MEDICINES AND PUBLIC HOSPITALS: THE IMPACT OF THE IMPLANTATION OF PHARMACY AND THERAPEUTIC COMMITTEES.

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ABSTRACT

Introduction: The implementation of essential drug policies and evaluation of technological incorporation are still far from being a reality in SUS hospitals and other health institutions. The Brazilian Pharmacy and Therapeutics Committees (CFT) present difficulties related to their institutionalization in services, disclosure of work, correct training of multidisciplinary team and mainly to the monitoring and evaluation of their performance. **Objective**: To verify the economic and access impacts, besides the essentiality levels of the lists of medicines of a public hospital network after the implantation of Pharmacy and Therapeutics Committees (CFT). **Methods**: This work was developed based on the Health Research Evaluation, where the implementation of CFT was promoted through the so-called situational strategic planning between the period from October 2010 to March 2012. **Results**: A reduction of 27.8% in the total number of items was observed, a 13.6% increase in the percentage of items belonging to Rename, 10.5% in the WHO list and 14.7% indicated by clinical guidelines. In economic analysis, it was observed a reduction of approximately 12% of the list costs, demonstrating the great potential of contribution to optimize public resources. **Conclusions**: The incentive to implement CFT, present in only 12.5% of Brazilian municipalities, and the promotion of essential drug policies, are alternatives to minimize the intense pressure for the incorporation of sanitary technologies, sometimes questioned in the public health system.

Keywords: Essential Medicines; Pharmacy and Therapeutics Committee; Pharmaceutical care; Rational Use of Medications.

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INTRODUCTION

Since the 1970s, many countries have initiated essential drug policies, primarily through the adoption of drug relationships with prior analysis of the best scientific evidence available and without market influences. These actions, largely associated with therapeutic and economic gains, follow policy guidelines of the World Health Organization (WHO) which has published its model list for member countries since 1977.[1]

Despite some advances at federal level, such as the approval of the National Policy on Health Technology Management (PNGTS) and the promulgation of Law 12,401/2011, which provides for therapeutic assistance and the incorporation of health technologies in the Unified Health System (SUS), it is observed that the implementation of essential drug policies and evaluation of technological incorporation are still far from being a reality in hospitals and other health institutions of SUS.[2]

A study of 250 public and private hospitals in several Brazilian regions showed that only 29 hospitals had commissions responsible for incorporating drugs, often referred to as Pharmacy and Therapeutics Committees (CFT). Yet in only nine of these hospitals, these committees functioned regularly, that is, with at least one meeting every two months. These data contrast with national and international recommendations and the reality of developed countries. In the USA, for example, CFT is present in 99.3% of hospitals and its functioning is a conditional factor for accreditation processes.[3,4]

When comparing the few existing information on Brazil's CFTs with those of developed countries, it can be observed that the Brazilian women present difficulties related to their institutionalization in services, dissemination of work, correct formation of multidisciplinary team and mainly to the monitoring and performance evaluation.[4]

At the hospital level, this situation tends to be more worrying due to its characteristic of intense technological density and the lack of national regulation that guarantees the selection of medicines and inputs based on scientific criteria with proven efficacy and safety, at the lowest possible cost and better treatment of the target population.

Although drug selection is already an internationally well-known activity, there are still few publications in the Latin American region demonstrating the effective impact of the implementation of CFT in health services.[5] The objective of this article is to demonstrate the economic impacts on access, as well as changes in the level of essentiality of drug relations after the implementation of these committees in public hospitals.

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METHODS:

This work was developed based on the Health Research Evaluation, which promoted the implementation of drug incorporation committees, called on Pharmacy and Therapeutics Commissions (CFT) through the so-called situational strategic planning between the period of October 2010 to March 2012.[6]

The study was carried out in a statewide network composed of 12 public hospitals with different sizes and specialties and a mobile emergency service (prehospital service), managed by a state foundation, with exclusive service to SUS. The research project to carry out this study was submitted and approved by the research ethics committee of the Federal University of Sergipe.

