Economic evaluation of active microbiology laboratory to inform decision-marking on ongoing investments

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Content

1. Overview

This practical session is designed to provide an overview to economic evaluation using a decision tree model. The practical session describes the basic concepts of decision tree model with an example on evaluation of the cost-effectiveness of active microbiology laboratory services compared against no active microbiology laboratory in a hospital in a LMIC. While the example presented here has two comparison groups, the same concept can be expanded to more than two groups. Participants are expected to have some basic understanding on how to program in the R language.

The session is organised around three simple exercises plus one optional & more challenging exercise. The exercises require participants to read, understand & edit R code, and interpret outputs. The exercises are organised as below:

1. Structure of a decision tree model and how to populate the parameter values
2. Estimating and interpreting ICER in R
3. Deterministic sensitivity analysis
4. Probabilistic sensitivity analysis (optional)

1.1 Practical session materials

The code for the practical session can be found at https://github.com/Cherrylim128/economic_evaluation_tutorial.git and is available for R software. A pre-print of a paper making use of an expanded version of the model used in this practical can be found at https://www.medrxiv.org/content/10.1101/2024.05.14.24307355v1.

1.2 Background: AMR burden and hospital microbiology laboratory service

The emergence of antimicrobial resistance (AMR) is a global health threat, and the burden of AMR is highest in low- and middle-income countries (LMICs) with limited healthcare resources to respond to and monitor the spread of resistance. Routine use of blood culture for microbiologically-informed targeted antibiotic treatment in the

patients tested would be expected to lead to patients being treated with effective antibiotics in a more timely manner and hence improve patient outcomes and shorten lengths of stay. There are also potential cost savings, for example if targeted antibiotics are cheaper than those prescribed empirically (before lab results are available) or if better antibiotic prescribing leads to reduced healthcare costs. However, it is uncertain whether these benefits are sufficient to make the intervention cost-effective. While local hospital active microbiological testing may provide many benefits, including providing information to support infection prevention and control programmes and to develop local empirical antibiotic guidelines, the model considers only the health benefits arising from improved treatment of suspected bloodstream infection in hospital inpatients in this practical.

1.3 Decision tree model

There are multiple modelling approaches which can be used to perform cost-effectiveness analysis, including Markov models, mechanistic models, and decision-tree models. The choice of which approach to use depends on the aim of the evaluation and the context (i.e. type of intervention, mechanism of disease in question) of the problem.

In this practical, we will use a decision-tree model. There are eight basic steps in using such a decision-tree model:

1. define the problem
    a. Specify the decision-maker (i.e. policy-maker, a healthcare centre, or a patient)
    b. Objective of the decision (i.e. to maximise quality-adjusted life expectancy or to minimise costs)
2. identify all the decision alternatives
    a. In this practical, our decision alternatives are i) active microbiology laboratory service and ii) no active microbiology laboratory service
3. list all the possible outcomes of each decision alternative
4. define the relevant time horizon

5. draw a decision tree to map out the pathways of events leading from the initial decision to the relevant outcomes including decisions and chance events
6. quantify uncertainty by assigning probabilities to each chance outcome
7. quantify values in costs by assigning a cost to each event; similarly, quantify effectiveness by assigning a health outcome measure to outcomes
8. calculate the expected value of each decision alternative

An useful tool to draw decision trees is https://silverdecisions.pl/. The key components of a decision tree are:

- a root node, which is the starting point
- decision nodes, which represents choices to be made between different interventions
- chance nodes, which represents probabilities of different outcomes
- branches, which shows the decision pathways (note that each branch is assigned a cost)
- one or more endpoints or terminal nodes, which represents final outcome

Essentially, a decision tree is a method to map out potential decision pathways, and each pathway has an associated cost and probability. The costs and probabilities from the pathways can be summarised to compare the overall costs and effectiveness between interventions. It is important to note that in a typical cost-effectiveness analysis, we are interested in combining both the costs (in monetary terms) and effectiveness measures (which quantify health outcomes, typically DALYs or QALYs, which we will look into in the next section) of interventions of interest.

1.4 Key parameters

As mentioned above, in a decision tree model of cost-effectiveness, we are interested in comparing the cost and effectiveness between two or more interventions. Hence, cost and effectiveness measures are the key parameters we are interested in.

- Cost: while straightforward to understand, it can be challenging to find data to inform the analysis. In some cases may need to consider the appropriate

currency to use, purchasing power conversion (if cost data is extrapolated from different settings) etc. In this practical, we will use US dollars (USD) as a unit of cost.

