

**Análisis coste-efectividad Bayesiano con dos medidas
de efectividad: el plano de aceptabilidad
coste-efectividad.**

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Análisis coste-efectividad Bayesiano con dos medidas de efectividad: el plano de aceptabilidad coste-efectividad.

Abstract

Cost-effectiveness analysis (CEA) compares cost and outcome of two or more technologies. However, there is no consensus about which measure of effectiveness should be used in each analysis. Clinical researchers have to select an appropriate outcome for their purpose, and this choice can have dramatic consequences in the conclusions of the analysis. In this paper we present a Bayesian cost-effectiveness framework to carry out CEA when more than one measure is considered. In particular, we analyse the case in which we have two measures of effectiveness, one binary and the other continuous.

Decision-making measures, such as the incremental cost-effectiveness ratio, incremental net-benefit and cost-effectiveness acceptability curves, are used to compare costs and one measure of outcome. We propose an extension of cost-acceptability curves, the cost-effectiveness acceptability plane, as a suitable measure for decision taking.

The models were validated using data from two clinical trials. In the first one, we compared four highly active antiretroviral treatments applied to asymptomatic HIV patients. As measures of effectiveness, we considered the percentage of patients with undetectable levels of viral load, and changes in quality of life, measured according to EuroQol. In the second clinical trial we compared three methadone maintenance programmes for opioid-addicted patients. In this case, the measures of effectiveness considered were quality of life, according to the Nottingham Health Profile, and adherence to the treatment, measured as the percentage of patients who participated in the whole treatment programme.

Key Words: Bayesian Analysis, Cost-Effectiveness, Cost-utility, Measures of Effectiveness.

1 Introduction

There is no consensus about which measure of effectiveness should be used in cost-effectiveness analysis (CEAC). Thus, researchers have to choose between alternative measures of effectiveness on the basis of specific objectives. However, the choice of this measure of effectiveness can have dramatic consequences on the results as to which treatment is more cost-effective. Quality Adjusted Life Years (QALYs) and Disability Adjusted Life Years (DALYs) have been proposed as a way of expressing effectiveness in common units of health-related value. However, these measures are not suitable to measure the effectiveness of a large number of treatments or technologies. In many studies [1-5] more than one measure of effectiveness

to compare technologies is considered. Generally, in such studies a complete CEA is carried out for each measure of effectiveness. However, these analyses do not take account of the correlation between measures of effectiveness; neither do they provide a single measure for decision-taking, considering all measures of effectiveness. In this paper we propose a CEA framework for more than one measure of effectiveness from a Bayesian point of view. In particular, we analyse the case in which we have two measures of effectiveness, one binary and the other continuous.

Spiegelhalter *et al.* [6] and Jones [7] were the first to discuss the Bayesian approach for statistical inference in the comparison of health technologies. Since then, many studies have proposed the Bayesian approach to compare treatment options by means of cost-effectiveness analysis [8–15].

The standard measure used to compare the cost and effectiveness of treatments is the incremental cost-effectiveness ratio (ICER). Nevertheless, this measure presents severe interpretation problems, as well as difficulties in estimating the confidence or credibility intervals. The incremental net benefit (INB) has been proposed as an alternative to ICER [11–16]. The INB of treatment 1 versus treatment 0 is defined as

$$INB(R_c) = (\mu_1 - \mu_0) - \frac{(\gamma_1 - \gamma_0)}{R_c} = (\Delta\mu) - \frac{(\Delta\gamma)}{R_c}, \quad (1)$$

in units of effectiveness, or

$$INB(R_c) = R_c \cdot (\mu_1 - \mu_0) - (\gamma_1 - \gamma_0) = R_c \cdot (\Delta\mu) - (\Delta\gamma), \quad (2)$$

in units of costs.

The value R_c is interpreted by O’Hagan and Stevens [13] as the cost that decision-takers are willing to accept in order to increase the effectiveness of the treatment applied by one unit. Thus, analysing whether the alternative treatment is more cost effective than the control treatment is equivalent to determining whether $INB(R_c)$ is positive. In practice, it is not a simple matter for the decision-taker to determine a single R_c , and so a cost-effectiveness acceptability curve (CEAC) is constructed. This curve provides a graphical representation of the probability of the alternative treatment being preferred ($\text{Prob}(INB(R_c) > 0)$) for each value R_c . This interpretation of the CEAC, in terms of probability, is only possible when the Bayesian approach is adopted [9]. All these measures of decision-making are defined to compare one measure of effectiveness and cost for each treatment.

