

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

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**Abstract:** In this study, we developed a computational algorithm under stochasticity by using Markov-cycle tree and Monte Carlo simulations for patients coming into a hospital and being suspected of leptospirosis. 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.

**Keywords:** Markov-cycle tree; Monte Carlo simulations; Leptospirosis.

## 1 Introduction

Leptospirosis is a neglected zoonotic disease 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 [1,2,3]. 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 [4].

Transmission of leptospirosis occurs in humans through contact with infected animals or soil and water contaminated by infected animals' urine. [1,5]. 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 [3,6,7]. 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 [8,1].

In humans, antibiotic therapy is the most common and effective method as compared with vaccination to provide immunity against leptospirosis and doxycycline is potentially the best option for initial antimicrobial treatment [9,6]. 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 [10,7]. In this study, three diagnostic tests are used; Polymerase Chain Reaction based assay (PCR), Microscopic Agglutination Test (MAT), Rapid screening tests.

In this study, our goal is to determine a treatment strategy for patients coming into a hospital and being suspected of leptospirosis. 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 2 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.

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## 2 Model Formulation

A computational algorithm of cost-effectiveness analysis 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, the assumptions we made;

- 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.

Recall that the physicians know whether the patient has severe or mild symptoms and whether the patient is late or early case. Therefore, we start with classifying the patients according to their known features and there are four different classes;

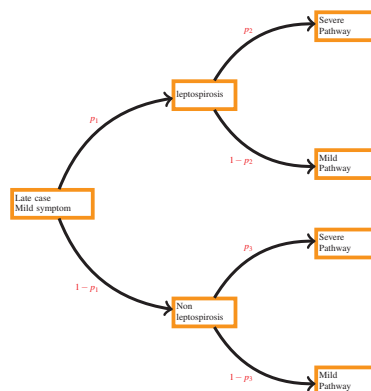
- Late case, severe symptoms patients.
- Late case, mild symptoms patients.
- Early case, severe symptoms patients.
- Early case, mild symptoms patients.

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

### 2.1 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.

Similarly, 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 1 shows the diagram of patient identification for late case, mild symptoms patients, where  $p_1$  is the probability of having leptospirosis for late case, mild symptoms class patients,  $p_2$  is the conditional probability of leptospirosis patients in late case, mild symptoms class moving to severe pathway, and  $p_3$  is the conditional probability of non-leptospirosis patients in late case, severe symptoms class moving to severe pathway.



**Fig. 1:** The diagram for identifying late case, mild symptoms patients.

The process is similar for other three classes. 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 1, for instance the first patient has leptospirosis and is on severe pathway.

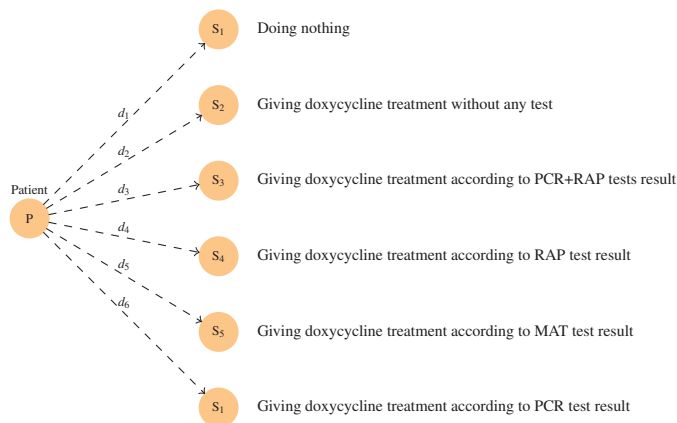
Patient	leptospirosis	Pathway
1	Yes	Severe
2	No	Severe
3	No	Mild
4	No	Severe
5	Yes	Mild
⋮	⋮	⋮
⋮	⋮	⋮
⋮	⋮	⋮

**Table 1:** Patients' identification beyond the known class.

### 2.2 Decision Process

There are six choices for the physicians to make a decision. We have assigned each choice with a probability  $d_i$  where  $i = 1, 2, \dots, 6$  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 1 at each distribution. Therefore, the cost function depends on the distributions in the model.

Figure 2 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;  $(1, 0, 0, 0, 0, 0)$ ,  $(0, 1, 0, 0, 0, 0)$ ,  $(0, 0, 1, 0, 0, 0)$ ,  $(0, 0, 0, 1, 0, 0)$ ,  $(0, 0, 0, 0, 1, 0)$ ,  $(0, 0, 0, 0, 0, 1)$ . 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. 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, we use Monte Carlo method [14] :



