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Article

# Economic impact of pharmaceutical interventions in a medium complexity Brazilian university hospital

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Clinical pharmacists have been increasing their participation mainly through actions aimed at patient care, with international studies demonstrating favorable cost-benefit ratio from pharmacists interventions. However, there are few studies carried out in Brazil about the subject. This study aims to assess the economic impact of pharmaceutical interventions (PIs) in a hospital setting performed in October 2018. Each performed PI was registered and associated with the direct cost of drugs for economic impact analysis. A total of 185 PIs were evaluated, comprising 106 patients. The most intervened drugs were antibiotics, presenting the greatest economic impact, R$2,370. The total economic impact was R$2,578, mainly in the Pediatric Intensive Care Unit that represented R$1,701. Regarding the economic impact by PI as the "Suspension of drug without indication" saved R$1,360 while the "Inclusion of required drugs" cost R$807. It was estimated that the savings would be R$30,936 and, if PIs were performed at day zero, the savings would be R$79,728 per year. An average of 1.75 PI per patient was performed with an economic impact of R$14 per PI. Our results showed that clinical pharmacist's role in the evaluation of pharmacotherapy is important for patients' health and represents a positive economic impact.

**Keywords:** Pharmaceutical intervention. Direct costs. Economic impact. Hospital setting.

## INTRODUCTION

Clinical Pharmacy is defined by the American College of Clinical Pharmacy as a health science discipline in which pharmacists provide patient care that optimizes medication therapy and promotes health, wellness, and disease prevention. It comprises the analysis of exams, interactions and drug incompatibilities, dosage, among other responsibilities, being essential in the assessment of the clinical conditions of the inpatient (American College of Clinical Pharmacy, 2008).

This assessment is the prescription risk-benefit analysis that the pharmacist executes as part of his professional routine and which is discussed with the multidisciplinary team during medical visits (Correia *et al.*, 2017). It is essential to prevent and resolve Medication Errors and Adverse Drug Reactions (ADRs), with Pharmaceutical Intervention (PI) being the way the pharmacist suggests changes in medical procedures (Aguiar et al., 2018).

A PI is any action taken by a pharmacist that directly results in a change in the patient management or therapy (Gallagher, McCarthy, Byrne, 2014; Mongaret *et al*., 2018). The Pharmaceutical Society of Australia (2018) adds that it is a pharmaceutical activity directed to the most effective use of the medication. Moreover, according to the Brazilian Consensus on Pharmaceutical Care, a PI is "a planned, documented and performed act with the user and health professionals, which aims to solve or prevent problems that may interfere with pharmacotherapy, being an integral part of the pharmacotherapeutic monitoring process" (Pan-American Health Organization, 2002).

A quality indicator is a common management tool to track performance and identify areas of improvement (Boutin *et al.*, 2019). Monitoring of PIs in institutional management may be used as a quality indicator, since it

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permits the assessment of outcomes in monetary indicators (Cazarim *et al*., 2020). This allows the evaluation of multidisciplinary teams as to the implementation of therapeutic protocols and compliance with institutional quality standards, as well as in the evaluation of costs (Nunes *et al*., 2008; Finatto, 2011).

Several studies evaluate the presence of the pharmacist in different hospital and outpatient services, showing the importance of this professional in the health sectors (Klopotowska *et al*., 2010; Gallagher, McCarthy, Byrne, 2014). Tasaka *et al.* (2018) conducted a study that comprised the collection of PIs from 20 hospitals over two years with the aim of analyzing potential Drug Related Problems (DRPs). During this period, 2,376 PIs were performed (68,2% of which in elderly patients), the majority of which were related to overdose, followed by omission of prescription medication, contraindications and duplicated prescription. It was observed that of the total of IFs performed, 1,678 DRPs were avoided. The study showed that the pharmacist plays an important role in the safety of elderly patients and in the prevention of DRP.

Daupin *et al.* (2019) carried out a prospective cross-sectional study in the oncology department of a university hospital with 800 beds, in order to assess the impact of PIs in the safety of patients on chemotherapy. For one month, all chemotherapy prescriptions were evaluated by the pharmacist, assessing the need to perform PIs. A total of 1,346 prescriptions were evaluated and 129 PIs were performed, and 69.8% of these PIs had a significant impact on patient safety. A great number of PIs were also observed on day 1 of chemotherapy and a large number was related to the type of tumor. This study highlights the importance of the pharmacist in maintaining the safety of prescriptions of cancer patients caring.

