BMJ Open

Trends in hypertension and diabetes medicines utilization following changes in patient cost sharing in the "Farmácia Popular" program in Brazil

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017308
Article Type:	Research
Date Submitted by the Author:	20-Apr-2017
Complete List of Authors:	Emmerick, Isabel; ENSP/Fiocruz, Nucleuos for Pharmaceutical Policies Campos, Monica; Fundacao Oswaldo Cruz, Luiza, Vera Lucia; National School of Public Health/ Oswaldo Cruz Foundation, Nucleus for Pharmaceutical Policies; Home, Chaves, Luisa; UFRJ Macaé, ; Escola Nacional de Saude Publica - Sergio Arouca, Bertoldi, Andrea D. Ross-Degnan, Dennis; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine
Primary Subject Heading:	Public health
Secondary Subject Heading:	Health services research, Health policy, Cardiovascular medicine, Diabetes and endocrinology
Keywords:	chronic illness, non-communicable diseases, health services, medicines utilization, patient cost sharing, medication adherence

Trends in hypertension and diabetes medicines utilization following changes in patient cost sharing in the "Farmácia Popular" program in Brazil

Isabel Cristina Martins Emmerick, ScD

Research Fellow, Pharmaceutical Policy Research Fellowship, Department of Population Medicine, Harvard Medical School & Harvard Pilgrim Health Care Institute. Landmark Center, 401 Park Drive Suite 401 Boston, MA 02215·

Mônica Rodrigues Campos, PhD

Department of Social Sciences, Sergio Arouca National School of Public Health, Oswaldo Cruz Foundation.1480 Rua Leopoldo Bulhões #905, Manguinhos, Rio de Janeiro 21041-210, Brazil

Vera Lucia Luiza, ScD

Department of Medicines and Pharmaceutical Services Policies, Sergio Arouca National School of Public Health, Oswaldo Cruz Foundation. 1480 Rua Leopoldo Bulhões #624, Manguinhos, Rio de Janeiro 21041-210, Brazil

Luisa Arueira Chaves, MSc

Phamacy Department, Federal University of Rio de Janeiro, Macaé Campus. Av. Aluizio da Silva Gomes, #50, Granja dos Cavaleiros, Macaé, 27930-560, Brazil - Rio de Janeiro Federal University – Macaé Campus.

Andréa Dâmaso Bertoldi, PhD

Postgraduate Program in Epidemiology, Federal University of Pelotas. Rua Marechal Deodoro 1160, 96020-220, Pelotas, Brazil.

Dennis Ross-Degnan, ScD

Department of Population Medicine, Drug Policy Research Group, Harvard Medical School & Harvard Pilgrim Health Care Institute. Landmark Center, 401 Park Drive Suite 401 Boston, MA 02215

Corresponding Author:
Isabel Emmerick, Research Fellow
Pharmaceutical Policy Research Fellowship
Department of Population Medicine
Harvard Medical School & Harvard Pilgrim Health Care Institute
Landmark Center, 401 Park Drive Suite 401 Boston, MA 02215
Phone: 1-617-509-9510, Fax: 1-617-859-8112
isabel_emmerick@harvardpilgrim. org; emmerick. isabel@gmail. com

Key words: chronic illness, non-communicable diseases, health services, patient cost sharing, medicines utilization, medication adherence

Running Title: Trends in hypertension and diabetes medicines utilization

Words and tables count

Number of tables: 03

Number of figures: 01

Words (Abstract): 230

Words (Text): 2980

Appendix: 02

Abstract

Objectives: Brazil launched the "Farmácia Popular" (FP) program in 2004 to improve access to essential medicines and expanded the program in 2006 to include private pharmacies. This paper describes changes in utilization and continuity of coverage for oral hypoglycemic (OH) and antihypertensive (AH) medicines following changes in patient cost sharing in the FP program.

Study Design: Interrupted time series study using retrospective administrative data.