For the development of the work, five CFTs were officially established, structured according to the degree of complexity of the units and services offered (Table 1). The researchers, who also composed the commissions, through participant observation carried out the monitoring and recording of all activities, collecting the minutes of meetings, dispatches and internal communications, opinions and other documents produced.

Table 1 – Structure of the implanted CFT and participating units.

Committee	Unit Characterization	Units	Members
CFT 01	Local Hospitals (up to 40 beds)	04 (30.8%)	09
CFT 02	Regional Hospitals (40 to 150 beds)	05 (38.4%)	11
CFT 03	Exclusive maternity service	02 (15.4%)	12
CFT 04	Large hospital with specialties (600 beds)	01 (7.7%)	15
CFT 05	Pre-hospital care service	01 (7.7%)	07

The commissions had a multidisciplinary character, with members appointed jointly by the service management and state management according to their degree of representativeness and technical-scientific recognition. State supporters participated in more than one CFT and established exchanges of information and experiences among different committees. Throughout the process, 54 professionals participated, including 20 doctors from various specialties, 15 pharmacists, 14 nurses and 05 from other professions related to care, purchasing and management.

Members signed terms where they declared no conflicts of interest. Only one professional cannot participate in the process for declaring an ethical impediment.

All stages of CFT implementation and drug selection activities were based on WHO recommendations on Drug and therapeutics committees: a practical guide, in a literature review of the main indicators used in health services and detailed in a previous study that deals with the process of institutionalization.[5–7] The CFT met at least monthly and weekly maximum, considered appropriate by the said guide that recommends a minimum meeting every two months to consider the committee with regular operation.

As there were initially no records of lists of drugs officially established in the evaluated services, a list was drawn up that included the items included in the purchase processes (price registration records) and those in stock (verified through physical inventory).

The commissions used this initial list as the starting point for the beginning of the evaluation and selection of medicines. The drugs followed the nomenclature of the Brazilian Common Denomination – DCB[8] and were categorized according to the Anatomical Therapeutical Chemical Classification – ATC.[9]

The rules of operation of the CFT, criteria and flows for inclusion and exclusion of items were previously defined by means of specific resolution. All CFT decisions were recorded in minutes signed by participants. The decisions with greater potential of budgetary or clinical impact were preceded by elaboration of technical-scientific opinion, according to model established by the Ministry of Health.[10]

After finalization of the selection process by the commissions, the drug relations produced by each of the CFTs were collected in a single general list, which was approved by the hospital network management, becoming the first hospital medicine list in the state.

All analyzes in this study were based on the comparison between the initial list of October 2010 (prior to the implementation of CFT) and the March 2012 list of medicines (after selection by the CFT).

The parameters used to verify the changes during this period were chosen for their pertinence and feasibility of measurement, belonging to two basic categories: 1) economic and access impacts and 2) changes in the level of essentiality. The parameters were defined according to a survey of previous literature indicators, recommendations of the WHO Pharmacotherapy Committee Guide[5,7] and limitations of obtaining survey data.

For analysis of economic and access impacts the total number of drugs was verified before and after the implementation of the CFT, besides the inclusions and exclusions by group of medicines during the period.

The percentage of items with availability of generic drugs in the market and the presence of drugs with a current patent or a single national producer were verified using the database of the National Sanitary Surveillance Agency (Anvisa), the National Institute of Industrial Property (INPI) and/or production exclusivity documents contained in the unenforceability proceedings.

The changes in the demand for costs were also analyzed by means of the analysis of tangible direct health costs,[11] in this case, restricted to the value of the medicines obtained through consumption records and prices recorded in the institution's bidding processes, thus not including possible expenses with additional inputs related to their preparation, transport, storage and inventory management. The lack of adequate records in the surveyed units made it impossible to obtain data on other direct and indirect expenses, thus becoming a limitation of this study. All figures were restated by the National Broad Consumer Price Index (IPCA) for amounts referring to April 2018.

