

## Cost-Minimization and Budgetary Impact of the Use of Cycloserine in the Treatment of Resistant Tuberculosis

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### Abstract

**Objective:** To carry out a cost-minimization and budgetary impact assessment for the incorporation of cycloserine as a second-line drug in the treatment scheme for multidrug-resistant tuberculosis in the Brazilian Unified Health System (SUS).

**Methods:** The analysis of cost-minimization and budgetary impact followed the recommendations of the Methodological Guideline for Economic Evaluation and the Methodological Guideline for the Assessment of Budgetary Impact. A model was proposed using a simple decision tree with a base case composed of two scenarios: the reference one, using terizidone as a second-line medication standardized by the Ministry of Health in the therapeutic regimen of patients with MDR-TB, and the alternative scenario, using cycloserine.

**Results:** The safety outcomes were not considered to be adverse effects. No studies were found that assessed the cure rate outcome. A single study estimated the relative risk (RR) for treatment failure or relapse outcome for longer MDR-TB regimens, suggesting that cycloserine and terizidone have the same efficacy, considering the analyzed outcomes.

**Conclusion:** Cycloserine can be cost-effective. It must be considered that the incremental cost of incorporating cycloserine can be R\$ 2,829,825.60, with a budgetary impact that can reach more than R\$ 12 million, resulting in an increase of 26% to 29% in public spending in 5 years. These resources could be applied to other measures that may represent greater benefits for these patients.

**Keywords:** Cycloserine; Terizidone; Tuberculosis; Cost-Benefit Analysis; Budgetary Impact Analysis

### Introduction

Tuberculosis (TB) is a serious disease that has affected humanity since the most remote times, with found archaeological suggestive evidence of bone tuberculosis since the Neolithic period. With the industrial revolution, at the end of the 18<sup>th</sup> century, the epidemiological circumstances of urban households, with great levels of poverty, bad nutrition and crowding, made it easier to spread the disease [1].

It is estimated that in 2015 about 10.4 million people developed tuberculosis (TB), 580 thousand of them in the form of multidrug-resistant TB or rifampicin-resistant TB (TB-RR) and, in the same year, 1.4 million people died from the disease. At the same time, about 6.1 million new TB cases were reported that year. The Americas region represents 30% of the global burden of the disease, with 268 thousand new cases registered [2].

The pharmacological presentation of the drugs currently in use for the basic treatment scheme for TB are fixed-dose tablets combined in two types: 4 in 1 (Rifampicin, Isoniazid, Pyrazinamide and Ethambutol - RHZE) or 2 in 1 (Rifampicin and Isoniazid - RH). The basic regimen for children lesser 10 years old consists in the use of three drugs for the intensive phase (Rifampicin, Isoniazid, pyrazinamide - RHZ), and two drugs for the maintenance phase (RH), with individualized pharmacological presentations (tablets and/or suspension) [2,3].

For the treatment of adults and adolescents (over 10 years old) is established 2RHZE/4RH, indicated for new cases of tuberculosis or retreatment (recurrence and reentry after discharge with active disease), in all pulmonary and extrapulmonary clinical presentations, except the meningoencephalic and osteoarticular form [2,3]. In Brazil, in 2017, according to the Special Tuberculosis Treatment Information System (SITE-TB), while 246 new cases of monoresistance were reported, 80 cases of polyresistance were diagnosed and followed and the cases of multidrug resistance or resistance to rifampicin reached 713 cases with 2 cases of extensive resistance [2].

As rifampicin is the most active drug against the TB bacillus, schemes without it in its composition, whether due to resistance or intolerance, necessarily requires the use of second-line drugs, which requires treatment with a longer duration, with greater potential for toxicity and a worse prognosis [2,3].

First-line drugs, those used predominantly in the basic treatment regimen, are more effective and less toxic. Second line drugs, such as ethionamide and prothionamide, cycloserine and terizidone and paraminosalicylic acid (PAS), are less effective, more toxic and require a longer treatment period. For the drug treatment of MDR-TB, the Ministry of Health (MS) adopts the Directly Observed Treatment strategy in Short Course (DOTS), and uses a drug regimen that includes rifampicin, isoniazid, streptomycin, capreomycin, ethambutol, pyrazinamide, levofloxacin and terizidone (from group C), instead of ethionamide [2-4].