Methods: Monthly program participation (PP) and proportion of days covered (PDC) were the two outcome measures. The open cohort included all patients with two or more dispensings for a given study medicine in 2008-2012. The interventions were an increase in patient cost sharing in 2009 and zero patient cost sharing for key medicines in 2011.

Results: A total of 3.6 and 9.5 million patients receiving treatment for diabetes and hypertension, respectively, qualified for the study. Before the interventions, PP was growing by 7.3% per month; median PDC varied by medicine from 50-75%. After patient cost sharing increased in 2009, PP reduced by 56.5% and PDC decreased for most medicines (median 60.3%). After the 2011 free medicine program, PP surged by 121,000 new dispensings per month and PDC increased for all covered medicines (80.7%).

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.

Strengths and limitations of this study

- This paper contributes to our understanding of the impacts of sequential national policies in Brazil's *Farmácia Popular* (FP) program that were intended to improve access to medicines for non-communicable diseases in a middle-income country.
- Reduced program participation when patient cost sharing was increased and dramatic increases when key essential medicines were dispensed free of charge in private sector pharmacies provide important evidence about the impact of financial barriers on strategies to improve adherence to use of chronic medicines.
- The analysis uses the strongest quasi-experimental design - Interrupted Times Series (ITS) with segmented regression analysis - to evaluate policy impacts.
- The study is limited to patients treated under the FP program and not the entire population in Brazil. Overlaps between the FP program and other medicines provision mechanisms in the country including public sector health facilities could not be analyzed.
- The analyses of medicine utilization are based on dispensed amounts and enable us to evaluate average availability over time, but not actual adherence to treatment, overuse of medicines, or potential diversion outside of the program.

Background

Brazil has three main mechanisms by which individuals obtain access to medicines: out-of-pocket purchase in private pharmacies, provision in public health facilities, and the "Farmácia Popular" (FP) program. For out-of-pocket purchase, there are about 63,000 private pharmaceutical outlets all over the country, although the wealthier Southeast region was responsible for 51.9% of sales in 2013. [1] Medicines have been offered free-of-charge in all levels of public health care facilities since the 1970s. [2] The National Essential Medicines List, comprising 840 items in 2014, is the reference list for public coverage. [3]

FP, a new medicines subsidy program created in 2004,[4] has evolved in four phases. First, FP was implemented only in government-owned pharmacies to address persistent shortages of medicines in public health facilities. Medicines were sold at cost price plus operating cost, with selling prices 64-90% lower than the private market. [5] In the second phase, beginning in 2006 ("Aqui tem Farmácia Popular", AFP-I), a limited list of essential medicines was authorized to be sold in private pharmacies contracted by the Ministry of Health. The government paid either 90% of a government-established reference price for each medicine or 90% of the selling price, whichever was less; patients paid the remaining value not covered by the government. In the third phase beginning in 2009 (AFP-II), administrative changes were introduced to improve accountability and reference prices were reduced for most medicines, resulting in increases in the patient's share. [4] In the fourth phase starting in February 2011 ("Saúde Não Tem Preço", SNP), hypoglycemic and antihypertensive medicines began to be offered free-of-charge to patients in both government-owned and contracted private pharmacies, with the government paying a fixed negotiated price per medicine. In 2014, FP accounted for about 2.4 billion "reais" (1.09 billion USD) in government expenditures. [6]

Hypoglycemic (OH) and antihypertensive (AH) medicines were covered in all phases of FP program as part of broad ranging government initiatives to address these two non-communicable diseases. [7] One measure of private sector FP's contribution to control of these two illnesses is the proportion of days covered (PDC) by medicines dispensed by private FP pharmacies. PDC is a commonly-used refill-based measure of treatment adherence; [8–12] in this study, it refers to consistency of dispensing from the FP program, since there are other unobserved sources of medicines available to patients.

This paper aims to analyze changes in program participation and PDC for OH and AH medicines following changes in cost sharing during the AFP-II and SNP phases of the private sector FP program, using AFP data from January 2008 through December 2012. Comparable patient-level data are not available to evaluate changes in utilization of the public sector FP program.

