## Full title

Adoption of new therapies in the treatment of hepatitis: a verification of the accuracy of Budget Impact Analysis to guide investment decisions

## Short title

Adoption of new therapies in the treatment of hepatitis: A verification of BIA accuracy

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**ABSTRACT**

**Objectives** Whilst there are good Budget Impact Analysis (BIA) guidelines, studies still register potential bias. Consequently, there is a need to still point out weaknesses and improve their accuracy. To do this, we compared the results between theoretical and Real-World Evidence (RWE) expenditures for medicines for hepatitis C: boceprevir (BOC) and telaprevir (TVR). Whilst both are currently not recommended in treatment guidelines following recent developments, this is an emblematic case because for four years these medicines consumed considerable resources. **Methods** Theoretical results and RWE expenditures were compared regarding the incorporation of BOC and TVR in 2013-2014 into the Brazilian Public Health System. Theoretical values were extracted from Commission for Technology Incorporation Report and RWE expenditures were extracted from the administrative data records using deterministic-probabilistic linkage. **Results** The estimated number of patients treated (BOC+TVR) was 13,012 versus 7,641 (real). The estimated purchase price for BOC was US$6.20 versus US$11.07 (real) and for TVR was US$42.21 versus US$84.09 (average/real). The estimated budget impact was US$285.16 million versus US$128.58 million (real). **Conclusion** This study demonstrates appreciable divergence (US$156.58 million) between the theoretical budget impact and RWE expenditures due to underestimated purchase prices and overestimated populations. The greater the degree of accuracy the more reliable and usable BIAs become for decision making.

**KEYWORDS**

*Affordability; Brazil, Budgetary Impact Analyses; Budgetary Impact Model; Economic Evaluation; Health Technology Assessment; Medicines, Hepatitis C*

## 1. Background

Ensuring access to new healthcare technologies requires a wide range of evidence, particularly in the case of high-cost technologies where opportunity costs are a key consideration [1]. In some cases, high-cost medicines are effective and cost-effective; however, due to their budget impact and co-payment issues they are not available to patients especially in countries with

public health systems. This applies to trastuzumab in low-and middle-income countries (LMICs), biological medicines for immunological disease among Central and Eastern European (CEE) countries [2-4], and new medicines for hepatitis C across countries [5,6]. We are even seeing developed countries struggling to fund new and expensive medicines for disease areas such as oncology exacerbated by limited health gain for most new cancer medicines [7,8]. These challenges will grow leading to suggestions for new pricing models to enhance their affordability [9].

Budget Impact Analysis (BIA) is part of a Health Technology Assessment (HTA) for a new medicine or device in order to know if the new technology is not only safe, effective, and efficient but it will also be affordable to payers and users of healthcare in the country. BIAs seek to estimate, over the short and medium term, the economic consequences of new potential technologies to health authority decision makers to help with investment decisions and subsequent budget allocation decisions [10-15]. In this way, BIAs become essential for the decision-making process regarding new technology incorporation [16], with such analyses used by countries and regions in Europe when undertaking yearly forecasts to improve their budgeting and resource allocation [17-19].

This is particularly important for new high-priced medicines for oncology and orphan diseases with, as mentioned, often limited health gain, which currently comprise the majority of new medicines [7,8,20]. Medicines for complex diseases now comprise approximately 50% of global expenditure on medicines and growing at an annual compounded rate of 3 to 6% [9,21], which is a continued concern given competing demands. In addition, new oncology medicines are increasingly launched with limited clinical information with health authorities required to make investment decisions with incomplete data in this emotive disease area [9, 22,23]. These concerns have resulted in, as mentioned, proactive models to improve the managed entry of new medicines including new oncology medicines [24-27] given existing levels of unmet need, exacerbated by the recent COVID-19 pandemic [28].

However, published studies have cast concerns about the level of quality, the results, and the conclusions of BIAs published in scientific journals, which impacts on their utility in practice [11,13,29]. This is mainly due to the lack of standardization and the low adherence to suggested requirements contained within the methodological guidelines developed for these analyses [30-33]. Such concerns in the methodological application of BIAs can generate bias and unrealistic estimates. This can subsequently compromise the entire process of decision making among health authority personnel working within finite resources and multiple competing demands.

In Brazil, for a new technology to be incorporated into the Brazilian Health Unified System (SUS, acronym in Portuguese), HTA studies must be performed including a BIA. One such analysis occurred in 2012 for the incorporation of new protease inhibitors for the treatment of chronic hepatitis C into the Brazilian Public Healthcare System. At the time, the prevalence of hepatitis C in Brazil was up to 2.1% of the population aged between 10-69 years [34]. Between 2009 and 2011, the cost of treating approximately thirty thousand patients in Brazil reached US$ 383.41 million (US$ 12,780 per patient). However, despite an investment of USD 231.12 million approximately eighteen thousand patients (60%) were still not being treated without the new protease inhibitors and not reaching the desired sustained virological response [35].

Consequently, in 2013 boceprevir (BOC) and telaprevir (TVR) were incorporated by SUS. There were side-effect and other concerns with these medicines, forerunners of newer protease inhibitors, which may have limited their use in practice [36-38]. This was addressed with the development of new direct-acting antiviral medicines including sofosbuvir and simeprevir, which showed high cure rates and fewer side-effects with shorter treatment durations compared with BOC and TVR [27,39].

Consequently, the objective of this study is to compare the estimated values and real-world evidence (RWE) expenditures concerning the budget impact of the incorporation of the protease inhibitors BOC and TVR into SUS in 2013 and 2014. The findings can be use to suggest additional methodological issues associated with BIAs that need to be addressed to promote a higher

degree of accuracy for future BIAs. This is especially important in this field with suggestions of the considerable budget impact of the newer direct-acting antiviral medicines if all eligible patients were treated [40]. In addition, concerns with the excessive profitability for potentially a cure for an infectious disease with estimates of gross profit levels at 99%, although lower in countries such as Brazil through public negotiations [39,41,42].

