

Table 3.22: Evaluating each strategy with respect to the number of deaths, DALYs and hospital costs in average of 100 runs for late case, mild symptoms class

Strategy	Deaths	DALYs	Hospital cost
Doing Nothing	17	359	$2,412,720
Doxycycline without test	10	220	$1,061,786
PCR+Rapid	9	195	$2,258,662
Rapid	9	206	$2,225,596
MAT	9	202	$2,356,267
PCR	14	295	$2,398,347

Table 3.23: Evaluating each strategy with respect to the number of deaths, DALYs and hospital costs in average of 100 runs for early case, severe symptoms class

Strategy	Deaths	DALYs	Hospital cost
Doxycycline without test	81	1668	$12,000,000
Treatment	47	994	$6,186,124
PCR+Rapid	39	828	$10,534,490
Rapid	66	1367	$11,077,886
MAT	62	1278	$11,669,869
PCR	41	851	$11,154,008

Table 3.24: Evaluating each strategy with respect to the number of deaths, DALYs and hospital costs in average of 100 runs for early case, mild symptoms class

Strategy	Deaths	DALYs	Hospital cost
Doing Nothing	17	351	$2,377,560
Doxycycline without test	9	205	$1,015,295
PCR+Rapid	8	183	$2,117,789
Rapid	14	292	$2,178,337
MAT	13	272	$2,392,194
PCR	8	185	$2,258,733

Table 3.25: The number of deaths, DALYs and hospital costs results from an average of 100 runs for late case, severe symptoms class with respect to each distributions

Distribution	Deaths	DALYs	Hospital cost
1	83	1696	$12,000,000
2	66	1373	$9,165,376
3	50	1045	$6,339,539
4	63	1307	$11,519,943
5	47	981	$8,694,488
6	44	911	$11,045,011
7	65	1343	$11,555,707
8	47	983	$8,725,963
9	45	938	$11,069,599
10	46	961	$11,092,345
11	64	1328	$11,687,955
12	47	988	$8,857,481
13	44	927	$11,200,985
14	46	952	$11,226,681
15	45	939	$11,358,581
16	75	1543	$11,859,370
17	58	1209	$9,028,780
18	55	1142	$11,368,549
19	56	1171	$11,394,998
20	56	1167	$11,532,941
21	67	1385	$11,710,060

Table 3.26: The number of deaths, DALYs and hospital costs results from an average of 100 runs for late case, mild symptoms class with respect to each distributions

Distribution	Deaths	DALYs	Hospital cost
1	16	348	$2,407,320
2	14	293	$1,734,414
3	10	222	$1,060,733
4	13	272	$2,331,568
5	9	208	$1,657,969
6	9	192	$2,259,596
7	13	278	$2,315,821
8	10	210	$1,635,066
9	9	198	$2,242,134
10	9	204	$2,226,056
11	13	272	$2,379,555
12	10	213	$1,710,933
13	9	196	$2,309,306
14	9	203	$2,290,536
15	9	201	$2,356,484
16	15	318	$2,399,400
17	12	257	$1,725,987
18	11	242	$2,326,502
19	11	242	$2,307,808
20	11	248	$2,374,977
21	13	285	$2,392,039

Table 3.27: The number of deaths, DALYs and hospital costs results from an average of 100 runs for early case, severe symptoms class with respect to each distributions

Distribution	Deaths	DALYs	Hospital cost
1	83	1707	$12,000,000
2	66	1358	$9,082,943
3	48	1010	$6,178,789
4	62	1283	$11,268,048
5	45	937	$8,360,356
6	40	848	$10,522,540
7	75	1550	$11,528,385
8	58	1201	$8,627,555
9	54	1122	$10,793,127
10	67	1391	$11,060,510
11	73	1494	$11,821,991
12	56	1166	$8,912,578
13	51	1069	$11,083,174
14	65	1340	$11,355,726
15	62	1285	$11,649,412
16	62	1280	$11,567,241
17	44	928	$8,657,731
18	41	855	$10,832,447
19	54	1122	$11,102,453
20	52	1075	$11,397,321
21	41	860	$11,142,325

Table 3.28: The number of deaths, DALYs and hospital costs results from an average of 100 runs for early case, mild symptoms class with respect to each distributions

