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ORIGINAL RESEARCH ARTICLE

# Budget Impact Analysis of Risperidone Use and Adverse Event Monitoring in Autism Spectrum Disorder in Brazil: Assessment of Theoretical Versus Real Data

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## Abstract

**Background and aims** Risperidone is used in autism spectrum disorder (ASD) to manage aggressive behavior. Budget impact analysis (BIA) assists managers in promoting more sustainable health systems; however, it is unclear whether BIAs underestimate or overestimate the estimates derived from real-world data. This study aimed to compare the estimated BIA values of risperidone use and the monitoring of adverse events in ASD using theoretical and real data.

**Methods** Analyses were conducted based on the clinical protocol and the Brazilian therapeutic guidelines for ASD. The perspective adopted was that of the Unified Health System (SUS), considering a time horizon of 5 years. Three possible scenarios were considered based on the maximum daily dose of risperidone. Expenses related to the acquisition of risperidone and the monitoring of adverse events were taken into account using health databases in Brazil. For the calculation based on theoretical data, the prevalence of ASD was estimated using information from the scientific literature and the Brazilian demographic census. The model calculated from real data was obtained by analyzing the linear trend of the number of users assisted in the SUS from 2017 to 2021.

**Results** The population estimated by the theoretical model compared with the model calculated from the real data was higher. Likewise, the 5-year budgetary impact of the theoretical model versus the model calculated from the real data was higher, with statistical significance in all scenarios ($p < 0.001$). In the real data model, the most economically advantageous scenarios were Scenario 1 for children (International dollars [I$] 7,630,040.73) and Scenario 3 for adults (I$60,329,288.17). Estimated expenditures for monitoring adverse events ranged from 17 to 74% in children and from 50% to 63% in adults.

**Conclusions** The data revealed significant differences in population and cost estimation between theoretical data and real-world data. The expenses associated with monitoring adverse events represented a substantial expenditure estimate for the SUS.

## Key Points for Decision Makers

The model calculated using theoretical data estimated significantly higher costs associated with risperidone utilization in autism spectrum disorder in Brazil in comparison with the model calculated using real data.

The estimate expenses associated with monitoring adverse events of risperidone in autism spectrum has an important budgetary impact in Brazil.

Decision-making guided by real data is a promising trend and in this case, our findings can encourage stakeholders to prioritize the use of such data whenever they are available.

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## 1 Introduction

Autism spectrum disorder (ASD) is a group of heterogeneous neurodevelopmental conditions characterized by early-onset communication disorders, impaired social interaction, and repetitive and stereotyped behaviors and interests [1]. It is estimated that around 52 million people are living with ASD worldwide [2]; however, this estimate may vary in developing countries due to limited access to mental health services [3]. ASD is the leading cause of disability in children under 5 years of age [2]. Psychosocial interventions can benefit patients and improve their quality of life [4]. However, some individuals with ASD exhibit aggressive behavior, characterized by the presence of irritability, self-mutilation, and self-harm [5]. In such cases, pharmacological treatment with second-generation antipsychotics is recommended in combination with psychosocial interventions [6].

Aggressive behavior is a primary cause of psychiatric hospitalization in individuals with ASD [7] and results in substantial costs for public and private health services [8]. The prevalence of aggressive behavior in individuals with ASD is high, but varies considerably between studies (ranging from 8 to 68%) due to differences in the definition of aggressive behavior, measurement methods, and sample characteristics [9]. Although further investigations are needed to determine the exact prevalence of aggressive behavior in ASD, it is well established that this condition causes harm to individuals, family members, and caregivers [10]. ASD is a medical condition with significant social and healthcare costs, amounting to over $35 billion, which includes expenses related to medical services, outpatient and clinical care, general dental services, medication use, behavioral therapy/support, family support, and special education [11].

Treatment costs pose a significant barrier to accessing comprehensive healthcare for this population, leading to increased expenses associated with psychiatric hospitalizations [12, 13]. Given the wide range of financial costs and treatment options, which are not always aligned with public health interests, health systems, particularly those with universal coverage, require tools that optimize resources [14]. Risperidone and aripiprazole are second-generation antipsychotics that have demonstrated efficacy in managing aggressive behavior [15]. In Brazil, risperidone is the only medication recommended for managing aggressive behavior associated with ASD, specifically for children aged ≥ 5 years of age [16].

Budget impact analyses (BIAs) can assist managers, particularly in environments characterized by mounting social pressure and economic interests, such as Health Technology Assessments (HTA). In this sense, the BIA is the stage of HTA that assesses whether a specific safe and effective technology is economically feasible for a health system, particularly one that aims to achieve or sustain universal health coverage [17]. Good BIA guidelines have been developed by institutions and systems associated with HTA, including Australia, Canada, the UK, and Brazil [18]; however, there are concerns regarding the quality and reliability of the estimates used in these BIAs [19]. In addition to this, there is a growing recognition that data from epidemiological studies and clinical trials are insufficient for effectively enhancing sustainable mental health services for individuals with ASD [20, 21].