Given this context, this study is lead by the following question: Within the scope of the National Tuberculosis Control Plan, the replacement of cycloserine by terizidone in the treatment of patients with MDR-TB, aged over 10 years old, coinfectd or not by the HIV virus, can reduce treatment costs from the perspective of SUS considering the 5-year time horizon? In this perspective, the main objective for this work was to conduct a cost-minimization and budgetary impact assessment for the incorporation of cycloserine as a second-line medication in the treatment scheme for multidrug-resistant tuberculosis on SUS.

### Methods

This is a Technological Health Assessment (HTA) understood as a comprehensive way to explore the technical (almost always clinical), economic and social short and long-term consequences for the use of health technologies. As well as their direct, indirect, desirable and undesirable effects [2], whose purpose is to prevent damage and ensure that technologies are safe, as well as to guarantee that they are effective, bring benefits and have been used properly, among other objectives.

The study's problem emerged from the possibility of treating MDR-TB cases with the replacement of terizidone, the standard medicine and therapeutic scheme proposed by the Ministry of Health which is already registered with the National Health Surveillance Agency (ANVISA), for cycloserine, which is not registered in the agency, but for been biocompatible, has the same safety and efficacy as terizidone, however, with a higher acquisition cost. The study adopted a cost-minimization economic analysis and a budgetary impact analysis to estimate if the incorporation of cycloserine by SUS could minimize the costs of treating MDR-TB.

Both analyses were designed following the recommendations of the Methodological Guideline for Economic Evaluation and the Methodological Guideline for the Analysis of Budgetary Impact [4,5]. A model was proposed using a simple decision tree, to compare the drugs in terms of cost-minimization, considering that there is no difference in their effectiveness as biocompatible ones. Considering the outcomes, both of them increased the cure rate and reduced the mortality and treatment failure or relapse rates.

As a case of cure, was considered an individual with bacteriologically confirmed tuberculosis at the beginning of treatment, who had a negative result on sputum smear or culture in the last month of treatment and on at least one previous occasion. It was defined as a case of treatment failure or relapse, the individual who had a sputum smear or positive culture in the fifth month or later during treatment. And the treatment abandonment was considered when the individual interrupted the treatment for tuberculosis for a period longer than 30 days after the scheduled date of return to self-administered treatment or 30 days after the last dose ingested in DOT. Finally, it was established the death caused by tuberculosis and occurred during treatment as death from tuberculosis.

The base case was composed of two scenarios: the reference one, using terizidone as a second-line medication standardized by the Ministry of Health for the therapeutic regimen of patients with MDR-TB, and the alternative one, using cycloserine instead. It considered the perspective of SUS (from Brazil), that determines the National Tuberculosis Control Plan. The study population consisted of a hypothetical cohort of patients of both sexes, aged over 10 years, diagnosed with MDR-TB, co-infected or not by the HIV virus, assisted by SUS, eligible for the use of terizidone as second-line drug for the treatment of MDR-TB.

The study population was estimated by the method of measured demand for the analysis of cost minimization as well as the analysis of budgetary impact. The DAF reported that between 2017 and 2018, in Brazil, an average of 716 patients were treated with terizidone, out of 1892 patients diagnosed with MDR-TB.

By the epidemiological method, considering 2018 as the reference year for the consultation of the data from the Ministry of Health in the Information System for Notifiable Diseases - Sinan, it appears that, out of the 87,292 patients registered with confirmed cases of tuberculosis, 98.2% were over 10 years old<sup>1</sup> and the prevalence rate of MDR-TB was estimated at 1.1% of the total cases of tuberculosis registered at Sinan between the years 2016 and 2018, with a number of patients very close to the estimated by the measured demand, a total of 943 patients.

