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The Expected Value of Perfect Information of COVID-19 Treatment Using Discrete Event Simulation

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Abstract

The Value of Perfect Information (EVPI) and also Sample Information (EVSI) are necessary for calculating the expected economic benefit of a research based on evidence about the cost and efficacy of novel therapies. The EVPI determines the maximum value resulting from soliciting data to decrease the uncertainties and the expected loss in case of providing ineffective treatment. In general, an inefficient decision will waste health resources that may be better spent elsewhere, thereby deteriorating health outcomes. In this article, the value of information resulting from reducing uncertainty will be applied in assessing two COVID-19 treatments, namely, the standard care and vaccines. A discrete event simulation model is introduced to expand the usage of EVPI calculations to medical applications with various sources of uncertainty as the case of COVID-19. Our simulation results show that further testing and vaccine validation will be of insignificant value if the response rate on vaccine is higher than 85%. The purpose of this study is to provide a step-by-step guide to the computation of the value pre-testing in the context of healthcare decision-making. Worked scenarios were presented for COVID-19 in UAE. The study can serve as a useful template for various decision-making problems in medical settings.

Keywords: Value of Information; Decision Making; HealthCare; Simulation; COVID-19.

1. Introduction

The coronavirus epidemic (COVID-19) has wreaked havoc on society and economy all over the world (Sizhong S. 2022; Timelli L. et al., 2021). As of January 2022, almost 300 million illnesses and five million fatalities had been documented worldwide (WHO, 2022). Despite public health authorities enforcing preventative measures like mask use, illnesses and casualties continue to accumulate (Sylvia H. et al., 2021; Hisrael P. et al., 2022). Fig. 1 shows the number of cases and deaths due to COVID-19 as of 16 January 2022.

To confront the pandemic, universal immunization against COVID-19 is required in the light of the terrible situation and the proliferation of new variants of the virus. Although different vaccines have been produced, unfortunately, vaccination reluctance has put several immunization initiatives at risk (Winter T. et al., 2022; Marta C. et al., 2022; Merkley E. et al., 2022).

The direct medical expenditures incurred, simply during the illness, might be as high as $163.4 billion in the United States of America (Michele et al., (2021). This estimate excludes medical costs associated with post-infection care or the worsening of unrelated diseases as a result of postponement of preventive care and diagnosis (Michele K. et al., 2021).

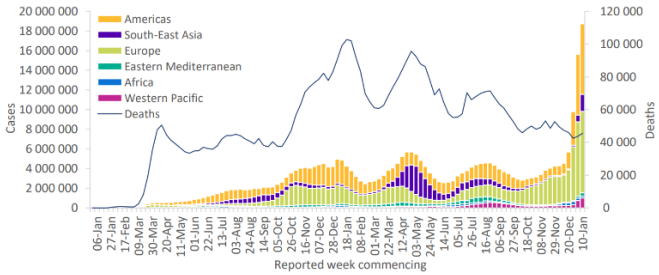

Fig. 1: Covid-19 cases and deaths as of 16 January 2022, from WHO, 2022.

There are now some newly suggested COVID-19 vaccinations. In new vaccines, there are numerous factors to consider, including the feasibility of use in clinical settings, cost and effectiveness (Sookaromdee P., and Wiwanitkit V. 2021). The cost and efficacy of various vaccinations may be major factors in the choice to deploy a new immunization (Hotez P. and Bottazzi M. 2020). Furthermore, a vaccination that is suitable for clinical use which is easy to store and administer, should be chosen. Due to unknown outcomes, adverse reactions, and responses, people may not be entirely immune even after receiving vaccinations. Therefore, it is important to establish methods to evaluate information and tests that can reduce such uncertainties. The valuation of information on uncertainties in COVID-19 treatments will be the main focus of this paper.

The paper is organized as follows: Section 2 explains the EVPI followed by a brief about finding the EVPI via simulation in Section 3. Section 4 explains the proposed model and in section 5, the decision problem is laid out. Section 6 demonstrates the discrete event model followed by the results and conclusions in sections 7 and 8,

2. Expected Value of Perfect Information

Value of Information (VOI) is a decision-making approach that classifies and positions the areas of a decision model where more information is anticipated to be valuable. VOI, in particular, identifies the possible advantage that might be realized if the condition of a previously unknown variable is known before the choice is taken (Constantinou B. 2018).