To date, only the BIA conducted by Zimmerman et al. has specifically examined the use of risperidone in ASD [22]; however, this analysis only considered the adult population. Given that antipsychotics are among the most commonly prescribed medications for ASD and entail significant costs for health systems, there is a need for BIAs that specifically focus on expenditures related to these drugs [23].

The real-world data in BIA has witnessed significant growth in recent years. A systematic review examined the incorporation of real-world data in economic evaluations and identified 93 studies that primarily utilized information systems, such as administrative databases, to capture direct medical costs, efficacy outcomes, and population estimates [24]. When these data are incorporated into the BIA, they provide more precise estimates [25]. However, there are barriers to the utilization of real-world data, including challenges related to missing data, limited availability of professionals to compile data in clinical practice, and the need for training researchers in the use of such data [24]. Therefore, it is necessary to compare models calculated using theoretical data and real data to identify potential limitations in the estimates derived from each method. This will ultimately lead to greater accuracy in the BIA, facilitating informed decision making.

This study aimed to compare the estimated BIA of risperidone utilization and the monitoring of adverse events in ASD using both theoretical and real data.

## 2 Methods

### 2.1 Study Design

This was a comparative BIA based on the model calculated using real data for risperidone in the Unified Health System (SUS) and the model derived from theoretical epidemiological data obtained from the scientific literature.

### 2.2 Study Setting

The SUS guarantees universal access and comprehensive coverage to all Brazilian citizens. The financial resources for funding the system come from taxes and contributions collected by the federal government, states, and municipalities

[26]. Until 2011, the HTAs were conducted by a sectoral committee within the Ministry of Health in Brazil. Subsequently, the National Commission for the Incorporation of Technologies in the SUS (CONITEC) was established and took over this responsibility [27]. The treatment of chronic diseases in Brazil is regulated by specific clinical protocols and therapeutic guidelines (PCDT).

Brazilian patients with ASD can have free access to risperidone through an administrative process conducted by the SUS. This process verifies and authorizes the treatment request in accordance with the PCDT [28]. Patients receive their medications on a monthly basis and undergo regular reassessments to ensure continued funding and usage. Through its computerized system, the SUS can monitor user fees, medical prescriptions, and costs.

Some international clinical guidelines recommend the use of risperidone for managing irritability associated with ASD [6, 29]. Currently, risperidone is included in the Specialized Component of Pharmaceutical Assistance (CEAF) for children and adults; its incorporation into the SUS took place in 2014 and 2016 for children and adults, respectively [16]. In ASD, the use of risperidone is guided by the 'PCDT for Aggressive Behavior in ASD' [16], which was implemented in February 2022, specifically when non-pharmacological interventions prove to be ineffective.

## 2.3 Criteria

### 2.3.1 Time Horizon and Perspective

This study had a time horizon of 5 years (2022–2026) and adopted the perspective of the SUS.

### 2.3.2 Scenarios

Three possible scenarios were adopted for children and adults (Table 1) taking into account the recommended daily doses in milligrams, i.e. 2 mg/day for children and 3 mg/day for adults, as indicated [16]. The scenarios were validated through two online meetings involving specialists, SUS managers, and health professionals who provide care for patients with ASD.

### 2.3.3 Costs with Risperidone

Based on the defined scenarios, the expenses with the acquisition of risperidone per patient per month were calculated for both age groups. The purchase price was obtained from the Health Price Bank (municipal purchases) and the Integrated General Services Administration System (state purchases). The filters used included purchase years between 2017 and 2021, the type of purchase (administrative or not informed), and the Catalog of Materials (CATMAT) corresponding to risperidone in the concentrations specified in the PCDT of Aggressive Behavior in ASD [16]. These concentrations include 1 mg/mL (BR0284106), 1 mg (BR0272839), 2 mg (BR0268149), and 3 mg (BR0284105). The values recorded in the SUS Procedures, Medications, and OPM Table Management System (SIGTAP) were as follows: International dollars (I$) 0.018 for the 1 mg presentation, I$0.019 for the 2 mg presentation, I$0.067 for the 3 mg presentation, and I$3.53 for the 30 mL vial oral solution (weighted average of the values obtained until May 2021). Among the retrieved data, any instances where the concentration of risperidone 1 mg/mL differed from the 30 mL vial were excluded since it lacks a code in the Management System of the Table of Procedures, Medications, and Orthotics/Prostheses and Special Materials from the SUS (SIGTAP). Furthermore, data filters were applied to exclude records with errors in the filling for the CATMAT of risperidone in tablet form when the supply unit was indicated as vial-ampoule. Additionally, records with a purchase quantity of < 100 units of pills or < 10 bottles of oral solution were excluded since these quantities are typically associated with acquisitions through legal processes (judicialization) and therefore would not accurately reflect the real expenses of the SUS [30].