## 2. Research design and methods

### 2.1. Study setting

The right to healthcare in Brazil is included in the Federal Constitution and guaranteed through social and economic policies aimed at reducing the risk of diseases and other illnesses through providing universal and equal access to public health activities and services for all citizens [43] including new healthcare technologies. In order to make this right feasible, SUS was established in Brazil as one of the largest public health systems in the world, offering comprehensive and universal health care free of charge [44]. The system is funded by the federal, state, and municipal governments, through tax revenues and social contributions (taxes for specific social programs) [45]. The population has access to medicines for chronic diseases through administrative requests based on the clinical guidelines established for each disease area and subsequent treatment. Some of the medicines, including those available for the treatment of hepatitis C, are purchased and distributed by the Brazilian Ministry of Health (MoH) to the States, which in turn are responsible for all the logistics, from storage to dispensing them to patients.

The National Commission for Technology Incorporation for SUS (Conitec) is a Department of the MoH responsible for undertaking analyzes regarding the incorporation, exclusion, or alteration of technologies used by SUS. Conitec includes representatives of SUS management hierarchy and from Civil Society, which includes the Federal Council of Medicine and patient representatives through the National Health Council [46]. Following the precepts of

accountability for the SUS as well as HTA, at the end of each analysis, Conitec issues a technical opinion [47]. This is in the form of a Recommendation Report, which includes the results of studies and recommendations concerning the evaluated technologies including a BIA [48]. The HTAs are performed based on the best evidence available in the literature and RWE, considering aspects of efficacy, accuracy, effectiveness, and safety of technology, as well as comparative economic evaluations of costs and benefits in relation to existing technologies [49]. Conitec has adopted a series of methodological guidelines. These include the Brazilian recommendations for BIA studies [50], in accordance with key international publications [10-14,51,52]. It is important that Conitec and the Government can defend their positions as patients can seek funding for new medicines not approved by Conitec and funded by SUS via the courts [53,54], with subsequent evaluations undertaken by HTA agencies in Brazil to defend the Government position [55,56].

**2.2. Study design**

In order to achieve the proposed objective, the theoretical results and RWE expenditure will be compared regarding the incorporation of BOC and TVR protease inhibitors for the treatment of chronic hepatitis C in Brazil into SUS between in 2013 and 2014. These medicines were chosen as exemplars because for four years these treatments consumed appreciable financial resources across the world. They also paved the way for funding newer direct-acting antiviral medicines including sofosbuvir with their improved effectiveness and safety [27,39].

2.2.1. Values for the theoretical model

The theoretical values adopted for the comparison are derived from the Conitec Report (2012) [35] regarding SUS incorporation of protease inhibitors (BOC and TVR) for the treatment of patients with chronic viral hepatitis C in genotype 1, with fibrosis F3 (advanced fibrosis) or F4 (cirrhosis), "treatment virgins" or for retreatment (recurrent, partial response or non-response to conventional treatment). The proposed therapeutic regimen of BOC and TVR was compared

with the standard treatment at the time, which included the antiviral drugs pegylated interferon (INF) and ribavirin (RBV) [57]. The estimation of the population for the comparative analysis was calculated based on SUS data, considering care provided in the previous years, the scientific literature, local epidemiological bulletins, studies of the prevalence of different hepatitis C virus genotypes in Brazil, as well as data from retreatment obtained in patient care centers.

The methodology adopted by Conitec to undertake the BIA considered only the acquisition costs of BOC and TVR. Costs related to human resources, inputs for managing adverse events, as well as costs associated with complications due to disease progression such as decompensated cirrhosis, liver cancer, and transplants, were not considered in the estimate. Costs related to other medicines such as antiviral drugs (INF; RBV) and also those to treat the adverse effects of treatment including epoetin alpha (EPO) were measured but not computed in the BIA. The report estimates the treatment costs for 2013, setting two possibilities for the purchase value of the medicines. The first possibility, with higher values, adopted for the calculations the Maximum Sale Price to the Brazilian Government (PMVG, acronym in Portuguese) [58] for the acquisition of these medicines. The second possibility used the same parameters but considered a discount of at least 30% in the purchase prices of medicines obtained through negotiations with suppliers. The PMVG established for BOC and TVR used international purchasing parameters from nine countries, which also undertook public purchases of the medicines being analyzed.

The theoretical calculation considered an increase of two thousand new treatments in 2014 with an increase in expenses of approximately US$ 46.7 million without discriminating quantities and values for each of the medicines. It is important to document that for its analysis, Conitec did not adopt the Brazilian BIA guidelines. This though reinforces the purpose of this present study, i.e., to point out weaknesses in the BIAs and to promote a higher degree of accuracy to enhance their future use.

Inclusion criteria: Patients with mono-infection with the hepatitis C virus; genotype 1; advanced hepatic fibrosis (F3 or F4) or evidence by imaging or endoscopic methods of cirrhosis; compensated liver disease (Child-Pugh score > 6, classes B and C); patients without prior treatment (treatment virgins) or patients with prior treatment failure (recurrent, partial or non-responders); and no prior PI treatment.

Exclusion criteria: Patients with HIV or viral hepatitis B co-infection; prior liver transplants.

2.2.2 Real-world Evidence (RWE) expenditures

The real-world values came from the administrative data records of the MoH through which all hospital and outpatient procedures of SUS are registered and paid on a national level.