Methods

Intervention

The study interventions are two changes in patient cost sharing in AFP. In April 2009, the government reduced reference prices for most FP medicines by an average of 24.5 %, resulting in an immediate increase in patient copayment from an average of 2.45 "reais" to 3.88 "reais" per 30 days dispensing, a relative increase of 58.4%. In February 2011, the government made all

covered medicines for hypertension and diabetes free to patients, reimbursing pharmacies according to a set of negotiated prices.

Data source and study population

There have been no changes in FP eligibility criteria during the program. To have a medicine dispensed at any FP private pharmacy, a patient must present a valid prescription and a national ID. Medicines were dispensed on a monthly basis, although prescriptions were valid for 120 days. Over time, the number of participating private sector pharmacies has expanded substantially, especially in some regions. [4]

Data are derived from an electronic point-of-sales dispensing program implemented in 2006 in FP retail pharmacies. Available data include patient and pharmacy identifiers, patient age and gender, facilities geographic location, date of dispensing, name and quantity of medicine dispensed, daily-prescribed dose, MoH reimbursement, and patient copayment. For this paper we use data on dispensings of hypertension and diabetes medicines from January 2008 to December 2012. Dispensing data are of good quality and relatively complete, with duplicate cases accounting for less than 0.005% and individual-level missing data at less than 0.05%. We excluded encounters with missing data from all analyses.

Patients are included only if they received two or more dispensings for a given medicine during the study period. Patients with a single dispensing were considered occasional buyers and not actually participating in the AFP program. We assumed patients were participating from the date of the first dispensing until 120 days after the last dispensing in a sequence, which is the period of prescription validity; we then excluded patients from analysis until a new dispensing occurred.

Analysis

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. 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). The number of days covered by a dispensing was defined as the amount of medicines dispensed divided by the prescribed daily dose. Days of therapy remaining in hand from prior dispensings were used to extend the number of days covered; possible overuse due to overlapping dispensings was not evaluated. [12]

We calculated monthly PDC as the number of days of therapy available during a month divided by the number of days in the month, with PDC thus varying between 0% and 100%;[12] the calculation for the first month of treatment considered only the days after the first dispensing. The median, 25th and 75th percentile PDCs represent aggregate values across all patients who were in an episode of treatment with that medicine during the month.

Statistical methods

We used interrupted time series (ITS) segmented linear regression models to determine the effect of the FP policy changes on the two study outcomes. In estimating effects, ITS models

adjust for pre-existing trends in the period before the policy change. Segmented linear regression models were constructed using the *prais* command in STATA v12.

ITS models included three segments, one per program period, with 15, 22, and 23 monthly observations, respectively. The baseline segment was fit with an intercept and a variable estimating trend. We estimate each policy effect by one variable representing the change in level of the outcome immediately after the policy and a second representing the change in trend of the post-policy segment. Patients experienced the changes in cost sharing only when they presented to fill a prescription after the policy change. We thus defined a post-policy implementation period of two months for participation and six months for PDC (to account for the 120-day refill period); these periods were excluded in the ITS models so that we could estimate stable post-intervention effects.

We retained all parameters in the models regardless of statistical significance. We highlight the results with $p<0.05$. We also tested logarithmic trend terms to accommodate possible non-linear trends during each post-intervention segment, selecting the best model using the BIC and AIC goodness of fitness criteria. [13] For the trends in metformin 500mg, atenolol 25mg, and enalapril 5mg dispensing after the 2009 increase in cost sharing, the natural log of trend represented a better model fit. We tested the adequacy of each model by residual analysis. To create single number summaries of policy effects, we calculated estimates of the relative changes in outcomes compared to expected values based on prior trends in April 2010 and February 2012, about one year after the two cost sharing interventions.

Results

A total of 6,032,380 and 14,392,076 patients who received any OH or AH, respectively, from the FP program comprised the dataset; of these, 3,611,512 (59.9%) and 9,534,333 (66.25%) patients received two or more dispensings (Table 1). The mean age was 57 years for both diabetes and hypertension patients, with females comprising about 60% of patients; the Southeast region represented the majority of patients in the program. Patients with two or more dispensings did not differ significantly from those with a single medication fill in age, gender or region.

