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Budgetary impact of incorporating clarithromycin in the treatment of respiratory infection associated with COVID-19

Impacto presupuestario de la incorporación de claritromicina en el tratamiento de la infección respiratoria asociada a COVID-19

Impacto orçamentário da incorporação da claritromicina no tratamento de infecção respiratória associada à COVID-19

Cássio Maia Pessanha[1]
ORCID: 0000-0002-7296-5923
Isabella Barbosa Meireles[1]
ORCID: 0000-0001-7744-1128
Carla Coura[1]
ORCID: 0000-0002-7185-7437
Juliana Batista de Souza[1]
ORCID: 0000-0002-1093-3715
Antônio Augusto de Freitas Peregrino[2]
ORCID: 0000-0002-6617-480X
Roberto Carlos Lyra Silva[3]
ORCID: 0000-0001-9416-9525

[1]Hospital Federal Cardoso Fontes. Rio de Janeiro, Brazil.
[2]Universidade do Estado do Rio de Janeiro. Rio de Janeiro, Brazil.
[3]Universidade Federal do Estado do Rio de Janeiro. Rio de Janeiro, Brazil.

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Corresponding author:
Cássio Maia Pessanha
E-mail: cassiopessanha@yahoo.com.br

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Abstract

This study aimed to estimate the budgetary impact of using clarithromycin as a supporting macrolide in the empirical treatment scheme for patients with Severe Acute Respiratory Syndrome. Budget impact analysis was carried out from the perspective of the Unified Health System, using the Brazilian Budget Impact Analysis Worksheet. Three alternative scenarios and one reference scenario were evaluated. The cost over five years in the baseline scenario was R$2,504,887.92. The incorporation of clarithromycin in alternative scenarios may represent an average incremental cost greater than 22% of the budget available for the acquisition of azithromycin in five years, and its offer to all patients in the hospital may be economically unfeasible, without prejudice to the care of other demands.

Descriptors: Pandemic, COVID-19, Unified Health System, Budgetary Impact Analysis, Drug Therapy.

Resumén

Este estudio tuvo como objetivo estimar el impacto presupuestario del uso de claritromicina como macrólido de apoyo en el esquema de tratamiento empírico para pacientes con síndrome respiratorio agudo severo. El análisis de impacto presupuestario se realizó desde la perspectiva del Sistema Único de Salud, utilizando la Hoja de Trabajo de Análisis de Impacto Presupuestario de Brasil. Se evaluaron tres escenarios alternativos y un escenario de referencia. El costo a cinco años en el escenario base fue de R $ 2.504.887,92. La incorporación de claritromicina en escenarios alternativos puede representar un costo incremental promedio superior al 22% del presupuesto disponible para la adquisición de azitromicina en cinco años, y su oferta a todos los pacientes del hospital puede resultar económicamente inviable, sin perjuicio de la atención de otras demandas.

Descriptores: Pandemia, COVID-19, Sistema Único de Salud, Análisis de Impacto Presupuestario, Quimioterapia.

Resumo

Objetivou-se estimar o impacto orçamentário do uso da claritromicina como macrolídeo coadjuvante no esquema de tratamento empírico de pacientes com Síndrome Respiratória Aguda Grave. Realizada análise de impacto orçamentário na perspectiva do Sistema Único de Saúde, utilizando a Planilha Brasileira de Análise de Impacto Orçamentário. Foram avaliados três cenários alternativos e um de referência. O custo em cinco anos no cenário de referência foi de R$2.504.887,92. A incorporação da claritromicina nos cenários alternativos pode representar um custo incremental médio superior a 22% do orçamento disponível para a aquisição de azitromicina em cinco anos, podendo ser economicamente inviável a sua oferta para todos os pacientes no hospital, sem que houvesse prejuízo no atendimento de outras demandas.

Descritores: Pandemias; COVID-19; Sistema Único de Saúde; Análise de Impacto Orçamentário; Terapia Medicamentosa.

Introduction

In November 2019 an outbreak of respiratory disease, caused by the new coronavirus (SARS-CoV-2), was detected in the city of Wuhan, China. In a few months, thousands of cases of COVID-19 were confirmed, which resulted in countless deaths. In March 2020, the new coronavirus had spread to hundreds of countries, continuing to cause respiratory illness and death, especially in risk groups such as the elderly, pregnant women, immunocompromised and others. This epidemic stands out for its rapid spread, severity, and difficulties to contain it.