A national cohort based on the population of patients undergoing chronic hepatitis C treatment was constructed from January 2000 to October 2015 using a deterministic-probabilistic linkage approach and using the data records contained in the following databases: Hospital Information System (SIH, Acronym in Portuguese), Outpatient Information System (SIA, acronym in Portuguese) and Mortality Information System (SIM, acronym in Portuguese). The deterministic-probabilistic linkage was assessed by linking data that presented a reliable unique identifier (deterministic), and for the others by weighing the identifiers, second degree of certainty and (probabilistic) precision of the pairing [59-65]. The probability failure for this technique varies from 2 to 5% of the total data [66], which does not compromise the validity or quality of this study.

Inclusion criteria: According to SUS guideline [57] dated July 2011, patients treated by the SUS, according to parameters regulated by the Clinical Protocol and Therapeutic Guidelines for Viral Hepatitis C and Coinfections, identified according to the following ICD-10 codes – International Classification of Diseases, 10$^{th}$ Revision: B 17.1 – acute viral hepatitis C; B 18.2 – chronic viral hepatitis C; B 18.2 – chronic viral hepatitis C associated with B 18.1 – chronic viral hepatitis B; and, B 18.2 – chronic viral hepatitis C associated with B 20 – 24 – HIV disease.

Exclusion criteria: None.

**2.3. Variables and sources**

To obtain the results of the theoretical model, the following variables were extracted from Conitec's report: Number of patients receiving BOC and TVR treatment; Purchase value of these medicines; Annual cost of BOC and TVR; Annual cost of other medicines; Total annual cost of drug treatment; and the value of the annual budget impact.

In order to obtain the results in regarding RWE expenditure of these two medicines, the data for the following variables were extracted from the data records contained in the SIH, SIA and SIM databases: 1. User profile (age, sex, treatment start and end dates, and ICD 10); 2. Treatment data and comorbidities (dates for beginning and end of procedures, line of medicines and procedural care, amounts and values spent on procedures and medicines). 3. Gender, age category, region of residence, diagnosis according to ICD-10 codes, medicines used, and respective therapeutic class and calendar year period. Variables were also used for events that occurred during follow-up, including medicines changes, comorbidity, and death. The medicines included in the established therapeutic regimens were categorized as antivirals, with distinction for BOC and TVR, and the others were classified as other pharmacological groups. Outpatient procedures included, in addition to medicines, laboratory tests and diagnostic procedures. Categorical variables were reported by frequency distribution. For continuous variables, the mean and standard deviation (SD) and cost per patient were calculated by stratified follow-up time alongside demographic and clinical variables. The average expenditure per patient was calculated for each follow-up year, by health resource category.

**2.4 Monetary values**

The costs of outpatient and hospital procedures were based on the values recorded in the SIH and SIA databases. The costs of the medicines were determined by the purchase price recorded by the Brazilian government during the analyzed period [67]. All monetary amounts were

converted to US dollars adjusted by Purchasing Power Parity (PPP) according to figures provided by The World Bank [68] by calendar year. The following exchange rates were considered: 1 USD = 1,5590 BRL (2012) = 1,6493 BRL (2013) = 1,7473 BRL (2014).

### 2.5 Criteria employed to compare the outcomes

The most advantageous results for SUS were adopted from the theoretical model, in other words, the acquisition prices of BOC and TVR with a 30% discount in relation to PMVG. It is important to note that, as established by the hepatitis C treatment protocol, BOC and TVR should not be used concomitantly. In this way their cost values can be added for comparison purposes unlike the other antiretroviral medicines.

For 2013, specific values were estimated for each of the medicines; however, for 2014 a general estimate was presented. Consequently, for 2013, theoretical results and RWE expenditures individually for the BOC and TVR were compared. These included: Number of treatments; Unit purchase value and Cost Hospital; Outpatient; Diagnostic Procedure; Medicines). Additionally, for both of them over the study years, the accuracy of the findings were compared to the total number of treatments; total costs medicines (BOC and TVR); and total incremental budgetary impact.

### 2.6 Ethical clearance

This study was approved by the Research Ethics Committee of the Federal University of Minas Gerais – Brazil (44121315.2.0000.5149).

## 3. Results

### 3.1 Outcomes of the budgetary impact theoretical calculation

A total of 1,251 treatments with BOC were estimated to 2013, at a total cost of medicines of US$ 40.50 million, of which US$ 28.71 million was only for BOC, at a unit cost of US$ 6.20. The total estimate for TVR was 4,255 treatments and the total cost of medicines of US$ 130.62 million, of which US$ 90.52 million was only for TVR at the unit cost of US$ 42.21 (Table 1). The

report did not specify presented data and values for 2014; however, considered that there would be two thousand new cases, with an indication of the use of protease inhibitors resulting in an incremental budget impact of US$ 46.71 million (Table 3).

**3.2 Outcomes recorded by real-world evidence (RWE) expenditures**

Demographic and clinical characteristics of the patients with viral hepatitis C and co-infections treated through SUS between January 2000 and October 2015, as well as the annual average cost according to the different classifications, for the RWE expenditures are shown in Table 2. According to the data, 27,466 (57.6%) of the patients were men, with an average annual treatment cost of US$ 4,473.72 versus US$ 4,436.06 for treating women with hepatitis C. An appreciable proportion of (35.6%) who started treatment were between the ages of 46 and 55 years. The treatments with the highest average annual cost (US$ 4,640.26) were those performed in patients between 56 and 65 years of age: 13,573 (28.5%) treatments. Most of the treatments (59.4%) were administered in the southeast region of the country (the most developed in Brazil) responsible for more than 55.0% of Brazilian GDP. The pharmacological group most used were the antiretroviral medicines (except BOC and TVR) at 89.3% of treatments prescribed with an average annual cost per patient of US$ 3,988.90 followed by antiretroviral medicines including TVR for 4,072 (8.5%) treatments with average annual cost of US$ 9,588.16. A similar pattern was found regarding medicines used at the beginning of the treatment: antiretroviral drugs (except BOC and TRV) were used in 38,222 (80.1%) treatments with an average annual cost per patient of US$ 3,888.43 followed by antiretroviral drugs including TVR used in 3,937 (8.3%) treatments with average annual cost of US$ 9,606.85. Among treated patients, the main cause of death was viral hepatitis (27.4%), with an average annual cost of US$ 5,503.37 followed by malignant neoplasia of the digestive organs (10.6%), costing US$ 10,409.76, and liver diseases (10.3%) costing US$ 8,320.35.