### 2.3.4 Costs of Monitoring Examinations

Costs of monitoring tests related to adverse events associated with risperidone were extracted from SIGTAP (Table 1). The same values were adopted for both the model calculated from theoretical data and the model based on real data.

## 2.4 Population Estimation

### 2.4.1 Model Calculated from Real Data

The population of individuals with ASD using risperidone was extracted from retrospective data (2017–2021) available in the Open Room on Health Intelligence (SABEIS). This database collects information on medication dispensation throughout Brazil in accordance with the PCDT.

The SABEIS platform encompasses all medication users within the SUS. This platform retrieves data from DATASUS, extracting, transforming, and loading information from the SUS system into a tabulated file (flat file). Data on medications, from the CEAF, including risperidone, are sourced from the Outpatient Information System (SIA) and the National Register of Health Establishments (CNES), which are managed by the Specialized Secretariat for Health Care (SAES/MS) [31].

**Table 1** Parameters adopted in the budget impact analysis

| | |
|---|---|
| General characteristics of the adopted model | |
| Type of clinical condition | Chronic |
| Type of intervention | Continued pharmacological |
| Effect of the intervention on the disease | Reduces irritability |
| Criteria | |
| Characterization of the clinical condition and intervention under analysis: | |
| Condition name | ASD |
| ICD-10 classification | F84.0—infantile autism; F84.1—atypical autism; F84.3—other childhood disintegrative disorder; F84.5—Asperger's syndrome; F84.8—other pervasive developmental disorders |
| Prevalence of ASD | 1.0% (0.3–2%) [36] |
| Prevalence of aggressive behavior | 30% (8–68%) [37] |
| Population covered by the SUS | 70% [35] |
| Characteristics of the analysis | |
| Perspective | Brazilian SUS |
| Time horizon | 5 years (2022–2026) |
| Mid-cycle correction | Not applicable |
| Identification of model scenarios | |
| Children and teenagers (0–18 years of age): | |
| Scenario 1 (I$15.71 per patient/per year) | 1 tablet of risperidone 2 mg |
| Scenario 2 (I$28.57 per patient/per year) | 2 tablets of risperidone 1 mg |
| Scenario 3 (I$203.90 per patient/per year) | Risperidone 1 mg/mL vial (30 mL) |
| Adults (over 18 years of age): | |
| Scenario 1 (I$42.85 per patient/per year) | 3 tablets of 1 mg |
| Scenario 2 (I$44.28 per patient/per year) | 1 tablet of 2 mg + 1 tablet of 1 mg |
| Scenario 3 (I$24.28 per patient/per year) | 1 tablet of 3 mg |
| Monitoring examinations | |
| Costs associated with monitoring adverse events (I$42.08 per patient/per year) | Consultation and monitoring of adverse events, anthropometric measurements and blood pressure (three times a year): I$17.85<br>Lipid profile (3 times a year): I$14.73<br>Fasting blood glucose (3 times a year): I$2.22<br>Blood count (twice a year): I$3.26<br>Prolactin level measurement (once a year): I$4.02 |

*ICD-10* International Classification of Diseases, Tenth Revision, *ASD* autism spectrum disorder, *SUS* Unified Health System

Although this is administrative data and has limitations related to potential bias due to missing data, it can be considered an Observational Medical Outcomes Partnership—Common Data Model [31]. This is because it captures care contacts, including the date of medication dispensation, medication information, and diagnosis, which are individually recorded and associated with the encrypted National Health Card (CNS). These records also contain information on sex and age [31].

We included patients registered in the SABEIS database with a confirmed diagnosis of ASD based on the International Statistical Classification of Diseases, Tenth Revision (ICD-10) and Related Health Problems, as specified in the PCDT (Table 1).

Based on retrospective data regarding the utilization of risperidone for the treatment of patients with ASD between 2017 and 2021, we applied a linear trend analysis to estimate the population of individuals with ASD who would be using risperidone in the next 5 years (2022–2026). We opted for the linear trend approach due to the progressive dissemination of this treatment technology within the SUS since 2017, which has been facilitated through programs aimed at expanding access [32] [33]. Consequently, it is reasonable to anticipate a linear upward trend in this context [34]. The retrospective population data (2017–2021) are openly accessible in the Open Science Framework (https://osf.io/8fmjq/).