The time horizon used in the analysis was demarcated in 5 years, as required by the technical area of the Ministry of health, considering the natural history of TB-MDR. The method used to estimate costs was based on micro-costing approaches. Only the direct medical costs of treatment related to the costs of acquiring cycloserine and terizidone were considered for the offer of a treatment with these drugs to a cohort of 716 patients during 20 months of treatment. With the monthly consumption of 84,221 capsules of 250 mg from each medicine in the respective base case scenarios.

The costs of routine outpatient follow-up, laboratory tests and radiodiagnosis, hospitalization and human resources involved were not considered, seeing that they would be the same in both scenarios. The cost of the acquisition of cycloserine was obtained from rates for May 2019, found in the Global Drug Facility - GDF and the cost for the acquisition of terizidone was informed by the Department of Pharmaceutical Assistance and Strategic Inputs - DAF of the Secretariat of Science, Technology and Strategic Inputs form de the Ministry of health - SCTIE/MS. The price for the 250 mg tablet of cycloserine was estimated at USD 1.66 per capsule. The price of the blister containing 100 capsules may vary from USD 19.25 to USD 26.80, according to the Global Drug Facility (GDF) catalog on May 2019<sup>2</sup>.

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<sup>1</sup><http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sinanet/cnv/tubercbr.def>

<sup>2</sup><http://www.stoptb.org/assets/documents/gdf/drugsupply/GDFMedicinesCatalog.pdf>

the Department of Pharmaceutical Assistance and Strategic Inputs<sup>3</sup> reported that the price of terizidone, 250 mg tablet, in the contract no. 114/2017, signed with the company<sup>4</sup> for the purchase of 1,155,050 capsules of the drug, was € 1,105/capsule. The price paid by the Ministry of Health for a terizidone capsule was R \$ 4,000. The total price of the contract was R\$ 4,620,315.51<sup>5</sup>. DAF also reported that the average monthly consumption (CMM) of the drug in 2018 was 84,221 capsules. For this economic analysis, the dollar and euro values were converted to Real, considering the official quotation of the respective currencies closed on May 2, 2019.

The assumptions made in this study for carrying out the cost-minimization and budgetary impact analysis, based on the evidence found in the results of the literature review and official information passed on by the Ministry of Health and international bodies, are described in table 1.

Variables	Estimatives	Sources
Effectivity of cycloserine a- Treatment failure or relapse outcome; b- Death outcome.	RR 0.6 IC 95% (0.4 - 0.9) RR 0.6 IC 95% (0.5 - 0.8)	WHO
Effectivity of terizidone a- Treatment failure or relapse outcome; b- Death outcome.	RR 0.6 IC 95% (0.4 - 0.9) RR 0.6 IC 95% (0.5 - 0.8)	WHO
Cycloserine cost	R\$ 6,58	GDF <sup>1</sup> 250 mg dose
Terizidone cost	R\$ 4,90	DAF <sup>2</sup> 250 mg dose
TB treatment cost	R\$ 82,40	SIGTAP (2019 <sup>th</sup> daily rate)
Treatment abandonment rate	10,80%	Brasil
Mortality rate	3,85% 3,64% - 6,68%	DATASUS (2016 to 2018)
Cure rate	70,07% 51,72 - 71,04	DATASUS (2016 to 2018)
TB-MDR incidence rate	0,52 /100.000 citizen	Brasil, 2017 (consideraing 2018 and 1100 new cases)
TB-MDR prevalence rate	1,1% 1,19 - 1.90	DATASUS (2016 to 2018)
Average number of patients/year undergoing MDR-TB treatment	1013	DAF (2017 and 2018)
Average of patients/year using terizidone	716	DAF (2017 and 2018)
Monthly consumption of terizidone	84.221 capsules	DAF
Duration of treatment	20 months	Brasil, 2018

**Table 1:** Assumptions made in the analyzes. **Source:** The authors.

<sup>1</sup>Global Drug Facility (GDF), november 2018 (USD 1,66/capsule and dollar exchange rate at R\$ 3,965 on 5/2/2019).

<sup>2</sup>General Coordination of Pharmaceutical Assistance and Strategic Medicines - CGAFME, of the Secretariat of Science, Technology and Strategic Inputs - SCTIE / Ministry of Health - MS.