The performance of PIs, in addition to their clinical impact on the evaluation of pharmacotherapy and maintaining the patient safety, also plays an important role in reducing operating costs (De Rijdt, Willems, Simoens, 2008).

The importance of the pharmacist in the hospital environment is discussed in several studies that address the rational use of drugs and the impact of this professional on clinical outcomes and the cost reduction of inpatient care (Sjölander *et al*., 2019; Perlman *et al*., 2019). For example, Aguiar *et al.* (2018) conducted a retrospective observational study in an oncology hospital, covering the period from July to August of 2016, in which they evaluated the economic impact of pharmaceutical evaluation in detecting and preventing prescription errors of antineoplastic agents. From the 6,104 prescriptions evaluated, 275 (4.5%) had errors. Having intercepted the errors represented savings of R$54,081.01 and the expenses of R$20,863.36 resulted in a positive balance of R$33,217.65, therefore each PI saved R$126.78. This study shows how few implementations, such as the analysis of prescriptions, are able to identify and prevent DRPs, in addition it can also promote a substantial cost saving for health services.

At the *Hospital Universitário da Universidade de São Paulo* (HU-USP/SP), the Clinical Pharmacy Service has been in service since 1991. Initially the service was established in the Women's Health Unit and after 1998 it expanded to all inpatients care units, which comprise Adult Intensive Care Unit (Adult ICU), Surgical Unit, Internal Medicine Unit, Pediatric General Unit, Pediatric Intensive Care Unit (Pediatric ICU), Neonatal Intensive Care Unit (Neonatal ICU), in addition to Pharmacovigilance (Storpirtis *et al*., 2008).

The roles performed by clinical pharmacists have patient safety as the main focus, ranging from admission to hospital discharge. The service performed by the clinical pharmacy team at the HU-USP/SP represents an important impact on clinical outcomes, however, the economic impact that those professionals promote is still superficial (Storpirtis *et al*., 2008).

Thus, studies that assess the impact of PIs in the clinical and economic scope are essential to better understand the importance of the pharmaceutical professional (Sjölander *et al*., 2019; Perlman *et al*., 2019).

The aim of this research is to evaluate the economic impact of pharmaceutical interventions in a medium complexity Brazilian university hospital.

## MATERIAL AND METHODS

The study was carried out in a secondary care university hospital in the city of São Paulo (*Hospital Universitário da Universidade de São Paulo* - HU-

USP/SP), containing 188 active beds, which serves the population of Butantã district, about 400,000 inhabitants, as well as students, university employees and their families through public health system (*Sistema Único de Saúde* - SUS).

The Clinical Pharmacy Service has eight pharmacists and sixteen pharmacy residents who carry out pharmacotherapeutic follow-up for all inpatients and if it is necessary they perform PIs. These interventions are recorded in the hospital's electronic shift-change record ranked according to the classification prepared by the Clinical Pharmacy Service (Chart I), and transcribed to a database, called "Database of PIs", which includes the following data: date of the PI, inpatient care unit, anonymized hospital record, age, gender, medication and the classification of PIs.

**CHART I –** Classification of pharmaceutical interventions that have a direct economic relationship.

| CATEGORY | |
|---|---|
| Dosage | Correction of dosage - reconciliation |
| | Correction for rounding dose |
| | Correction of subdose |
| | Correction of overdose |
| | Correction of exceeded maximum daily dose |
| | Renal/hepatic dosage adjustment |
| | Correction of administration frequency |
| | Sequential therapy (intravenous to oral) |
| Presentation | Drug presentation - substitution |
| Interaction | Drug interaction detected |
| Safety | Item forgotten to be suspended |
| | Item forgotten to be prescribed |
| | Renal function lab test request |
| | Drug dosing |
| | Vancomycin adjustment by PK/PD |
| Requirement | Suspension of drug without indication |
| | Drug substitution |
| | Inclusion of required drug |
| | Non-standard drugs - substitution/suspension |
| | Adjustment to therapy protocol |
| Parenteral nutrition | PN - item inclusion on prescription |
| | PN - item suspended (not suitable for treatment) |
| | PN - substitution of item |
| | PN - final volume correction |
| | PN - composition correction |
| | PN - dosage correction |
| | PN - osmolarity correction |

**CHART I –** Classification of pharmaceutical interventions that have a direct economic relationship.

PK/PD: pharmacokinetic/pharmacodynamic; PN: parenteral nutrition. From the *Hospital Universitário da Universidade de São Paulo's* Clinical Pharmacy Service (Oct/2018).