### 2.4.2 Model Calculated from Theoretical Data

Delimitation of the population for the theoretical data was conducted using population projections from the Brazilian

Institute of Geography and Statistics (IBGE) for each year, with the data stratified for children and adolescents as well as adults. From the population projection, the prevalence of individuals with ASD was calculated, along with those diagnosed with ASD exhibiting aggressive behavior. Among patients with aggressive behavior associated with ASD, a coverage rate of 70% by the SUS was considered [35]. Retrospective data (2017–2021) used to estimate the BIA from the theoretical model are available in electronic supplementary material (ESM) 1. Table 1 provides an overview of the general parameters adopted in the analysis.

### 2.5 Budget Impact Calculation

The methodology outlined in the Methodological Guidelines—Manual BIA for the Brazilian Health System was utilized, employing the corresponding spreadsheet [38]. Based on the population delimitation and expenditures per patient, the budgetary impact per year was calculated.

### 2.6 Economical Adjustments

Adjustments for inflation and discount rate are not recommended in BIAs [18]. However, the purpose of the BIA is to provide information for current financial planning; therefore, the value obtained in a BIA represents a present value and will be used by the manager in budget estimates for the current financial year, without adjustments for inflation or influenced by discounts. Considering the short time horizon of the research, the fact that the values of inputs and procedures are not annually updated by the SUS, and that the BIA results should reflect the real impact at the time of analysis, no discounts, updates, or indexing were applied.

All data were processed in Brazilian currency (R$) and converted to international dollars (I$) using the purchasing power parity methodology [39]. This methodology provides an alternative approach to the exchange rate and is particularly useful for international comparisons. It allows for the measurement of how much a given currency can purchase, independent of market influences or economic policies that determine the exchange rate. It takes into account various factors, such as differences in income and cost of living.

### 2.7 Statistical Analysis

Descriptive statistics were employed to characterize the expenses associated with risperidone and monitoring adverse events in the three scenarios, as well as the estimated population in both the theoretical and real data methods. A parametric Student's *t*-test was used to compare the theoretical and real data methods across scenarios. A significance level of $p < 0.05$ was adopted.

### 2.8 Data Availability

The data utilized for this BIA, including the sensitivity analysis considering the range of prevalence, are accessible in the Open Science Framework (https://osf.io/8fmjq/).

## 3 Results

### 3.1 Population

Between 2022 and 2026, real data estimated a total of 132,004 children and 908,943 adults with ASD exhibiting aggressive behavior to be served, respectively (Table 2). On the other hand, theoretical data suggested a population of 471,746 children and 1,637,478 adults to be assisted. In both populations of children and adults, theoretical data were higher, with statistical significance in all years ($p < 0.001$). Our sensitivity analyses (ESM 2) showed that the population estimated from the extreme prevalence ranges (ASD 0.3–2%; aggressive behavior: 8–68%) remained significantly different from the real data.

#### 3.1.1 Comparison of Budget Impact between Theoretical Data and Real Data

Total SUS expenditures over the course of 5 years, depending on the scenario, ranged from I$7,630,040.73 to I$32,471,936.35 for children and I$60,329,288.17 to I$78,508,148.17 for adults, based on real data. On the other hand, considering theoretical data, the total expenses for SUS ranged from I$27,267,667.60 to I$116,045,771.98 for children and I$108,684,353.29 to I$ 139,094,659.00 for adults. Similar to the population, expenditures estimated by theoretical data were higher for both children (Table 3) and adults (Table 4). Sensitivity analyses (ESM 3) with extreme prevalence showed significant differences in budgetary impact in all scenarios and both populations.

#### 3.1.2 Comparison of Budget Impact between Scenarios

The findings in the tables suggest that scenarios 1 and 3 are the most economically beneficial for the SUS to serve children and adults, respectively, with the lowest monetary value. The costliest scenario for the SUS among children was associated with the use of risperidone in oral solution (scenario 3).

Spending on monitoring adverse events represented an important estimate of expenditure for the SUS, ranging from I$5,555,692.16 to I$19,854,516.17 for children and I$38,254,958.17 to I$68,917,030.43 for adults over a period of 5 years. Estimated expenditures for monitoring adverse events ranged from 17% to 74% in children and 50% to 63% in adults.