We propose an extension of INB (units of costs) for two measures of effectiveness. In this case, decision-takers should define two willingnesses to pay for each measure of effectiveness (R_{1c} and R_{2c}). The INB is now defined as

$$INB(R_{1c}, R_{2c}) = R_{1c} \cdot (\mu_{11} - \mu_{10}) + R_{2c} \cdot (\mu_{21} - \mu_{20}) - (\gamma_1 - \gamma_0) = R_{1c} \cdot \Delta\mu_1 + R_{2c} \cdot \Delta\mu_2 - \Delta\gamma, \quad (3)$$

In a similar way to CEAC, the cost-effectiveness acceptability “plane” (CEAP) can provide the probability of obtaining a positive INB for each R_{1c} and R_{2c} in a 3-D graphical representation.

The willingness to pay for each measure of effectiveness may not be independent. Thus, if one is willing to pay a large sum for the first effectiveness, the willingness to pay for the other could be smaller. This relationship is specific for each analysis. In this case, the possible combination of (R_{1c}, R_{2c}) would not be \mathbb{R}^2 but $\{(R_{1c}, R_{2c}) \in \mathbb{R}^2 / R_{2c} = f(R_{1c})\}$.

It is common that, when there are two measures of effectiveness, one of them was considered as the main measure of effectiveness, and the other as a secondary effectiveness. In that case, Equation (3) can be rewritten as:

$$INB(R_{1c}, R_{2c}) = R_{1c} \left(\Delta\mu_1 + \frac{R_{2c}}{R_{1c}} \cdot \Delta\mu_2 \right) - \Delta\gamma \quad (4)$$

where the decision-taker should define the willingness to pay for the main measure of effectiveness (R_{1c}), and the relative weight of the secondary measure of effectiveness (R_{2c}/R_{1c}). The interpretation of this second term can be that an increase of one unit in the secondary effectiveness would be equivalent to an increase of R_{2c}/R_{1c} units of the main effectiveness. We will adopt the expression (3) in the rest of the article.

Section 2 presents the model for the particular case in which two measures of effectiveness are considered. The first is defined by a binary variable defining whether an objective has been achieved, and the second one is continuous. Section 3 includes two practical applications. The first example compares four highly-active antiretroviral treatments applied to asymptomatic HIV patients. The measures of effectiveness considered were the percentage of patients with undetectable levels of viral load, and the change in quality of life, measured according to EQ-5D. The second example compares three methadone maintenance programmes for opioid-addicted patients. In this case, the measures of effectiveness considered were the adherence to the treatment, measured as the percentage of patients who completed the whole treatment programme, and quality of life, according to the Nottingham Health Profile (NHP). In Section 4, some conclusions are drawn.

2 Model specification

Given a sample of n patients, we obtained data on costs (c_{ij}) and two measures of effectiveness (e_{1ij} and e_{2ij} for each patient i receiving treatment j). The number of patients receiving treatment j is denoted by n_j . Each patient received one of the T treatments to be compared, $n = \sum_{j=1}^T n_j$. We consider the particular case in which one outcome (e_{1ij}) is defined by a binary variable. Therefore, $e_{1ij} = 1$ if the outcome for patient i in treatment group j was good, and $e_{1ij} = 0$ otherwise. The second outcome (e_{2ij}) is continuous, and so we assume it to be normally distributed. We also recognize the skewness in the cost data; thus it is realistic to assume that the cost is log-normally distributed [13,17].