- Effectiveness measured in mortality: this is also conceptually straightforward but it can be challenging to find data for the parameter input.
- Effectiveness measured in Disability-adjusted life-years (DALYs): calculated from mortality, length of hospitalisation, disability weights, and number of years lost for deaths. DALYs are calculated by estimating the sum of the years of life lost due to premature mortality (YLLs) and equivalent years of life lost due to time lived in states of less than full health, which is also known as the years of healthy life lost due to disability (YLDs). The YLLs are calculated as the number of deaths multiplied by a loss function specifying the years lost for deaths as a function of the age at which death occurs. This value is country-specific. YLDs are calculated from the length of hospitalisation after the day of diagnosis with suspected bloodstream infection (here we assume a patient regains full health after being treated and discharged from hospital) multiplied by a disability weight. This value is disease-specific and a data source to find a relevant value is from the Global Burden of Disease (GBD) Study estimates. One DALY is the loss of one year of full health.

1.5 Measurement of cost-effectiveness

A measurement of cost-effectiveness is the incremental cost-effectiveness ratio (ICER), which is calculated by dividing the difference in calculated costs between the interventions to be evaluated and the control (i.e. standard of practice) by the corresponding difference in health outcomes (Equation 1).

When the ICER is less than what we are willing to pay per outcome gained, we conclude that the new intervention is cost-effective (even if it is not cost saving). In this practical, we will use DALYs and the number of deaths averted as measures of health outcomes in the cost-effectiveness analysis.

Equation 1:

$$\frac{Cost\ with\ active\ microbiology\ laboratory - cost\ with\ no\ microbiological\ testing}{DALYs\ with\ no\ active\ microbiology\ testing\ service - DALYs\ with\ active\ microbiology\ testing\ services}$$

1.6 Overview of a simple decision tree model for the practical session

We consider two comparison arms and calculate expected costs and health-related outcomes including mortality and length of hospitalisation associated with each arm (Figure 1). In the active microbiology laboratory testing system arm, a patient with suspected bloodstream infection will have one set of blood cultures (two bottles) taken, and be started on empirical antibiotic therapy (ceftriaxone combined with gentamicin) before any potentially causative organism is identified. If bacterial pathogens are identified from those cultures, then definitive therapy based on the antibiotic susceptibility of the organisms may lead to the antibiotic regimen being changed. In the second arm, in which there is no microbiological testing, the patient would again be empirically treated, but any changes in treatment would be driven by clinical condition alone, without microbiological testing results.

We assume a patient is considered for antibiotic treatment adjustment after three days of empirical treatment. The adjustment depends on which comparison arm they are under (Figure 1). For patients in the active microbiology laboratory arm, in which blood culture was performed, antibiotic treatment changes would depend on the results of the blood culture. For patients in the no microbiology testing service arm, antibiotic treatment changes would depend on changes in clinical condition. We consider three possible changes to the antibiotic treatment received following initial empirical treatment:

- Stepping up, which is changing from ceftriaxone and gentamicin to meropenem and vancomycin
- Stepping down, which is switching to an oral antibiotic
- No change, which is continuing to receive the same antibiotic treatment.

Let's take a look at the R code for the analysis!

Load packages

In this practical, we will use the following packages: "dplyr", "ggplot2", and "brms". The master script, "practical_cea_7Feb2025.R", contains the codes to call the decision tree model to perform the deterministic and probabilistic sensitivity analyses.

The first section of the code loads the libraries needed for this practical:

```
# packages ----
library(dplyr)
library(ggplot2)
library(brms)
```

The second section defines the hypothetical population:

```
# Define the basic population to infer ----
N = 1000 # number of the individual patients
num_bottle = 2 # number of blood bottles coll
length_empiric = 3 # number of days of empiri
length_targeted = 7 # number of days of targe
```

The third section calls the decision model:

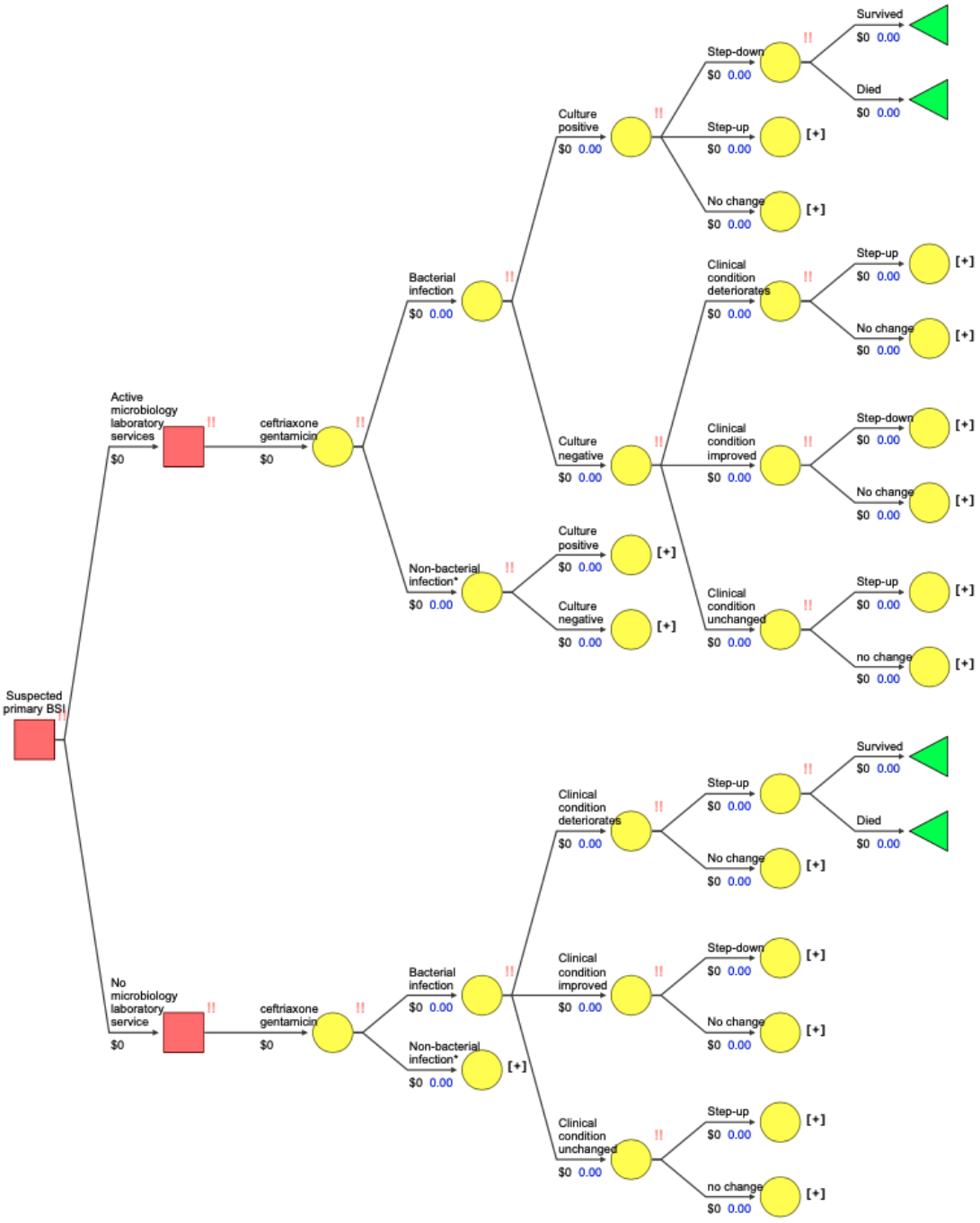
```
# Decision tree model ----
source("practical_cea_decisiontree.R")
```

We will now take a close look at the "practical_cea_decisiontree.R" script.

2. Exercise 1: Decision tree model and populating parameter values

This part will look at how a decision tree model is coded in the R program, and then at how parameter values can be populated in the model to estimate measurements of cost-effectiveness of interest. We begin by looking at the "practical_cea_decisiontree.R" script, which codes the majority of the decision tree model shown in Figure 1.

Figure 1. Decision tree



The circles in Figure 1 represent chance nodes and squares represent decision nodes. We will start by looking at the branch of “active microbiology laboratory services”. There are 18 pathways in this branch.