As a result, the World Health Organization (WHO) declared a pandemic for the new coronavirus on March 11, 2020, and since then, countries have been making huge efforts to contain the outbreak and reduce the lethality caused by the disease. The main measure instituted for pandemic control was social isolation accompanied by surveillance of cases based on constant epidemiological analysis.[1]

The clinical profile of the disease is not fully established, requiring further investigation and time for its characterization. Thus, clinical evaluation and treatment have been established based on the definitions of flu syndrome (SG) and severe acute respiratory syndrome (SRAG), based on the Ministry of Health's Influenza Protocol.[2,3]

In this context, SARS presents itself as one of the most common complications, being defined by the presence of dyspnea or the following signs of severity: peripheral oxygen saturation (SpO2) lower than 95% in room air; signs of respiratory distress or increased respiratory rate assessed according to age; worsening in the clinical conditions of the underlying disease; hypotension in relation to the patient's usual blood pressure; individual of any age with acute respiratory failure during the seasonal period.

Despite the rapid advance of this pandemic, specific drugs against its etiological agent have not yet been identified. There is a consensus, however, that pharmacological measures (or not) should be implemented for the clinical management of patients.

Patients with SARS symptoms should receive an antimicrobial regimen associated with influenza treatment until the etiology is established. Empirical use should be considered based on the suspicion of associated bacterial infection, or in those cases where there is a suspicion of healthcare-related infection (HAI) and should follow the local recommendation for treatment based on the sensitivity profile and using drugs with spectrum for multiresistant bacteria.[3-6]

Nationally, the recommendation for the management of community-acquired pneumonia (CAP) is the use of third generation cephalosporins (ceftriaxone or cefotaxime) or ampicillin/sulbactam associated with a macrolide (azithromycin or clarithromycin) during the treatment of hospitalized patients (infirmary/intensive care unit).[7]

Macrolides are commonly used in the treatment of respiratory tract infections, with particular activity against atypical pathogens, in addition to Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis.[8] Among them, clarithromycin is an active antimicrobial against typical and atypical respiratory pathogens, including mycobacterial infections. It is considered more active, presenting greater bioavailability compared to azithromycin (55% vs 37%) and reaching peak serum concentration more quickly (1.8 hours vs 2.5 hours).[9]

The COVID-19 pandemic presents unusual situations in the 21st century, if the absence of specific treatments was not enough. It threatens the entire global supply chain, especially that linked to healthcare products and medicines.[10] Since its inception, interruptions in the supply chain and the reduction in stocks of strategic supplies and medical equipment have worried health facility managers, regardless of the available financial resources.[11]

The shortage of drugs is a major public health problem, and the COVID-19 pandemic has the potential to further aggravate the lack of essential drugs - which can compromise the quality of care and pose a threat to patient safety when the healthcare system is overwhelmed by extremely critical patients.

They are drugs of different classes, especially sedatives, anesthetics, and neuromuscular blockers – those commonly needed in patients who are on mechanical ventilation. Concomitant use should be considered in patients with respiratory failure due to other etiologies, who require intensive care and undergo emergency surgery under general anesthesia.

The pandemic affected the entire drug manufacturing and export process, revealing the fragility of the sector's supply chain. Many active pharmaceutical ingredients (IFA) used in the production of these drugs come from countries affected by COVID-19, such as China. In addition, many generic drugs are manufactured and imported from other countries, such as India, which are also heavily impacted by the current pandemic.[12,13]

It is necessary for managers to consider the need for strategic planning to ensure global production, access, protection and monitoring of supply chains in the face of an inevitable shortage, rising costs and national hoarding, which is why the impact should also be considered. budget that may result in the incorporation of technological alternatives.[10]

In the case of drugs, considering the variety of macrolides available on the Brazilian market, different alternatives could be considered as a therapeutic option for the treatment of patients with SARS, which can generate uncertainties regarding the best available alternative in terms of efficacy and security and in terms of economic viability.

Two of the uncertainties that are always present in the resource allocation process and that must be considered concern how much the incorporation of a technology can impacts the budget, and what is the opportunity cost of this incorporation. Opportunity cost refers to the benefit potentially lost from adopting one intervention over another.[14]

It is believed that the study results can support decision-making, providing managers with an estimate of

the budgetary economic impact resulting from the incorporation of these drugs, helping to allocate resources in times of the current pandemic in the SUS.