## Eligibility criteria

Only categorized PIs from October 2018 Database suggested by pharmacists and accepted by the healthcare team and those with a direct economic relationship were included in this study.

PIs that did not have a direct economic relationship or the necessary information for a complete assessment were excluded from analysis.

## Variables

The types of variables present in this study were continuous quantitative (Age, drug cost, administered dose, length of stay), discrete quantitative (Frequency and duration of the treatment) and nominal qualitative (Genre, route, PI date, type of PI, drug).

**Data collection and analysis**

The considered PIs were those contained in the “Database of PIs”. For the calculation of costs, acquisition prices of standard medicines were used. These were obtained from the hospital’s management system, considering the average price of the last three acquisitions obtained through bids. For non-standard drugs used in the Hospital, the values were collected from the online platform KairosWeb, considering the maximum values for the state of São Paulo during the month of August 2019. These data were compiled in the spreadsheet “Database of Drugs”. For the calculations, the “General Database” was created collecting the information from the “Database of PIs” and the “Database of Drugs”, in which anonymized patient information, drug costs, pharmacotherapies and PIs performed were compiled (Figure 1).

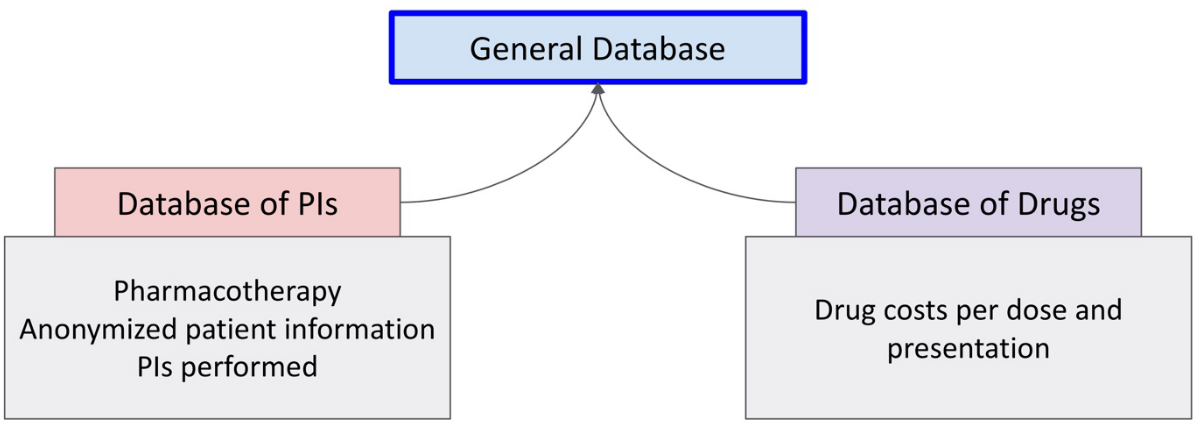


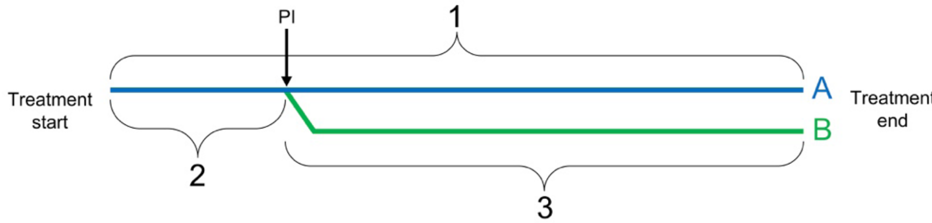

**FIGURE 1 -** Flowchart for data analysis. The arrows indicate that both PIs and Drugs Databases are compiled into the General Database.

The data analysis allowed the creation of Tables I, II and III, which are the basis for the results of this study.

The evaluation of direct costs of PIs is a type of economic analysis that allows the evaluation of the costs of an intervention by calculating the difference between the cost of the previous therapy and the one implemented by the PI. Likewise, it is possible to assess the cost of a therapy that was suspended (Yasunaga *et al*., 2017).

For the calculation of the economic analysis, regarding a single use vial, one dose was equivalent to the price of an entire bottle. Even if the patient has not used the full bottle, especially in the case of pediatric patients, it will not be used in another patient due to the inherent risks of handling the product in the absence of an adequate environment.