During the baseline period prior to the cost sharing changes, patients filled an average of 1.1 and 2.7 million dispensings per medicine per year for DM and HTN, respectively; dispensings were growing at an average rate of 7.4 % per month for the medicines analyzed (Figure 1, Table 2). Metformin 850mg was the most widely used OH medicine and had the highest rate of growth, while metformin slow release had the smallest monthly number of dispensings (Appendix 1); enalapril was the most widely used AH medicine and propranolol the least widely used, but utilization of all AH medicines was growing rapidly (Appendix 2).

Prior to the increased cost sharing, PDC levels for studied medicines were relatively stable; by March 2009, one month before the AFP-II policy, median PDC levels for OH and AH medicines were 64.2 and 70.4%, respectively. Median PDC levels varied across covered medicines from 63.3% (metformin slow release) to 78.7% (captopril 25mg) (Figure 1, Table 3, Appendix 1, and Appendix 2).

Table 1. Patients participating in Brazil's "Farmácia Popular is Available Here" program, total and with two or more dispensings versus one dispensing, by gender, age and region, 2008 to 2012.

		Total		Two or more dispensings		One dispensing only	
DIABETES							
Age (n; mean (SD))		6,026,058	55.5 (15.1)	3,608,677	56.8 (14.0)	2,417,381	53.6 (16.5)
Gender (n, %)	Female	3,602,944	59.7%	2,168,131	60.0%	1,434,813	59.3%
	Male	2,413,718	40.0%	1,433,895	39.7%	979,823	40.5%
Region (n, %)	North	169,330	2.8%	79,517	2.2%	89,813	3.7%
	Northeast	849,184	14.1%	444,653	12.3%	404,531	16.7%
	Southeast	3,769,151	62.5%	2,336,807	64.7%	1,432,344	59.2%
	South	885,391	14.7%	540,572	15.0%	344,819	14.2%
	West-Center	359,324	6.0%	209,963	5.8%	149,361	6.2%
Total		**6,032,380**	**100.0%**	**3,611,512**	**100.0%**	**2,420,868**	**100.0%**
HYPERTENSION							
Age (n; mean (SD))		14,374,244	55.8 (15.1)	9,525,183	56.7 (14.3)	4,849,061	53.97 (16.4)
Gender (n, %)	Female	8,636,053	60,0%	5,777,649	60.6%	2,858,404	58.8%
	Male	5,714,487	39,7%	3,728,721	39.1%	1,985,766	40.9%
Region (n, %)	North	469,739	3,3%	232,250	2.4%	237,489	4.9%
	Northeast	2,121,308	14,7%	1,201,133	12.6%	920,175	18.9%
	Southeast	8,290,832	57,6%	5,714,243	59.9%	2,576,589	53.0%
	South	2,562,095	17,8%	1,780,678	18.7%	781,417	16.1%
	West-Center	948,102	6,6%	606,029	6.4%	342,073	7.0%
Total		**14,392,076**	**100,0%**	**9,534,333**	**100.0%**	**4,857,743**	**100.0%**

Table 2. Baseline level and trend in monthly number of dispensings (DISP)[a] per 100,000 for hypoglycemic and antihypertensive medicines, and changes in level and trend by stage of the "Farmácia Popular" program, Brazil, 2008 to 2012.