In 2013, there were a total of 269 treatments with BOC, with a total cost for medicines of US$ 2.10 billion, of which US$ 1.31 billion was only for BOC, at a unit cost of US$ 11.07. For TVR,

there were 1,128 treatments, at a total cost of medicines of US$ 23.56 billion, of which US$ 20.99 billion was just as TVR, at a unit cost of USD 87.48. In 2014, the total number of treatments with BOC was 1,581, with a total cost for medicines of US$ 23.93 billion, of which US$ 15.76 billion was only for BOC at a unit cost of US$ 11.07. For TVR, there were 4,663 treatments, at a total cost of medicines of US$ 109.23 billion, of which US$ 90.65 billion was just as TVR, at a unit cost of US$ 80.70 (Table 1).

**3.3 Comparing outcomes**

3.3.1 Number of treatments

The estimated number of patients for BOC treatment in 2013 was 4.7 times higher than the number of patients actually treated by SUS (1,251 *vs*. 269) and for TRV was 3.8 times higher (4,255 *vs*. 1,128) (Table 1). Theoretical results estimated an increase of two thousand new treatments in 2014; however, they did break down the specific quantities for treatment with either BOC and TVR.

3.3.2 Unit purchase value and cost medicines

The average annual purchase values of these medicines by the Brazilian government for BOC was 1.8 times higher than estimated purchase values (US$ 11.07 *vs.* USD 6.20). For TVR, the difference was 2.1 times more in 2013 and 1.9 times more in 2014 (US$ 87.48 in 2013 and US$ 80.70 in 2014 vs. US$ 42,21) (Table 1). The theoretical analysis adopted the purchase price of BOC and TVR with discounts of 30%. However, if compared to purchase values without the discount, the prices of new technologies to the Brazilian government for BOC was 1.2 time more than the estimated purchase values (US$ 11.07 *vs*. US$ 9.13) and between 1.3 and 1.4 for TVR (US$ 87.48 by 2013 and US$ 80.70 by 2014 *vs*. USD 62.06).

3.3.3 Cost BOC & TVR

For treatment with BOC, the differences between estimated and RWE expenditure values were 22.1 times higher than 2013 (US$ 28.71 million *vs*. US$ 1.30 million) and for treatment with TVR

were 4.3 times higher (US$ 90.52 million *vs.* US$ 20.88 million) (Table 1). Theoretical results estimated an increase in expenses of approximately US$ 46.7 million in 2014; however again this did not include the specific values for treatment with either BOC or TVR.

3.3.4 Hospital and Diagnostic Procedure Cost

These costs have not been estimated.

**3.4 - Accuracy of the findings for BOC and TVR of hepatitis C**

3.4.1 Number of treatments

The estimated number of treatments was 70% higher than the actual situation (13,012 vs.7,506), with a difference of 4,109 (294%) in the first year and 1,262 (20%) in the second (Table 3).

3.4.2 Total costs of medicines

The estimated cost of treatments was 122% higher than the actual situation (US$ 285.16 million vs. US$ 128.58 million), with a difference of US$ 97.05 million (438%) in the first year and US$ 59.53 million (56%) in the second year (Table 3).

3.4.3 Total incremental budgetary impact

The estimated incremental budget impact was 122% higher than the actual situation (US$ 285.16 million vs. US$ 128.58 million), with a difference of US$ 156.58 million in two years (Table 3).

## 4. Discussion

For a health system to provide effective and cost-effective treatment for its population, it is important to consider the scenario where the increase in public spending on high-cost medicines threatens access to medicines for other priority areas including infectious diseases such as hepatitis C [39,40,69]. European health authorities are struggling to fund new high-priced medicines in all suggested populations, and this situation is likely to worsen given ageing populations and the continued launch of new premium prices medicines [2,9,37,70,71]. BIA can

assist with decision making on new medicines by presenting to key stakeholder groups the potential financial consequences of incorporating a new technology into the healthcare system as part of their decision making [19]. In this sense, it is necessary to promote a greater degree of accuracy in BIAs to assist healthcare managers and others in their decision making. Budget forecasting should be as accurate as possible given the many competing demands from new high-priced medicines and finite resources within universal healthcare systems [17,19] However, under no circumstances should a BIA on its own be used as an instrument to convince a healthcare system to incorporate a new technology. Wider considerations are necessary including cost-effectiveness analyses and cost consequence considerations.

Consequently, this study analyzed the incorporation of BOC and TVR for the treatment of hepatitis C into the public health system in Brazil (middle-income country) comparing the results from theoretical estimates with those from actual RWE expenditures. The value of this exemplar was heightened by the fact that the BIAs undertaken for government agencies did not present all the key features advocated by the Brazilian guidelines for BIAs [50], which are of fundamental importance to their future. A time horizon of 3 to 5 years, evaluation of uncertainties, and validation were not considered. In addition, the analysis of scenarios, considering the treatments available at the time, the possible alternatives and the rate of diffusion of any new technology, as well as variations of the market share, were also not considered [50,72]. This is a major concern since the Brazilian budget impact guideline for medicines resemble international ones and cover an appreciable number of categories and recommendations from nine national and transnational BIA guidelines [73,74].

### 4.1. Purchase price

The prices of new medicines for hepatitis C on the international market are seen as expensive [39,40,75], and made it impossible to authorize treatment on a large scale as this could potentially threaten the sustainability of healthcare systems especially in LMICs [39,40,76]. This

was made worse by increasing knowledge of the low costs of goods for new direct-acting antiviral medicines [39,40,71].