<sup>3</sup>General Coordination of Pharmaceutical Assistance and Strategic Medicines - CGAFME, of the Secretariat of Science, Technology and Strategic Inputs - SCTIE / Ministry of Health - MS.

<sup>4</sup>General Coordination of Pharmaceutical Assistance and Strategic Medicines - CGAFME, of the Secretariat of Science, Technology and Strategic Inputs - SCTIE / Ministry of Health - MS.

<sup>5</sup>The Euro price at the time of the contract was formalized in R\$ 3.62

For the cost-minimization analysis the costs of acquiring cycloserine and terizidone, the monthly consumption of terizidone and the duration of treatment were considered (Table 1). The variables imputed in the decision tree are described in table 2. No evidence was found about the difference in the effectiveness of the evaluated technologies and the outcomes for the reduction of treatment failure or relapse rates and reduction of the mortality rate. Only one outcome, the reduction of mortality rate, was used as a variable in the analysis, considering it as a critical outcome.

Name	Description	Values
Cons_Med_Mensal	Average monthly drug consumption	84.221 (unit)
Cost_Cicloserina	Cost of a 250 mg cycloserine tablet	6,58 (reais)
Cost_Terizidona	Cost of terizidone 250 mg tablet	4,90 (reais)
Efet_Reduo_Mort_Interv	Effectiveness of interventions for the mortality outcome	0.6 (%)
Temp_Tratamento	Duration of treatment	20 (months)

Table 2: variables imputed in the decision tree.

Source: The authors.

Results

After the Roll Back of the Decision Tree, as shown in figure 1, the incorporation of cycloserine, minimized the costs of treating MDR-TB in the base case.

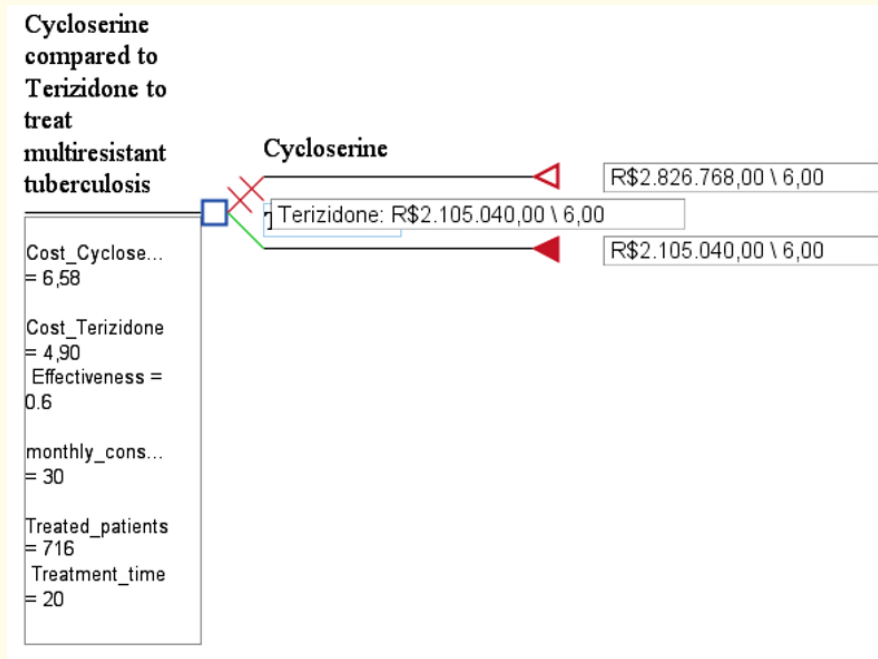


Figure 1: Decision tree after roll back. Source: The authors

The result in the cost-minimization analysis shows that the replacement of terizidone by cycloserine in the therapeutic scheme of MDR-TB, in the base case, may represent an incremental cost for the Ministry of Health, in order of R\$ 2,829,825.60 to meet a monthly consumption of 84,221 capsules of the drug. To address the uncertainties and assess the vigour of the model, two sensitivity analyses were performed. The Tornado Diagram, to assess the impact of variables on the model results, and a Decision Tree, to assess the impact of the number of TB-MDR patients treated annually [6].