	Baseline		AFP-II (April 2009)					SNP (February 2011)		
	Level (DISP)	Trend	DISP (March 2009)	Level AFPII (April 2009)	Trend AFPII	%relative Change (AFPII) (April 2010)	DISP (Jan 2011)	Level SNP (Feb 2011)	Trend SNP	%relative change (SNP) (Feb2012)
Oral Hypoglycemic	2.45	0.16	4.85	**-2.12 (-3.13;-1.1)**	**-0.15 (-0.24;-0.06)**	**-54.5**	3.23	**4.39 (3.47;5.31)**	**0.40 (0.33;0.47)**	**262.0**
Glibenclamide 5mg	0.58	0.04	1.25	**-0.67 (-0.99;-0.35)**	**-0.05 (-0.07;-0.02)**	**-63.7**	0.66	**1.22 (0.93;1.52)**	**0.10 (0.07;0.12)**	**350.2**
Metformin 850mg	1.14	0.07	2.19	**-1.01 (-1.43;-0.59)**	**-0.06 (-0.1;-0.03)**	**-55.4**	1.43	**1.98 (1.6;2.36)**	**0.15 (0.12;0.18)**	**239.8**
Metformin 500mg	0.51	0.02	0.73	**-0.26 (-0.48;-0.05)**	-0.02 (-0.04;0.00)	**-48.7**	0.46	**0.68 (0.48;0.88)**	**0.04 (0.03;0.06)**	**258.9**
Metformin slow release	0.23	0.03	0.67	-0.16 (-0.38;0.06)	-0.02 (-0.04;0.00)	**-39.2**	0.69	**0.47 (0.27;0.66)**	**0.12 (0.1;0.13)**	**226.5**
Oral Antihypertensive	6.94	0.51	14.58	**-7.28 (-12.1;-2.45)**	**-0.5 (-0.93;-0.06)**	**-60.1**	8.56	**15.91 (11.45;20.37)**	**1.5 (1.16;1.84)**	**371.9**
Losartan 50mg	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Atenolol 25mg	1.59	0.09	2.90	**-1.1 (-1.68;-0.52)**	**-0.1 (-0.15;-0.04)**	**-53.3**	1.81	**1.87 (1.34;2.4)**	**0.21 (0.17;0.25)**	**242.4**
Propranolol 40mg	0.45	0.04	1.03	**-0.64 (-0.99;-0.29)**	**-0.04 (-0.07;-0.01)**	**-72.8**	0.37	**0.76 (0.43;1.1)**	**0.05 (0.03;0.07)**	424.7
Hydrochlorothiazide 25mg	1.31	0.14	3.46	**-2.05 (-3.14;-0.97)**	**-0.14 (-0.24;-0.04)**	**-67.6**	1.75	**4.15 (3.16;5.14)**	**0.4 (0.33;0.48)**	**481.1**
Captopril 25mg	1.42	0.11	3.12	**-1.8 (-2.42;-1.17)**	**-0.13 (-0.18;-0.07)**	**-69.3**	1.29	**1.92 (1.34;2.51)**	**0.08 (0.03;0.12)**	**244.3**
Enalapril 5mg	2.18	0.12	4.04	**-1.42 (-2.04;-0.8)**	**-0.13 (-0.18;-0.07)**	**-50.0**	2.78	**1.93 (1.36;2.5)**	**0.13 (0.09;0.17)**	**123.1**

significant values p<0.05 are highlighted in bold
NA - no applicable
The number of dispensings was divided by 100,000.
[a] DISP – number of dispensings

Table 3. Baseline median and trend in monthly Proportion of Days Covered (PDC) for hypoglycemic and antihypertensive medicines, and changes in level and trend by stage of the "Farmácia Popular" program, Brazil, 2008 to 2012.