In view of the above, the question of this research was defined as follows: what is the budgetary impact and the opportunity cost of using clarithromycin in the management of patients with SARS, considering a time horizon of 5 years?

The aim of this study, therefore, was to carry out a budget impact analysis of the use of clarithromycin as the macrolide of choice associated with ceftriaxone in the empirical treatment scheme for pneumonia in patients with SARS, from the perspective of the Unified Health System (SUS).

Methodology

This is a Health Technology Assessment (HTA) study that can be understood as a comprehensive way of researching the technical (almost always clinical), economic and social, short- and long-term consequences of the use of health technologies, as well as its direct and indirect effects, both desirable and undesirable.[15]

The problem of the study emerged from the possibility of empirically treating secondary infections in patients with SARS by COVID-19 using clarithromycin associated with third-generation cephalosporin (ceftriaxone), replacing another macrolide (azithromycin) - whose safety and efficacy are similar in the scheme proposed therapeutic.

The study was designed as a budget impact analysis and used the Brazilian Budget Impact Analysis Worksheet (PBIO), following the recommendations of the Economic Evaluation Methodological Guideline and the Budget Impact Analysis Methodological Guideline. The time horizon used in the analyzes was 5 years.[14,16]

The base case was composed of two scenarios: the reference, which uses azithromycin as the macrolide of choice in the empirical treatment scheme for pneumonia in SARS patients, and alternative scenarios, using clarithromycin.

The perspective of the study was that of the SUS at the local level.

The study population consisted of a hypothetical cohort of patients of both sexes, aged 10 years or older, diagnosed with SARS by COVID-19, assisted by SUS, in a medium-sized federal hospital in the public health network. located in the city of Rio de Janeiro.

The cohort was estimated using the measured demand method, considering the number of individuals who demanded treatment with azithromycin during their stay in that hospital. During the first four months of 2020, a total of 152 patients used azithromycin, which is why this was considered the measured demand and the size of the cohort in the analysis.

The method used for cost estimation was based on the micro costing approach. Only the cost of each drug in the base case was considered. Other direct medical costs of treatment were not considered. The costs are related to the acquisition of clarithromycin and azithromycin to offer treatment with these drugs to a cohort of 152 patients for 7 days, requiring 14 vials of clarithromycin 500 mg or 7 vials of azithromycin 500 mg.

Likewise, the cost of acquisition of ceftriaxone (adjuvant treatments), which is common in the association both in the reference and alternative scenarios, was considered. For the studied cohort, during 7 days of treatment, 14 vials of ceftriaxone would be needed per individual.

The costs of laboratory tests and radiodiagnosis, hospital admission and the human resources involved were not considered, as they would be the same in both base-case scenarios, since there is no difference in effectiveness between the technologies evaluated.

The drug acquisition costs were obtained from the Hospital Management System HOSPUB (version 13.0.0.1), used in the studied institution. The average prices of vials of clarithromycin 500 mg, azithromycin 500 mg and ceftriaxone 1 g were, respectively, R$ 24.98; BRL 25.76; and R$7.81 (amounts verified in the HOSPUB system, on June 6, 2020).

The assumptions made in this study to carry out the budget impact analysis, based on the evidence found in the results of the literature review, official information, and records in hospital management systems, are described in Chart 1.

Chart 1. Assumptions made in the analyses. Rio de Janeiro, RJ, Brazil, 2020

Time horizon: 5 years	**Reference scenario:** 25% use of clarithromycin
	Alternative scenario 1: 90% use of clarithromycin
Population sample: 152 patients (measured demand)	**Alternative scenario 2:** 75% use of clarithromycin
7 days of treatment (14 vials of clarithromycin 500 mg or 7 vials of azithromycin 500 mg)	**Alternative scenario 3:** 50% use of clarithromycin
No discount fee	**Average inflation for the period:** 4%

For the purposes of calculating the budget impact, the Ministry of Health's Brazilian Budget Impact Sheet for Health Technologies was used, developed for pharmaceuticals, available for download on the website of the Brazilian Health Technologies Network, and the Budget Impact Manual.[14,16]

Results

This study analyzed the budgetary impact and opportunity cost of incorporating clarithromycin as an alternative drug therapy in the treatment of patients with COVID-19 infection, over a five-year time horizon, from the perspective of a medium-sized hospital in the federal network.