Figure 2 shows the equation used to calculate the economic impact from a pharmaceutical intervention. Letter A represents the full treatment without the PI and letter B the treatment changed after the intervention. The cost of the full treatment without the PI is represented by the number 1, while the cost of the full treatment including the change by the PI is represented by the numbers 2 + 3. From this equation it is possible to compare the costs of different treatments, evaluating the economic impact from a PI (Saokaew, Maphanta, Thangsomboon, 2009).




$$Economic\ impact = \underbrace{\left[\frac{\$A}{dose} \times \frac{doses}{day} \times duration\ of\ full\ treatment\right]}_{1} - \left[\underbrace{\left(\frac{\$A}{dose} \times \frac{doses}{day} \times duration\ before\ PI\right)}_{2} + \underbrace{\left(\frac{\$B}{dose} \times \frac{doses}{day} \times duration\ after\ PI\right)}_{3}\right]$$

**FIGURE 2 -** Treatment timeline and the equation used to calculate the economic impact of a pharmaceutical intervention. Letters A and B are the different treatments and the numbers 1, 2 and 3 are the period costs. Letter A is the treatment without PI and letter B is the treatment after PI. Number 1 represents the period cost of the full treatment without PI, number 2 is the period cost before PI and the number 3 is the period cost after PI (adapted from Saokaew, Maphanta, Thangsomboon, 2009).

It is important to explain the difference between real economic impact and estimated economic impact, which was used in this work, as well as the difference between costs without PI and costs if PI since the first day of therapy.

The real economic impact was considered to be the value calculated by the equation in Figure 2, in which the duration of the full treatment and the duration of treatment after PI were performed. The economic impact was also calculated as if the PI had been performed on the first day of treatment, before the intake of the first dose, describing a quantitative assessment of the likely results that we called "estimated economic impact". For its calculation, the equation mentioned above was not used, but the difference between the PI cost from day zero and the cost without PI (Rascati, 2010). Also, the real economic impact can be calculated by the sum of the negative and positive real economic impact, and the estimated economic impact by the sum of the negative and positive estimated economic impact.

Cost without PI is the cost of treatment without PI performed, it is the treatment as prescribed without intervention from the pharmacist. Cost if PI since the first day of therapy represents the cost of the treatment changed by the PI being prior to the first dose intake, so it is the cost of treatment with PI performed from the beginning of therapy.

In addition, the economic impact can be subdivided into negative (the sum of PIs that increased costs, thus decreasing the economic impact) and positive (the sum of PIs that decreased costs, thus increasing the economic impact).

In this study, the differences between the real, estimated, positive and negative economic impacts of PIs were analyzed, separating the analysis by PI, inpatient care unit and drug class for better comprehension.

### Evaluation by the research ethics committee

This research project was approved on both Research Ethics Committees of the *Faculdade de Ciências Farmacêuticas da Universidade de São Paulo* (CAAE 16398719.0.0000.0067) and *Hospital Universitário da Universidade de São Paulo* (CAAE 16398719.0.3001.0076).

## RESULTS

From the 387 PIs observed in October 2018, 202 were excluded, 138 due to the lack of direct economic correlation and 64 for not presenting complete information that enabled the cost assessment. Thus, 185 IFs were analyzed.

It is important to notice that some PIs were performed on the same patient, thus, the total number of patients differs from the total number of PIs, being 106 and 185, respectively.

The average time of treatment until the PI was 3 ± 4.5 days, with the shortest time being 0 days and the longest being 31 days. The most prevalent intervened drugs were: 27% antibiotics; 10% anticoagulants; 10% antacids; 10% anti-inflammatories; 6% non-opioid analgesics and 5% antihypertensive drugs. Antibiotics, anticoagulants and antacids represent almost 50% of the medications intervened in October.

## Cost analysis

In October 2018, the analysis of the 185 PIs showed that the real and the estimated economic impact of the PIs were R$2,578 and R$6,644, respectively, of these, 21 PIs resulted in cost reduction and 64 in cost increase, with an average cost per intervention of R$14.

The average cost per dose of medication was R$4.49 ± 7.16, with the lowest cost being R$0.04 and the highest cost being R$33.10.

## Analysis by drug class

The PIs performed on antibiotics represented about 92% of the real economic impact (R$2,370 from a total of R$2,578) or 58% of the positive real economic impact (R$2,370 from a total of R$4,114). It could reach a value of 98% (R$6,515 out of a total of R$6,644) if we consider the estimated economic impact or 74% of the positive estimated economic impact (R$6,515 out of a total of R$8,789), among the drug classes analyzed. In turn, anticoagulants increased the cost by R$290 on the real economic impact and R$602 on estimated economic impact, as shown on Table I.