**Fig. 2:** The choices of physicians with probabilities.

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

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  $j = 0, 1, 2, 3, 4, 5$

### 2.3 Evaluation of Each Strategy

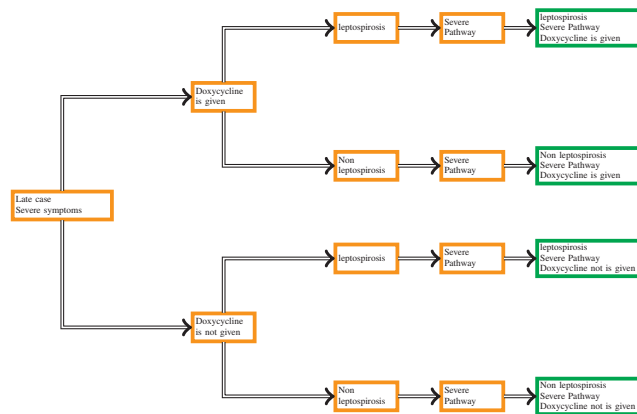
After the algorithm decides the choice of the strategy, the model uses the sensitivity and specificity of the tests to find out the tests' result. To decide whether the test result is positive or negative for a patient having leptospirosis in Table 1, a random number is drawn for the patient from an 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 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.

### 2.4 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 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. 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, severe symptoms:



**Fig. 3:** The diagram of each strategy for late case, severe 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.

### 2.5 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. The goal is to find the best choice for the physicians in Figure 2 that minimizes each of these cost values.

Note that no matter which strategy that the physician uses, the patients in Table 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. The goal is to minimize the following objective function of the distributions for a particular cost value, then we can achieve our goal

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

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:

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

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 [12, 13]. 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 2 and 3 are found based on these situations. The values in these tables are adjusted according to the expert opinions [12, 13].

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

**Table 2:** YLDs values.

Recall that an accurate test confirmation reduces the overall cost, as discussed earlier in subsection 2.4. Therefore, we need to use the weight factor in Table 3 for the values in Table 2 to reduce the DALYs values for the patients with accurate test results. The values in Table 3 are adjusted according to the expert opinions [12, 13] and the studies in [7, 4].

Table 3 represents the weight factors on YLDs costs for the patients accurately detected. In addition, 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.

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:** Weight factors on YLDs due to accurate test confirmation.

**DEATHS:** The number of deaths is 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 1, if the random number is less than the probability of deaths for their feature then we assume the patient dies. Table 4 represents the 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

**Table 4:** Probability of deaths.

We also need to use the weight factor for the patients accurately detected, therefore, Table 5 represents 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

**Table 5:** Weight factors on the death probabilities due to accurate test confirmation.

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

- 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 6 and 7. Table 6 represents the dollar cost of doxycycline and the tests, and Table 7 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 [12, 13] and the studies in [15, 7].

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

**Table 6:** The treatment costs.

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 7:** Costs of hospital stays.

Finally, accurate test confirmation reduces also the cost of hospital.

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

**Table 8:** Weight factors on hospital cost due to accurate test confirmation.

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 is counted for patients with confirmed tests. We chose reasonable values in Table 9.

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

**Table 9:** Monetary costs for supportive treatment.

### 2.6 Combined Cost Function

Before we move to the simulations, one can combine the functions of distributions  $c_1(d), c_2(d), c_3(d)$  to form the following total cost function of DALYs, deaths, hospital costs in order to make final decisions,

$$\mathcal{T}(d) = ac_1(d) + bc_2(d) + c_3(d),$$

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 one may evaluate the total cost function for some different values of  $a$  to see how these different values change the final decision.

### 3 Simulations and Results

In this section, we show some of the simulation results with available parameters for six simple distributions. The model is run with 1000 patients for each class. The parameters used in these simulations are given in Table 10 and 11 and the values in Table 11 are adjusted according to the expert opinions [12, 13] and a hospital results in Thailand [7].

Tests	Sensitivity Late case	Sensitivity Early case	Specificity Late case	Specificity Early case	Reference
PCR	34%	86%	99%	100%	[15, 2, 1]
MAT	82%	41%	100%	95.7%	[8, 17, 6]
LFA	81%	34%	96%	88 %	[15, 7]

**Table 10:** Sensitivity and specificity of tests.

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 11:** 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

#### 3.1 Simulations with Respect to DALYs, Death and Monetary Cost

The model has been run with 1000 patients and six simple distributions. Tables 12-15 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 2 - 11.



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 12:** Evaluating each strategy for late case, severe 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 13:** Evaluating each strategy for late case, mild 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 14:** Evaluating each strategy for early case, severe 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 15:** Evaluating each strategy for early case, mild symptoms class.

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.

### 3.2 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 2-11.

The results show 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.

### 3.3 Simulations with Different Prevalences

The parameters given in Tables 2-11 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 [7]. 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.

The results suggest 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.

### 3.4 Simulations with Combined Costs

Finally, we want to see the results of total cost functions,  $\mathcal{T}(d)$  that was discussed in the subsection 2.6. 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 2-11 and then find the best strategy that gives minimum total cost value of the average cost of 100 runs.

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.

## 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 [12, 13] and the studies in [15, 7]. 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.

The 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.

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