The option for a time horizon of five years considered that the course of the current pandemic would be reasonably long – since the discovery of vaccines and the immunization of the entire world population would be slow processes.

The analysis of the budgetary impact was carried out considering the scenarios described in Chart 2. The average rate of 4% of inflation was applied cumulatively over the time horizon (3% in the first year and 4% in subsequent years). No discount rates applied.

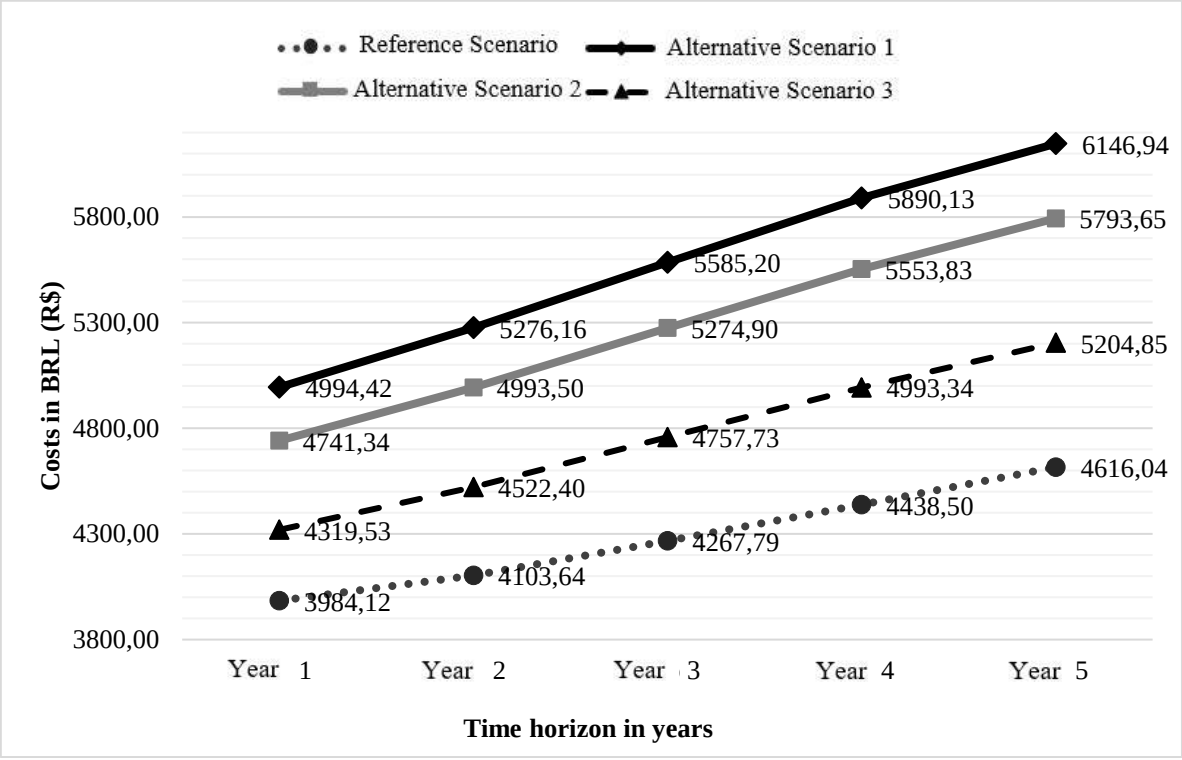
The cost per treatment with empirical antibiotic therapy in patients with SARS was considered at an estimated value of R$ 459.06 (average price informed by the HOSPUB system), without considering any restriction on the use of clarithromycin by the population of interest, initially defined by the demand method measured (152 patients). No factors that could impact the demand of patients for the drug were considered.

Chart 2. Scenarios considered in the sensitivity analysis. Rio de Janeiro, RJ, Brazil, 2020

Reference scenario	25% use of clarithromycin
Alternative scenario 1	90% use of clarithromycin
Alternative scenario 2	75% use of clarithromycin
Alternative scenario 3	50% use of clarithromycin

The 5-year time horizon considered that the demand for clarithromycin will be 83% in the first year, assuming that, in that year, 17% of patients will continue to receive the azithromycin that remained in the stock, after the acquisition of clarithromycin. In the following years, 2nd, 3rd, 4th, this demand would increase to 90%, 95% and 99%, respectively. From the 5th. year, the demand would be 100%.