	Baseline			AFP II (April 2009)				SNP (February 2011)		
	Level (PDC)	Trend	PDC (Mar 2009)	Level AFP II (Change at the intervention)	Trend AFP II	% relative change (AFP II) (April 2010)	PDC (Jan 2011)	Level SNP (Change at the intervention)	Trend SNP	% relative change (SNP) (Feb 2012)
Oral Hypoglycemic	59.67	0.30	64.22	**-8.1 (-12.85;-3.36)**	0.28 (-0.12;0.67)	**-9.0**	67.21	**4.88 (0.37;9.39)**	**-0.43 (-0.79;-0.07)**	2.5
Glibenclamide 5mg	61.40	0.56	69.75	**-15.23 (-19.65;-10.81)**	-0.07 (-0.43;0.3)	**-20.4**	65.73	**6.23 (2.03;10.42)**	**-0.35 (-0.68;-0.01)**	**5.3**
Metformin 850mg	59.02	0.38	64.74	**-10.41 (-15.3;-5.52)**	0.21 (-0.2;0.62)	**-12.8**	66.08	**3.84 (-0.81;8.49)**	**-0.37 (-0.74;-0.01)**	1.7
*Metformin 500mg	56.24	0.05	57.04	-1.75 (-7.23;3.73)	**2.87 (0.07;5.67)**	6.7	64.41	**8.56 (2.9;14.22)**	-0.15 (-0.77;0.46)	**11.2**
Metformin slow release	61.09	0.15	63.29	0.61 (-10.35;11.57)	0.16 (-0.75;1.06)	2.6	69.67	**11.09 (0.61;21.56)**	-0.43 (-1.25;0.4)	11.0
Oral Antihypertensive	63.98	0.45	70.74	**-10.63 (-14.7;-6.55)**	0.22 (-0.12;0.55)	**-11.9**	73.48	**4.87 (1;8.73)**	**-0.57 (-0.88;-0.27)**	1.0
Losartan 50 mg	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
*Atenolol 25mg	64.88	0.02	65.15	-0.70 (-5.53;4.13)	**3.4 (1.03;5.78)**	9.1	74.27	**10.63 (6.6;14.67)**	-0.14 (-0.49;0.21)	**12.6**
Propranolol 40 mg	61.34	1.07	77.40	**-26.21 (-32.49;-19.93)**	**-0.73 (-1.25;-0.21)**	**-34.3**	63.00	**11.63 (5.66;17.6)**	-0.23 (-0.71;0.24)	**14.8**
Hydrochlorothiazide 25mg	56.88	0.82	69.22	**-18.17 (-22.91;-13.43)**	-0.12 (-0.51;0.28)	**-23.8**	67.25	**10.1 (5.6;14.6)**	**-0.53 (-0.89;-0.17)**	**8.4**
Captopril 25mg	63.81	0.99	78.66	**-23.07 (-28.85;-17.29)**	**-0.52 (-1;-0.04)**	**-29.2**	69.11	**5.86 (0.37;11.35)**	-0.38 (-0.82;0.06)	4.2
*Enalapril 5mg	70.16	0.02	70.39	-2.91 (-7.74;1.93)	**2.56 (0.18;4.95)**	3.0	74.93	**7.79 (3.75;11.83)**	-0.02 (-0.37;0.34)	**10.0**

significant values p<0.05 are highlighted in bold
NA - no applicable
*it was used the Log of the AFP II trend

Cost sharing increases (AFP-II) April 2009

After patient copayments increased, OH dispensings declined immediately by -2.12 per 100,000 (95% CI [-3.13, -1.10]) compared to 4.85 per 100,000 in March 2009, immediately before the policy (Table 2). In addition, the previous upward monthly trend in participation flattened to nearly zero (slope change -0.15 per month, [-0.24, -0.06]). By one year after the policy, dispensings had declined by 54.5% [-65.9%,-43.0%] compared to where they would have been had baseline trends continued. Similarly, dispensings of AH medicines declined by -7.8 per 100,000 [-12.1,-2.45] from their level of 14.6 per 100,000 immediately before the AFP-II policy. As with OH medicines, the previous monthly increase in participation of 0.51 declined by -0.5 [-0.93, -0.06]. After one year, participation was 60.1% [-76.1, -44.2] lower than expected based on prior trends. (Table 2)

After AFP-II, rates of monthly dispensing for most studied medicines followed similar patterns. Dispensing had been increasing by 1,600 (metformin 500mg) to 14,000 (hydrochlorothiazide 25mg) fills per month prior to the increased cost sharing. After AFP-II implementation, there were immediate reductions in participation and flattened rates of dispensing that persisted over time. By one year after the intervention, in April 2010, all medicines had experienced significant relative decreases varying from 39.2% for metformin slow release to 72.8% for propranolol 40mg. (Table 2)

