A Comparative Study for Cost-Utility Analysis Methods: An Application to a Case Study on Multicomponent Vaccine against Meningococcal B Disease

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Abstract: The aim of this study is to explore and compare the results of application of three different modelling techniques used to perform Cost-utility Analysis in Health Economics and Health Technology Assessment (HTA). The three modelling techniques described are Decision Tree, Markov model and Discrete Event Simulation. For each of these modelling techniques was evaluated the introduction of a multicomponent serogroup B meningococcal vaccine. The preliminary cost-utility analysis herein developed considers societal perspective, and evaluates the impact of vaccination on Italian infants less than one year of age. The models validation and the Incremental Cost-Effectiveness Ratio (ICER) resulting from each technique are reported, in preliminary results each modelling technique gives different ICER, depending on the modelling technique.

1 INTRODUCTION

In Health Economics and Health Technology Assessment (HTA) the use of modelling techniques is strongly recommended for the introduction of a new device, drug, clinical pathway, vaccine or other instruments that can have an impact on patients' health and on National Health Service (NHS) budgets. For the decision-maker, usually represented by NHS, it is important to know the incremental cost-effectiveness of the technology that represents the change in cost and effectiveness achieved by the new technology compared with current practice. In international literature the main modelling techniques applied to evaluate the introduction of new technologies are: Decision Tree, Markov Model and Discrete Event Simulation. Each technique has its strength and weak characteristics that enable the method to be the best to fit the analysis.

While in the literature the use of Decision Tree and Markov models are the main techniques applied for Cost Effectiveness Analysis (Muennig and Bounthavong, 2016), the adoption of DES is recent.

Decision trees are simple and directed graph without recursion and they represent a formal way to describe decisions, embodying the paradigm of decision analysis. Each decision can be divided into three components: the decision node (the representation of the moment when the decision maker has to do a choice between competing strategies), the decision strategy (represented by the set of actions or events consequent to a certain decision) and the outcome nodes (which represent the outcome in cost and effectiveness).

Even if it is the simplest method of analysis, the use of decision trees (Aleem et al., 2009) presents some limitations from the perspective of performance and outcome analysis. Firstly simplification errors may occur when measuring the final outcome of treatment decisions with values such as quality-adjusted life years (Van der Velde, 2005; Naglie et al., 1997). It is also difficult to perform adequately an analysis considering the variation of some parameters during a long time horizon in a clinical environment (Aleem et al., 2009) and various factors (including expenses and patient preferences for medical services) are involved in the decision-making process, and these cannot be accurately reflected in a decision tree (Burch et al., 2012; Bhandari et al., 2003).

Markov models are cyclic directed graphs used when a decision problem has the exposure to some

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risks or events is variable or changes during a certain time horizon. Most of Markov models used in healthcare are semi-Markov state transition models, where state transitions can vary during the time horizon (Stahl, 2008).

DES is a very flexible modelling method in which entities may interact or compete with each other for resources in a system. Every interaction between entities (with each other or with the resources in the system) is an event. Every interaction changes the state of the entity involved and of the system as a whole (Stahl, 2008).

The time between each event can be handled probabilistically, using fixed time increments, or both, depending on the nature of the system being modelled. DES are composed by entities, attributes, queues and resources. In a simulation model entities are objects characterised by attributes, usually entities are represented by patients or element of a chain, such as products, that can interact with the other entities inside the system. Entities are the main element of the simulation and are generated in the beginning of the model or during the execution.

Attributes are specific characteristics of each entity, represent the information of the entity such as the chronic disease of a patient, the health status if we consider patients as entities. Attributes can vary during the simulation and they are very important in the simulation when the entity interact with other entities inside the system or when some events occurs.