Below is the R script to calculate the probability of each pathway. A useful exercise is to check if you understand which parts of the code below correspond to which pathways in Figure 1.

```
#/////// Pathway for active microbiology lab service arm /////// # ----
### Expected probabilities for each pathway
# infection caused by bacteria
#- culture positive
ep1 <- p.bact * p.bact_culture_pos * p.CefGen_culpos_stepdown
ep2 <- p.bact * p.bact_culture_pos * p.CefGen_culpos_stepup
ep3 <- p.bact * p.bact_culture_pos * p.CefGen_culpos_nochange
#- culture negative
ep4 <- p.bact * (1-p.bact_culture_pos) * p.CefGen_bact_culneg_deter * p.CefGen_culneg_deter_ste
ep5 <- p.bact * (1-p.bact_culture_pos) * p.CefGen_bact_culneg_deter * p.CefGen_culneg_deter_noc
ep6 <- p.bact * (1-p.bact_culture_pos) * p.CefGen_bact_culneg_impro * p.CefGen_culneg_impro_ste
ep7 <- p.bact * (1-p.bact_culture_pos) * p.CefGen_bact_culneg_impro * p.CefGen_culneg_impro_noc
ep8 <- p.bact * (1-p.bact_culture_pos) * p.CefGen_bact_culneg_nocha * p.CefGen_culneg_nocha_ste
ep9 <- p.bact * (1-p.bact_culture_pos) * p.CefGen_bact_culneg_nocha * p.CefGen_culneg_nocha_noc
```

```
# not bacterial infection
#- culture positive
ep10 <- p.nobact * p.nobact_culture_pos * p.CefGen_culpos_stepdown
ep11 <- p.nobact * p.nobact_culture_pos * p.CefGen_culpos_stepup
ep12 <- p.nobact * p.nobact_culture_pos * p.CefGen_culpos_nochange
#- culture negative
ep13 <- p.nobact * (1-p.nobact_culture_pos) * p.CefGen_nobact_culneg_deter * p.culneg_deter_st
ep14 <- p.nobact * (1-p.nobact_culture_pos) * p.CefGen_nobact_culneg_deter * p.culneg_deter_no
ep15 <- p.nobact * (1-p.nobact_culture_pos) * p.CefGen_nobact_culneg_impro * p.culneg_impro_st
ep16 <- p.nobact * (1-p.nobact_culture_pos) * p.CefGen_nobact_culneg_impro * p.culneg_impro_no
ep17 <- p.nobact * (1-p.nobact_culture_pos) * p.CefGen_nobact_culneg_nocha * p.culneg_nocha_st
ep18 <- p.nobact * (1-p.nobact_culture_pos) * p.CefGen_nobact_culneg_nocha * p.culneg_nocha_no
```

The second branch is the “no active microbiology laboratory services”. There are 12 pathways in this branch. Below is the R script to calculate the probability of each pathway. An useful exercise is to check if you understand which parts of the code below correspond to which pathways in Figure 1.

```
#/////// Pathways for no microbiology laboratory services arm /////// # ----
#/ ceftriaxone/gentamicin ----
# Bacterial infection
np1 <- p.bact * p.CefGen_bact_nocul_deter * p.CefGen_nocul_deter_stepup
np2 <- p.bact * p.CefGen_bact_nocul_deter * p.CefGen_nocul_deter_nochange
np3 <- p.bact * p.CefGen_bact_nocul_impro * p.CefGen_nocul_impro_stepdown
np4 <- p.bact * p.CefGen_bact_nocul_impro * p.CefGen_nocul_impro_nochange
np5 <- p.bact * p.CefGen_bact_nocul_nocha * p.CefGen_nocul_nocha_stepup
np6 <- p.bact * p.CefGen_bact_nocul_nocha * p.CefGen_nocul_nocha_nochange
checkpoint2_bact_cefgen <- np1 + np2 + np3 + np4 + np5 + np6
# Non-bacterial infection
np7 <- p.nobact * p.CefGen_nobact_nocul_deter * p.CefGen_nocul_deter_stepup
np8 <- p.nobact * p.CefGen_nobact_nocul_deter * p.CefGen_nocul_deter_nochange
np9 <- p.nobact * p.CefGen_nobact_nocul_impro * p.CefGen_nocul_impro_stepdown
np10 <- p.nobact * p.CefGen_nobact_nocul_impro * p.CefGen_nocul_impro_nochange
np11 <- p.nobact * p.CefGen_nobact_nocul_nocha * p.CefGen_nocul_nocha_stepup
np12 <- p.nobact * p.CefGen_nobact_nocul_nocha * p.CefGen_nocul_nocha_nochange
```

Exercise 1.1. Write a line of R code in the script to calculate the probability within the “active microbiology laboratory services” arm of the decision tree, that a patient with

suspected primary BSI has a bacterial infection, is culture positive and subsequently steps down from the empiric antibiotic treatment.

Exercise 1.2. Write a line of R code in the script to calculate the probability within the "no active microbiology laboratory services" arm that a patient with suspected primary BSI has a bacterial infection, has an unchanged clinical condition three days after starting initial treatment, and has no change in treatment from the initial empiric antibiotic treatment.

3. Exercise 2: Estimating and interpreting ICER

We have now seen how the decision tree model is coded in R. Let's start populating the parameter values to do some analysis.