We present the joint distribution for the unknown parameters in our model. First, we consider that for each treatment group there is a probability ϕ_j of a good outcome ($e_{1ij} = 1$). With this aim, let $(e_{2ij}, \log(c_{ij}))$ follow a multivariate normal distribution, $(e_{2ij}, \log(c_{ij})) \sim N(\mu_{1j}, \Sigma_{1j})$, while if $e_{1ij} = 0$, then $(e_{2ij}, \log(c_{ij})) \sim N(\mu_{2j}, \Sigma_{2j})$. For this representation, the mean effectiveness of treatment j for each measure of effectiveness is

defined for the following expression $(\phi_j, \phi_j \cdot \mu_{1j}[1] + (1 - \phi_j) \cdot \mu_2[1])$, where $a[b]$ denotes the component b of vector or matrix a . Similarly, the mean cost of treatment j is defined for $\delta_j = (\phi_j \cdot \exp(\mu_{1j}[2] + \Sigma_{1j}[2, 2]/2) + (1 - \phi_j) \cdot \exp(\mu_{2j}[2] + \Sigma_{2j}[2, 2]/2))$. The unknown parameters comprise $\Delta_j = (\phi_j, \mu_{1j}, \Sigma_{1j}, \mu_{2j}, \Sigma_{2j})$.

We propose a general prior structure: beta distribution for parameters ϕ_j for $j = 1, \dots, T$, multivariate normal distribution for vectors μ_{1j} and μ_{2j} for $j = 1, \dots, T$ and inverse Wishart distribution for the variance–covariance matrix Σ_{1j} and Σ_{2j} for $j = 1, \dots, T$. In the examples shown in this paper, we assume prior ignorance about the parameters of interest.

The posterior distribution of the coefficients does not have a closed–form expression, so numerical techniques are needed. We use Markov-chain Monte Carlo (MCMC) methods to approximate the posterior distribution and estimate posterior means and variances and Bayesian credible intervals. The necessary computation routines are coded in the software package WinBUGS (<http://www.mrc-bsu.cam.ac.uk/bugs/welcome.shtml>). The complete code for the examples is freely available upon request to the authors.

3 Empirical applications

3.1 Example 1

The data used in this section were obtained from a real clinical trial in which a comparison was made between two highly–active antiretroviral treatment protocols applied to asymptomatic HIV patients [18]. We obtained data on the direct costs (of drugs, medical visits and diagnostic tests), on the effectiveness, based on clinical variables (percentage of patients with no detectable virus load) and on health–related life–quality variables, using EQ–5D.

In this exercise, we compared four three–way treatment protocols, d4T+3TC+IND, d4T+ddl+IND, AZT+3TC+IND and AZT+ddl+IND. Two alternative measures of effectiveness were employed. The first one considered was the percentage of patients who, at the end of the treatment programme, presented undetectable levels of viral load. Effectiveness, therefore, can only be expressed as one of two values, 1 if the viral load is undetectable, otherwise 0. The second effectiveness measure was the improvement in the patient’s life quality, measured as the improvement on a visual analogue scale (VAS) using EQ–5D instrumentation. Table 1 summarises the statistical data.

Please insert Table 1 about here

Diffuse priors are utilized for the parameters of interest. We ran 40000 replications following first a burn-in phase of 10000 replications.

The posterior means and standard deviations of the true mean effectiveness and cost for each treatment group are presented in Table 2.

Table 2

The cost–effectiveness acceptability curve (CEAC) is a decision–making measure. It represents the probability of choosing treatment 1 versus treatment 0 for each willingness to

pay for an increase in effectiveness of one unit (R_c). In the present study, a CEA is carried out for two measures of effectiveness. In such a case, the decision-maker must fix two different willingnesses to pay for each outcome considered (R_{1c} and R_{2c}). The value R_{1c} can be interpreted as the cost that decision-takers are willing to accept in order to increase the proportion of patients with undetectable viral load by one percent. Similarly, the value R_{2c} can be interpreted as the cost that decision-takers are willing to accept in order to increase the improvement in VAS by one unit. The graphical representation of the probability of obtaining a positive INB for each pair of values (R_{1c} , R_{2c}) defines the cost-effectiveness acceptability plane (CEAP).

Most cost-effectiveness analysis compares two alternative technologies, namely the control treatment and the new treatment. In this example, we compare four treatments. To present how a cost-effectiveness analysis for two treatments would be carried out, we compare the treatments d4T+3TC+IND and d4T+ddl+IND. The results are shown in Figure 1.