**Table 2** Comparison of estimated population from real and theoretical data

| Year | Model calculated from real data | Model calculated from theoretical data | *p*-value | Model calculated from real data | Model calculated from theoretical data | *p*-value |
|---|---|---|---|---|---|---|
| | Children [$n = 132,004$] | Children [$n = 471,746$] | < 0.001 | Adults [$n = 908,943$] | Adults [$n = 1,637,478$] | < 0.001 |
| 2022 | 19,586 | 96,700 | < 0.001 | 139,354 | 325,860 | < 0.001 |
| 2023 | 23,040 | 95,402 | < 0.001 | 158,185 | 330,105 | < 0.001 |
| 2024 | 26,346 | 94,130 | < 0.001 | 182,025 | 334,197 | < 0.001 |
| 2025 | 29,927 | 92,889 | < 0.001 | 207,191 | 338,135 | < 0.001 |
| 2026 | 33,105 | 92,625 | < 0.001 | 222,188 | 309,181 | < 0.001 |
| Average (±SD) | 26,400.8 (5364.6) | 94.349,2 (1716.6) | < 0.001 | 181.788,6 (34,041.4) | 327,495.6 (11,213.9) | < 0.001 |

*SD* standard deviation

## 4 Discussion

### 4.1 Main Findings

The findings of this study suggest that conducting a BIA based on theoretical data may result in a different population estimate and cost estimate compared with using real data. In our study, the estimates derived from the theoretical model were higher when compared with the model calculated from real data. Both the theoretical and real models exhibited significant differences, even after conducting sensitivity analyses. Furthermore, with regard to the use of risperidone in ASD, the monitoring of adverse events entails a considerable expense for the SUS.

Considering that the result of a BIA aids managers in making decisions regarding health system coverage, understanding potential divergences between these different models can assist in proposing and refining BIAs that

**Table 3** Budget impact analysis in different scenarios among children, considering real-world and theoretical data

| Model calculated from real data | | | | | Model calculated from theoretical data | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Year | Population | Risperidone (I$) | Monitoring examinations (I$) | Total (I$) | Population | Risperidone (I$) | Monitoring examinations (I$) | Total | *p*-Value |
| Scenario 1: Risperidone (I$15.71 per year); monitoring examinations (I$42.08 per year) | | | | | | | | | |
| 2022 | 19,586 | 307,780.00 | 824,321.89 | 1,132,101.89 | 96,700 | 1,519,571.43 | 4,069,842.06 | 5,589,413.49 | < 0.001 |
| 2023 | 23,040 | 362,057.14 | 969,691.43 | 1,331,748.57 | 95,402 | 1,499,174.29 | 4,015,212.75 | 5,514,387.03 | < 0.001 |
| 2024 | 26,346 | 414,008.57 | 1,108,832.05 | 1,522,840.62 | 94,130 | 1,479,185.71 | 3,961,677.70 | 5,440,863.41 | < 0.001 |
| 2025 | 29,927 | 470,281.43 | 1,259,546.67 | 1,729,828.10 | 92,889 | 1,459,684.29 | 3,909,447.36 | 5,369,131.64 | < 0.001 |
| 2026 | 33,105 | 520,221.43 | 1,393,300.12 | 1,913,521.55 | 92,625 | 1,455,535.71 | 3,898,336.31 | 5,353,872.02 | < 0.001 |
| Total | 132,004 | 2,074,348.57 | 5,555,692.16 | 7,630,040.73 | 471,746 | 7,413,151.43 | 19,854,516.17 | 27,267,667.60 | < 0.001 |
| Scenario 2: Risperidone (I$28.57 per year); monitoring examinations (I$42.08 per year) | | | | | | | | | |
| 2022 | 19,586 | 559,600.00 | 824,321,89 | 1,383,921.89 | 96,700 | 2,762,857.14 | 4,069,842.06 | 6,832,699.21 | < 0.001 |
| 2023 | 23,040 | 658,285.71 | 969,691.43 | 1,627,977.14 | 95,402 | 2,725,771.43 | 4,015,212.75 | 6,740,984.17 | < 0.001 |
| 2024 | 26,346 | 752,742.86 | 1,108,832.05 | 1,861,574.90 | 94,130 | 2,689,428.57 | 3,961,677.70 | 6,651,106.27 | < 0.001 |
| 2025 | 29,927 | 855,057.14 | 1,259,546.67 | 2,114,603.82 | 92,889 | 2,653,971.43 | 3,909,447.36 | 6,563,418.79 | < 0.001 |
| 2026 | 33,105 | 945,857.14 | 1,393,300.12 | 2,339,157.26 | 92,625 | 2,646,428.57 | 3,898,336.31 | 6,544,764.88 | < 0.001 |
| Total | 132,004 | 3,771,542.86 | 5,555,692.16 | 9,327,235.02 | 471,746 | 13,478,457.14 | 19,854,516.17 | 33,332,973.32 | < 0.001 |
| Scenario 3: Risperidone (I$203,90); monitoring examinations (I$42.08 per year) | | | | | | | | | |
| 2022 | 19,586 | 3,993,678.67 | 824,321.89 | 4,818,000.56 | 96,700 | 19,717,590.48 | 4,069,842.06 | 23,787,432.54 | < 0.001 |
| 2023 | 23,040 | 4,697,965.71 | 969,691.43 | 5,667,657.14 | 95,402 | 19,452,922.10 | 4,015,212.75 | 23,468,134.84 | < 0.001 |
| 2024 | 26,346 | 5,372,074.86 | 1,108,832.05 | 6,480,906.90 | 94,130 | 19,193,555.24 | 3,961,677.70 | 23,155,232.94 | < 0.001 |
| 2025 | 29,927 | 6,102,257.81 | 1,259,546.67 | 7,361,804.48 | 92,889 | 18,940,509.43 | 3,909,447.36 | 22,849,956.79 | < 0.001 |
| 2026 | 33,105 | 6,750,267.14 | 1,393,300.12 | 8,143,567,26 | 92,625 | 18,886,678.57 | 3,898,336.31 | 22,785,014.88 | < 0.001 |
| Total | 132,004 | 26,916,244.19 | 5,555,692.16 | 32,471,936.35 | 471,746 | 96,191,255.81 | 19,854,516.17 | 116,045,771.98 | < 0.001 |