To verify the degree of essentiality of the lists, they were evaluated in comparison with the National Relation of Essential Medicines (Rename) 2010, updates of Rename 2012 and 2014[12–14] and 18th WHO Reference List.[15] At this point, it was also verified if the items were indicated by the Clinical Protocols and Therapeutic Guidelines of the Ministry of Health (PCDT)[16] and/or protocols elaborated by the different Societies of Specialties affiliated to the Brazilian Medical Association: The Guidelines.[17]

RESULTS AND DISCUSSION:

Economic and Access Impacts

The lack of previously established criteria for incorporating technologies into health units results in a deregulation of the therapeutic arsenal, creating lists of drugs inflated with items of questionable utility. This problem was verified in the target services of the study, which initially counted with a total number of 716 medicines and, after implementation of the selection process, had 516 items, a reduction of 27.8%, as observed in Table 2.

Table 2 – Quantitative items before and after the selection of drugs by CFT.

Medication Groups (ATC/WHO Classification 2012 Index)	Before CFT	After CFT	% reduction
Digestive System and Metabolism (A)	102	68	33.3%
Blood and Hematopoietic Organs (B)	35	29	17.1%
Cardiovascular System (C)	66	51	22.7%
Anti-infectives (J)	138	90	34.8%
Antineoplastic and Adjuvant (L)	112	87	22.3%
Musculoskeletal System (M)	40	30	25%
Nervous System (N)	114	86	24.6%
Respiratory System (R)	24	19	20.8%
Several (V)	85	56	34.1%
Total Medications	716	516	27.8%

Drugs still lacking consolidated evidence, duplicity of alternatives for the same treatment without differential advantages and presentations with pharmaceutical forms not adapted to hospital use were the main reasons for the exclusion of 225 items throughout the process. The percentage of reduction exceeded the expectations of the researchers and managers involved in the process, being considered a relevant result despite the lack of comparative studies in the literature.

Reis e Perini (2008) and Magarinos-Torres et al. (2011) have already shown that the decrease in the number of items is a gain for pharmaceutical assistance. The operation of hospital pharmacy logistics processes is favored when fewer drugs are available. Patients are also benefited because attending in units without excess medications are less vulnerable to adverse events related to supply failures due to the variety of circulating items and exposure to more drugs with limited information about their safety.[18,19]

Among the classes evaluated, it can be verified that the group that had the highest percentage of reduction in the number of items were the anti-infectious ones. Reducing the range of available antimicrobials is a measure that helps to minimize the worrying effect of microbial resistance and hospital infection rates. International studies have shown that antibiotic access control policies have led to the prescription and rational use of antibiotics, including in developing countries.[20]

The constant interaction with Hospital Infection Control Commissions (CCIH) during the process was crucial for this result, in line with the Brazilian consensus on the rational use of antimicrobials, which recommends that every hospital should have a CFT and a CCIH and these two committees should be responsible for the standardization and control of the use of antimicrobials in the institution.[21]

During the analysis of the excluded items, the percentage reduction of 43.9% in the number of drugs presented in association or "Fixed Dose Combinations" (FDC) was observed, from 41 (5.7%) presentations, included in the initial list, to 23 (4.4%).

Although at times they are related to improved adherence and increased therapeutic effect, the use of FDC should be avoided. The WHO recommends that "most essential medicines should be formulated as monofrugics. Fixed-dose combinations should be selected only when there is definite advantage over compounds administered separately in terms of efficacy, safety, compliance, and delay in developing resistance in malaria, tuberculosis and HIV/AIDS".[22,23]

This precaution is justified because CFT is associated with a greater number of interactions and adverse reactions that can motivate many hospitalizations. In addition, these combinations, by the small number of producers, also often have a higher cost than single drug preparations.[22]

Besides the exclusion of items with greater potential for harm to the patient, the process of drug selection also promotes access to essential treatments. During the study, 25 drugs were included, some of which were used in conditions not previously contemplated, as in the case of malignant hyperthermia, in the treatment of the acute phase of acute myocardial infarction and in the treatment of patent ductus arteriosus in neonates. After inclusion in the list, the items entered the bidding processes of the institution and became available on the network.

The inclusion of drugs for certain specialized therapies in the hospital treatment list, with such an evaluation of their degree of essentiality, epidemiological importance, quality and safety, also contributes to avoid later judicial processes. In a study carried out in the state of Rio de Janeiro, it was verified that almost 70% of the lawsuits came from patients treated in hospitals and clinics agreed to the SUS.[24]

Other parameters evaluated were the percentage of items that had current patents/exclusive producer and the availability of generic drugs. During the study, 32 drugs with a patent/exclusive producer were excluded and there was an increase of approximately 5% in the generic percentage of the cast (Table 3).