The Expected Value of Perfect Information (EVPI) offers a collective estimate representing the expected benefit when we have perfect knowledge about the states of all the variables in the decision problem. However, when uncertainties pile up on top of each other, finding the EVPI can be difficult such as the case of COVID-19. Here, only sampling and simulation can be helpful to address such a problem. While a decision analyst is usually more concerned with the value of obtaining extra information on particular individual factor than with the total worth of all variables, the EVPI provides the maximum possible value one can gain from any kind of information.

Unlike the EVPI, calculating the expected value of sample information of continuous variables is more challenging which will be addressed in future work, however, in this paper, a discrete event simulation model is proposed to estimated the EVPI. Due to uncertainties in the results of standard care and vaccination in dealing with COVID-19, the value of information becomes crucial in the decision of whether to implement vaccines and or consider only standard care. The purpose of this paper is to address the possible uncertainties of such health care problem in order to value the different treatment options if uncertainties are eliminated.

2.1. Decision Trees

A decision tree depicts all potential arrangements of decision junctions, potential events and observations in a given sequence on a tree assembly to describe a decision problem. The decision and chance nodes of a decision tree are represented by rectangles and circle, respectively. Each decision node outgoing arc symbolizes a decision alternative, and each chance node outward arc represents a result labeled by name and the associated probability.

The benefit nodes are positioned at the leaves of the tree which do not have outward arcs. Accordingly, each route from the root to the leaf reflects a decision situation with a series of decisions and possible events. Due to their ease of use and simple calculation, decision trees have become popular modeling tools. The size of a decision tree, on the other hand, can expand exponentially as the number of variables or states grow. In this article, we will use decision trees to value two types of COVID-19 treatment, namely, standard care and vaccination.

2.2. Expected Value of Perfect Information of continuous variables

In the field of health economics, Bayesian decision models are becoming progressively prominent. Many EVPI and EVSI algorithms have been established particularly for Bayesian models using Monte Carlo simulation and sampling methods. The conditional probability distributions and functions of each parameter are generally represented by a series of mathematical equations in these models.

Estimating the EVPI is the first step in value of information analysis. It's the projected benefit per patient of a trial with an infinite sample size, yielding complete knowledge of all (total) unknown parameters, effects and characteristics. Such a research, albeit hypothetical, would eliminate confusion regarding the net benefit of each intervention. The EVPI finds the ceiling of the expected cost of a future study. Studies with a finite sample size or studies that evaluate only a subset of factors all have a lower expected benefit than the EVPI.

As a result, extra research is not justified if the EVPI does not surpass the fixed cost of research. On contrast, if the overall EVPI exceeds the fixed cost of research, additional research may be justified. However, the EVPI depends on uncertainty, in simple terms, the anticipated loss associated with uncertainty is the probability of being "incorrect" multiplied by the

average result of being incorrect (the opportunity loss), which is equivalent to the EVPI. For instance, the expected incremental net benefit (INB) of the following payoffs of two course of actions and four states of nature is 225 as shown in Table 1. The expected loss is $0.05 \times (-750) + 0.25 \times (-250) = -1000$, which is in essence the EVPI.

Table 1: An example of incremental net benefit.

	State 1	State 2	State 3	State 4	
Probabilities	0.05	0.25	0.4	0.3	Expected benefit
Decision $d \in \boldsymbol{D}$	Probability of state $\theta \in \boldsymbol{\theta}$				$E_\theta\{B(d,\boldsymbol{\theta})\}$
New treatment	250	750	1250	1750	1225
Standard treatment	1000	1000	1000	1000	1000
INB	-750	-250	250	750	225

Fig. 2 shows the incremental net benefit of Table 1. If the mean of the INB distribution is positive, the expected loss is $-\sum_i p_i \times INB_i | INB_i \leq 0$. On contrast, if the mean of INB distribution is negative the expected loss is $\sum_i p_i \times INB_i | INB_i \geq 0$. Alternatively, this can be put in a continuous form as follows:

$$EVPI = -\Gamma(\bar{x}) \int_{-\infty}^{0} x f(x) dx + (1 - \Gamma(\bar{x})) \int_{0}^{\infty} x f(x) dx \qquad (1)$$