Distribution	Deaths	DALYs	Hospital cost
1	16	343	$2,382,240
2	12	268	$1,698,841
3	9	209	$1,017,930
4	12	262	$2,250,224
5	9	197	$1,575,007
6	8	180	$2,121,139
7	15	315	$2,284,441
8	11	248	$1,596,552
9	11	233	$2,153,397
10	13	280	$2,181,301
11	14	306	$2,391,607
12	10	227	$1,707,746
13	10	218	$2,257,765
14	13	270	$2,288,239
15	12	260	$2,394,730
16	12	261	$2,323,538
17	9	199	$1,646,112
18	8	184	$2,194,030
19	11	231	$2,221,111
20	10	228	$2,331,371
21	8	186	$2,264,019

3.3.4 Simulations with different prevalences

The parameters given in Tables 3.3-3.12 are mostly country dependent. The prevalence of leptospirosis is between 0.4 and 0.5 in some tropical regions, however, it varies from 0.1 to 0.2 in the most countries [60]. In this subsection we want to see how the results vary based on the prevalence of leptospirosis. Therefore, we vary the prevalence of leptospirosis from 0.1 to 0.5 by keeping all other parameter values the same and find the best strategies giving the minimum values based on the number of deaths, DALYs and hospital costs with respect to each prevalence.

In Tables 3.29-3.32, the first column refers to the prevalence of leptospirosis, the second column refers to the strategy giving the minimum number of deaths with respect to the prevalence, the third column refers to the strategy giving the minimum DALYs with respect to the prevalence and fourth columns refers to the strategy giving the minimum hospital cost with respect to the prevalence.

The results suggests the strategy giving doxycycline treatment according to PCR+Rapid tests result gives the minimum number of deaths and DALYs up to 0.2 prevalence, then the best strategy with respect to three cost values when the prevalence is higher than 0.2 is giving doxycycline treatment without any test.

3.3.5 Simulations with combined costs

Finally, we want to see the results of total cost functions, $\mathcal{T}(d)$ that was discussed in the subsection 3.2.7. Since it is hard to determine the monetary cost per DALYs a, we have varied it from \$10,000 to \$20,000 and find the best strategies giving the minimum costs for each of this value. We run the model 100 times with 1000 patients and the parameters in Tables 3.3-3.12 and then find the best strategy that gives minimum total cost value of the average cost of 100 runs.

The tables 3.33-3.36 show the results. The first column refers to monetary costs per DALYs, a, one can thinks as the monetary loss for one year if a patient is not economically productive. The second column refers to the strategy giving the minimum total cost with respect to monetary costs per DALYs, a. The third column refers total monetary cost, $\mathcal{T}(d)$.

Table 3.29: The strategy giving the minimum the number of deaths, DALYs and hospital costs with respect to each prevalence for late case, severe symptoms

Prevalence	Deaths	DALYs	Hospital cost
0.1	PCR+Rapid	PCR+Rapid	Doxycycline without test
0.2	PCR+Rapid	PCR+Rapid	Doxycycline without test
0.3	Doxycycline without test	Doxycycline without test	Doxycycline without test
0.4	Doxycycline without test	Doxycycline without test	Doxycycline without test
0.5	Doxycycline without test	Doxycycline without test	Doxycycline without test

Table 3.30: The strategy giving the minimum the number of deaths, DALYs and hospital costs with respect to each prevalence for late case, mild symptoms

Prevalence	Deaths	DALYs	Hospital cost
0.1	PCR+Rapid	PCR+Rapid	Doxycycline without test
0.2	Doxycycline without test	Doxycycline without test	Doxycycline without test
0.3	Doxycycline without test	Doxycycline without test	Doxycycline without test
0.4	Doxycycline without test	Doxycycline without test	Doxycycline without test
0.5	Doxycycline without test	Doxycycline without test	Doxycycline without test

Table 3.31: The strategy giving the minimum the number of deaths, DALYs and hospital costs with respect to each prevalence for early case, severe symptoms

Prevalence	Deaths	DALYs	Hospital cost
0.1	PCR+Rapid	PCR+Rapid	Doxycycline without test
0.2	PCR+Rapid	PCR+Rapid	Doxycycline without test
0.3	Doxycycline without test	Doxycycline without test	Doxycycline without test
0.4	Doxycycline without test	Doxycycline without test	Doxycycline without test
0.5	Doxycycline without test	Doxycycline without test	Doxycycline without test

Table 3.32: The strategy giving the minimum the number of deaths, DALYs and hospital costs with respect to each prevalence for early case, mild symptoms

Prevalence	Deaths	DALYs	Hospital cost
0.1	PCR+Rapid	PCR+Rapid	Doxycycline without test
0.2	PCR+Rapid	PCR+Rapid	Doxycycline without test
0.3	Doxycycline without test	Doxycycline without test	Doxycycline without test
0.4	Doxycycline without test	Doxycycline without test	Doxycycline without test
0.5	Doxycycline without test	Doxycycline without test	Doxycycline without test