For BIA to be a powerful tool in the financial management process of health systems, the estimated costs of the new technology should be as close to reality as possible, with calculations that use reliable sources to reflect the local reality [11,12,14,30]. The BIA must consider the context in which the analyzed technology is being launched into the international market and the prices that could potentially be charged. Likewise, establishing the possible cost of acquiring a new technology for any health care system ideally requires more accurate analysis. To help with this, it is necessary to consider not only potential prices in the international market, but the specificities of the market being analyzed, as well as to know as far as possible price behavior during the process of incorporating new technologies into any healthcare system [33,77,78]. Apparently, all of this was observed by the Brazilian system in 2015 when it obtained considerable discounts on the purchase of new antivirals for hepatitis C in relation to other similar countries such as South Africa [42].

However, in 2013 and 2104 the theoretical values for the purchase of BOC and TVR were much lower than RWE expenditures at 78% for BOC and between 91% and 107% for TVR. If considering the purchase of BOC and TVR without the application of any discount, the more expensive estimates would increase the theoretical budget impact to US$ 175.3 million [35], which would be an overestimate of 7.9 times in 2013 and 1.6 times in 2014 respectively.

**4.2. Number of treatments**

Population calculations are one of the main weaknesses of any BIA [30]. The population of interest can be estimated by the epidemiological method or by measuring demand [13]. For both methods, aspects that influence the size of the treated population or changes in population characteristics should be considered so that budget impact estimates are not skewed [32]. An overestimated population calculation greatly elevates treatment cost estimates, providing the health system manager with information on the volume of budget resources that is potentially

far removed from reality. In this sense, the greater the distortion of the population, the lower the study's degree of accuracy with the potential for denying effective medicines due to concerns with the potential budget impact for this new technology versus other candidates.

In the present study, theorical results for the Brazilian population were estimated by measuring demand, considering the population data in the healthcare system and using treatment records from previous years. However, the calculation did not consider any type of population transition between the standard treatment and the new treatment. Consequently, during the first year a significant difference (4,109; 294%) was registered between the estimated number and the number of patients who actually received the new treatments. This difference dropped to 20% in the second year; however, it remained significant: 1,262 treatments. A similar result was reported by Sooksriwong & Chanjaruporn (2011) who also revealed appreciable differences between theoretical BIA and an empirical study for the treatment of lung cancer [79]. Their results revealed that the impact per patient was constant in the theoretical BIA while that of the RWE expenditures increased over the time [79]. A previous study undertaken in Europe (de Bruijn et al, 2016) with BOC and TVR showed initial acceleration in their use; however, impacted by issues of physician preference and side-effects [37]. Their prescribing though appreciably tailed off in anticipation of the new direct-acting antiviral medicines with their improved effectiveness and appreciably reduced side-effect rate [37].

For BIAs to be more accurate, population calculations should estimate a transition from patients currently being treated with standardized regimens to the new treatment, especially in the first year of incorporation, when rates of adherence to the new treatment are typically lower [80]. Among the factors that must be considered are lack of knowledge among patients regarding the availability of the new technology, patient comfort in maintaining the previous standard treatment, the possibility of a lack of adaptation to the new treatment, the processes and the entire logistics chain involving purchase, distribution, storage, professional training, and dispensing of the medicines, as well as the use of medicines already delivered to patients or still

stored in in the warehouses of the healthcare system [26,70,81,82]. Especially with chronic disease treatments, the transition between treatments should be considered since substitution of a particular medicine may compromise adherence to future therapy [83].

**4.3. Budget Impact**

When the estimates of the purchase price of the new technology and the potential number of treatments available are unrealistic, this becomes a major aggravating factor regarding the possible lack of accuracy for future assessments. This happened in this present study. The purchase price was underestimated by 78% for BOC (US$ 6.20 x US$ 11.07) and on average 99.2% for TVR (US$ 42.21 x US$ 84.09) (Table 3). On the other hand, the total number of treatments were overestimated by 70.3% (7.641 x 13.012) (Table 3).

Based on 2012 figures, the real budget impact in 2013 with BOC and TVR to treat 1,397 patients was US$ 22.18 million, but the estimated impact was US$ 119.23 million to treat 5,506 patients (Table 3), i.e. overestimated by US$ 97.05 million (the estimated was 5.4 times greater than reality). The real budget impact in 2014 with BOC and TVR to treat 6,244 patients was US$ 106.41 million, but the estimated impact was US$ 165.96 million to treat 7,506 patients (Table 3), i.e., overestimated by US$ 59.53 million (the estimated was 1.5 times greater than reality).

A similar result was reported by Iwanczuk et al. (2015) when comparing estimated BIAs and actual reimbursement claims and expenditures of the Polish government for BOC and TVR for patients with chronic hepatitis C genotype 1 [84]. The estimated values were 1.88 times higher than first year and 1.36 times higher than second year, while the estimated population size was 53% higher in the first year and 38% higher in the second year. Similarly, Geenen et al. (2019) using hepatitis C as a case study to quantify the accuracy of the Budget Impact predictions used in Dutch reimbursement decision-making, and to characterize the influence of market-dynamics on the actual Budget Impact, showed that the published estimates provide a substantial overestimation of the RWE expenditures of between €153 and €275 million [77].

These figures, estimated or real, are significant for any healthcare system, especially for the Brazilian public health system, which invested heavily in the treatment of hepatitis C. Considering the purchases made by the MoH, the estimated annual expenditure for the treatment of hepatitis C increased from US$ 23.47 million in 2006 to US$ 283.82 million in 2015 [69]. However, it is not just the cost that must be analyzed. The planning of the incorporation of any new technology is of fundamental importance for the sustainability of healthcare systems. In the present study, the health system manager projected an increase in costs with BOV and TVR between 2013 and 2014 of US$ 128.58 million, but in fact had to bear US$ 285.16 million (122% more than planned) (Table 3). This means available resources for other priority medicines will have been compromised.