Where, $f(x)$ is the prior density function of the incremental net benefit, $\bar{x}$ is the mean of the incremental net benefit density function and $\Gamma(\bar{x})$ is a binary function, where $\Gamma(\bar{x}) = 1$ if $\bar{x} \geq 0$ and $\Gamma(\bar{x}) = 0$ if $\bar{x} < 0$. For example if the benefit of the standard treatment is 1500AED instead of 1000, the mean INB will be -275, and hence, the first part of equation (1) will be valid and the EVPI will equal to 75.

The main challenge in using (1) is the unavailability of the function $f(x)$, particularly when many uncertain parameters are involved like the case of COVID vaccination. Therefore, other but approximate methods can be found to estimate the EVPI as illustrated shortly.

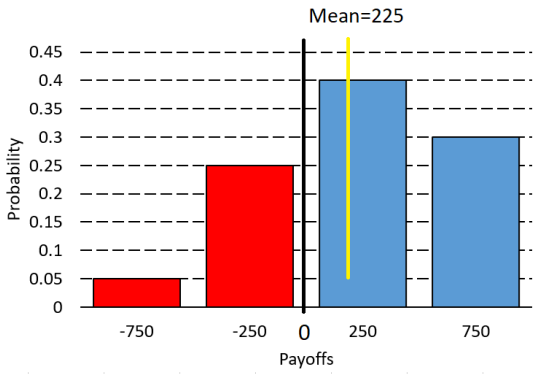

Fig. 2: An example of incremental benefit of Table 1.

3. EVPI via Simulation

Suppose in a typical decision-making model that the decision alternatives are denoted by D and the unknown parameters by θ with the joint *pdf* of $P(\boldsymbol{\theta})$. In such a model, we seek to find the benefit $B(d,\boldsymbol{\theta})$ of the decision d in D. With this, each alternative predicted benefit is:

$$E_\theta\{B(d,\boldsymbol{\theta})\} = \sum_\theta B(d,\boldsymbol{\theta}) P(\boldsymbol{\theta}) \qquad (2)$$

If we don't know the value of any model parameter, we compute the anticipated benefit of each alternative and choose the alternative with the highest expected value, i.e.,

$$\max_d [E_\theta\{B(d,\boldsymbol{\theta})\}] \qquad (3)$$

which is represented in the last column of Table 1. If we could have perfect knowledge on all uncertain parameters in the decision problem, we would be able to adjust our actions to optimize the result and minimize the losses incurred by the uncertainty in the model. The anticipated benefit with perfect information is determined as follows:

$$E_\theta\left(\max_d [B(d,\boldsymbol{\theta})]\right) = \sum_\theta P(\boldsymbol{\theta}) \max_d [B(d,\boldsymbol{\theta})] \qquad (4)$$

The difference between the maximum expected value with perfect information and the highest expected value without perfect information is the expected value of perfect information (EVPI).

$$EVPI(\boldsymbol{\theta}) = E_\theta\left(\max_d [B(d,\theta)]\right) - \max_d [E_\theta\{B(d,\theta)\}] \qquad (5)$$

The above formula can be easily implement in a simulation model as compared to (1).

4. The Decision Making Model

Assume a novel treatment for a health condition is offered to substitute a current treatment. The decision is whether to use the new treatment instead of the old. According to economic theories, this decision should be made based on whether it will achieve a net gain, taking into consideration the opportunity cost of the new treatment (i.e., the worth of health sacrificed somewhere else in the system to make space for the newly proposed treatment). The incremental net benefit of the proposed treatment is used to calculate this, which is basically a rearranged version of the incremental cost-effectiveness ratio decision rule.

The value of information statistics can be calculated in two ways: analytically, which usually requires normality assumptions among parameters, and numerically (through simulation), which relaxes some of the assumptions like the normal distribution of observations; however, it can be time consuming, requiring many hours of computational time. The analytical solutions tend to assume that the mean INB

is a simple linear composition of incremental mean cost and outcomes, that is: $b = \Psi Q - c$, where b is the benefit, Q is the gain, Ψ is the willingness to pay and c is the cost. Throughout this research, outcomes are measured in Quality-Adjusted Life-Years (QALYs).