Events are actions or things that can occur inside the simulation environment or to an entity (e.g. an infection or a virus that change the health status of a patient). Resources are represented by service providers for entities inside the model. Most of the resources are limited (e.g. the nurses of a Cardiology Unit or the MRI machines inside a Radiology department). When resources are used by entities, other entities have to wait, creating a queue. Queues are managed following several rules, depending also on the modeller choice (e.g. priority queues, First In - First out, Last In – First out). All the elements above described work and interact and compete in a specific frame of time, usually it is the period time to represent the system. (Karnon et al., 2002)

The disadvantage of cost-effectiveness analysis limitations and inaccuracies of Markov models are easily avoided with the use of DES. In literature several studies describe the principles and the methodologies of decision-analytical modelling for Health Technology Assessment (Sun and Faunce, 2007).

In this study three modelling techniques were applied to verify the cost utility of the introduction of a new multicomponent vaccine for the *Neisseria meningitidis serogroup B* (NmB) in the Italian NHS context.

The *Neisseria meningitidis* (Nm) is a gram negative bacterium that cause meningitis or other forms of meningococcal diseases. Even if the incidence of this disease in Italy has low values, the diseases caused by Nm represent a public health problem that produce a sensible economic impact on the society (Anonychuk et al., 2013; Davis et al., 2011). The incidence of disease is variable within the geographical areas (Harrison et al., 2009), since after the introduction of meningococcal serogroup C vaccination, the serogroup B has become the main agent of meningococcal disease. The disease most affects children under one year of age are mainly affected. In Italy, about 60% of typed cases of meningococcal disease are now caused by NmB (European Centre for Disease Prevention and Control, 2010; Istituto Superiore di Sanità, 2014).

2 MODEL DESCRIPTION

In order to perform the technique comparison on Cost-utility evaluation three models with three techniques were developed: Decision tree, Markov and DES models. The three techniques were developed using respectively TreeAge® Pro 2015, Microsoft Excel® 2013 and Lanner Witness® 2016.

2.1 Decision Tree Model

The decision tree herein presented (Figure 1) belongs to a previous study developed for economic evaluation of Bexsero® vaccine in Italy (Gasparini et al., 2016).

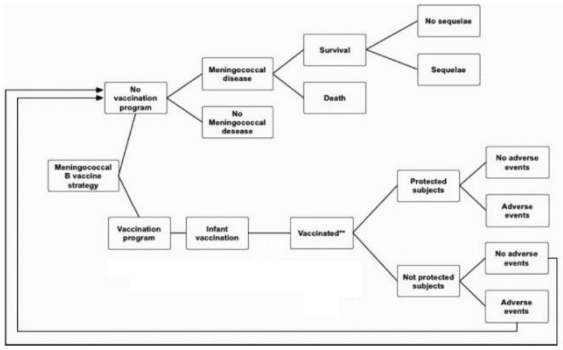

Figure 1: Decision tree model.

The tree is composed firstly by the choice node where begin the two branches representing the strategies: "Vaccinate infant Italian population" and "Not vaccinate infant Italian population". Vaccinated infants can be immunised or not immunised against *NmB*, immunisation depends on the effectiveness of the vaccine. If infants are immunised then they can have adverse events or not, usually represented by allergic reactions or flue. Infant not immunised for the missed effectiveness of the vaccine can have adverse event or not, but they have the same conditions and risks of infants that do not participate to vaccination program.

Infants that are not immunised can live their entire life without contracting the disease. If an infant has the NmB disease, there can be three different health status: Death, Survive with sequelae (the consequence of the disease represented by chronic diseases or disabilities) and Survive without sequelae.

The list of possible sequelae are: Amputation with substantial disability, Anxiety, Arthritis, Depression, Motor Deficits, Blindness, Epilepsy or Seizure, Severe Neurological Disability, Mental retardation (cognitive problems), Hearing loss with cochlear implantation, Moderate/Severe bilateral Hearing loss, Moderate/Severe unilateral Hearing loss, Renal Failure, Chronic migraine, Skin necrosis, Scars and Severe Speech or communication problem.

2.2 Markov Model

Markov models are widely adopted into Cost-Effectiveness Analysis. The model herein developed is split into two sub-models: Vaccination program (Figure 2) and No Vaccination program (Figure 3).