Figure 1. Evolution of annual costs per patient/scenarios. Rio de Janeiro, RJ, Brazil, 2020



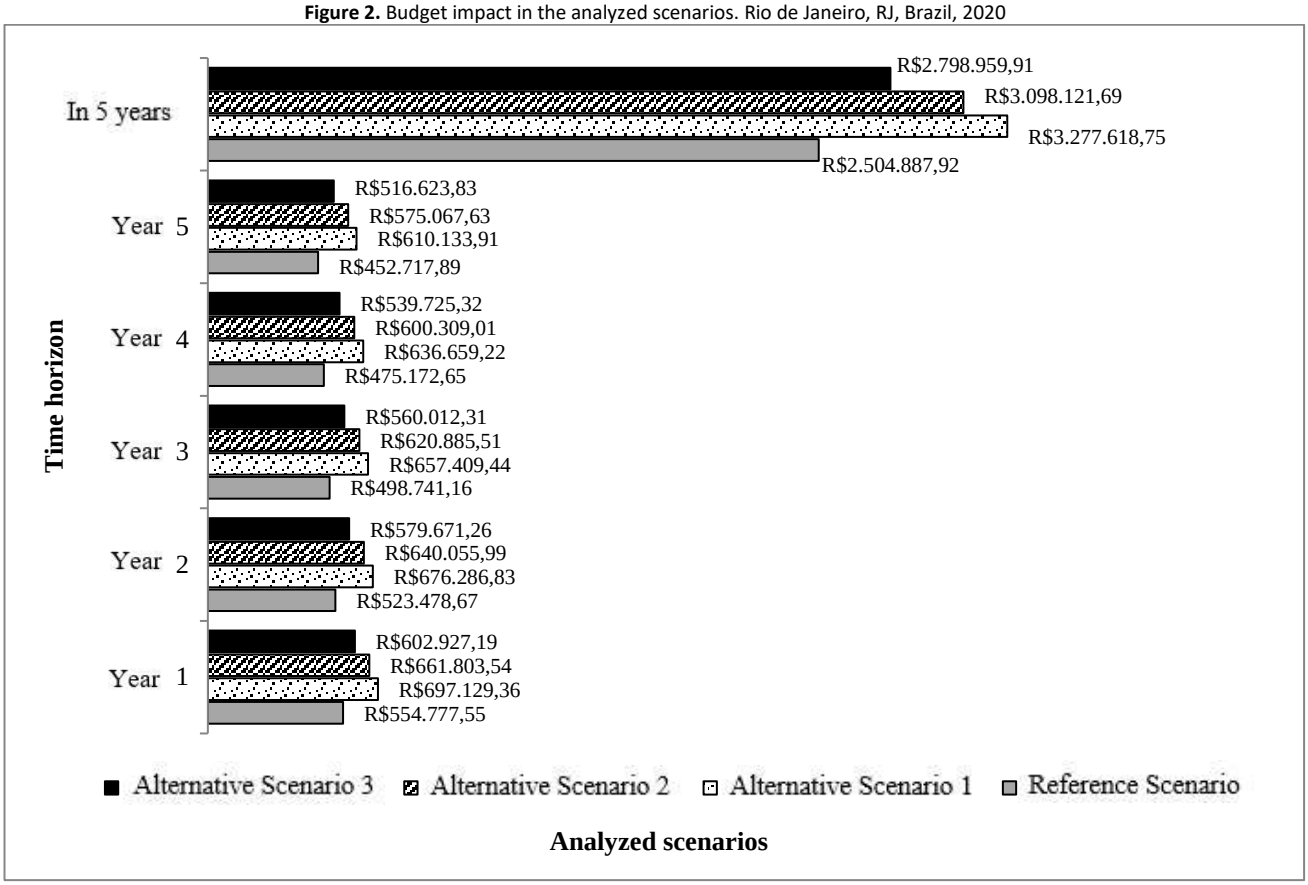
These estimates are real-world and refer to the demand for medicines to treat 152 patients who were treated during the first four months of 2020 in a medium-sized hospital in the public health network in Rio de Janeiro.