*I$* International dollars

**Table 4** Budget impact analysis in different scenarios among adults considering real-world and theoretical data

| Model calculated from real data | | | | | Model calculated from theoretical data | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Year | Population | Risperidone (I$) | Monitoring examinations (I$) | Total (I$) | Population | Risperidone (I$) | Monitoring examinations (I$) | Total (I$) | *p*-Value |
| Scenario 1: Risperidone (I$42.85 per year); monitoring Examinations (I$42.08 per year) | | | | | | | | | |
| 2022 | 139,354 | 5,972,314.29 | 5,865,033.83 | 11,837,348.11 | 325,860 | 13,965,428.57 | 13,714,568.10 | 27,679,996.67 | < 0.001 |
| 2023 | 158,185 | 6,779,357.14 | 6,657,579.80 | 13,436,936.94 | 330,105 | 14,147,357.14 | 13,893,228.69 | 28,040,585.83 | < 0.001 |
| 2024 | 182,025 | 7,801,071.43 | 7,660,941.07 | 15,462,012.50 | 334,197 | 14,322,728.57 | 14,065,449.93 | 28,388,178.50 | < 0.001 |
| 2025 | 207,191 | 8,879,614.29 | 8,720,110.10 | 17,599,724.39 | 338,135 | 14,491,500.00 | 14,231,189.72 | 28,722,689.72 | < 0.001 |
| 2026 | 222,188 | 9,522,342.86 | 9,351,293.37 | 18,873,636.22 | 309,181 | 13,250,614.29 | 13,012,593.99 | 26,263,208.28 | < 0.001 |
| Total | 908,943 | 38,954,700,00 | 38,254,958.17 | 77,209,658.17 | 1,637,478 | 70,177,628.57 | 68,917,030.43 | 139,094,659.00 | < 0.001 |
| Scenario 2: Risperidone (I$44.28 per year); monitoring examinations (I$42.08 per year) | | | | | | | | | |
| 2022 | 139,354 | 6,171,391.43 | 5,865,033.83 | 12,036,425.25 | 325,860 | 13,723,009.81 | 13,714,568.10 | 27,437,577.91 | < 0.001 |
| 2023 | 158,185 | 7,005,335.71 | 6,657,579.80 | 13,662,915.52 | 330,105 | 13,901,780.38 | 13,893,228.69 | 27,795,009.07 | < 0.001 |
| 2024 | 182,025 | 8,061,107.14 | 7,660,941.07 | 15,722,048.21 | 334,197 | 14,074,107.62 | 4,065,449.93 | 28,139,557.55 | < 0.001 |
| 2025 | 207,191 | 9,175,601.43 | 8,720,110.10 | 17,895,711.53 | 338,135 | 14,239,949.43 | 14,231,189.72 | 28,471,139.16 | < 0.001 |
| 2026 | 222,188 | 9,839,754.29 | 9,351,293.37 | 19,191,047.65 | 309,181 | 13,020,603.62 | 13,012,593.99 | 26,033,197.61 | < 0.001 |
| Total | 908,943 | 40,253,190.00 | 38,254,958.17 | 78,508,148.17 | 1,637,478 | 68,959,450.87 | 68,917,030.43 | 137,876,481.30 | < 0.001 |
| Scenario 3: Risperidone (I$24.28 per year); monitoring examinations (I$42.08 per year) | | | | | | | | | |
| 2022 | 139,354 | 3,384,311.43 | 5,865,033.83 | 9,249,345.25 | 325,860 | 7,913,742.86 | 13,714,568.10 | 21,628,310.95 | < 0.001 |
| 2023 | 158,185 | 3,841,635.71 | 6,657,579.80 | 10,499,215.52 | 330,105 | 8,016,835.71 | 13,893,228.69 | 21,910,064.40 | < 0.001 |
| 2024 | 182,025 | 4,420,607.14 | 7,660,941.07 | 12,081,548.21 | 334,197 | 8,116,212.86 | 14,065,449.93 | 22,181,662.79 | < 0.001 |
| 2025 | 207,191 | 5,031,781.43 | 8,720,110.10 | 13,751,891.53 | 338,135 | 8,211,850.00 | 14,231,189.72 | 22,443,039.72 | < 0.001 |
| 2026 | 222,188 | 5,395,994.29 | 9,351,293.37 | 14,747,287.65 | 309,181 | 7,508,681.43 | 13,012,593.99 | 20,521,275.42 | < 0.001 |
| Total | 908,943 | 22,074,330.00 | 38,254,958.17 | 60,329,288.17 | 1,637,478 | 39,767,322.86 | 68,917,030.43 | 108,684,353.29 | < 0.001 |

