PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Retrospective interrupted time series examining hypertension and diabetes medicines utilization following changes in patient cost sharing in the “Farmácia Popular” program in Brazil
AUTHORS	Emmerick, Isabel; Campos, Monica; Luiza, Vera Lucia; Chaves, Luisa; Bertoldi, Andrea D.; Ross-Degnan, Dennis

VERSION 1 – REVIEW

REVIEWER	ANIBAL GARCIA-SEMPERE CSISP-FISABIO Foundation for Biomedical Research of the Region of Valencia, Spain
REVIEW RETURNED	11-May-2017

GENERAL COMMENTS	This is a potentially interesting paper that aims to examine the impact of changes in cost sharing for essential diabetes and hypertension medicines on the volume of use and continuity of use of those medicines. Authors employ adequate interrupted time series analyses to address the assessment and obtain that increased cost sharing was associated to level and trend decreases in use and continuity of use, and that eliminating cost sharing translated into opposite effects. The authors conclude that cost sharing affects use and continuity and that essential medicines should be exempt from cost sharing. Main comments. Abstract. Objectives. instead of giving information on the initial launch of the program, it is more inyteresting for the reader to know that "in 2008 and in 2011, the program Farmacia Popular changed the cost sharing status of OH and AH medicines". Conclusion. Some caution should be considered with regard causal inference due to limitations of the study. Also the risk of patients should be taken into consideration when stating recommendations with regards free drug access (would it be socially desirable to eliminate cost sharing for anyone? or only for high risk patients?) Introduction I assume that the list of Essentials medicines of AFP-I and II include the drugs that are subject to evaluation in the study. Please clarify. If medicines are available at the public health facilities at no cost, why would patients use the two other mechanisms? Geographical access barriers? Shortages? Please clarify.

	What does “OH and AH were covered in all phases of FP” mean? Methods Typically the methods section should start by a “design” subheading section. Intervention. It would be interesting to know what the copayment changes for the drugs under study were and not averages. Also the prices and patient share would be interesting. Is there a price/copayment gradient in the impact of changes in cost sharing? I understand we miss government-pharmacies data: ok reported in limitations. DM: only metformin and glibanclamide, no DDP-4 and others. Hypertension: more comprehensive (BBloquers, diuretics, ECAIs and one ARBII), but also missing various compounds of different therapeutic classes that are substitutes. Effects of possible drug substitution (if therapuetic alternatives are listed, which I do not know) should be referred. Data source Its is said that patients receiving only one dispensing are not considered as participating in the program, but they are included in the results and table 1. Please either change methods or eliminate from results. Also the criterion for considering a patient as participating in the program is receiving at least two dispensations in a period of 5 years (2/60), which seems a weak indicator of participation (58/60 months may be receiving the medication through the other two mechanism). Analysis The way PDC is calculated and used in the study is confusing to me. As the three mechanisms to access drugs seem to be substitutive, when increases in cost sharing in the AFP program translate to decreases in PDC this can be due to the use of the other mechanisms were drugs are dispensed at lower cost, or at FP program in public pharmacies? It is explained at the paper but still. Maybe using an acronym like PrFP-PDC (PDC by the private FP program drugs) could be less counterintuitive. Or maybe just do not call this PDC (it is more something like “continuity of use of the PrFP program”). Statistical methods Is the number of observations sufficient to perform ITS SLR analysis? Losartan for instance can not be analized and maybe it should be excluded from analysis (striking growth of utilization figures may be kept but in the discussion section only)

	Discussion In the discussion and particularly the limitations section, authors should relate issues affecting this kind of studies. Internal validity considerations present in ITS studies (as inferential validity) and technical aspects with regards studies with drug dispensing (stockpiling effects before changes in cost sharing, for instance) should be elaborated. Caution should be employed with regard causal inference due to study limitations. PDC used in the study is not really PDC and this shoulkd be reflected when discussing about PDC levels and outcomes. When discussing about eliminating cost sharing for essential medicines, it is interesting to consider also the risk of patients (appropiateness of prescription) in terms of desirable policies for the rational use of drugs. References International evidence with regard the impact of cost sharing on the use and adherence to essential medicines and on outcomes is wide and the authors may want to use more references to support their comparative statements.