The evolution of the annual cost in the reference scenario per patient, considering economic adjustments, is described in Figure 1. In the reference scenario, the cost of using azithromycin can vary over the 5 years, from R$3,984, 12 in the first year, at R$ 4,616.04 in the fifth.

In alternative scenario 1, which considers the use of clarithromycin instead of azithromycin to treat 90% of COVID-19 cases that could require antibiotic therapy, costs can range from R$4,994.42 in the first year, to R$6,146, 94, in the fifth year.

The budgetary impact, considering the reference scenario and each of the 03 possible alternative scenarios (alternative scenario 1, alternative scenario 2 and alternative scenario 3) is described in Figure 2.

Figure 2. Budget impact in the analyzed scenarios. Rio de Janeiro, RJ, Brazil, 2020



In the analysis, the following variables were considered: population considered; annual incidence of the disease; weighted annual mortality for the scenario; average population/year; cost/scenario per individual/year; Gross Budget Impact (IO) for the scenario; Inflation-adjusted Budget Impact.

In five years, the inflation-adjusted budget impact was R$2,504,887.92 in the baseline scenario. In alternative scenario 1, it was R$ 3,277,618.75; in alternative scenario 2, the cost was R$ 3,098,121.69; and in alternative scenario 3, the cost was R$2,798,959.91 (Figure 2).

The incremental or differential budget impact informs the additional cost of incorporating clarithromycin into the base case compared to using azithromycin.

To estimate the incremental budget impact in the base case, the differences in budget impact values between two scenarios were calculated. The alternative scenarios were compared with each other and in relation to the reference scenario. The results are shown in Figure 3.

In the alternative scenarios, compared to the reference scenario, the variation in average percentage terms over 5 years was 11.9% ± 2% (alternative scenario 3 versus reference scenario) to 31% ± 3% (alternative scenario 1 versus scenario of reference).

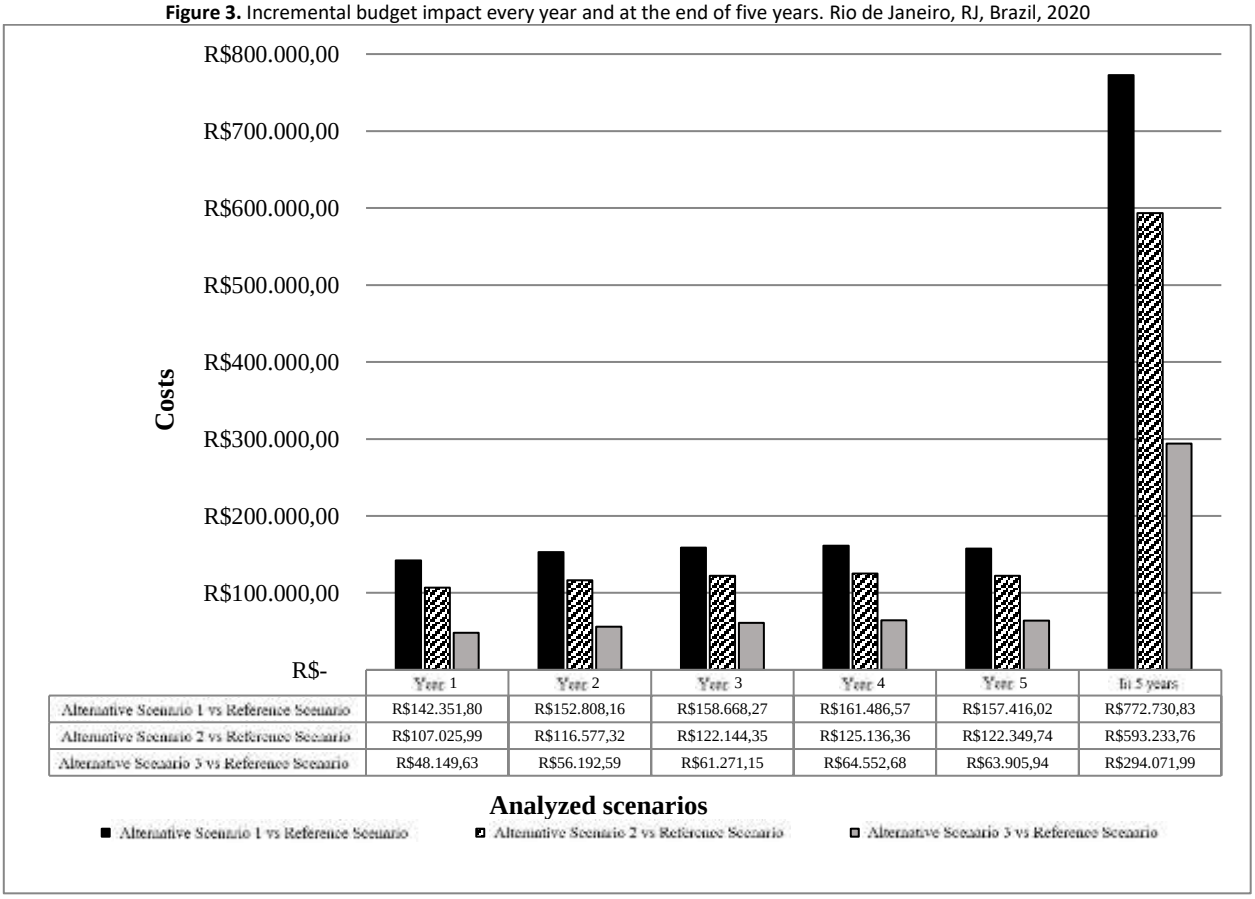
The incremental cost after 5 years, in absolute numbers, reached values in the order of R$ 772,730.83 in the comparison between alternative scenario 1 and the reference scenario. In the comparison between alternative scenario 2 and the reference scenario, the incremental cost was BRL 593,233.76 and, in the comparison between alternative scenario 3 and the reference scenario, the incremental cost was R$ 294,071.99.