After patient copayments increased and substantial numbers of patients left the program, median PDC declined for OH medicines by 8.11% [-12.85%, -3.36%] and for AH medicines by 10.61% [-14.7%, -6.55%]. While the AFP policy remained in effect (until December 2010), median monthly PDC tended to increase slightly among participating patients (OH medicines: 0.28 per month [-0.12, 0.67]; AH medicines: 0.22 [-12, 0.55]). By one year after the policy, median PDC had declined for OH medicines by 9.0% [-18.0%, -5.8 %] and for AH medicines by 11.9% [-26.3,-14.4] relative to where they would have been had baseline trends continued. (Table 3)

Changes in PDC following increased cost sharing varied across medicines. PDC for five of the nine medicines covered decreased by 12.8% (metformin 850mg) to 34.3% (propranolol 40mg). However, four medicines actually experienced small nonsignificant increases in PDC for patients remaining in the program by a year after the cost sharing increase. (Table 3)

Availability of free medicines (SNP) – February 2011

After the SNP implementation, dispensings of OH medicines increased by 4.39 per 100,000 [3.47, -5.31] compared to 3.23 per 100,000 in January 2011, immediately before the policy (Table 2). Additionally, there was an upward monthly trend in dispensings of 0.40 per month [0.33, 0.47] contrasting with the previous flattened trend. By a year after the policy, dispensings had increased by 262% [130.7, 393.3] compared to where they would have been had previous trends continued. AH medicines followed the same pattern; dispensings increased by 15.9 per 100,000 [11.45, 20.37] from their level of 8.6 per 100,000 immediately before the SNP policy. Participation increased by 1.5 [1.16, 1.84] per 100,000 per month. After one year, participation was 372% (57.2, 686.6) higher than expected based on prior trend. (Table 2)

After SNP, rates of monthly dispensing for most medicines followed similar patterns, varying from an immediate increase in participation of 47,000 (metformin slow release) to 415,000 (hydrochlorothiazide 25mg) fills per month; increases in trend of monthly dispensing persisted over time. By one year after the free medicines policy, in February 2012, significant relative increases varied from 226% to 481% for metformin slow release and hydrochlorothiazide 25mg, respectively. (Table 2)

Losartan was added to the medicines reference list in October 2010; by the time of SNP implementation four months later, there were only about 10 thousand dispensings. By one year after medicines became free to patients, losartan dispensings had increased to more than 2 million dispensings. In comparison, its therapeutic competitors captopril and enalapril had only 700,000 and 1 million dispensings, respectively, in February 2012. (Appendix 2)

After SNP and the substantial influx of patients, median monthly PDC increased for OH medicines by 4.88% [0.37%, 9.39%] and for AH medicines by 4.87% [1.00%, 8.73%], and remained relatively constant until the end of the study period (December 2012). (Table 3) Changes in PDC varied by medicine; six of the nine medicines covered increased significantly by 5.3% (glibenclamide 5mg) to 14.8% (propranolol 40mg), but three experienced only small, nonsignificant increases by the year after the free medicine policy. (Table 3).

Discussion

Coverage policies in "Farmácia Popular", a publicly-financed program designed to increase access to essential medicines in Brazil, have evolved over time. Patient cost sharing increased by 58% in 2009, resulting in immediate decreases in program participation and PDC. In contrast, rapid increases in both outcomes followed implementation of a 2011 policy to make essential medicines for diabetes and hypertension free to patients.

Program participation for hypertension and diabetes follow the prevalence profile of these two diseases in the country. [14] The majority of AFP patients are from the wealthier Southeast region where there is a higher density of participating pharmacies; [4] this may imply increasing socioeconomic disparities in access to treatment for diabetes and hypertension, especially now that medicines are available for free. Other studies that have evaluated access to medicines for hypertension[15] and diabetes[16] through the Health has No Price program have concluded that the intervention contributed to increased access to these medicines in Brazil.

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.