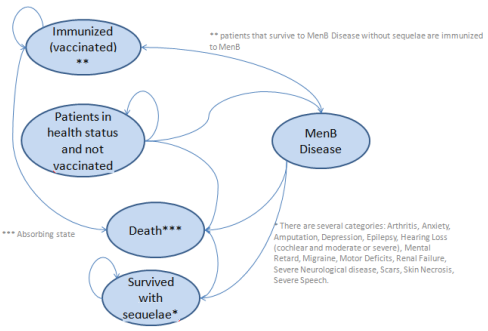

Figure 2: Markov model for vaccination program.

The first model is composed by five status: Patients in health status and not vaccinated, Immunized (vaccinated), MenB disease, Death and Survived with sequelae. Firstly all infants are in a good health status and are not vaccinated. If the infant

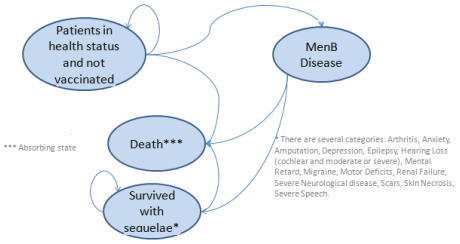

Figure 3: Markov model for no vaccination program.

population is vaccinated then there can be two status: infant that are immunized change the status into "Immunized", while not immunized infants are still in the previous status. Infants that will have NmB disease pass through the transitional status "MenB Disease" and consequently transferred into one the following health status: "Death" if infant dies, "Survived with sequelae" if infant survives with sequelae and "Patients in health status and not vaccinated" if infant survives without sequelae. The No Vaccination program model has the same configuration but it is not considered the "Immunized" health status for the missing vaccination program. The absorbing state for each model is "Death".

2.3 Discrete Event Simulation Model

Simulation enables to develop models built to determine the response of a system to changes in its internal structure and inputs. It can reproduce a simplified representation of a dynamic process that is too complex for a direct analysis, considering that it is a cheaper and simple tool for analysts.

Two DES sub-models were developed: the first sub-model shown in Figure 4, represents and describes the clinical pathway that infants have to follow when they are vaccinated (vaccination model). The second sub-model, shown in Figure 5, describes the actual scenario where all the infants are not vaccinated against NmB (the so-called "comparator").

2.3.1 Vaccination Model

Infants when are vaccinated can be immunized or not, considering the effectiveness of the vaccine. If the vaccine is effective then the infant is immunized and protected for lifetime. If vaccine is effective then there can be adverse or not adverse events (high body temperature or allergic reaction). Infants not immunized can acquire the NmB during their life of survive without contracting the disease. If infants acquire the NmB disease can die, survive without

sequelae or survive without sequelae. The description of the pathway for vaccinated infants is shown in Figure 4.

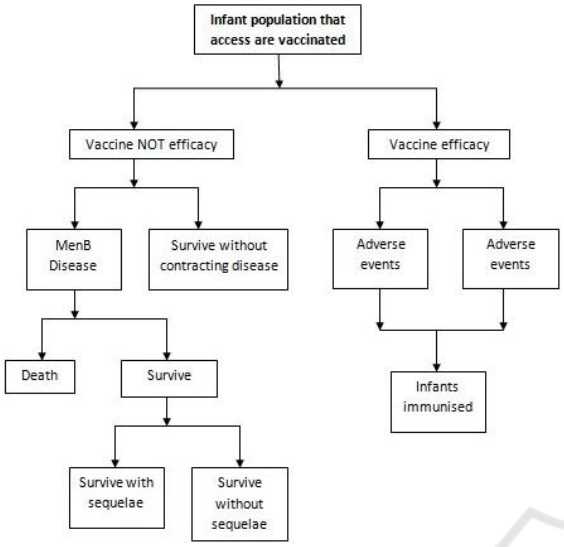

Figure 4: Flow chart for Vaccination model.