*I$* International dollars

provide more accurate measurements of costs within the context of HTA.

## 4.2 Comparison with Previous Studies

The estimate of people to be served in this study was almost four times higher in theoretical data when compared with real-world data. These differences arise due to the nature of the data. The theoretical model of BIA in this study was calculated based on estimates from epidemiological studies. This means that these data depend on the availability of robust population surveys with methodological quality, which are scarce for ASD, particularly in low- and middle-income countries such as Brazil [40]. On the other hand, our real model was calculated using retrospective data on risperidone dispensing in the SUS, representing a more accurate estimate. The population of interest is one of the essential variables for the robust calculation of BIA and is necessary to provide an accurate estimate of the number of people who are likely to be treated with the technology [41].

Measured demand and epidemiological methods (with variables of prevalence, incidence, restrictions, and additional demands) can be used for the calculation but the latter tends to overestimate the budgetary impact. Similar to our results, other studies have found population discrepancies when comparing real data and theoretical data, despite having been constructed following the main international guidelines [17, 42, 43].

Among the factors that can influence population discrepancies between theoretical and real-world values in BIA, the scarcity of reliable theoretical data stands out, especially from population surveys [35, 37]. In the case of Brazil, the country where this study was conducted, Azevedo and Mendonça point out that factors such as the geographic scope, scarcity of trained human resources to conduct surveys, selective losses of specific groups due to social and racial inequalities, and low population adherence make it challenging to carry out robust studies [45].

ASD is a clinically underreported condition. This underreporting is influenced by socioeconomic factors, racial and

ethnic disparities, sex, and access to health services [46–48]. Furthermore, lower rates of ASD are reported in contexts with limited resources, which can compromise the availability of reliable theoretical data [49]. These challenges, inherent to the clinical condition, also undermine the sensitivity of budget impact analyses that solely rely on theoretical data [8].

As the estimation of the budgetary impact is associated with a specific population and the costs associated with serving that population, any inaccuracies in calculating these variables can lead to significant differences in the estimates. In this regard, we identified significant differences when comparing the models calculated using theoretical and real data. Our study revealed that the projected expenditures based on theoretical data calculations exceeded the real data values by more than I$8,604,534.35. These results align with the findings presented by Faleiros et al., who reported an overestimation of data by almost US$5 billion [43], and Snider et al., who identified a 25-fold discrepancy between theoretical and real data [50].

This study is one of the first to compare BIA results from models calculated using theoretical and real data. Geenen et al. highlighted a similar situation in a BIA conducted to inform decisions regarding access to 10 oncology drugs in The Netherlands, where the estimated value was €140.7 million, while only €82.1 million was actually spent [51]. With the objective of comparing the estimated values provided by pharmaceutical companies when assessing the costs of recommended medicines in Wales, Keeping et al. revealed that total spending was overestimated by 41–62% over a span of 3 years [52]. Similar discrepancies were reported by Broder et al. [53]. This is a concern because health system managers often depend on BIAs to establish drug coverage policies and assess their impact on their financial outcomes [50]. Our findings further highlight these potential variations.