**TABLE I -** Economic impact analysis by drug class

| Drug class | Number of PIs | Real economic impact (R$) | Estimated economic impact (R$) |
|---|---|---|---|
| Antibiotics | 49 | 2,370 | 6,515 |
| Anticoagulants | 18 | -290 | -602 |
| Antacids | 17 | -55 | -38 |
| Anti-inflammatories | 17 | 294 | 432 |
| Non-opioids analgesics | 10 | -56 | -61 |
| Antihypertensives | 09 | 23 | 22 |
| Antiemetics | 08 | 117 | 139 |
| Others | 57 | 177 | 237 |
| **TOTAL** | **185** | **2,578** | **6,644** |

PI: pharmaceutical intervention. From the *Hospital Universitário da Universidade de São Paulo's* Clinical Pharmacy Service (Oct/2018).

### Analysis by pharmaceutical intervention

The economic impact analysis by PI is shown in Table II.

**TABLE II -** Economic impact analysis by pharmaceutical intervention

| Pharmaceutical Intervention | Quantity | Total treatment cost (R$) | | | | Real economic impact (R$) | Average of real economic impact (R$) | Estimated economic impact (R$) |
|---|---|---|---|---|---|---|---|---|
| | | With PI | | PI since first therapy day | | | | |
| | | Total | By PI | Total | By PI | | | |
| Inclusion of required drug | 30 | 0 | 0 | 807 | 27 | -807 | -27 | -807 |
| Correction of subdose | 19 | 1,592 | 84 | 2,805 | 148 | -592 | -31 | -1,213 |
| Renal/hepatic dosage adjustment | 6 | 498 | 83 | 546 | 91 | -108 | -18 | -48 |
| Item forgotten to be prescribed | 9 | 451 | 50 | 411 | 46 | -29 | -3 | 40 |
| Correction of dosage - reconciliation | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 |
| Sequential therapy (intravenous to oral) | 2 | 23 | 11 | 7 | 4 | 6 | 3 | 16 |
| Correction for rounding dose | 8 | 309 | 39 | 172 | 22 | 51 | 6 | 137 |
| Drug presentation - substitution | 2 | 168 | 84 | 51 | 26 | 108 | 54 | 117 |
| Non-standard drugs - substitution/suspension | 5 | 175 | 35 | 252 | 50 | 160 | 32 | -77 |
| Item forgotten to be suspended | 4 | 297 | 74 | 0 | 0 | 192 | 48 | 297 |
| Correction of administration frequency | 22 | 1,454 | 66 | 1,280 | 58 | 255 | 12 | 174 |
| Correction of overdose | 24 | 2,133 | 89 | 937 | 39 | 467 | 19 | 1,196 |
| Drug substitution | 13 | 1,961 | 151 | 1,193 | 92 | 562 | 43 | 768 |
| Correction of exceeded maximum daily dose | 5 | 1,925 | 385 | 953 | 191 | 953 | 191 | 972 |
| Suspension of drug without indication | 35 | 5,072 | 145 | 0 | 0 | 1,360 | 39 | 5,072 |
| ***Subtotal – negative economic impacts*** | - | - | - | - | - | *-1536* | - | *-2145* |
| ***Subtotal – positive economic impacts*** | - | - | - | - | - | *4114* | - | *8789* |
| **TOTAL** | **185** | **16,059** | **87** | **9,415** | **51** | **2,578** | **14** | **6,644** |
| **TOTAL estimated impact annually** | **2220** | **192,798** | **87** | **112,980** | **51** | **30,956** | **14** | **79,728** |

PI: pharmaceutical intervention. From the *Hospital Universitário da Universidade de São Paulo's* Clinical Pharmacy Service (Oct/2018).

The PI "Suspension of drug without indication" type (medication prescribed unnecessarily and for this reason subsequently suspended) was responsible for the real savings of R$1,360 and an estimated savings of R$5,072. Then the PIs "Correction of exceeded maximum daily dose" and "Drug substitution" (prescribed dose exceeded the maximum permitted daily dose and replacement of medication with similar indication for example, ranitidine and omeprazole), with combined real and combined estimated savings, respectively, of R$1,515 and R$1,740. These three PIs were responsible for 70% (R$2,875) of the positive real economic impact, from a total of R$4,114. However, the PIs "Inclusion of required drug" and "Correction of subdose" were responsible for 91% (R$1,399) of the negative real economic impact of all PIs (R$1,536), respectively representing R$807 and R$592, also, the total negative estimated impact was R$2,145.