Please insert Figure 1 about here

The first CEAC shows the results of cost-effectiveness analysis when the measure of effectiveness is the proportion of patients with undetectable viral load. Treatment d4T+3TC+IND has a mean effectiveness of 0.65 units, versus 0.54 units obtained by treatment d4T+ddl+IND. The mean cost of treatment d4T+3TC+IND is estimated as 7124 euros, while that of treatment d4T+ddl+IND is estimated as 7278 euros. Therefore, in mean terms, the first treatment is more effective and cheaper. The CEAC shows probabilities greater than 90% of choosing treatment d4T+3TC+IND for each R_{1c} considered.

If we consider the change in VAS as the measure of effectiveness, different results would be obtained. The mean change in VAS for d4T+ddl+IND is 4.83, while that of treatment d4T+3TC+IND is 4.56. The cheaper treatment (d4T+3TC+IND) would be preferred for a willingness to pay less than 564.55 euros. For a higher willingness to pay, we would prefer the more effective treatment (d4T+ddl+IND).

Very different conclusions are obtained if we use one or the other measure of effectiveness. Figure 1 also shows the CEAP. This graph shows the probability of d4T+3TC+IND being more cost-effective than d4T+ddl+IND for each combination of (R_{1c} , R_{2c}). To simplify interpretation of this graph, the contour plots are shown. The probability of accepting treatment d4T+3TC+IND increases for lower levels of R_{2c} and for higher levels of R_{1c} .

Finally, Figure 2 shows the cost-effectiveness analysis results for the four treatments.

Figure 2

The CEAC shows the probability of accepting each treatment for each value of R_{1c} or R_{2c} when only one measure of effectiveness is considered. Thus, if we take the percentage of patients with undetectable viral load as the measure of effectiveness, the preferred treatment will be AZT+3TC+IND for a willingness to pay of less than 183.45 euros, and

d4T+3TC+IND in the other case. If the change in VAS is used as the measure of effectiveness, the preferred treatment will be AZT+3TC+IND for a willingness to pay of less than 3945 euros, and d4T+ddl+IND in the other case

Figure 2 also shows which treatment is preferred for each area of the plane (R_{1c} , R_{2c}) and the probability of accepting such a treatment in each particular case. We have called this graph the cost-effectiveness acceptability plane frontier (CEAPF). For high values of R_{2c} and low values of R_{1c} the preferred treatment is d4T+ddl+IND. Table 2 shows this is the treatment that obtains highest levels of improvement of VAS. Alternatively, for a high willingness to pay for an improvement in the proportion of patients with undetectable viral load, the preferred treatment is d4T+3TC+IND. For low levels of willingness to pay, and when the two measures of effectiveness are similarly valued, the preferred treatment is the cheaper one, AZT+3TC+IND. CEAPF also shows the contour plots for the probability of choosing one or the other treatment.

3.2 Example 2

Data were obtained from a multicentre study to compare three methadone maintenance programmes (MMP) (high, medium and low intensity) for opioid-addicted patients [19]. A 12-month follow-up study of 586 patients beginning methadone treatment at five Drug Care Centres in Barcelona was performed. The Nottingham Health Profile (NHP) was used to measure quality of life. The difference between the NHP value at the start of treatment and the value one month later was used as the effectiveness measure. One of the main variables of analysis for treatments for addicted patients is the degree of adherence, and so we determined whether the patient continued the treatment during the twelve months of analysis. These two measures were analysed in order to obtain a complete Bayesian cost-effectiveness analysis.

Table 3 shows the posterior means and standard deviations of the true mean effectiveness and cost for each treatment group.

Table 3

The high-intensity programme presents higher levels of effectiveness, but is the most expensive treatment. Figure 3 shows this treatment to be preferred for high levels of R_{1c} and R_{2c} . The low-intensity programme is only chosen for low levels of willingness to pay, because it is the cheapest. The medium-intensity programme is more expensive than the low-intensity one, but obtains higher levels of continuous effectiveness.