For the first sensitivity analysis, the Tornado Diagram (Figure 2), was used to identify the variables that most impact incremental cost, in the cost-minimization model, considering the average monthly consumption of drugs in the base case, on which, was applied a reduction of 10.80% in the determination of the lowest monthly consumption, referring to the rate of treatment abandonment (75,125,131 to 84,221.00 capsules). Regarding the cost of the alternatives, one tablet of cycloserine and terizidone, knowing that they are drugs paid in foreign currency, a discount rate of 5% was applied to define the lowest amount paid: R\$ 6,251 to R\$ 6.58 for cycloserine and R\$ 4.665 to R\$ 4.90 for terizidone. For the treatment time it was considered a minimum of 18 and a maximum of 20 months.

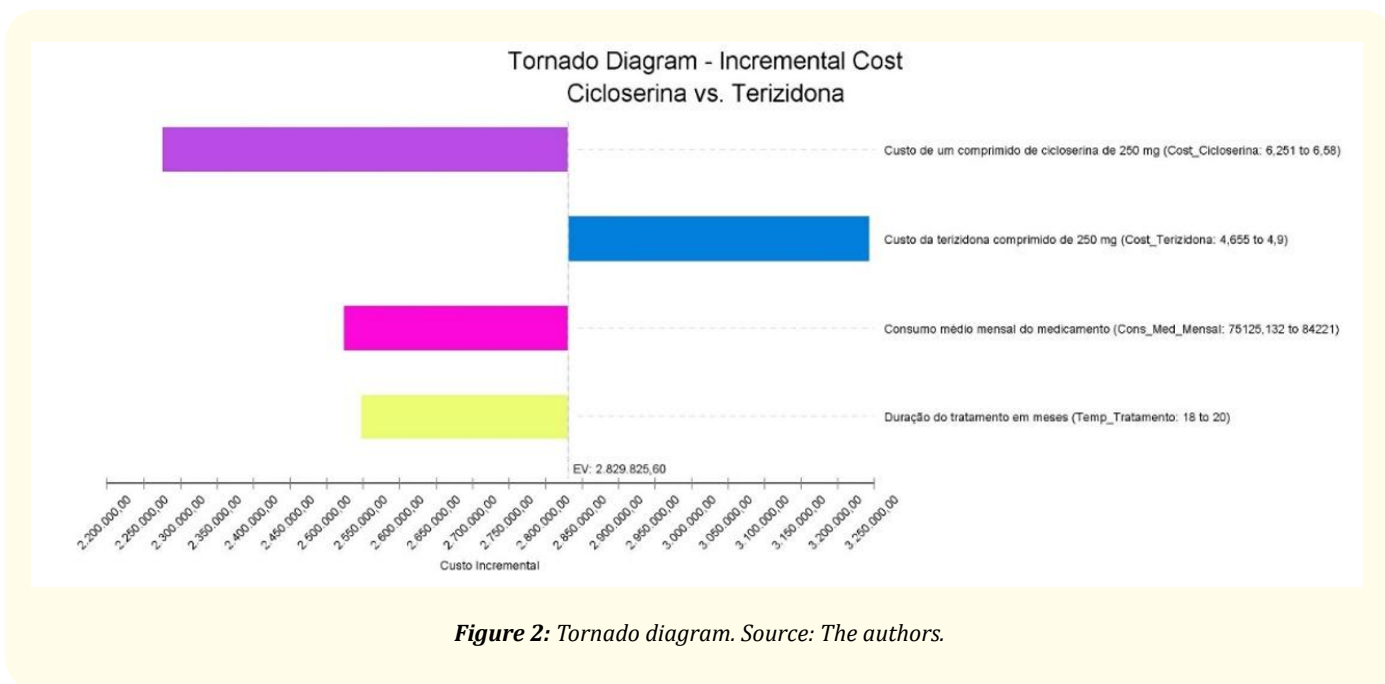


Figure 2: Tornado diagram. Source: The authors.