## Analysis by inpatient care unit

The economic impact analysis and the characterization of PIs by inpatient care unit, gender and age of the patients is shown in Table III.

There were more PIs performed on the Pediatric General, Adult General and Surgical units. Furthermore, the real average economic impact per PI and per patient were R$14 and R$24, respectively.

**TABLE III -** Characterization of the pharmaceutical interventions and economic impact analysis by inpatient care unit

| Inpatient care unit | Number of PIs | | | | | | Number of patients | | | | | | Total cost (R$) | | Real economic impact (R$) | Average real economic impact by PI (R$) | Average real economic impact per patient (R$) | Estimated economic impact (R$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | Gender | | | | Age average (years old) | Total | Gender | | | | Age average (years old) | Without PI | PI since first therapy day | | | | |
| | | F | | M | | | | F | | M | | | | | | | | |
| | | # | % | # | % | | | # | % | # | % | | | | | | | |
| Nursery | 4 | 1 | 25 | 3 | 75 | 0.03 | 3 | 1 | 33 | 2 | 67 | 0.03 | 271 | 298 | -2 | -1 | -1 | -27 |
| Surgical | 65 | 17 | 26 | 48 | 74 | 52 | 33 | 13 | 39 | 20 | 61 | 54 | 3,142 | 2,704 | 129 | 2 | 4 | 438 |
| Adult General | 33 | 14 | 42 | 18 | 55 | 63 | 22 | 11 | 50 | 11 | 50 | 60 | 1,711 | 1,776 | 25 | 1 | 1 | -65 |
| Pediatric General | 32 | 13 | 41 | 19 | 59 | 3.6 | 19 | 8 | 42 | 11 | 58 | 3.9 | 1,506 | 856 | 300 | 9 | 16 | 650 |
| Women's Health | 2 | 2 | 100 | 0 | 0 | 25 | 2 | 2 | 100 | 0 | 0 | 25 | 4 | 4 | 0 | 0 | 0 | 0 |
| Adult ICU | 27 | 14 | 52 | 13 | 48 | 60 | 17 | 11 | 65 | 6 | 35 | 60 | 3,016 | 2,264 | 279 | 10 | 16 | 751 |
| Neonatal ICU | 5 | 5 | 100 | 0 | 0 | 0.1 | 3 | 3 | 100 | 0 | 0 | 0.1 | 301 | 93 | 146 | 29 | 49 | 208 |
| Pediatric ICU | 17 | 8 | 47 | 9 | 53 | 4 | 7 | 4 | 57 | 3 | 43 | 4.8 | 6,108 | 1,420 | 1,701 | 100 | 243 | 4,689 |
| **TOTAL** | **185** | **74** | **40** | **110** | **60** | **-** | **106** | **53** | **50** | **53** | **50** | **-** | **16,059** | **9,415** | **2,578** | **14** | **24** | **6,644** |
| **TOTAL estimated impact annually** | **2,220** | **888** | **40** | **1,320** | **60** | **-** | **1,272** | **636** | **50** | **636** | **50** | **-** | **192,798** | **112,980** | **30,935** | **14** | **24** | **79,728** |

PI: pharmaceutical intervention; F: female; M: male; ICU: intensive care unit. From the *Hospital Universitário da Universidade de São Paulo's* Clinical Pharmacy Service (Oct/2018).

Performing the economic analysis of PIs by inpatient care unit, an economic impact of R$2,578 was noticed, reducing the expenses of the Pediatric ICU by R$1,701 (65.9%), of the Pediatric General unit by R$300 (11,6%) and of the Adult ICU by R$279 (10.8%). If the intervention had been performed on the first day of prescription, the estimated impacts would have been R$4,688 (71%), R$650 (10%) and R$751 (11%), respectively, of the total R$6,644.

In summary, in the assessed month the real economic impact was R$2,578 and the estimated economic impact was R$6,644, extrapolating annually it would be R$30,936 and R$79,728 respectively. Also, regarding the cost of treatments, with PI was R$9,415 and without PI was R$16,059, and extrapolating annually, it would be R$112,980 and R$192,798, respectively.