REVIEWER	James X. Zhang, PhD, MS The University of Chicago
REVIEW RETURNED	26-Jun-2017

GENERAL COMMENTS	This is an interesting study with topical importance. The authors developed an interrupted time series study using retrospective administrative data and found that cost sharing is a barrier to continuity of treatment. This finding has important implications for pharmaceutical practice and policy globally, as making essential medicines free to patients may substantially increase participation and continuity of treatment. I have some minor comments: 1. Abstract: Conclusion: “Cost sharing is a barrier to continuity of treatment in Brazil’s private sector FP program; making essential medicines free to patients substantially increased participation and continuity of treatment to clinically beneficial levels.” Please clarify what you mean by “clinically beneficial levels.” Also, “substantially increased participation” has a very strong causal implication that the time-series approach does not necessarily support. Please consider revising in a more reserved tone. 2. Methods: “The primary outcome variables were the number of monthly dispensings of AFP program medicines and the monthly median proportion of days covered (PDC) for participating patients.” (Line 34, Page 5). Did the dispensings all have the same supply length (e.g. 30-day supply, 60-day supply)? Please clarify, as this may have important implications for the outcome measure of the number of monthly dispensings.

	3. Methods: “Medicines covered by the program include four to treat diabetes (glibenclamide 5mg, and metformin 500mg, 850mg, and slow release 500mg) and six for hypertension (atenolol 25mg, propranolol 40mg, hydrochlorothiazide 25mg, captopril 25mg, enalapril 5mg, and losartan 50mg).” (Line 37, Page 5) Is it possible that patients switch from one medication to another among those 10 medications? If so, what would be the implication to the study? Please clarify in either Methods or Discussion. 4. Discussion: “PDC is usually used in the literature as a proxy for treatment adherence. [9,12,17] In this paper, PDC measures consistency of filling in the AFP program. Since prescriptions can be filled in either public or private FP pharmacies, available data is insufficient to determine the actual level of prescription filling in the program; the observed PDC can be thought of as measuring a minimum level of program adherence.” (Line 43, Page 11) Does this mean that there is differential missingness in data between the public and private FP pharmacies? Please clarify and discuss the implication for potential bias in the study. 5. Other potential limitations: is off-label use of anti-diabetes drugs an issue in Brazil? The study seems to have an implicit assumption that all drugs are intended for the treatment of diabetes. Please discuss potential implications for the results/conclusions of the study if off-label use is an issue.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Comment:

Objectives. Instead of giving information on the initial launch of the program, it is more interesting for the reader to know that "in 2008 and in 2011, the program Farmacia Popular changed the cost sharing status of OH and AH medicines". Conclusion. Some caution should be considered with regard causal inference due to limitations of the study. In addition, the risk of patients should be taken into consideration when stating recommendations with regards free drug access (would it be socially desirable to eliminate cost sharing for anyone? or only for high-risk patients?)

Response:

The abstract was adjusted to address the reviewer’s comments. With regards to the conclusions comment, we clarify that access to medicines in Brazil is considered as a right, so risk evaluation is not considered regarding free access to medicines. According to the country’s legislation, all individuals in need should have access to the medicines that they require.

Comment:

I assume that the list of Essentials medicines of AFP-I and II include the drugs that are subject to evaluation in the study. Please clarify.

Response:
The medicines evaluated in this study were part of this list. Nevertheless, the medicines list covered in the program include other therapeutic class that were not evaluated in this study. The paper Emmerick *et al*. (2016) details the content of the list in each phase of the program and an explicit statement to it was included in the introduction. Additionally, the introduction was adjusted to clarify the essential medicines list content.

Comment:
If medicines are available at the public health facilities at no cost, why would patients use the two other mechanisms? Geographical access barriers? Shortages? Please clarify.

Response:
Despite of being free of charge the medicines in the public health facilities, the medicines are not always available. Additionally to obtain medicines in the public health facilities, it is needed a prescription from the public sector. Since some people in Brazil use private health care, they can not obtain their medicines in the public health facilities, being FP an alternative to them. However, these questions are relevant and further studies need to investigate it and this was not the objective of this study.

Comment:
What does “OH and AH were covered in all phases of FP” mean?

Response:
As mentioned previously, the FP program covers other diseases’ medicines. We clarified in the text that the OH and AH medicines evaluated were the ones present in the program’s list. Furthermore the medicines to treat hypertension and diabetes were present in the program’s list in all phases of the program and during the study period.

Comment:
Typically the methods section should start by a “design” subheading section.

Response:
We added a design subheading and adjusted the text accordingly.

Comment:
It would be interesting to know what the copayment changes for the drugs under study were and not averages. Also the prices and patient share would be interesting. Is there a price/copayment gradient in the impact of changes in cost sharing?