**4.4. Effectiveness and affordability**

In addition to analyzing budget results, it is important to question efficiency in planning and spending. Between 2009 and 2011, the Brazilian government spent US$ 231.12 million on Hepatitis C treatments, without the use of protease inhibitors and 18 thousand patients did not achieve a sustained virological response [35].

Between 2013 and 2014, treatments with BOC and TVR accounted for US$ 128.59 million, enabling 7,641 patients to obtain a sustained virological response (Table 3).

In 2016, with the arrival of the new direct-acting antiviral medicines (sofosbuvir, daclatasvir and simeprevir) BOC and TVR were excluded from the Brazilian guideline as well as other countries. [40]. In accordance with the incorporation process in SUS, a new HTA was produced and a new Recommendation Report [85] was issued. It recommended that new antiviral drugs would have a more favorable safety and efficacy profile, with performance for all genotypes and greater ease of treatment, i.e., shorter, with fewer daily tablets, no mandatory use of other antiretroviral medicines and other medicines to treat the adverse effects of previous treatments. In addition, the costs of the new treatments would be lower than the costs with BOC and TRV [86], which turned out to be the case with successful negotiations [42]. It should

be noted that these considerations should have been included in the BIAs for BOC and TVR given the fact that the increased effectiveness and reduced side-effects of the new direct-acting antiviral medicines was already known since these medicines were already being launched across countries.

The new Recommendation Report for Brazil evaluated approximately 15,000 treatments for different genotypes, whilst the new direct-acting antiviral medicines would be responsible an annual cost increase in 2015 of between USD 250.81 million and USD 358.13 million [85]. However, the MoH costs with Hepatitis C treatments in 2015 were 2.3 times that of 2014 and it spent USD 508.13 million on sofosbuvir, simeprevir, daclatasvir and boceprevir alone [69]. Despite the increase in the effectiveness and safety of the new treatments, once again information confronts theoretical results and RWE.

BIAs are currently an important tool to assist discussions regarding accessibility budgetary thresholds, especially in the negotiations between healthcare systems and the pharmaceutical industry regarding the purchase price of medicines or other financial agreements that help determine the price and expenditures for a specific population regardless of the actual number of patients treated [16,77]. BIAs can also help shape any discussions of potential discounts and rebates during managed entry agreements to enhance the chances of reimbursement [85,87]. In this sense, BIAs that are produced with the highest degree of accuracy possible, trying to establish precise scenarios as close as possible to reality, help with making decisions that preserve system sustainability whilst trying to address unmet need [74,88,]. This is working will within European countries including Sweden with their comprehensive system for introducing new medicines and monitoring their effectiveness and safety in practice including prescribing against agreed criteria [24,26,27,81]. We are also seeing similar developments in Scotland with their comprehensive databases [18]. Bilinski et al. (2017) claim that HTA enables policymakers to develop a better set of high value programs for specific contexts. Despite this, they found that among the articles cataloged in the Tufts Medical Center Global Health Cost-Effectiveness

Analysis (GHCEA) only 12 of 284 articles included a formal BIA and only 37 of the 384 of the articles included an informal BIA [78]. For the BIA to be reliable and used more often in decision making, they need to be conducted with a higher degree of accuracy in order to establish the population that will benefit, particularly in relation to the transition between standardized treatment and the new technology being incorporated. The accuracy of BIAs is especially in LMICs that will have accessibility and affordability problems for new medicines [2-4, 9,70].

**4.5. Policy implications**

Economic evaluations, followed by research in health insurance and financing, access and equity analysis, cost-effectiveness analysis, and price regulation issues have become a recurring theme among scientific publications [89]. In the context of health policies, the results from these studies support decision-making processes on the incorporation of new technologies. In this sense, BIA and cost-effectiveness are important tools adopted by many governments since 1990 for the approval and reimbursement of new medical technologies [90].

Currently, BIA has been shown to be fundamental for managers in the price negotiations of new technologies [69], being considered in the main Asian economies, including China and Japan, a matter of standard procedure [91]. This is a trend worth noting as the average overall growth rate of healthcare expenditure in Asian countries is 7% per year, well above Western Europe (3.9%) and North America (5.4%) [92]. This is likely to accelerate with ageing populations among Asian countries including China and Japan.

BIAs are especially important in developing countries were there are scarce financial resources and important unmet population health needs. These countries must seek a substantial improvement in the effectiveness and efficiency of their health expenditures given increasing demands of the population [93]. This is because increases in expenditures do not always result in improvements in health outcomes [94]. The search for efficiency in healthcare has two important consequences. Firstly, it enhances the sustainability and affordability of healthcare systems. Secondly, it helps avoid the catastrophic consequences to families caused by financial

expenditure on healthcare (direct costs) as well as any loss of salary and income as well as time of the patient and caregiver (indirect costs) [95-97]. Consequently, it is essential that available resources are used as wisely as possible.

BIA is a forecast / estimate and it does not perfectly correspond to future reality; consequently, many countries use it as a complement and not as the main reason for decision making. However, any lack of confidence in BIA is exacerbated when studies, point to a low degree of accuracy between theoretical and practical results. Concerns can start to be addressed by the need for greater methodological rigor for population and cost predictions, enhanced treatment modeling, as well as greater cognizance of the metrics for exchange, treatment sequences and patient behavior patterns.

Regarding the sustainability of health systems, the realization and results of a BIA cannot be restricted to the final areas (health care). It is essential that planning and financial areas participate in the process of new medicine incorporation. Population data and the costs of medicines are extremely sensitive to expert help as seen for instance in Sweden [24]. However, what actually contributes to budget planning for health systems are the forecasts of values and periodicity of disbursements that will occur with potential purchases. It must be made clear that the financial budget impact actually occurs on the budget and not on healthcare.