## DISCUSSION

In this work, the proposal was to use the method developed by Saokaew, Maphanta and Thangsomboon (2009) to analyze the economic impact of Pharmaceutical Interventions performed at the hospital. This method was chosen as it presents a well-defined form of data evaluation without requiring major adaptations (Rodrigues *et al.*, 2019). This is the first study carried out at HU-USP/SP that evaluated the economic impact of PIs in the hospital's inpatient care units.

The sample characterization in relation to the intervened drug classes showed that almost half of the PIs were related to only three drug classes, antibiotics, anticoagulants and antacids, with more than 25% of the PIs being related to the adjustments of antibiotic therapy. Anticoagulants and antacids had the most interventions due the need for prophylaxis, venous thromboembolism and for stress ulcers, performed respectively. Therefore, dosage should be constantly changed. In addition, antibiotic therapy is also one of the most altered therapies during the hospitalization of patients, since depending on the response to the antibiotic and the growth of different bacteria in collected cultures. There is also a constant need to evaluate the choice of the antibiotic, as well as its doses, since the antibiotic is selected according to its bacterial coverage and often the patient's renal function.

The study by Tasaka *et al.* (2018), which evaluated 2,376 PIs, with the objective of understanding which types of PIs were more prevalent, analyzing the incidence of PIs by drug classes, concluded that the most intervened drug classes are in decreasing order antibiotics, chemotherapy, antacids and anticoagulants, during the 2 years of his research in 20 hospitals in a Japanese city. Such study highlights the similarity between the findings in our study that certain drug classes are more susceptible to pharmaceutical interventions, reducing undesirable effects in patients and promoting savings to hospital. This study differs from ours in relation to the use of antineoplastic drugs, which are not used in our hospital, and that the study was carried out in partnership with 20 hospitals, besides, a much larger sample size was used than in our study.

Analyzing the economic impact of the PIs by drug classes, over 90%, both of real and estimated economic impact, of all PIs were related to antibiotic therapy adjustment; 25% of PIs were responsible for almost the entire economic impact of PIs in October 2018, a similar result to the study by Yasunaga *et al.* (2017) which presented both the largest number of PIs and the greatest economic impact related to antibiotic adjustment. In their study, carried out in a single Japanese hospital for a period of one year, it was observed that the 1,452 PIs evaluated allowed savings of US$876,017, with 37.1% (US$325,080) of this amount being attributed to the PIs related to antibiotic infusion. This study differs from ours, since it also evaluates the costs associated with adverse drug reactions and not only the costs of medications as performed in our study.

Nobrega and Lima (2014) found similar results to those in our study, in which four types of PIs had a greater role in the real economic impact, two that increased the costs, "Inclusion of required drug", "Correction of subdose", and two that decreased the costs, "Correction of exceeded maximum daily dose" and "Suspension of drug without indication". In addition, two PIs did not have an economic impact on the total number of PIs, these being "Correction of dosage - reconciliation" and "Sequential therapy (intravenous to oral).

Patients admitted to medium complexity hospitals represent the picture of Brazilian health, high incidence of trauma, vascular and respiratory diseases, and HU-USP/SP is not far from this reality (Brasil, 2019a). In this regard, most standardized drugs in the hospital are part of the list of essential drugs of the public system, such as antihypertensive drugs, analgesics, antacids, anti-inflammatories and anticoagulants, drugs that have a low cost of acquisition, except antibiotics, which, despite being essential drugs, still have a high cost (Brasil, 2019b).

Both interventions “Inclusion of required drug” and “Correction of subdose” are based on the introduction of more medication to the treatment, either by introducing a new drug or by adding the dose needed to complete the treatment’s effectiveness. Likewise, the interventions “Correction of exceeded maximum daily dose” and “Suspension of drug without indication” also have the main objective of changing the amount of medication administered to the patient, however, differently from the first two, these aim a reduction of doses or suspension of treatment, for example when the dose administered is causing adverse events or if the length of treatment has already ended and there is no justification for its continuation (De Rijdt, Willems, Simoens, 2008; Rodrigues *et al.*, 2019).

The study by Rodrigues *et al.* (2019), which evaluated 522 PIs performed by the Clinical Pharmacy service in the Neurology unit of a Brazilian public tertiary hospital for three years, found that most PIs are for the introduction of drugs (27.5%) and the second most performed PIs are related to drug suspension (16.7%) which corroborates the findings of our studies that also presented these two types of interventions as the most frequent in our study, “Suspension of drug without indication” with 18.9% and “Inclusion of required drug” with 16.2% incidence.