Table 3.33: The strategy giving the minimum cost with respect to each monetary cost per DALYs and total cost with this strategy for late case, severe symptoms

Cost per DALYs, a	Strategy	Total cost
\$10,000	Doxycycline without test	\$26,840,847
\$12,000	Doxycycline without test	\$30,372,956
\$14,000	Doxycycline without test	\$35,087,189
\$16,000	Doxycycline without test	\$39,098,882
\$18,000	PCR+Rapid	\$43,316,477
\$20,000	PCR+Rapid	\$45,650,849

Table 3.34: The strategy giving the minimum cost with respect to each monetary cost per DALYs and total cost with this strategy for late case, mild symptoms

Cost per DALYs, a	Strategy	Total cost
\$10,000	PCR+Rapid	\$5,240,307
\$12,000	PCR+Rapid	\$6,250,289
\$14,000	PCR+Rapid	\$6,991,394
\$16,000	PCR+Rapid	\$7,753,733
\$18,000	PCR	\$8,701,316
\$20,000	PCR+Rapid	\$9,444,138

Table 3.35: The strategy giving the minimum cost with respect to each monetary cost per DALYs and total cost with this strategy for early case, severe symptoms

Cost per DALYs, a	Strategy	Total cost
\$10,000	Doxycycline without test	\$25,690,212
\$12,000	Doxycycline without test	\$29,866,772
\$14,000	PCR+Rapid	\$33,408,709
\$16,000	PCR+Rapid	\$36,570,175
\$18,000	PCR+Rapid	\$40,369,244
\$20,000	PCR+Rapid	\$43,837,258

Table 3.36: The strategy giving the minimum cost with respect to each monetary cost per DALYs and total cost with this strategy for early case, mild symptoms

Cost per DALYs, a	Strategy	Total cost
\$10,000	Doxycycline without test	\$5,111,084.6
\$12,000	Doxycycline without test	\$5,924,353.6
\$14,000	Doxycycline without test	\$6,764,999
\$16,000	PCR+Rapid	\$7,362,403.9
\$18,000	Doxycycline without test	\$7,920,482.4
\$20,000	PCR+Rapid	\$8,853,438.6

The results show the strategy giving doxycycline treatment without any test gives the minimum total cost value for the monetary cost per DALYs from \$10,000 to \$16,000, then the strategy giving doxycycline treatment according to PCR+Rapid tests result gives the minimum total cost for the monetary cost per year higher than \$16,000 for late case, severe symptoms class.

The results show more precise strategy giving doxycycline treatment according to PCR+Rapid tests result gives the minimum total cost for late case, mild symptoms class.

The results show the strategy giving doxycycline treatment without any test gives the minimum total cost value for the monetary cost per DALYs from \$10,000 to \$12,000, then the strategy giving doxycycline treatment according to PCR+Rapid tests result gives the minimum total cost for the monetary cost per year higher than \$12,000 for early case, severe symptoms class.

The results show the strategy giving doxycycline treatment without any test gives the minimum total cost value for the monetary cost per DALYs from \$10,000 to \$14,000, then the best strategy switches between giving doxycycline treatment according to PCR+Rapid tests result and giving doxycycline treatment without any test for the monetary cost per year higher than \$14,000 for early case, mild symptoms class.

3.4 Conclusion

We have developed a stochastic computational model of cost-effectiveness and early detection of leptospirosis for the patients suspected of leptospirosis. Most of parameters used in the simulations of the model are adjusted according to the expert opinions [43, 24] and the studies in [48, 60]. Note that our results and conclusions completely depend on these parameter values. However, our model is applicable with different set of parameters and will determine a different best strategy with different set of parameters.

Four strategies were discussed in this study: PCR+Rapid, Rapid, MAT and PCR. The performance of each test depends on whether the patient is late or early case. The ranking of the strategies in order of the number of true positives is PCR+Rapid, MAT, Rapid and PCR from highest to lowest for late case patients, but for early case patients, the corresponding order is PCR+Rapid, PCR, MAT and Rapid. The ranking of the strategies in order of the number of accurate actions is MAT, Rapid, PCR+Rapid and PCR from highest to lowest, for late case patients, however, for early case patients the corresponding order is PCR, MAT, PCR+Rapid and Rapid. We may conclude that PCR itself does not perform well for late case patients, but does perform well for early case patients this coincides with the results in [48]. In addition, MAT does not give many false positive results particularly in late case patients.