2.3.2 No Vaccination Model

The second DES model (Figure 5) describes the actual scenario where infants are not vaccinated and consequently not immunized against NmB. If the National Health Service does not include vaccination, infants can live their whole life without contracting the disease. If during their life they acquire the disease, then infants can have two possible outcomes: death or Survive. Survivors are divided into two different categories: without or with sequelae.

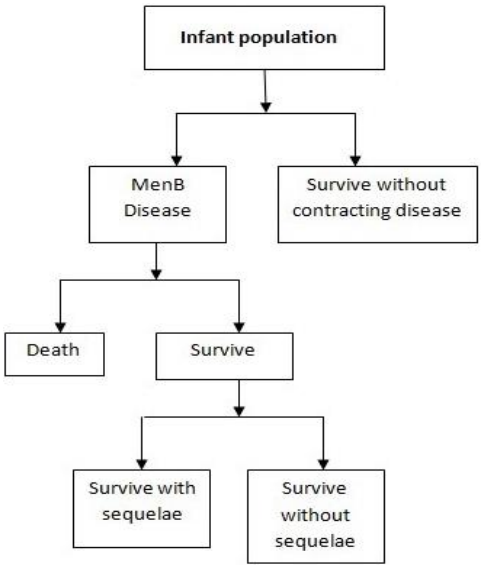

Figure 5: Flow chart for No Vaccination model.

2.3.3 Elements of DES Model

Infants are entities in the model and correspond to the number of infants born in a year.

Once infants are generated by the simulator, then they are sent to the "Vaccination" queue, where the "Vaccination" resource distribute infants into "Adverse Events", "No Adverse Events" and "No Vaccination" queues. These queues contain respectively infants that had adverse events after the vaccination cycle, that had not any adverse event and that were not immunized by the vaccine (unprotected).

This last resource named "No Vaccinated Flow" collects patients that are not vaccinated or unprotected and submit them to the "Incidence" resource, that distribute entities into "Disease" and "No Disease" queues. Infants that have the disease are hospitalized and the resource "Effect of Disease" distribute them into "Deaths", "Survival with No Sequelae", "Sequelae" (with the different sequelae reported previously) queues. The distribution of elements inside the model follows the probability distributions described in Gasparini et al. (2016).

3 CASE STUDY

3.1 General Characteristics

The three modelling techniques were applied to the Italian epidemiological scenario of 2012. Data used in this study refer to a previous study (Gasparini et al., 2016) where a Cost-Utility Analysis was performed using a decision tree model.

3.2 Model Parameters, Costs and Utilities

A detailed specification of data, incidence of disease, model assumptions, cost and outcome values and distribution is herein reported.

The main parameters and assumption respect the criteria given by Italian guidelines for economic evaluation in healthcare (AIES, 2009; Capri et al., 2001). The adoption of discount rate for both costs and utilities is needed to evaluate the relative values during the long time horizon. The probability of disease is provided by the Italian Institute of Healthcare (Istituto Superiore di Sanità) and it is related to NmB cases occurred annually in Italy from 2007 to 2012. The vaccine herein evaluated is supposed to give a full lifetime protection. In Table 1 general model parameters are reported.

Table 1: General model parameters.

Parameter	Value
Probability of disease	0.0000023
Vaccine compliance	0.9
Discount rate for costs and utility	0.03
Probability of death	0.0673
Probability of Amputation with substantial disability	0.01
Probability of Anxiety	0.068
Probability of Arthritis	0.025
Probability of Depression	0.05
Probability of Motor deficits	0.019
Probability of Blindness	0.004
Probability of Epilepsy or Seizure	0.02
Probability of Severe Neurological disability	0.021
Probability of Mental retardation (cognitive problems)	0.254
Probability of Hearing loss requiring cochlear implantation	0.02
Probability of Moderate/severe bilateral hearing loss	0.05
Probability of Moderate unilateral hearing loss	0.05
Probability of Skin necrosis	0.015
Probability of Scars	0.03
Probability of Severe speech or communication problems	0.037
Probability of Renal failure	0.019
Probability of Chronic migraine	0.10
Probability of Survive without sequelae	0.402

Outcomes were measured using Quality Adjusted Life Years (QALYs), one of the main measures of the value of health outcomes. The classification system assumed for QALY was EuroQoL EQ-5D. In Table 2 are reported annual health outcomes for all the health status related to the NmB sequelae, death and survival.