Table 3 - Percentage of Medicines with Patents/Exclusive and Generic Producers.

Medication Groups (ATC/WHO Classification 2012 Index)	Medications - Formerly CFT		Medications - After CFT	
	Patents/ Exclusive Producer	Generic	Patents/ Exclusive Producer	Generic
Digestive System and Metabolism (A)	04 (3.9%)	32 (31.4%)	01 (1.5%)	26 (38.2%)
Blood and Hematopoietic Organs (B)	03 (8.6%)	11 (31.4%)	03 (10.3%)	09 (31%)
Cardiovascular System (C)	07 (10.6%)	41 (62.1%)	03 (5.9%)	32 (62.1%)
Anti-infectives (J)	09 (6.5%)	90 (65.2%)	06 (6.7%)	65 (72.2%)
Antineoplastic and Adjuvant (L)	40 (35.7%)	40 (35.7%)	27 (31%)	34 (39.1%)
Musculoskeletal System (M)	06 (15%)	28 (70%)	03 (10%)	23 (76.7%)
Nervous System (N)	10 (8.8%)	72 (63.2%)	07 (8.1%)	60 (69.8%)
Respiratory System (R)	01 (4.2%)	18 (75%)	01 (5.3%)	15 (78.9%)
Several (V)	08 (9.4%)	10 (11.8%)	05 (8.9%)	08 (14.3%)
Total Medications	88 (12.3%)	342 (47.8%)	56 (10.9%)	272 (52.7%)

The WHO encourages policies to promote the use of generic medicines, which have lower prices and equivalent quality of reference medicines, as confirmed by bioequivalence and bioavailability tests.[25]

The promotion of generic drugs to the detriment of the use of patented products is associated with the reduction of health costs. Study conducted by Anvisa found that the share of patented products in total drug spending is 40% higher than generic drug costs.[26]

In the hospitals evaluated, the average values of monthly expenses with patented/exclusive producer were R$ 48,323.81, almost 12 times higher than the average generic expenses (R$ 4,061.60) during the study period.

The reduction of the total quantity of items purchased, the increase of the percentage of generics and the reduction of the percentage of items with a patent or exclusive supplier also contributed to the reduction of the demand for direct costs of the drugs after the implementation of the selection process through the CFT, as can be seen in Table 4.

Among the groups that contributed the most to a total reduction of 12%, Antineoplasics and Adjuvants accounted for 43% of the almost 1 million reduction in consumption demand before and after the implementation of CFT. Not coincidentally, this group stands out for having a higher percentage of the total expenditures of the evaluated network, both before (49.5%) and after (50.4%).

The area of oncology stands out for the high cost and technological sophistication. In the municipality of São Paulo, in 2005, the lawsuits for the acquisition of antineoplastic drugs accounted for 75% of the expenses with the acquisition of drugs by judicial determination.[27]

If we classify high-cost drugs as those that represent a monthly treatment value higher than one-third of the minimum wage, as proposed by some authors,[28] a reduction of these items was verified from 65 (9.1%) to 42 (8.1%) drugs. About 60% of the high-cost drugs identified during the study were classified as Antineoplastic and Adjuvant.

The careful monitoring of the selection of this group of drugs is fundamental given its high capacity to impact on the public budget. Another study from the state of São Paulo showed that only seven patented oncology

drugs were targeted by approximately 1220 lawsuits. More than 17% of applications had no scientific evidence for the indication mentioned in the lawsuit, which amounts to an inadequate expenditure of at least R $ 6.8 million.[29]

Table 4 – Cost analysis, consumption demand before and after the CFT.