Exercise 2.1. Run lines 20-255 in the practical_cea_7Feb2025.R script, and complete the table below using the output you see. Interpret the differences in mortality, DALY, and cost between the two arms.

Empirical antibiotic therapy	An active laboratory			No active microbiological testing			Incremental costs with an active laboratory	Number of deaths averted	DALYs averted with an active laboratory
	Costs ($)	DALYs	Mortality	Costs ($)	DALYs	Mortality			
Ceftriaxone and gentamicin									

Exercise 2.2. Calculate and interpret the ICER values.

Exercise 2.3. Run the model on a hypothetical population of 10,000 patients and interpret the estimated ICER values.

Exercise 2.4. Increase the number of blood bottles to 4 (i.e. 4 blood bottles collected per suspected bloodstream infection patient in active microbiology laboratory service arm). Run the model and interpret the results including the estimated ICER value.

4. Exercise 3: Deterministic sensitivity analysis

The estimates you have derived in Exercise 2.1 and Exercise 2.2 are based on point estimate input values that could be defined by various data sources. Some parameter input values are straightforward to derive from publicly available databases, for example the cost of antibiotic treatment. For other parameter input values, available data sources are limited; an example would be changes of a patient's clinical condition. In those situations, estimates and assumptions are needed for the input values. A logical next step is to explore how results would change when we vary those input parameters. In this exercise, we will perform deterministic sensitivity analysis and change one parameter value at a time and then generate plots to visualise the changes in results.

Exercise 3.1. Keep all other parameter values unchanged and edit the R script to complete the table below. Each row is a one run on the model of changing the value for proportion of bacterial infection among patients with suspected bloodstream infection (in short, we will call it prevalence of BSI in the table). Interpret the results.

Parameter name	Description	Value	Incremental costs with an active laboratory ($)	Number of deaths averted with an active laboratory	DALYs averted with an active laboratory
Prevalence of BSI	Base scenario	40%			
Prevalence of BSI	High prevalence	65%			
Prevalence of BSI	High prevalence	50%			
Prevalence of BSI	Low prevalence	30%			
Prevalence of BSI	Low prevalence	15%			

Exercise 3.2. Reset all other parameter values to the base scenario and edit the R code to complete the table below. Each row is a one run of the model changing the value for the probability of changing antibiotic prescription given a culture positive lab result in the hypothetical population.

Antibiotic change among culture positives	**Value**	**Incremental costs with an active laboratory ($)**	**Number of deaths averted with an active laboratory**	**DALYs averted with an active laboratory**
(base scenario) Probability of [i] stepping-down [ii] stepping-up [iii] no change	 [i] 0.06 [ii] 0.39 [iii] 0.55			
Probability of [i] stepping-down [ii] stepping-up [iii] no change	 [i] 0.02 [ii] 0.28 [iii] 0.70			
Probability of [i] stepping-down [ii] stepping-up [iii] no change	 [i] 0.05 [ii] 0.35 [iii] 0.60			
Probability of [i] stepping-down [ii] stepping-up [iii] no change	 [i] 0.07 [ii] 0.42 [iii] 0.51			
Probability of [i] stepping-down [ii] stepping-up [iii] no change	 [i] 0.13 [ii] 0.54 [iii] 0.33			
Probability of [i] stepping-down [ii] stepping-up [iii] no change	 [i] 0.20 [ii] 0.60 [iii] 0.20			

Exercise 3.3. Run lines 403-450 in practical_cea_7Feb2025.R to plot the results.

Exercise 3.4. Interpret the plot and describe which of the parameter values that we have performed deterministic sensitivity analyses on have the highest influence on the estimated ICER.

5. Exercise 4 (optional): Probabilistic sensitivity analysis

Probabilistic sensitivity analysis is a technique to account for uncertainties around the parameter inputs. These uncertainties can then be propagated across the pathways. The final analysis outputs will then include the levels of confidence around the key model estimates, including costs, DALY averted and ICER.

Exercise 4.1. Open the “practical_cea_probabilisticsen.R” script.

Exercise 4.2. Run lines 450-489 to plot an incremental cost-effectiveness plane. In the upper right quadrant, points below the broken diagonal line would be considered cost-effective for a willingness to pay to avert one DALY of $500, while points above this line would not be considered cost-effective at this threshold. Use this information to interpret the plot and state what decision you would make about investing to maintain active microbiology laboratory service if you were a policy-maker.

Exercise 4.3. Edit the “practical_cea_probabilisticsen.R” script to increase the uncertainties around each of the input parameter values. Plot the incremental cost-effectiveness plane and state how this plot differs from the plot in Exercise 4.2.