QALY value is a quantification of the health condition over a period of time. The score is used to quantify the value of medical treatments in economic assessment. For instance, an individual with an average health condition over one year can be assigned a value of one QALY, which is equivalent to excellent health condition over half a year. Alternatively, this is equivalent to living 2 years with a poor health condition. QALYs can be used to guide health insurance coverage decisions, program evaluations, treatment decisions, and future program priorities. Fig. 3 shows an instance of the increase in QALY profile upon intervention.

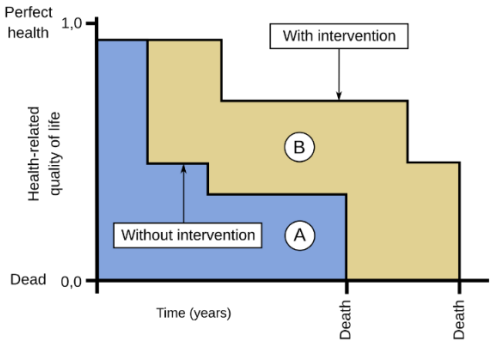

Fig. 3: The concept of QALYs.

5. The Decision Problem

The fundamental decision problem in the treatment of COVID-19 is whether to go for standard care or vaccination option. In our decision model, we found that a response on the standard treatment happens with a probability of Beta (70, 30) as shown in Fig. 4. The standard care of COVID-19 may include Hydroxychloroquine, 400mg BID×2 doses, then 200mg PO BID for 5 days OR Chloroquine Phosphate 500 mg PO BID for 5 days, other treatments include Pfizer's Paxlovid, Favipiravir, Remdesivir, etc. The gain in QALYs in case of response, regardless on standard treatment or vaccines is norm(6, 0.5) and the cost of standard care is estimated by 500AED (1AED is equivalent to $0.273 dollars at the time of study).

On the other hand, for vaccination, the vaccine is anticipated to significantly minimize the chance of catastrophic episodes. Those vaccinations are quite efficient, but they are also "reactogenic," meaning that they are likely to trigger an immunological response. In this research, vaccinations may come with side effects with a probability of Beta(40, 60).

According to the type of COVID-19 vaccination, different side effects may be noticed. Pfizer and Moderna vaccinations have the highest negative effects, (Meredith G. et al., 2022). The side effects of standard vaccines such as Pfizer and Senopharm include soreness at the injection site which seems to be the most typical and prevalent adverse effect. Fatigue, headache, muscular pains, chills, weariness, lethargy, tenderness, joint discomfort, and potentially a fever, are also some of the other adverse effects.

If a patient chooses the vaccination, she/he may experience side effects as illustrated above. With side effects, a loss in QALYs is estimated by norm(1, 0.2). The gain in QALYs for the vaccination arm is estimated by norm(6, 0.5) if no side effects are observed. On contrast, if side effects are experienced, the gain in QALYs will decrease by an amount of norm(1, 0.2). The cost of vaccine is estimated by 2500AED in UAE. An additional cost of Gamma(2.5,400)AED is needed to treat the vaccine side effects should they occur.