Costs reported in the model are annual costs in Euro (€) currency at January 2013 values, previous years costs were adjusted to January 2013 levels. Four categories were defined for costs: Direct costs related to meningococcal sequelae, Indirect costs related to meningococcal sequelae, Costs related to acute phase of disease and Costs associated to vaccination (Table 3).

The first category represents all the direct cost associated to sequelae (e.g. the direct cost of seizures), while the second category includes social costs that indirectly affect patients with the sequelae (e.g. the special education needed in school for children with cognitive problems, or the lost income of a parent that had to quit the job to follow the child with severe neurological disability).

Table 2: Health outcomes.

Health status	QALY
Death	0
Survive	1
Amputation with substantial disability	0.613
Anxiety	0.687
Arthritis	0.690
Depression	0.729
Motor deficits	0.830
Blindness	0.260
Epilepsy or Seizure	0.830
Severe Neurological disability	0.060
Mental retardation (cognitive problems)	0.541
Hearing loss requiring cochlear implantation	0.810
Moderate/severe bilateral hearing loss	0.910
Moderate unilateral hearing loss	0.910
Skin necrosis	0.900
Scars	1.000
Severe speech or communication problems	0.390
Renal failure	0.820
Chronic migraine	0.814

Table 3: Costs for economic evaluation.

Cost	Euro(€)
Amputation with substantial disability	7,339
Anxiety	1,146
Arthritis	1,184
Depression	3,192
Motor deficits	7,682
Blindness	4,076
Epilepsy or Seizure	2,272
Severe Neurological disability	94,880
Mental retardation (cognitive problems)	7,507
Hearing loss requiring cochlear implantation	6,327
Moderate/severe bilateral hearing loss	3,163
Moderate unilateral hearing loss	3,163
Skin necrosis	1,066
Scars	533
Severe speech or communication problems	9,796
Renal failure	56,126
Chronic migraine	892
Medical care: cost of hospitalization per case	7,900
Public Health Response	3,223
Acute phase lost productivity of parent or relatives	870
Acute phase lost productivity of patient	1,426
Special case education	14,556
Lost productivity of parent	24,500
Lost productivity of patient	24,500
Primary cycle of vaccination (4 doses)	200
Vaccine administration per dose	5.80
Hospitalization for 1 anaphylactic reaction	1175
Mild or moderate adverse event	3.40

The costs of acute phase of disease is the third category and it represents the costs bore by the national healthcare system and the society during both the hospitalisation and the treatment of the individuals that might be at risk of NmB (e.g. the DRG of hospitalisation and the chemoprophylaxis treatment). Also were considered indirect costs of parents and patient during the acute phase of the disease, represented by the missing income of parents and patient during the hospitalisation. The fourth and final category is the costs associated to vaccination, where are included the cost of the vaccine, the cost of administration of the vaccine, the costs of anaphylaxis reaction and the mild or moderate adverse event, usually managed with one box of paracetamol.

4 PRELIMINARY RESULTS

4.1 Model Validation

In order to perform a validation it is necessary to compare the model predictions with data used to in the simulation model (Eddy, 1985).

There is not a simple and universally applicable procedure to apply for model validation. Each case can be considered by itself, but to simplify it can be achieved identifying the desirable characteristics in the reporting of cost-effectiveness models (Mc Cabe and Dixon, 2000).

The first validation was done for the Decision tree model, where using the strategy of "No Vaccination" was checked if the results were corresponding in terms of incidence, deaths, survival with and without sequelae and number of patients with the sequelae. This first validation gave the same results as the actual epidemiological scenario without the vaccination program.