Response:
We agree and added this information in an Appendix and cited it in this method section. We did not investigate if there is a price/copayment gradient impact since this was not the objective of this study.

Comment:
I understand we miss government-pharmacies data.

Response:
This is true. We do not have a national database on government-pharmacies data. We addressed this in limitations text.

Comment:
DM: only metformin and glibanclamide, no DDP-4 and others. Hypertension: more comprehensive (BBloquers, diuretics, ECAIs and one ARBII), but also missing various compounds of different therapeutic classes that are substitutes. Effects of possible drug substitution (if therapeutic alternatives are listed, which I do not know) should be referred

Response:
The medicines included in the analysis are the medicines that are in the FP list. Since this was not clear, we have clarified this aspect in other sections of the paper (e.g. Introduction and analysis subheading of the methods section)

Comment:
Its is said that patients receiving only one dispensing are not considered as participating in the program, but they are included in the results and table 1. Please either change methods or eliminate from results. Also the criterion for considering a patient as participating in the program is receiving at least two dispensations in a period of 5 years (2/60), which seems a weak indicator of participation (58/60 months may be receiving the medication through the other two mechanism).

Response:
We have listed all of the patients in Table I to illustrate that we did not have selective missing, when we excluded them from the PDC analysis.Therefore, we believe we should maintain the table as it is because this illustration enhance the power of our findings, explicit the quality of the study and gives transparency to people evaluate the quality of the study and its findings. The patient participation as the PDC denominator changes every month. When patient has a dispensing he enter the program (and the analysis) and is kept in in analysis for 120 days (max time that the prescription is valid in Brazil) if the patient does not have a “new dispensing” during the 120 interval, the patient fall out of the analysis and it is not in the denominator anymore. It is an open cohort. The criteria aims to exclude those that only did one purchase and never returned. We revised the text to make it clear

Comment:
The way PDC is calculated and used in the study is confusing to me. As the three mechanisms to access drugs seem to be substitutive, when increases in cost sharing in the AFP program translate to decreases in PDC this can be due to the use of the other mechanisms were drugs are dispensed at lower cost, or at FP program in public pharmacies? It is explained at the paper but still. Maybe using an acronym like PrFP-PDC (PDC by the private FP program drugs) could be less counterintuitive. Or maybe just do not call this PDC (it is more something like “continuity of use of the PrFP program”).

Response:
We agree with your observation and this is a challenge in the Brazilian context. We aim at measuring PDC in the FP program in order to verify if people are becoming regular users of this access to medicines mechanism. Therefore, for us it is clear that the PDC measured is not for the whole Brazilian system, and only to the FP program and that is why we agree with your commentary. However, to change the acronym would make the text less clear to the readers and due to that we do not believe that changing the term would be adequate. Additionally, we prefer to maintain the term PDC because it is an indicator described in the scientific literature and to use it as it is become easier for the scientific community to compare results across the studies and makes clear the indicator calculation and its application.

Comment:
Is the number of observations sufficient to perform ITS SLR analysis? Losartan for instance can not be analized and maybe it should be excluded from analysis (striking growth of utilization figures may be kept but in the discussion section only)

Response:
According to Cochrane Effective Practice and Organisation of Care (EPOC, 2017; available at*http://epoc.cochrane.org/epoc-specificresources-review-authors*), it is considered an ITS study, researches that uses at least 4 or more observations before and after theintervention. That way, the number of observations used is adequate to perform an ITS analysis. Losartan was excluded from the analysis and excluded from the tables.

Comment:
In the discussion and particularly the limitations section, authors should relate issues affecting this kind of studies. Internal validity considerations present in ITS studies (as inferential validity) and technical aspects with regards studies with drug dispensing (stockpiling effects before changes in cost sharing, for instance) should be elaborated Response: The three points that could impact on internal validity have minimum effect in our results. The public FP arm accounts for only 2.2% of total PF dispensing facilities. Considering that patients are able to obtain medicines in other sources, we do not talk about adherence to treatment, but about to adherence to the program instead. The dispensings in FP program are monthly, for 30 days' supply, so no stockpiling is possible due the program rules. We stressed these issues in the Limitations text.

Comment:
Caution should be employed with regard causal inference due to study limitations. PDC used in the study is not really PDC and this should be reflected when discussing about PDC levels and outcomes.

Response:
We think that limitations are now more clearly
stated. Nevertheless, we they were already been taken in account in our Discussion. We already not talked about adherence to treatment, but about adherence to the program.