Figure 3

4 Conclusions

At present there is no consensus about which measure of effectiveness should be used in cost-effectiveness analysis. This implies that researchers have to choose between alternative measures of effectiveness, depending on their specific aims. In this paper, we propose an

alternative way of carrying out cost–effectiveness analysis with more than one measure of effectiveness, from a Bayesian point of view. In particular, we analyse the case in which we have two measures of effectiveness, one binary and the other continuous, although it could be applied when both measures of effectiveness are continuous. In the latter case, and assuming normality in both measures of effectiveness, the likelihood for both effectiveness and the log–transformation of the cost can be expressed as a multivariate normal distribution.

We propose the cost–effectiveness acceptability plane and the cost–effectiveness acceptability plane frontier as decision–making measures for comparing two or more than two treatments, respectively. Both graphs illustrate the more cost–effective treatment for each combination of R_{1c} and R_{2c} and the certainty about that decision, in terms of probability.

This model can be extended for more than two measures of effectiveness but the graphical interpretation of the results would not be easy or natural.

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Table 1: Statistical summary of costs (in euros) and effectiveness (change in VAS and percentage of patients with undetectable viral load).

	d4T+3TC+IND	d4T+ddl+IND	AZT+3TC+IND	AZT+ddl+IND
% patients with undetectable VL	0.65	0.54	0.53	0.60
Change in VAS (s.d.)	4.56 (15.12)	4.83 (13.78)	4.02 (14.29)	3.92 (13.04)
Costs in euros (s.d.)	7142.87 (1568.09)	7302.70 (1693.86)	6239.50 (926.46)	6228.99 (544.36)
n	269	95	91	25

Table 2: Posterior moments. Mean and standard deviation.

	d4T+3TC+IND	d4T+ddl+IND	AZT+3TC+IND	AZT+ddl+IND
ϕ	0.65 (0.03)	0.54 (0.05)	0.53 (0.05)	0.59 (0.09)
μ	4.54 (0.93)	4.83 (1.45)	4.03 (1.55)	4.00 (2.85)
δ	7124 (65.71)	7278 (103.20)	6247 (107.80)	6236 (116.80)

Table 3: Posterior moments. Mean and standard deviation.

	High-intensity	Medium-intensity	Low-intensity
ϕ	0.669 (0.03317)	0.6188 (0.03401)	0.6703 (0.03426)
μ	18.66 (1.941)	18.34 (1.76)	14.96 (1.709)
δ	711 (29.09)	641.8 (25.76)	541.6 (22.31)