Model validation was performed using the following values for "No vaccination" and "Vaccination" sub-models of Decision Tree, Markov and DES models. For model validation the following values were selected: the total number of infant in the model, the number of deaths for NmB disease, the number of sequelae, the number of infants without sequelae. In Table 4 the validation show a slight variation within the models. This small variation is given by the characteristics of each techniques, where events can happen at the end of a cycle or in a particular point in time.

Table 4: Model validation.

Value	Decision tree	Markov	DES
Infant population at the end of the simulation/cohort	531,372	531,372	531,372
No of deaths (Vaccine Model)	1	1	1
No of infants with sequelae (Vaccine Model)	90	90	89
# Survived without sequelae (Vaccine model)	11	12	12
# deaths (No Vaccine Model)	7	7	8
# infants with sequelae (No Vaccine Model)	43	42	43
# Survived without sequelae (No Vaccine model)	55	55	56

4.2 ICERs Comparison

Incremental Cost Effectiveness Ratio (ICER) is used in economic evaluation in health economics to evaluate a new technology (e.g. drugs, vaccines, therapeutics) and compare it with other technologies. The evaluation requires different results in order to confirm or not the introduction of a new technology, one of these results is the incremental cost-effectiveness ratio (ICER), which is the ratio of the change in costs of a new technology (compared to the alternative, such as doing nothing or using the best available alternative treatment) to the change in effects. For the three techniques the corresponding ICER were reported in Table 5.

Table 5: ICER values for DT, MM and DES techniques.

Modelling technique	Value (€)
Decision Tree	109,762
Markov Model	117,713
Discrete-Event Simulation	115,675

Considering a threshold value defined by the National Health Technology Assessment guidelines (Capri et al., 2001) of € 40,000.00, the introduction of vaccine is not advisable for the Italian epidemiological scenario.

The ICER values given by each technique are different and each variation in the result can be explained by the characteristics of model adopted for cost-utility evaluation. Decision tree is not able to represent the future events that depends on previous

events in the time (e.g. herd immunity). It is possible to achieve it with data approximation of these events, by modelling data with a detailed analysis, usually with the joint use of commercial spreadsheets and dedicated software, but these approximations can affect the final result.

The Markov Model can better represent the decision problem involving risk that is continuous over time, considering the timing of events and the possibility that events may happen more than once (Sonnenberg and Beck, 1993). As the ability of Markov models consists in representing repetitive events, time dependence of both probabilities and utilities that allow a more accurate representation of clinical reality for the model (Briggs and Schulper, 1998), the weakness is in the total missing of memory. The behaviour of the process subsequent to any cycle inside Markov models depends only on its description in that cycle. This means that the process has no memory for earlier cycles (Sonnenberg and Beck, 1993). Finally DES provides a flexible approach to represent complex systems (Law, 2007) and, its ability enable this technique to be one of the better techniques to perform Cost-Effectiveness analysis (Karnon et al., 2012, Caro et al., 2010). Events can happen in any moment in the time (not in the beginning of the end of the cycle as Markov models), being able to better represent reality.

5 CONCLUSIONS

The choice of modelling technique is very important in Health Technology Assessment for the economic evaluation and the study of impact of the introduction of a new technology in a National Healthcare System. In this study each of these techniques were applied to evaluate the introduction of a new vaccine against Neisseria meningitidis serogroup B. For each model developed was described the characteristics and the composition in detail. The three techniques were validated and it was computed the Incremental Cost Effectiveness Ratio (ICER) and compared to the Willingness to pay value of € 40,000.00.

The preliminary results show that the introduction of the vaccine is not advisable in Italy. The comparison between the three modelling techniques shows that ICERs resulting have some differences. The limitation of this study is represented by the adoption of the same assumptions for each of the technique. A further study aims at analysing the techniques with different model assumptions, and to evidence the main differences in terms of performance indicators.

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