Comment:
When discussing about eliminating cost sharing for essential medicines, it is interesting to consider also the risk of patients (appropriateness of prescription) in terms of desirable policies for the rational use of drugs

Response:
Some other controlling mechanisms, as the requirement of a prescription, max. monthly dispensing amounts, are able to overcome risks to rational. We highlighted that in the text.

Comment:
International evidence with regard the impact of cost sharing on the use and adherence to essential medicines and on outcomes is wide and the authors may want to use more references to support their comparative statements.

Response: We included a reference to a systematic review on this issue.

Comment:
Other potential limitations: is off-label use of anti-diabetes drugs an issue in Brazil? The study seems to have an implicit assumption that all drugs are intended for the treatment of diabetes. Please discuss potential implications for the results/conclusions of the study if off-label use is an issue.

Response:
Some medicines, such as antidiabetics to weight loss, are likely to have off-label use. FP does not require information on the medicines indication, neither patient diagnosis. Therefore, we cannot assure that all medicines addressed in this paper were really use for their primary indications, but this was not the purpose of this study. Then, we think that introduce this issue in the paper text would not help clarity.

Reviewer 2

Comment: Abstract: Conclusion: "Cost sharing is a barrier to continuity of treatment in Brazil's private sector FP program; making essential medicines free to patients substantially increased participation and continuity of treatment to clinically beneficial levels." Please clarify what you mean by "clinically beneficial levels." Also, "substantially increased participation" has a very strong causal implication that the time-series approach does not necessarily support. Please consider revising in a more reserved tone.

Response:
The abstract was adjusted to address the reviewer's comments. By clinically beneficial levels we meant that PDC greater than 80% has a relation with reduced A1C level in patients with diabetes (Elhayany A, Vinker S, 2011; Lynch WD, Pesa J, Melkonian AK, *et al*, 2009;Nair KV, Miller K, Saseen J, *et al*, 2009; Asche C, LaFleur J, Conner C., 2011; Nichols GA, Rosales AG, Kimes TM, *et al.*, 2015). This was clarified in the abstract and detailed information on it is in other sections of the manuscript.

Comment:
"The primary outcome variables were the number of monthly dispensings of AFP program medicines and the monthly median proportion of days covered (PDC) for participating patients." (Line 34, Page 5). Did the dispensings all have the same supply length (e.g. 30-day supply, 60-day supply)? Please clarify, as this may have important implications for the outcome measure of the number of monthly dispensings.

Response:
All dispensings were for 30 days' supply. This was clarified in the text following this phrase.

Comment:
"Medicines covered by the program include four to treat diabetes (glibenclamide 5mg, and metformin 500mg, 850mg, and slow release 500mg) and six for hypertension (atenolol 25mg, propranolol 40mg, hydrochlorothiazide 25mg, captopril 25mg, enalapril 5mg, and losartan 50mg)." (Line 37, Page 5) Is it possible that patients switch from one medication to another among those 10 medications? If so, what would be the implication to the study? Please clarify in either Methods or Discussion.

Response:
Yes, it is possible that patient switch treatment. The way that we define, the patient was kept in the analysis for each medicine for 120 days after it's last dispensing. The implication is we underestimate the proportion of days covered. We have a lower value when the real coverage was higher. We have included it in the Discussion section as a limitation of the study.

Comment:
Discussion: "PDC is usually used in the literature as a proxy for treatment adherence. [9,12,17] In this paper, PDC measures consistency of filling in the AFP program. Since prescriptions can be filled in either public or private FP pharmacies, available data is insufficient to determine the actual level of prescription filling in the program; the observed PDC can be thought of as measuring a minimum level of program adherence." (Line 43, Page 11) Does this mean that there is differential missing ness in data between the public and private FP pharmacies? Please clarify and discuss the implication for potential bias in the study.

Response:
FThis is now better explained in the Limitation
text.
"The limitations of this study comprises that the patient-level utilization data are only available from private AFP pharmacies and not from government-owned pharmacies. Thus, this study does not evaluate the impact of these two cost-sharing interventions on utilization in the FP program as a whole or on the actual proportion of days covered for patients who filled prescriptions in both sectors. Nevertheless, the public arm accounts for about
2.2% of FP dispensing facilities [4]"

VERSION 2 – REVIEW

REVIEWER	James Zhang, PhD The University of Chicago
REVIEW RETURNED	22-Aug-2017

GENERAL COMMENTS	The authors have addressed the comments sufficiently.