The Diagram shows that the variables related to costs for the purchase of cycloserine and terizidone are those that most impact the model, considering the expected value (EV) for the incremental cost, of R\$ 2,829,825.60. The second sensitivity analysis aimed to address parametric uncertainty. For this, were substituted the variable Average monthly consumption of the drug (Cons\_Med\_Mensal) in the decision tree model, with the variable number of TB-MDR patients treated per year (Num\_Pac\_Trat), adding the variable amount of the dose of medicine received per month (Num\_Caps\_Mes). Therefore, this sensitivity analysis considered the cost of treating MDR-TB for a cohort of 716 patients and not the average consumption of drugs demanded monthly for the treatment of patients with MDR-TB in SUS.

To estimate the need for drugs to treat this cohort of patients, it was considered that each patient, over 30 days/month, received a daily dose of 250 mg of medicine, 01 capsule/day, during the 20 months of treatment, estimated from the average number of patients who received terizidone between the years 2017 and 2018 with no abandonment of the treatment. After the Rollback of the Decision Tree, the sensitivity analysis revealed that the option for cycloserine remains unable to minimize the costs of treating patients with MDR-TB, even if we consider the number of patients who received terizidone between 2017 and 2018 instead of the average monthly consumption (Figure 3).

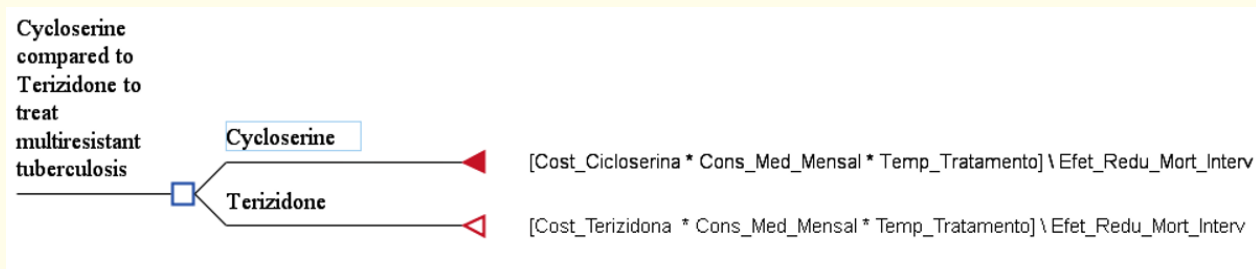


Figure 3: Decision tree after Roll Back in the sensitivity analysis. Sources: The authors.

The result in this sensitivity analysis shows that the replacement of terizidone by cycloserine in the therapeutic regimen of MDR-TB, in the base case may represent an incremental cost for the Ministry of Health, of R \$ 721,728.00, despite the fact that there was a reduction of R\$ 2,108,097.60 (75%) in relation to the incremental cost in the base case, to meet the monthly consumption of cycloserine, which was R\$ 2,829. 825.60. The 5% rate of inflation was applied cumulatively over the time horizon. No discount rates were applied. The cost of tuberculosis treatment per day was estimated at an estimated value of R \$ 82.40 (SIGTAP in 2019) and a restriction rate of 70.69% of the population of interest initially defined by the measured demand method (1013 patients). There were no factors that could impact the patient’s demand for the medication.

To clarify, the scenarios used were: Reference scenario = 100% use of terizidone; Alternative scenario 1: Worst scenario = 100% use of cycloserine; Alternative scenario 2: Treatment abandonment = 10.8% of treatment abandonment and Alternative scenario 3: Best scenario = 50% use of cycloserine. The 5-year time horizon took into account that, in the first year, the demand for cycloserine will be 85%, assuming the assumption that, in that year, 15% of patients would continue to receive terizidone, which remained in the stock, after acquisition of cycloserine. In the following years, 2<sup>nd</sup>, 3<sup>rd</sup> and 4<sup>th</sup>, this demand would increase to 90%, 95% and 99%, respectively. From the 5<sup>th</sup> year, the demand would become 100%. These estimates were arbitrary and considered that, of 1,155,050 terizidone capsules acquired in the last contract signed between the Ministry of Health and the supplier company (Collect Importation and comercy LTDA), only 37.20% (429,600 capsules) were used to treat, in average, 716 patients/year during the 20 months of treatment.