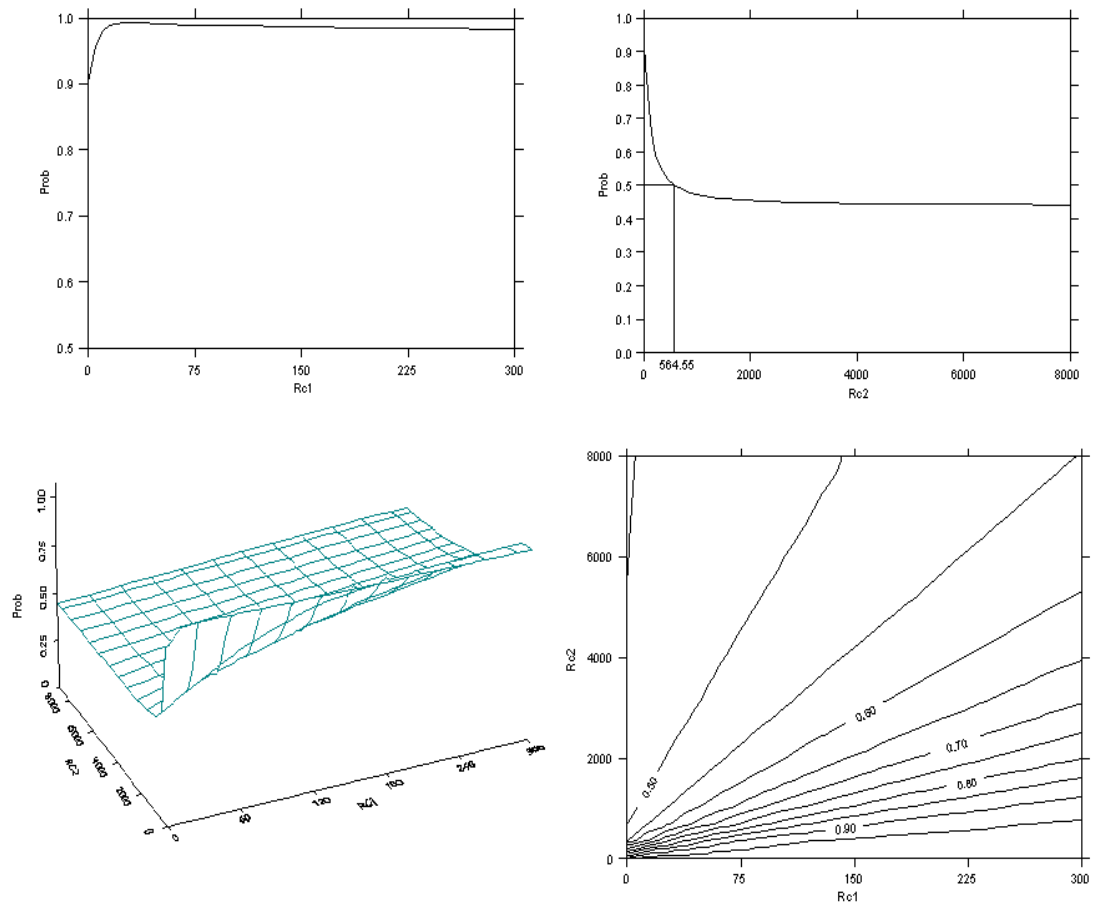


Figure 1: CEAC for d4T+3TC+IND versus d4T+ddl+IND for each effectiveness measure considered. CEAP for both effectiveness measures.