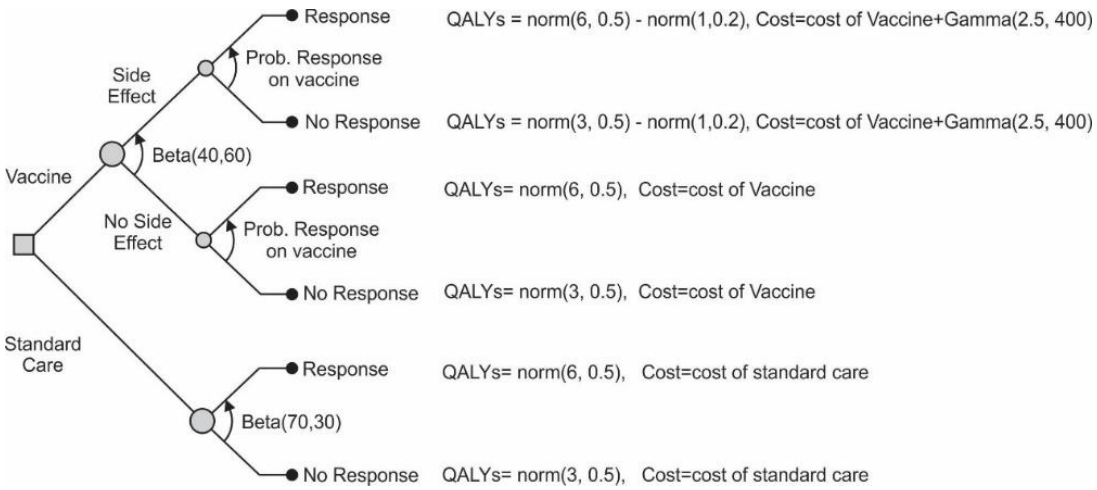

Fig. 4: The decision problem costs and QALYs for every arm in treating COVID-19.

Prior data on the efficacy of the new vaccines in the form of the log odds ratio (LOR) is available, but limited. Therefore, we use the following contingency table which was found on real cases in UAE-University of Sharjah Hospital as follows:

Table 2: Contingency table of the response on the two treatments.

	Response	No response
Vaccination	$A = 70$	$B = 30$
Standard treatment	$C = 60$	$D = 40$

The estimated Odds ratio of the contingency table is $O = \frac{A \times D}{C \times B}$. Note that, ln(Odds ratio) roughly follows a normal distribution with a mean of "$\ln(O)$" and a standard deviation of $\sigma = \sqrt{\frac{1}{A+0.5} + \frac{1}{B+0.5} + \frac{1}{C+0.5} + \frac{1}{D+0.5}}$. In terms of exact probabilities, the odds ratio is given by:

$$Odds\ Ratio = \frac{Odds\ of\ response\ on\ vaccine}{Odds\ of\ response\ on\ standard\ care}, \quad (6)$$

Where the odds of response on vaccine = probability of response on vaccine/(1- probability of response on vaccine) and the odds of response on standard care = probability of response on standard care/(1- probability of response on standard care). By plugging these two expressions in (6), we get:

$$Odds\ Ratio = \frac{\text{Prob. resp. on vaccine} \times (1 - \text{Prob.resp.on strd treatment})}{(1 - \text{Probability resp.on vaccine}) \times \text{Prob. resp. on strd treatment}} \quad (7)$$

To mimic the contingency table, the odds ratio will be sampled from $norm(\ln(e), \sigma)$. Denote the sampled ratio by $\mathcal{N}(\ln(e), \sigma)$, hence, the probability of response on vaccine is given by:

$$Probablity\ of\ response\ on\ vaccine = \frac{\mathcal{N}(\ln(e), \sigma) \times Prob.\ resp.\ on\ strd\ care}{Prob.resp.\ on\ strd\ care \times [\mathcal{N}(\ln(e), \sigma) - 1] + 1} \quad (8)$$

The side effects have a negative impact on one's quality of life, therefore, side effects will reduce the gained QALYs should they occur. The total cost end of each arm i is given by $c_{i,j}$, when patient i is treated through arm j, where j is either the standard treatment or vaccination. Let the QALYs of patient i in arm j be denoted by $Q_{i,j}$, with this, the net benefit of each patient in arm j will be:

$$b_{i,j} = \Psi Q_{i,j} - c_{i,j}, \quad (9)$$

where Ψ is the wiliness to pay per QALY. Therefore the average benefit of arm j is:

$$B_j = \frac{\sum_{i=1}^{n_j} b_{i,j}}{n_j}, \quad (10)$$

where n_j is the sample size in arm j.