Medication Groups (ATC/WHO Classification 2012 Index)	Before CFT	After CFT	Economy	Intragroup Reduction
Digestive System and Metabolism (A)	R$ 436,321.37	R$ 329,854.83	R$ 106,466.54	24%
Blood and Hematopoietic Organs (B)	R$ 587,274.63	R$ 562,126.40	R$ 25,148.23	4%
Cardiovascular System (C)	R$ 98,363.29	R$ 89,217.22	R$ 9,146.07	9%
Anti-infectives (J)	R$ 1,034,639.55	R$ 999,577.42	R$ 35,062.13	3%
Antineoplastic and Adjuvant (L)	R$ 3,863,313.96	R$ 3,460,332.78	R$ 402,981.18	10%
Musculoskeletal System (M)	R$ 181,757.95	R$ 132,686.61	R$ 49,071.34	27%
Nervous System (N)	R$ 412,810.20	R$ 361,862.81	R$ 50,947.39	12%
Respiratory System (R)	R$ 151,640.03	R$ 149,066.25	R$ 2,573.78	2%
Several (V)	R$ 1,024,761.71	R$ 773,706.11	R$ 251,055.60	24%
Total	R$ 7,790,882.69	R$ 6,858,430.43	R$ 932,452.26	12%

Impacts on Essentials

The selection activities in the hospitals evaluated also increased the level of essentiality of the role of medicines used. When comparing the initial list with the list elaborated by the CFT, there is a 13.6% increase in the percentage of items also included in Rename, a 10.5% increase in the number of items indicated by the WHO list and an increase of 14.7% of the drugs recommended by national protocols and guidelines (Table 5).

Considering that the selection of the medicines should observe regional epidemiological aspects, one could expect a higher agreement between the prescriptions with Rename (70.3%) and less agreement with the WHO list (51.3%). The lack of data to compare the adequacy in hospital services is a limiting factor of evaluation. However, when analyzing percentages of adequacy to Rename and WHO in primary care units in three other Brazilian states, we found values of 76.8% and 63%, respectively,[30] percentage not very far from those found in this study even if it is a hospital service that presents a higher degree of specialties and, therefore, greater potential to have items outside the lists of essential medicines.

If we considered together the indication by one of these three recommendations, of the 516 drugs in the final list, only 56 (11%) were not indicated by the Rename, WHO or Clinical Guidelines, which represents then that almost 90% of the final cast had agreement with national and international recommendations to promote the rational use of medicines.

Table 5 – Essentiality level of drug relations before and after CFT.

Medication Groups (ATC/WHO Classification 2012 Index)	% Medications - Formerly CFT			% Medications - After CFT		
	Rename	WHO	Guidelines	Rename	WHO	Guidelines
Digestive System and Metabolism (A)	59.8% (61)	41.2% (42)	47.1% (48)	75% (51)	50% (34)	67.6% (46)
Blood and Hematopoietic Organs (B)	57.1% (20)	25.7% (09)	68.6% (24)	75.9% (22)	27.6% (08)	79.3% (23)
Cardiovascular System (C)	66.7% (44)	50% (33)	59.1% (39)	74.5% (38)	49% (25)	68.6% (35)
Anti-infectives (J)	59.4% (82)	51.4% (71)	63% (87)	76.7% (69)	70% (63)	81.1% (73)
Antineoplastic and Adjuvant (L)	52.7% (59)	29.5% (33)	65.2% (73)	62.1% (54)	35.6% (31)	72.4% (63)
Musculoskeletal System (M)	52.5% (21)	50% (20)	77.5% (31)	63.3% (19)	66.7% (20)	93.3% (28)
Nervous System (N)	64.9% (74)	46.5% (53)	74.3% (85)	74.4% (64)	61.6% (53)	87.2% (75)
Respiratory System (R)	33.3% (08)	20.8% (05)	54.2% (13)	47.4% (09)	26.3% (05)	68.4% (13)
Several (V)	43.5% (37)	30.6% (26)	37.6% (32)	66.1% (37)	46.4% (26)	55.4% (31)
Total Medications	56.7% (406)	40.8% (292)	60.3% (432)	70.3% (363)	51.3% (265)	75% (387)

CONCLUSIONS

The inclusion of a new drug in lists receiving public funding is a critical time in which several circumstances, such as therapeutic improvement and increased expenditure, need to be considered.[31] Therefore, health professionals and managers should create strategies to ensure that the real advantages in patient's efficacy, safety, costs and needs are assessed in the incorporation processes, as previously noted by a qualitative baseline study in 2015 and now reinforced with quantitative results by this study.[32]