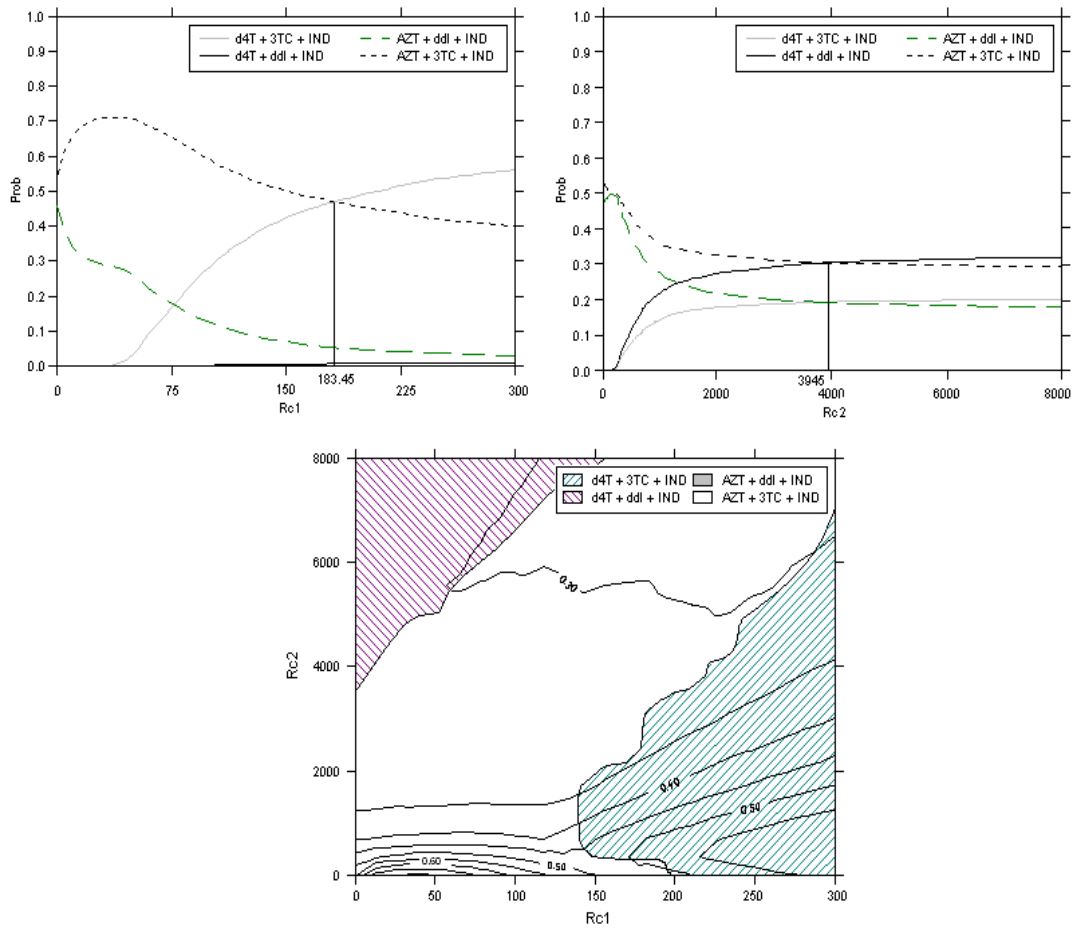


Figure 2: CEAC for four treatments for each effectiveness measure considered. CEAPF for four treatments.

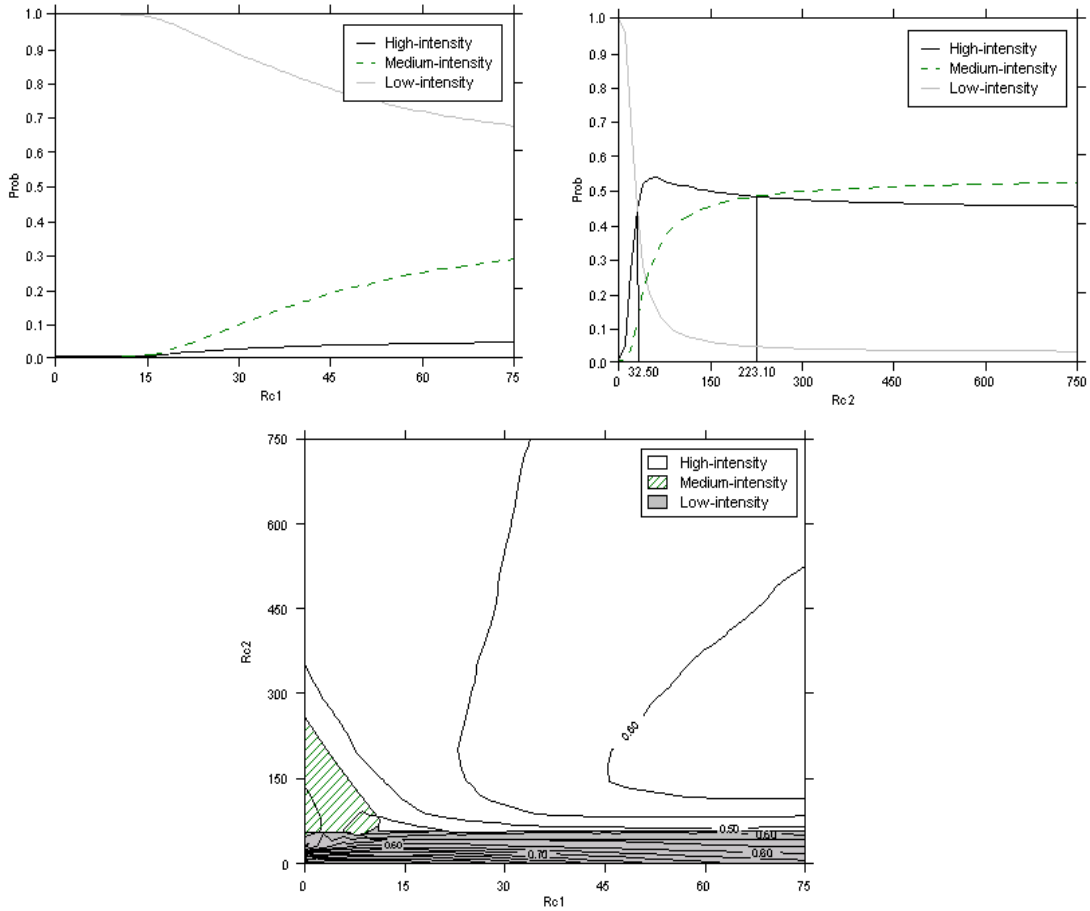


Figure 3: CEAC for four treatments for each effectiveness measure considered. CEAPF for four treatments.