6. Discrete Event Simulation Model

The expected value of perfect information which demonstrates the cap on how much gain one could achieve from eliminating the uncertainty in the problem. This makes the analytical and closed form solutions of EVPI particularly in the medical settings a challenging task. Thanks to simulation techniques that can help in finding such a quantity. In this work, we estimate the expected value of perfect information using discrete even simulation, particularly, using Arena 14.5. Here, we simulate the arrival of 1 million patients who have to decide between standard treatment of COVID-19 or vaccination. The model is depicted in Fig. 5 where each arrival, upon creation, is assigned different attributes and variables across its arm till the disposal block. To be able to compare the standard treatment vs. the vaccination, the entities are cloned for the two arms. For the standard treatment arm, the response probability of the treatment is given by a simulated data from the second row of the contingency table, that is Beta (60, 40).

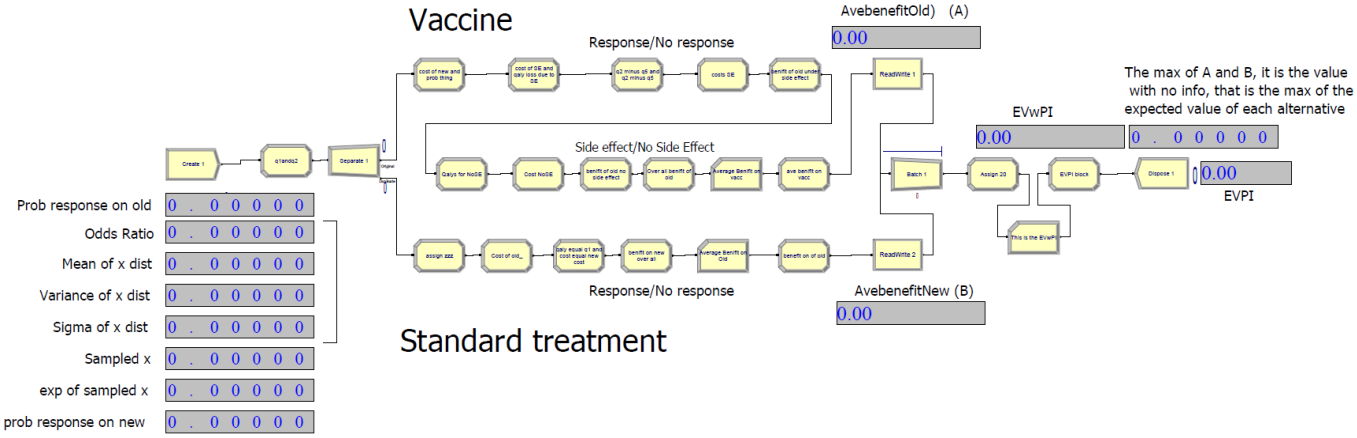

Fig. 5: Arena Simulation Model.

7. Results

By running the simulation model for 1million patients, the tally of the calculated variables is shown in Table 3. Following the equation of (5) to find the EVPI, it was found that, by eliminating all the uncertainty in the outcomes, the Expected Value with Perfect Information EVwPI= 96103.96AED, and that with no information, under uncertainty $\max_d[E_\theta\{B(d,\boldsymbol{\theta})\}]$ =95500.58AED, therefore, the EVPI= 5287.24AED. With 1million patients, the half width becomes extremely small leading to high confidence in the results as shown in Table 3. As a remark, the value of willingness to pay (Ψ) is 20,000AED.

Table 3: Results of a simulation run of 1Million patients using the contingency Table (2).

Expression	Average	Half Width	Minimum	Maximum
Average Benefit on Old	95,500.58	16,121.64	60,034.24	140,308.19
Average Benefit on vacc	90,816.72	21,089.84	46,335.62	133,741.35
EVwPI	96,103.96	16,162.80	60,650.86	140,308.19

To demonstrate the warm-up period of the model, Fig. 6 shows the statistics of the first 100 patients. Clearly the model average values stabilize after a small number of arrivals.

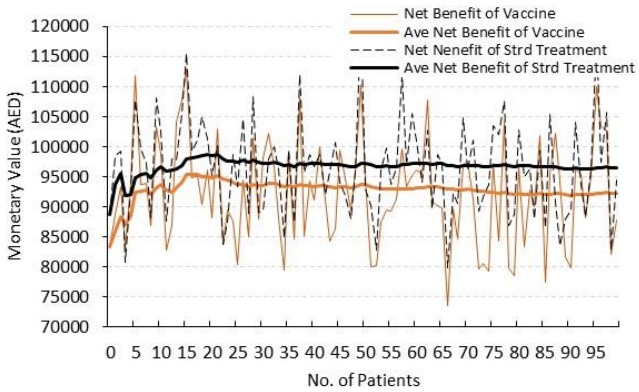

Fig. 6: Case by case and average benefit of the two treatments for 100 patients.