The Brazilian case is exemplary and indicates interesting points to be analyzed as a way of helping other countries especially those that provide universal healthcare or seeking to attain universal healthcare in line with the Millennium goals. Any BIA guideline adopted should be based on the best guidelines available and should cover most of the requirements necessary for a gold standard BIA [74]. However, most HTA analyzes carried out by CONITEC in Brazil do not use the aforementioned guideline and for this reason the 2014 Guideline has never been updated. Based on the reports presented, the science and technology manager makes the decision whether or not to carry out the incorporation of new technologies. The budget and financial planning sector does not participate in the discussions and becomes aware only when

it receives the request for the purchase of pharmaceutical assistance. It is necessary to understand that the sustainability of health systems is based on care, financial and management balance, with the participation of all areas involved: assistance, technology assessment and budgetary and financial planning. We will continue to make this point.

## 5. Conclusions

This study demonstrates an appreciable divergence (US$ 156.58 million in two years) between results theoretical and RWE for BIA of medicines for hepatitis C in Brazil. The main causes of the divergence are underestimated purchase prices and overestimated populations. If BIAs are performed according to the guidelines and to a high degree of accuracy, they can significantly contribute to the discussions about accessibility thresholds for healthcare systems and allow well-informed price negotiations between healthcare systems and the pharmaceutical industry especially in LMICs. This is particularly important in healthcare systems that provide universal healthcare and where there is still considerable unmet need. The greater the degree of accuracy between theory and the RWE expenditures, the more reliable and usable BIAs become. We understand that there are good established methodologies for BIA that can be improved. For this, it is essential that these are widely used, their results are compared with the findings in practice and any deviations are corrected so that their accuracy is improved to guide future investment decisions.

BIA support health authorities with the planning of budgets for new valued premium priced medicines. However, there are still concerns with the quality of studies. This study demonstrated that BIAs should estimate a transition of patients between the current standard and the new treatments while estimating more accurately likely purchase prices to obtain more accurate and reliable results for decision making. The most effective and promising strategies for BIAs in the future is the production of studies strongly committed to a high methodological quality, a low bias and greater accuracy.

## Key issues

- Budget Impact Analyses (BIA) seek to estimate the economic consequences of technologies to health authority decision makers to help with future budget allocation and investment decisions. However, there are concerns with the quality of current BIAs.
- To point out weaknesses and promote a higher degree of accuracy in BIA, this study compared the results from estimated and real-world evidence (RWE) expenditures for new medicines in the treatment of hepatitis C.
- The estimated population was 1.7 times higher than reality (7.641 patients). The total cost of drug treatment was 2.2 times higher in the estimates than the real-world situation (US$128.58 million), and the budget impact was overestimated by US$ 156.58 million.
- For BIA to become more accurate, population calculations should estimate a transition from current standardized treatments to the new treatment and the purchase price forecast must be more accurate where possible.
- The greater the degree of proximity between theory and RWE expenditures, the more reliable and usable BIAs become.

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To users of the health system.

## Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organizations or entities or any conflict of interest with the subject matter or objects discussed in this study.

## Geolocation information

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## Author contributions

Study design and governance: DRF; AAGJ; ENS; ACS. Write-up and ongoing critical review of the article: DRF; BBG; AAGJ. Materials/analysis tools: DRF; RGP; AAGJ. Ongoing study review and feedback regarding design, data collection, analysis and critical review of the manuscript: DRF; ENS; BBG; RGP; ACS; AAGJ. All authors had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

## Compliance with ethics guidelines

The real-life data were analyzed by means of a unique numerical identifier, which makes it impossible to distinguish between patients. The methodology, which followed the concepts of research ethics, was approved by the Research Ethics Committee of the Federal University of Minas Gerais – Brazil Under ETIC 0069.0.203.000-11.

## Consent for publication

Not applicable.

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Tables

Table 1 - Comparison of theoretical and RWE, costs of hepatitis C, SUS (2013 and 2014)

| | Estimated | Real-world evidence | |
|---|---|---|---|
| | 2013 | 2013 | 2014 |
| **Treatment: BOC** | | | |
| Number of patients (n) | 1,251 | 269 | 1,581 |
| Unit purchase value (USD) | 6.20 | 11.07 | 11.07 |
| **Cost (USD)** | **40,496,956.97** | **2,143,901.25** | **24,221,054.24** |
| Hospital cost | n/i | 268.70 | 9,284.29 |
| **Outpatient cost** | **40,496,956.97** | **2,143,632.55** | **24,211,769.95** |
| Diagnostic Procedure | n/i | 35,079.75 | 283,254.88 |
| **Medicines** | **40,496,956.97** | **2,108,552.80** | **23,928,515.07** |
| BOV | 28,708,030.44 | 1,300,653.44 | 15,761,050.87 |
| Other medicines | 11,788,926.53 | 807,899.36 | 8,167,464.20 |
| **Treatment: TVR** | | | |
| Number of patients (n) | 4,255 | 1,128 | 4,663 |
| Unit purchase value (USD) | 42.21 | 87.48 | 80.70 |
| **Cost (USD)** | **130,616,347.69** | **23,694,268.07** | **109,887,671.11** |
| Hospital cost | n/i | 4,457.77 | 23,825.99 |
| **Outpatient cost** | **130,616,347.69** | **23,689,810.30** | **109,863,845.12** |
| Diagnostic Procedure | n/i | 132,961.95 | 634,958.12 |
| **Medicines** | **130,616,347.69** | **23,556,848.35** | **109,228,887.00** |
| TRV | 90,518,919.72 | 20,877,281.17 | 90,646,378.07 |
| Other medicines | 40,097,427.97 | 2,679,567.18 | 18,582,508.93 |