The eventual incorporation of clarithromycin to serve 90% of the population of interest (alternative scenario 1) over 5 years may represent an increase in costs greater than 34.8% in relation to the costs in the reference scenario. The smallest increase observed in the analysis (11.4%) was in the total costs of offering clarithromycin to only 25% of the target population (alternative scenario 3).

Therefore, according to the assumptions made in the analysis, it is estimated that, annually, the costs revealed in the budget impact analysis for the eventual incorporation of clarithromycin in empirical antibiotic therapy in patients with SARS by SUS may vary between R$ 294,071.99 to R $772,730.83, depending on the scenarios compared.

The annual cost for incorporating clarithromycin, considering alternative scenario 1 and the reference scenario, ranged from R$ 142,351.80 (year 1) to R$ 157,416.02 (year 5). Considering alternative scenario 2 and the reference scenario, the variation was from R$ 107,025.99 (year 1) to R$ 122,349.74 (year 5). Finally, considering alternative scenario 3 and the reference scenario, the variation was from R$ 48,149.63 (year 1) to R$ 63,905.94 (year 5).

Figure 3. Incremental budget impact every year and at the end of five years. Rio de Janeiro, RJ, Brazil, 2020



	Year 1	Year 2	Year 3	Year 4	Year 5	In 5 years
Alternative Scenario 1 vs Reference Scenario	R$142.351,80	R$152.808,16	R$158.668,27	R$161.486,57	R$157.416,02	R$772.730,83
Alternative Scenario 2 vs Reference Scenario	R$107.025,99	R$116.577,32	R$122.144,35	R$125.136,36	R$122.349,74	R$593.233,76
Alternative Scenario 3 vs Reference Scenario	R$48.149,63	R$56.192,59	R$61.271,15	R$64.552,68	R$63.905,94	R$294.071,99

Discussion

The new coronavirus pandemic presented the world with a new scenario, full of uncertainty and a lot of fear. For health professionals, it provoked many questions regarding specifically how to prevent the spread of the disease and how to treat infected patients.

The pandemic also revealed how paradoxical it is that Brazil has one of the largest markets in the world, that it is the only country to have a universal health system that serves a population of over 200 million inhabitants (proposing equity and comprehensiveness), of having one of the largest chemical production parks in the world and, even so, experiencing serious restrictions in the development of the chemical and pharmaceutical sectors. During the pandemic, this paradox proved to be a huge weakness in our health system, which aims to be universal.