The sampled probability of the response on vaccine is shown in Fig. 7 over the 100 cases. The data points show an average around 0.7 as given by the contingency table. The probability of response on vaccine has been sampled from the contingency Table 2.

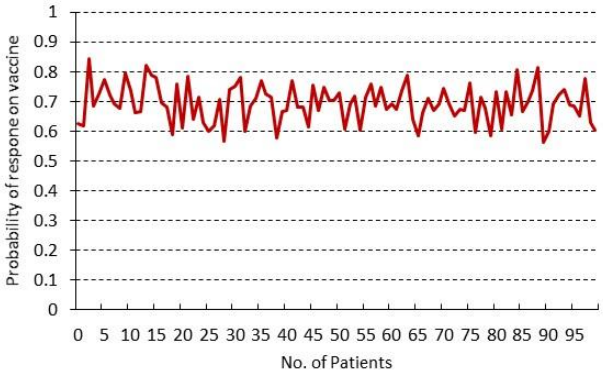

Fig. 7: Simulated probability of response on vaccine using the odds ratio in Table 2.

Due to high uncertainty in response, the model shows that higher benefits in the standard care are expected, i.e., 95500.58AED>90816.72AED. For this reason, we have run the model again by considering higher response rate on vaccines as in Table 4. The results of this scenario are shown in Table 5. Clearly, with higher response rate on vaccines, the expected gains of the vaccine arm will be higher than that in the standard care, i.e., 95500.58 vs. 102563.16AED. Better response rates on the vaccine will ultimately reduce the value of perfect information, which in turn reduces the value of sample information. That is, additional testing and sampling will be of less value when vaccinated patients demonstrate higher response rates. In fact the EVPI for this instance has dropped to 256.86AED.

Table 4: Modified contingency table

	Response	No response
Vaccination	A = 90	B = 10
Standard treatment	C = 60	D = 40

Table 5: Results of a simulation run of 1Million patients using the contingency Table 4.

Expression	Average	Half Width	Minimum	Maximum
Average Benefit on Old	95,500.58	16,121.64	60,034.24	140,308.19
Average Benefit on vacc	102,563.19	23,013.35	59,994.13	147,515.52
EVwPI	102,820.06	22,128.98	61,643.48	147,515.52

Although QALYs are roughly assessed in this article, more precise estimation will improve the estimate of the EVPI. The main advantage of this preliminary research is to build a discrete simulation system to model a decision tree of standard vs. vaccination options of COVID-19. This research will be extended to include the estimation of expected value of sample information.

8. Conclusions

This paper intended to give a "hands-on" approach to utilizing VoI as well as providing workable template to help scholars conduct their own research in valuing different treatments. The study implements two methodological approaches, namely the analytical and the numerical solutions. Each approach has its own set of pros and cons. The main benefit of the analytical technique is its short computational time and sound estimations that are free of noise. Simulation, on the other hand, suffers from the random noise that is inherent from random numbers generation.

The advantage of the numeric technique, on the other hand, is its flexibility in terms of the distributional forms of both input and output parameters; nevertheless, running enough simulation runs to minimize Monte Carlo errors is evidently effective. Comparisons of the outcomes of the analytical and numerical methods would be an interesting contribution to the literature. In the discrete event simulation model, we could extend the use of EVPI calculations to medical decision-making applications with a variety of sources of uncertainty for the case of COVID-19 vaccines. It was found that, further market testing and vaccine validation will be of insignificant value if the vaccination response rate is above 85%, according to our simulation results.

Finally, VoI is an approach for calculating the expected return on investment in research. It was shown that when the response rate on vaccine is not high, further tests will be of a value, however, when the response rate on vaccines is high, the investment on testing the vaccine hardly can be justified. This document, along with the Arena model is meant to serve as a useful template that may be easily modified to various decision scenarios.

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