De Rijdt, Willems and Simoens (2008) assessed the economic impact of PIs in a literature review from 1996 to 2007. It was evidenced that interventions that decrease costs, even representing a small percentage of the total PIs performed, generate significant economic impact. As evidenced, the intervention “Suspension of drug without indication” represents 33% (R$1,360) of the positive real economic impact (R$4,114) and 58% (R$5,072) of the positive estimated economic impact of all PIs (R$8,789), which represents only 18.9% of the total number of PIs in the study. If the real and estimated economic impacts are assessed, the savings provided by this PI alone would increase from R$1,360 to R$5,072. From this result, it can be inferred the importance, both financially and for the patients’ health, that this PI should be performed as soon as possible during the course of treatment. The suspension of medications should be carried out as soon as the treatment has ended to avoid the occurrence of adverse reactions, as well as prompting savings to the hospital.

In our study the average economic impact per PI was R$14. In this scenario, for each PI performed in October 2018 R$14 was saved, taking into account the real economic impact and the total number of PIs. If the analysis was made dividing the real economic impact by the number of patients in the study, the average increases to R$24. This value is below that found in the study by Klopotowska and collaborators (2010), which was from €26 to €40, which was carried out in a tertiary hospital in the Netherlands during the period of eight and a half months in order to assess the impact of the participation of the clinical pharmacist in the clinical discussions of the ICU in the reduction of prescription errors and ADRs, as well as the contribution of this professional to the reduction of costs to the hospital. The reason for this increase is due to the fact that more than one PI was performed per patient, more precisely 1.75 PI per patient.

In the analysis by inpatient care unit, it was calculated that the Pediatric ICU, Surgical unit and Adult ICU would have the highest costs related to treatments if the intervention had been performed. Shen *et al.* (2011) carried out a similar study when comparing, in the period of ten months in a Chinese tertiary hospital, groups of patients who received intervention from the pharmacist and who did not receive intervention related to antibiotic therapy. In his study it was observed that the intervention group represented a cost of US$1,142.30 while the other group had a cost of US$1,729.60, a US$ 587.30 savings from performed PIs.

The real economic impact extrapolated annually was R$30,936 while the estimated economic impact was R$79,728. It was observed that in most of inpatient care units PIs had a positive economic impact, that is, PIs promoted savings for the hospital. The same was demonstrated by Aguiar *et al.* (2018), that presented an annual savings of R$199,000 in their work, by Randolph *et al.* (2018) of US$138,000 and by Jourdan *et al.* (2018) of €252,000, despite that they have used different methods from ours, but still evaluating PIs in different hospital settings.

Comparing the estimated and real economic impacts, the Pediatric ICU had the greatest economic impact due to pharmaceutical interventions. This occurred due to the fact that some PIs in this unit have a much longer treatment time (25 days) than most PIs and more expensive drugs (antibiotics, especially meropenem and teicoplanin) were used. It was observed that some PIs had a relatively long treatment time and others had higher costs related to the intervened drugs, however, these few PIs in the Pediatric ICU had both factors, drastically influencing the final cost. This result can be explained by the small sample size used in the present study.

The study had limitations related to the small sample size and the evaluation of drugs only. In addition, it was not possible to assess health impacts regarding adverse drug events and economic impact of such events. Also, it was not possible to assess other types of costs such as direct medical, indirect and intangible costs, taking into account only direct costs. The economic impact found in this work reflects the importance of evaluating budget in a health institution, especially at HU-USP/SP, which receives financial resources exclusively from the government and serves the national health system. Every economic impact is beneficial for the institution and for patients, which can be translated into several improvements in departments, purchase of materials, structuring of surgical centers, obtaining higher cost drugs, hiring health professionals, among numerous improvements to be described.

Patient safety is always the priority in the health establishment, with periodic training of health teams, updating of protocols, double checking, prescription verification by pharmacists, with efforts to avoid adverse events to medications, thus reducing errors during the patient's hospitalization and consequently improving quality of life (Kwon *et al.*, 2016; Tasaka *et al.*, 2016).

## CONCLUSION

The present study showed that pharmaceutical interventions reduced costs related to drug therapy, mainly on the Pediatric ICU, as safety being the main category of intervention. It is of paramount importance, not only financially, but mainly for patients' health safety that clinical pharmacists should be included in therapeutic decisions. Besides, more economic studies including other types of costs are needed to better understand health-related costs in hospitals and the role of health professionals on this topic.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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