**Discussion**

The Tuberculosis Eradication Strategy proposes the inclusion of socioeconomic interventions basically focused on disease prevention and control and social protection for patients. Thus, it aims to minimize the high direct and indirect costs of treatment and eliminate the stigma and discrimination associated with certain population groups, aspects that need to be considered in the fight against tuberculosis in Brazil [2-9].

The current concern in SUS, could not be different, it is with the sustainability of the system, in which the ability to maintain health benefits over time is determinant for the quality of care and assistance provided to the population. We know about budget limitations and how much these limitations require managers to allocate resources efficiently. Therefore, it is not lawful for scarce resources to be allocated in the incorporation of therapeutic or diagnostic interventions that result in benefits of small or zero magnitude [3].

National studies that evaluated direct and indirect costs for patients, including multidrug-resistant forms, estimated a cost for family members and the health system to be approximately R\$ 293.91 and the average cost for families to be R\$ 3,119.40 per treated case. The costs for families could compromise from 33% to 48% of family income with expenses related to tuberculosis. For the treatment of a multi-resistant patient the cost was 27 times higher. The costs for public services corresponded to 65% in hospitalizations, 32% in treatment and only 3% in prevention. The costs for public services corresponded to 65% in hospitalizations, 32% in treatment and only 3% in prevention [7-10].

We cannot ignore the fact that the investments in the incorporation of new technologies to confront TB in the Health System (SUS) have favored the achievement of quality and effectiveness in the diagnosis and treatment of the disease [11].

These studies confirms that the costs of the disease, regardless of anything, must be known by managers and health professionals in the decision-making process, in order to obtain better results in relation to the control of the disease, seeking alternatives for the application of resources that can effectively contribute, also, to mitigate the financial impact for families, since intangible costs cannot be measured.

Studies of cost and economic implications related to economic assessments comprise a large group of methods used for the evaluation of health technologies. As no clinical evidence was found that cycloserine is not superior to terizidone, in terms of effectiveness, a cost-minimization assessment was then made, changing the initial proposal in this study. Although cycloserine and terizidone may be bioequivalent drugs, terizidone is analogous to cycloserine. As it were considered only efficacy outcomes, it may be that, in terms of safety, with regard to the occurrence of adverse reactions, one drug may be superior to the other and therefore offer greater benefits.

Two therapeutic strategies for the treatment of patients with MDR-TB were compared, each using one of these drugs with similar effectiveness for the analyzed outcomes in order to answer the following question: "Which alternative has the lowest cost in the treatment of patients with MDR-TB, cycloserine or terizidone?". The difference in costs between the alternative drugs that were assumed to produce equivalent results was calculated after conducting a systematic review, where differences were only in the costs incurred, with the lowest cost drug being preferable.

The cost-minimization analysis compared only the costs of medicines and the analysis of the budgetary impact was carried out, considering different possible scenarios. In the Decision Tree model used for cost-minimization analysis, it was possible to predict that the incorporation of Cicloserina may represent a cost increase of R \$ 2,829,825.60 to meet the demand of patients with MDR-TB, therefore being, the most cost-effective alternative. Sensitivity analysis demonstrated that the option for cycloserine continues to increase the costs of treating patients with MDR-TB. All the alternative scenarios purchased from the reference scenario resulted in cost increases ranging from 25.7% to 28.8% over the five-year time horizon.



The eventual incorporation of cycloserine to serve 100% of the population of interest (alternative scenario 1) in this horizon, represented the largest increase in costs in the analysis (28.8%). The smallest increase observed in the analysis (25.7%) was in the total costs of offering cycloserine for only 50% of the population of interest (alternative scenario 3). According to the assumptions adopted in the model, it is estimated that the values obtained in the analysis of the budgetary impact for eventual incorporation of cycloserine in the treatment of MDR-TB by SUS exceed R \$ 9 million in the 5-year time horizon, and may reach more 12 million, depending on the compared scenarios.