The health crisis showed the weaknesses of our Economic and Industrial Health Market. Brazil had enormous difficulties in the acquisition of medicines, personal protective equipment, biomedical equipment, in addition to the lack of adequate beds to provide the necessary care to patients with COVID- 19 - exposing weaknesses in various sectors that make up the health system supply chain.[17]

Since then, the current concern in SUS management is with the sustainability and efficiency of the system, ensuring the provision of assistance to the population even with the known budget limitations.

Therefore, it is not appropriate for resources that are already scarce to be allocated to the incorporation of therapeutic or diagnostic interventions that result in benefits of little or no magnitude, during a health crisis caused by a pandemic. The decision-making process regarding the incorporation of health technologies is subject to pressures of different orders. Therefore, the systematic and explicit use of economic evaluation methods in health can make this process more transparent, reducing the occurrence of biases and distortions.[14]

Based on this logic, the present study brought the discussion to the fore, evaluating the budgetary impact of the use of clarithromycin, if it were chosen as a macrolide associated with ceftriaxone in the empirical treatment of pneumonia in patients with SARS due to COVID-19.

Thus, our results revealed the dimension of the impact of choosing this component of treatment over a five-year period, from the perspective of the SUS. Choosing a more advantageous macrolide, with less impact on the budget, guarantees the manager the opportunity to better apply their financial resources and, consequently, treat more users.

To estimate the opportunity cost, three dimensions responsible for major concerns in the management of this pandemic were evaluated: personal protective equipment (PPE), respiratory equipment for the mechanical ventilation of patients in intensive care, and beds in intensive care units (ICU).

In this sense, if we consider the worst-case scenario studied (when we compare alternative scenario 1 vs. the reference scenario) it would be possible, for example, to acquire or fund, at the end of five years, a total of 150,924 units of face protection masks (type N95 or equivalent), 434

new equipment for mechanical ventilation or 4,830 ICU days - considering the support and intensive treatments necessary to maintain the lives of patients with COVID-19.[18,19]

In the best scenario studied, the one with the smallest estimated budget impact, it would be possible to acquire or fund, at the end of five years, a total of 57,436 units of face protection masks (type N95 or equivalent), 165 new equipment for mechanical ventilation or 1,838 daily ICU stays.

Assessing the opportunity cost helps us to understand that, when financial resources are scarce and, especially when living in a country whose health system is universal, such as in Brazil, before deciding to incorporate health technologies, necessary to reduce uncertainties in terms of costs and consequences.

The study showed that, if the country were able to meet 100% of the demand of patients who need clarithromycin as the antibiotic of choice in the empiric treatment scheme for Severe Acute Respiratory Syndrome, the costs could reach, in five years, the value of R $772,730.83.

Final Considerations

The fact that the entire demand for clarithromycin and azithromycin during the period analyzed in our estimate was considered, does not mean that all patients had a confirmed diagnosis of COVID-19 or had severe acute respiratory syndrome (SRAG), which could have overestimated the measured demand and the size of the analyzed cohort.

The fact that invoice prices were considered as a reference for the purchase of medicines is also a limitation of the study, since it may be overestimating or underestimating the costs only the efficacy outcomes, disregarding safety, even if the evaluated medicines are interchangeable. It is noteworthy, however, that the scientific literature referenced to describe the pharmacological characteristics of the evaluated drugs does not present differences in terms of adverse effects.

Given the limitations presented, the extrapolation of the results of this study should be done with due caution.

Access to medicines is an issue that deserves attention, especially in a universal health system such as in Brazil, where the demand is one of the most diversified, ranging from low to high-cost medicines, which is why managers should rely on the best evidence available to inform your decisions regarding the incorporation of this technology from the perspective not only of consequences, but also of costs.

In this sense, the population's access to medicines becomes a central issue for the viability and sustainability of the SUS, and this issue becomes more relevant in situations of pandemic as we currently live.

The results of this study reinforce the need to think about the costs of incorporating alternatives for the drug treatment of patients with COVID-19. The incorporation of clarithromycin in total or partial replacement of azithromycin represented an incremental cost that can be, on average, greater than 22% of the budget available for the acquisition of azithromycin, representing an additional average cost of R$ 1,106,691.05, to over 5 years.

The opportunity cost may be unfavorable to the incorporation of clarithromycin to meet 100% of the demand, unless there is no other alternative, given the availability of azithromycin on the market, which during the period of the COVID-19 pandemic has been presenting specific problems in the global supply chain.

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