For all the above, it can be concluded that the incentive to implement CFT, present in only 12.5% of Brazilian municipalities[33] and the promotion of essential drug policies is a real alternative to minimize the intense pressure for the incorporation of sanitary technologies, sometimes questioned in the public health system. In this study, it was possible to verify the benefits of rationalizing the list on broad fronts: reducing the total number of items, increasing the percentage of drugs recommended by clinical guidelines and relationships of essential drugs, increasing the percentage of generic items available and reducing items with patents. In addition, the implementation of CFT has had a direct impact on cost reduction, resulting from a process of organization of activities focused on the primary objective of promoting the adequate and safe use of medicines for the users of the health system.

Limitations in the health information registration and monitoring systems of the target services of this study did not allow to assess other impacts such as indirect costs, reduction of drug-related adverse events or clinical gains for certain groups of patients or reports of individual cases. Exploration work on these lines can be the subject of further studies, given the relevance of the theme to collective health.

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Conflito de Interesses

The authors declare that they don't have potential conflict of interest, including political and / or financial interests associated with patents or property, provision of materials and / or benefits of the pharmaceutical industry.

Colaboradores

RSS: coordinated the intervention work and was responsible for designing, designing or analyzing and interpreting the data and beginning the writing of the text. IMFL, GCC, EKCVK, EKM (*in memoriam*) and WBS: contributed to the writing of the article, relevant critical revision of the intellectual content and final approval of the version to be published. All are responsible for all aspects of the work in ensuring the accuracy and integrity of any part of the work.

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REFERENCES

1. Hogerzeil H. Essential medicines and human rights: what can they learn from each other? *Bull World Health Organ*, 2006, 84(5):371–5.

2. Silva H, Petramale C, Elias F. Avanços e desafios da política nacional de gestão de tecnologias em saúde. *Rev Saude Publica,* 2012, 46:83–90.

3. Osório-de-Castro CGS, Castilho SR. Diagnóstico da farmácia hospitalar no Brasil. ENSP/Fiocruz, editor. Rio de Janeiro; 2004.

4. Marques D, Zucchi P. Comissões farmacoterapêuticas no Brasil: aquém das diretrizes internacionais. *Pan Am J Public Heal,* 2006, 19(1):58–68.

5. Santana R et al. Indicadores da seleção de medicamentos em sistemas de saúde: uma revisão integrativa. *Pan Am J Public Heal*, 2014, 35(3):228–34.

6. Santana R et al. A institucionalização da seleção de medicamentos em hospitais públicos por meio do planejamento estratégico situacional. *Rev Adm Pública*, 2014, 48(6):1587–603.

7. World Health Organization. Drug and therapeutics committees: a practical guide. Holloway K, Green T, editors. Geneva; 2003.

8. Agência Nacional de Vigilância Sanitária. Manual das Denominações Comum Brasileira. Disponível em http://www.anvisa.gov.br/medicamentos/. 2013.

9. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment, 2015. Disponível em: http://www.whocc.no/atc_ddd_publications/guidelines/. 2015.

10. Brasil. Ministério da Saúde. Secretaria de Ciência Tecnologia e Insumos Estratégicos. Diretrizes metodológicas: elaboração de pareceres técnico-científicos. 4a edição. Brasília; 2014. 80 p.

11. Mota DM, Fernandes MEP, Coelho HLL. Farmacoeconomia: um instrumento de eficiência para a política de medicamentos do Brasil. *Acta Farm Bonaer*, 2003, 22(2):177–86.

12. Estratégicos BM da SS de CT e I. Relação Nacional de Medicamentos Essenciais: Rename 2010. Disponível em: http://portalsaude.saude.gov.br/images/pdf/2014/setembro/29/Rename-2010.pdf. 2010. p. 250.

13. Brasil. Ministério da Saúde. Secretaria de Ciência Tecnologia e Insumos Estratégicos. Relação Nacional de Medicamentos Essenciais: Rename 2012. Disponível em: http://portalsaude.saude.gov.br/images/pdf/2014/setembro/29/Rename-2013.pdf. 2012. p. 200.