The annual value of the impact, focusing on the alternative scenario 1 and the reference scenario, varied between R\$ R \$ 377,270.70 (2019) and R\$ 719,030.84 (2023). Although there are no defined thresholds for budgetary impact in Brazil and the values calculated in this budgetary impact analysis are well below R\$ 85 million, these values can be considered high for the system according to the distribution of values resulted from the history of drug recommendation reports evaluated by Conitec.

It should also be considered that new studies are suggesting that other drugs can be more effective in the treatment of tuberculosis and therefore saving resources for the incorporation of new drugs that can really offer greater benefits to the patient is a good example of thinking about the opportunity cost of investing in the incorporation of cycloserine [12,13].

Even if the results of this study could be considered feasible and valid and the results achieved could be used to inform the decisions of the Ministry of Health in the national level, given the information and knowledge learned until here, some limitations need to be considered and discussed. No methodological problems were found, but the scarcity and the reliability of the evidence obtained regarding the effectivity of the interventions is worth mentioning.

A single study, retrieved from the systematic review, assessed the efficacy of cycloserine and terizidone for the outcomes in reducing mortality rates and failure or relapse of treatment for MDR-TB regimens, demonstrating that there is no difference between medications. It is a study developed in a foreign country, which may compromise the power of extrapolating its results to the Brazilian reality, whose rate of treatment abandonment is still high.

The fact that this study considered only the efficacy outcomes without analyzing the safety ones, should be take as a limitation, even though the evaluated drugs are bioequivalent, and despite the fact that scientific literature referenced to describe the pharmacological characteristics of the drugs evaluated did not report a difference in terms of adverse effects for none of them.

### Conclusion

In the treatment of tuberculosis, rifampicin is still the main medication applied, for its bactericidal and sterilizing action, being essential for the cure in the standard treatment regimen.

For cases of multidrug resistance, the Ministry of Health has been using terizidone successfully for some years, and the rate of treatment abandonment is an obstacle to be overcome that directly impacts the cure rates of MDR-TB, which is the main evidence of the medicine's effectiveness. The effectivity of terizidone or cycloserine, for the two outcomes analyzed in this study (Reduced failure rates or treatment relapse and reduced mortality rate), according to studies recovered in the systematic review, did not show any difference in effectiveness between them (RR 0.6 IC 95% (0.4 - 0.9) and RR 0.6 CI 95% (0.5 - 0.8) respectively).

It is important to note that the present demand refers to the replacement of terizidone by cycloserine, without any change in the pharmacological regimen already recommended for the treatment of MDR-TB in terms of time or other medications used. Cycloserine can be cost-effective as well as terizidone, but for the Brazilian reality must be considered that the incremental cost of incorporating cycloserine can be R\$ 2,829,825.60, with a budgetary impact that can reach more than 12 million, determining an increase in public spending of 26% to 29% in 5 years.

Therefore, considering that no evidence was found to demonstrate the superiority of cycloserine over terizidone, with regard to the efficacy for the analyzed outcomes, and as the incorporation of cycloserine does not represent any increment of benefit to the treatment, but only in the costs, representing an impact of 26% to 29% in 5 years of increase in public spending, it is not cost-effective to replace terizidone with cycloserine. Thus, before deciding to incorporate cycloserine, which can even be cost-effective, but at a very high cost, the opportunity cost of a R\$ 12 million investment in 5 years must be considered.

When choosing to incorporate this medicine, SUS may, for example, have to stop investing in other actions within TB control programs that could facilitate the identification, for example, of the main risk factors to which patients are exposed with tuberculosis, with a higher risk of abandonment and, consequently, failing to adopt specific strategies to face this problem, thus avoiding new cases of MDR-TB and deaths.

It is believed that the results of this study may inform the decisions of the technical areas of the Ministry of Health, regarding the incorporation or not of cycloserine, considering that it would represent an increase in the costs of treating MDR-TB in SUS, without any additional benefit for the patients and with a budgetary impact that could compromise, in the perspective of cost-opportunity, the attendance and coverage of other demands in the system.

### Recommendation

In face of the results of the study, considering that there is no additional benefit, we do not recommend the incorporation of cycloserine as alternative for the treatment of MDR-TB in SUS.

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