Consistent with our expectations, our study revealed discrepancies between theoretical and real data, as well as variations across different scenarios, depending on the pharmaceutical form used. Regarding children, the most advantageous scenario resulted in a 5-year cost of I$3,460,986.48, while the least economically favorable scenario involved the utilization of risperidone oral solution. Extensive research has been conducted on the acceptability of oral medications among children for several years [54–56]. Although children are generally more inclined to accept oral solutions, a randomized controlled clinical trial demonstrated that both solid and liquid oral formulations were well received, and there was no significant preference between tablets and liquid formulations among children [57]. Ansah et al. and Bagenda et al. concluded that tablet formulations led to improved adherence in the pediatric population compared with liquid solutions [58, 59]. Spomer et al. compared uncoated placebo tablets with sweet syrup in hospitalized children and concluded that the acceptability of the tablets was at least as good as that of the syrup [60]. Although the BIA does not assess this aspect, it is crucial to consider that the most economically favorable treatments are not always well adhered to and accepted by patients. Therefore, additional studies are necessary to evaluate this aspect.

An important finding of this study was the cost of monitoring adverse events. Risperidone is not indicated for use in children under 5 years of age because of the limited evidence of safety in this population. For individuals with ASD, the estimated overall prevalence of adverse events associated with antipsychotic use is approximately 50%, often leading to discontinuation [61]. Adverse events, particularly metabolic and neurological events, should be monitored through laboratory tests and regular consultations with a multidisciplinary team [62]. A systematic review based on three randomized controlled clinical trials revealed that risperidone is effective in ASD. However, these benefits must be carefully balanced against its safety profile, which includes potential weight gain and increased prolactin levels [63]. Therefore, this BIA also provides a critical parameter for assessing the costs associated with monitoring adverse events associated with the use of risperidone in ASD.

### 4.3 Strengths and Limitations

This study stands out as one of the few that conducted a BIA using both theoretical and real data. The model utilized retrospective values (2017–2021) from the Brazilian population served by a significant and comprehensive SUS database called SABEIS, which holds the potential to provide valuable information for the SUS. Moreover, this study adhered to the Brazilian guidelines for BIA, which are aligned with international standards.

The model calculated from real data has certain limitations. The data utilized in this study were derived from the SABEIS database, which does not provide an estimate of the prevalence of ASD in Brazil. Instead, it represents the retrospective demand from the SUS for all patients with ASD and aggressive behavior who are prescribed risperidone in that country. In addition, Brazil does not have enough data to accurately assess real spending on monitoring adverse events. Therefore, we have adopted an ideal scenario in which all patients with ASD who use risperidone would undergo monitoring. The model calculated using theoretical data also has limitations, primarily attributed to the scarcity of population surveys on ASD in Brazil, as previously mentioned.

While analyzing risperidone costs, our model solely considers the direct expenses associated with procuring the medication, without accounting for the entire procurement

process. In addition, our study did not incorporate other potentially significant costs, such as those associated with preventing hospitalization and the utilization of health services, due to the limited availability of data on these aspects. This limitation should be acknowledged when interpreting the results.

### 4.4 Implications for Future Policy And Research

Our results demonstrated that the population and cost estimates in the BIA were considerably higher when comparing the model calculated from theoretical data with the model calculated from real data. These discrepancies remained even after sensitivity analyses were performed on the theoretical model, considering the extremes of prevalence. Such discrepancies can have consequences for the incorporation of new drugs and the management of health services, given the limited accuracy of theoretical data due to the factors previously discussed. In light of this, it is crucial to raise awareness among researchers conducting budget impact analyses to utilize real data whenever feasible.

Our findings align with other studies and underscore the importance of using real data in such analyses. To achieve this, efforts are required to develop strategies that enhance the availability of real-world data for meaningful economic evaluations.

## 5 Conclusion

The data revealed notable disparities in population and cost estimations between theoretical and real BIA data regarding the utilization of risperidone and the monitoring of adverse events in ASD. The cost values, represented in I$, associated with the monitoring of adverse events posed important expenses for the SUS.

The utilization of retrospective data proved valuable in achieving a more precise estimation of the target population for the technology and, subsequently, assessing its budgetary impact. Making decisions based on real data is an encouraging trend and, in this instance, the findings can contribute to the formulation of policy measures aimed at enhancing medication access for patients with ASD.

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## Declarations

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**Conflicts of Interest** Luis Phillipe Nagem Lopes, Alexander Itria and Luciane Cruz Lopes declare that they have no conflicts of interest.

**Ethics Approval** Ethical approval is not required for simulation-based studies in the present study's jurisdiction.

**Consent to Participate** Not applicable.

**Consent for Publication (from patients/participants)** Not applicable.

**Code Availability** The parameter values utilized in the model for this BIA are accessible in the published article (as well as its supplementary information files). The foundational data can be located on the Open Science Framework: https://osf.io/8fmjq/

**Data Availability** The data used for this BIA and the sensitivity analysis considering the prevalence ranges are available in the Open Science Framework (https://osf.io/8fmjq/).

**Author Contributions** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by LPNL and Alexander Itria. The first draft of the manuscript was written by LPNL and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.



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