14. Estratégicos BM da SS de CT e I. Relação Nacional de Medicamentos Essenciais: Rename 2014. 9a. http://portalsaude.saude.gov.br/images/pdf/2015/julho/30/Rename-2014-v2.pdf. Brasília; 2014. p. 230.

15. World Health Organization. 18th Model List of Essential Medicines. Disponivel em: http://www.who.int/medicines/publications/essentialmedicines/18th_EML_Final_web_8Jul13.pdf. 2013.

16. Brasil. Ministério da Saúde. Protocolos Clínicos e Diretrizes Terapêuticas. Disponível em: http://conitec.gov.br/index.php/protocolo-clinico-e-diretrizes-terapeuticas. 2015.

17. Associação Médica Brasileira (AMB). Projeto Diretrizes. Disponível em: http://projetodiretrizes.org.br/. 2015.

18. Reis AMM, Perini E. Desabastecimento de medicamentos: determinantes, conseqüências e gerenciamento. *Cien Saude Colet*, 2008, 13:603–10.

19. Magarinos-Torres R, Pagnoncelli D, Cruz Filho AD da et al. Vivenciando a seleção de medicamentos em hospital de ensino. *Revista Brasileira de Educação Médica*, 2011, 77–85.

20. Tunger O, Karakaya Y, Cetin CB, et al. Rational antibiotic use. *Journal of Infection in Developing Countries*, 2009, 88–93.

21. Brasil. Ministério da Saúde. Agência Nacional de Vigilância Sanitária. Consenso sobre o uso racional de antimicrobianos. Brasília; 2001.

22. Wannmacher L, Hoefler R. Combinações em doses fixas: comentários farmacológicos, clínicos e comerciais. *Uso Racion Medicam Temas Selecionados*, 2007, 4(7):1–6.

23. World Health Organization. Report of the WHO Expert Committee on the selection and use of essential medicines. 2007.

24. Messeder AM, Osorio-de-Castro CGS, Luiza VL. Mandados judiciais como ferramenta para garantia do acesso a medicamentos no setor público: a experiência do Estado do Rio de Janeiro, Brasil. *Cad Saude Publica*, 2005, 21(2):525–34.

25. Bertoldi AD, Barros AJD, Hallal PC. Generic drugs in Brazil: known by many, used by few. *Cad saude publica / Minist da Saude, Fund Oswaldo Cruz, Esc Nac Saude Publica*, 2005, 21(6):1808–15.

26. Agência Nacional de Vigilância Sanitária. Medicamentos com patentes de moléculas no Brasil. Disponível em: http://portal.anvisa.gov.br/. 2010.

27. Vieira FS, Zucchi P. Distorções causadas pelas ações judiciais à política de medicamentos no Brasil. *Rev Saude Publica*, 2007, 41(2):214–22.

28. Picon D, Beltrame A. Protocolos clínicos e diretrizes terapêuticas - medicamentos excepcionais. Brasília; 2002.

29. Lopes LC, Barberato-Filho S, Costa AC et al. Uso racional de medicamentos antineoplásicos e ações judiciais no Estado de São Paulo. *Rev Saúde Pública*, 2010, 44(4):620–8.

30. Pizzol T da SD, Trevisol DJ, Heineck I et al. Adesão a listas de medicamentos essenciais em municípios de três estados brasileiros. *Cad Saude Publica*, 2010, 26(4):827–36.

31. Organização Pan-americana de Saúde. O acesso aos medicamentos de alto custo nas Américas: contexto, desafios e perspectivas. 2009.

32. Lima-Dellamora E da C, Caetano R, Osorio-de-Castro CGS. The medicine selection process in four large university hospitals in Brazil: Does the DTC have a role? *Brazilian J Pharm Sci.*, 2015, 51(1):173–82.

33. Karnikowski MG de O, Galato D, Meiners MMM de A et al. Characterization of the selection of medicines for the Brazilian primary health care. *Rev Saude Publica*, 2017 Sep;51(suppl.2).