Three cost values were discussed in this study: deaths, DALYs and hospital cost. Each strategy gives different result, depending on the corresponding costs. We observe that choosing the strategy giving doxycycline treatment according to PCR+Rapid tests result is the best strategy respect to deaths and DALYs, and the strategy giving doxycycline treatment without any test is the best strategy respect to hospital costs for all four classes. We can conclude that the strategy giving doxycycline treatment according to PCR+Rapid tests is the most effective strategy when the hospital cost is not a factor.

We also observe that the best strategy depends on the prevalence of leptospirosis. When the prevalence of leptospirosis is below 0.2, the strategy giving doxycycline treatment according to PCR+Rapid tests result is the best strategy respect to deaths and DALYs, and the strategy giving doxycycline treatment without any test is the best strategy respect to

hospital costs for all four classes. However, when the prevalence of leptospirosis is higher than 0.2, then the strategy giving doxycycline treatment without any test is the best strategy respect to all three cost values for all four classes.

Based on the parameters in Tables 3.3-3.12 and vary the monetary cost per DALYs. The strategy giving doxycycline treatment without any test is the best strategy as long as the monetary cost per DALYs is not higher than $16,000 for late case severe symptoms class. The strategy giving doxycycline treatment according to PCR+Rapid tests is the best strategy as long as the monetary cost per DALYs is not too low for late case mild symptoms class. The strategy giving doxycycline treatment without any test is the best strategy as long as the monetary cost per DALYs is not higher than $12,000 for early case severe symptoms class. The strategy giving doxycycline treatment without any test is the best strategy as long as the monetary cost per DALYs is not higher than $14,000 for early case mild symptoms class.

The overall conclusion is that for all four classes, the strategy giving doxycycline treatment according to PCR+Rapid tests is the best strategy as long as the prevalence of leptospirosis is not high and the monetary cost per DALYs is not too low. When the prevalence of leptospirosis is high, the strategy giving doxycycline treatment without any test is always the best strategy for all four classes.

Early diagnosis of most diseases is crucial. However, the available technology is not always able to detect many diseases in early stages. Most patients suffer or lose their life due to late or inaccurate diagnosis. Some mathematical models can be developed with more complex computational algorithms and statistical methods to support the physicians' decision for early detection of diseases. Our model compares the treatment strategies based on their efficiencies and costs for the patients and for public health. The model indirectly maximizes the number of early detected leptospirosis cases and also minimizes the corresponding costs. The algorithm would be applicable to different types of diseases.

This chapter is collaboration with Prof. Suzanne Lenhart, University of Tennessee, Knoxville, Prof. Claudia Munoz-Zanzi, University of Minnesota, Minneapolis, Prof. Ben Fitzpatrick, Loyola Marymount University, Los Angeles, and Prof. Rudy A. Hartskeerl, Royal Tropical Institute in Netherlands, Amsterdam.

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Appendices

A Summary of Equations

Theorem .1. *If all the entries of NGM, K, are nonnegative and T is defined, then $T \geq 0$.*

Proof. Assume all the entries of K are nonnegative and T is defined. Since T is defined $\rho((I - P_i)K) < 1$ and so $(I - (I - P_i)K)^{-1}$ can be written

$$(I - (I - P_i)K)^{-1} = \sum_{n=1}^{\infty}((I - P_i)K)^n$$

since all the entries of K are nonnegative, the remaining entries after removing the targeted entries from K are nonnegative, therefore, the entires of $(I - P_i)K$ are nonnegative. Since all the entries of $(I - P_i)K$ are nonnegative, all the entries of $(I - (I - P_i)K)^{-1}$ are nonnegative. Therefore, the product of K and $(I - (I - P_i)K)^{-1}$ have all entries nonnegative and so T is nonnegative.

□

Vita

Ibrahim Halil Aslan was born on 2nd of February, 1986. He is the youngest son of Fadile Aslan. He started his studies at Suruc Ataturk ilk ogretim okulu in 1992. He entered the Faculty of Science in 2005 where, he received his Bachelor of Science, Special Degree in Mathematics with first class honor. In 2010, Ibrahim joined the Department of Mathematics, Faculty of Science at Gaziantep University. In 2012 he was granted study leave to pursue his higher studies and he started his graduate studies at the University of Tennessee, Knoxville, USA in 2014. There he was supported by a graduate teaching assistantship from the Department of Mathematics throughout his graduate studies. He graduated with a concurrent Masters Degree in December 2017, he graduated with his Ph.D in Mathematics 2019.