Table 2 – Real World Evidence: Demographic and clinical characteristics and average costs of patients with viral hepatitis C and Co-infections treated through SUS (2000 to Oct/2015)

| Parameter | N (%) | Average annual cost per patient USD (DP) |
|---|---|---|
| | 47677 | |
| **Cohort** | (100.00) | 4,457.81 (2,767.00) |
| **Sex** | | |
| Male | 27466 (57.61) | 4,473.72 (2,812.42) |
| Female | 20211 (42.39) | 4,436.06 (2,705.59) |
| **Age at the beginning of treatments, years, meanm +-DP** | 51.10 (10.82) | - |
| Male | 52.07 (11.47) | - |
| Female | 50.38 (10.26) | - |
| **Age range at the beginning of the treatment, years** | | |
| 0 - 17 years old | 148 (0.31) | 2,153.03 (2,251.16) |
| 18 - 25 years old | 394 (0.83) | 3,255.18 (2,376.55) |
| 26 - 35 years old | 3804 (7.98) | 4,205.38 (2,196.41) |
| 36 - 45 years old | 9008 (18.89) | 4,704.26 (2,405.26) |
| 46 - 55 years old | 16979 (35.61) | 4,321.90 (2,816.35) |
| 56 - 65 years old | 13573 (28.47) | 4,640.26 (3,047.04) |
| > 65 years old | 3771 (7.91) | 4,250.77 (3,117.68) |
| **Residence Region, beginning of cohort** | | |
| Southeast | 28388 (59.54) | 4,714.81 (3,109.28) |
| South | 11738 (24.62) | 3,055.72 (2,224.08) |
| Northeast | 3360 (7.05) | 8,419.69 (2,211.83) |
| North | 2238 (4.69) | 3,456.35 (2,546.59) |
| Midwest | 1953 (4.10) | 3,418.25 (2,726.40) |
| **Primary diagnosis, beginning of treatment** | | |
| Viral chronic hepatitis | 47287 (99.18) | 4,462.85 (2,778.12) |
| Other acute viral hepatitis | 390 (0.82) | 3,841.34 (1,529.66) |
| **Pharmacological group, begging of treatment** | | |
| Antiviral | 42594 (89.34) | 3,988.90 (1,904.69) |
| Antiviral+TVR | 4072 (8.54) | 9,588.16 (12,674.55) |
| Antiviral+BOC | 852 (1.79) | 7,405.32 (9,306.73) |
| TVR | 125 (0.26) | 14,436.30 (13,200.75) |
| BOC | 33 (0.07) | 5,802.02 (5,631.13) |
| **Medication, beginning of treatment** | | |
| EPO+RBV | 38222 (80.17) | 3,888.43 (2,047.59) |
| EPO+RBV+TVR | 3937 (8.26) | 9,606.85 (12,688.23) |
| alfainterferone+RBV | 1566 (3.28) | 2,180.20 (363.33) |
| EPO | 1563 (3.28) | 7,787.98 (1,623.42) |
| RBV | 1073 (2.25) | 3,284.58 (1,086.48) |
| EPO+BOC+RBV | 811 (1.70) | 7,526.83 (9,451.68) |
| EPO | 168 (0.35) | 6,822.94 (971.36) |
| TVR | 125 (0.26) | 14,436.30 (13,200.75) |
| Other medications | 212 (0.44) | 10,978.01 (10,563.89) |
| **Group CID10 - Deaths** | | |
| Viral hepatitis | 513 (27.43) | 5,503.37 (1,634.27) |
| Malignant neoplasias of digestive organs | 198 (10.59) | 10,409.76 (1,973.32) |
| Liver disease | 193 (10.32) | 8,320.35 (3,340.99) |
| Ischemic heart disease | 90 (4.81) | 2,4254.76 (3,366.80) |
| Cerebrovascular diseases | 84 (4.49) | 2,0957.26 (7,602.84) |

| | | |
|---|---|---|
| | | 79,178.56 |
| Diabetes mellitus | 65 (3.48) | (30,535.33) |
| Other groups cid death | 727 (38.88) | 37,393.03 (8,330.90) |

Table 3 - Accuracy of the findings theoretical and RWE for BOC and TVR of hepatitis C, SUS (2013 and 2014)

| | 2012 | 2013 | | 2014 | | Accumulated | |
|---|---|---|---|---|---|---|---|
| | RWE | RWE | Estimated | RWE | Estimated | RWE | Estimated |
| **mber of treatments (n)** | | | | | | | |
| tal treatments | 0 | 1,397 | 5,506 | 6,244 | 7,506 | 7,641 | 13,012 |
| **fference (theoretical vs. RWE)** | | | **4,109** | | **1,262** | | **5,371** |
| **presentativeness (theoretical vs. RWE)** | | | **294%** | | **20%** | | **70%** |
| **sts medicines BOC and TVR (USD)** | | | | | | | |
| tal cost | 0.00 | 22,177,934.61 | 119,226,950.16 | 106,407,428.94 | 165,935,421.99 | 128,585,363.55 | 285,162,372.15 |
| **fference (theoretical vs. RWE)** | | | **97,049,015.55** | | **59,527,993.05** | | **156,577,008.60** |
| **presentativeness (theoretical vs. RWE)** | | | **438%** | | **56%** | | **122%** |
| **remental Budget (USD)** | | | | | | | |
| tal Incremental Budget | 0.00 | 22,177,934.61 | 119,226,950.16 | 84,229,494.33 | 46,708,471.83 | 128,585,363.55 | 285,162,372.15 |
| **fference (theoretical vs. RWE)** | | | **97,049,015.55** | | **-37,521,022.50** | | **156,577,008.60** |
| **presentativeness (theoretical vs. RWE)** | | | **438%** | | **-45%** | | **122%** |