In the literature, about half of patients treated for chronic disease become no adherent within a year. [18] The consistency of prescription filling in the AFP program, particularly after medicines for diabetes and hypertension were made free to patients, suggest that private sector outlets are convenient and preferred by patients as a source of these free medicines.

The relationship between PDC levels and clinical outcomes is well-established in the literature. [19,20] For example, adherence to hypoglycemic treatment measured through administrative data has been found to be related to better glycemic control, fewer emergency department visits, and lower rates of hospital admission. [21] [22] [23] Many studies consider patients with PDC 80% or higher to be adherent to treatment;[21] lower adherence can lead to higher rates of adverse events, poor long-term health outcomes, and higher healthcare costs. [24] After SNP, rates of PDC were higher than 80% for well over half of patients taking OH and AH medicines, levels likely to have positive impact on clinical outcomes. One study that have analyzed the impact of full subsidy policies on medicines use have found similar effects on PDC as in our study. [11,25–28]

The relation between cost sharing and medication adherence has been widely studied. [29] In our study, all medicines with increased copayments in April 2009 experienced decreases in rates of dispensing and PDC. After SNP, we observed the opposite response; when patients had no cost sharing, program participation and PDC increased dramatically.

Although losartan is not a first-line treatment in the Brazilian guideline to treat hypertension,[30] it was included in the FP reimbursement list in 2010. Within a few months, losartan had become the most widely dispensed AH medicine. Coverage decisions in government subsidy programs should be consistent with treatment guidelines to encourage appropriate choice of therapy and more cost-effective treatment.

Our study has several limitations. Patient-level utilization data are only available from private AFP pharmacies and not from government-owned pharmacies in public sector facilities. Thus, it is impossible to 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. To make the estimates of PDC interpretable, we limited analysis of program impacts to patients who filled more than one prescription of a medicine in the FP private sector program; there were no relevant differences in characteristics between patients who filled only one prescription and those who used it more regularly. Additionally, we have no data on medicines that are not part of the program, so cannot evaluate the impact of FP program policies on use of other medicines used to treat diabetes and hypertension. Finally, as a result of the method chosen to calculate the PDC,[12] the possible overuse due to overlapping dispensings was not evaluated.

In conclusion, participation in the “Farmácia Popular” private sector program evolved in response to two cost sharing interventions implemented between 2008 and 2012. Increased patient cost sharing reduced participation, while full subsidy of key medicines in private pharmacies substantially increased participation; patients in the program achieved PDC levels that have been shown to improve health outcomes. Policy makers should consider reducing or removing cost sharing for essential medicines to treat chronic illness, while aligning subsidies to encourage greater use of first-line therapies.

Acknowledgements: The authors thank the Ministry of Health in Brazil for providing the data used in this study. Dr. Isabel Emmerick was supported by CNPQ process number 202246/2012-4 and the Pyle Fellowship of Harvard Pilgrim Health Care Institute.

Author contributions: All authors made substantial contribution to study conception, ICME MRC, DRD made substantial contribution to study design. ICME, VLL, MRC, LAC, ADB were responsible for data acquisition. ICME, MRC and DRD were responsible for data analysis. All authors contributed to interpretation of data. ICME drafted the article and is guarantor. All authors provided critical revisions for important intellectual content and approved the final version.

Conflicts of interest: Dr. Emmerick, principal investigator, reports grants from World Health Organization Access to Medicines Research Network, during the conduct of the study. Dr. Campos, Dr. Luiza, Dr. Chaves, Dr. Bertoldi and Dr. Ross-Degnan report personal fees from World Health Organization Access to Medicines Research Network, during the conduct of the study; Dr. Luiza also reports personal fees from Oswaldo Cruz Foundation (Fiocruz), outside the submitted work.

Funding: Research grant from the World Health Organization Alliance for Health Policy and Systems Research. Dr. Emmerick is supported by the Pyle Fellowship of Harvard Pilgrim Health Care Institute. Dr. Ross-Degnan is supported in part by the Health Delivery Systems Center for Diabetes Translational Research (HDS-CDTR) [NIDDK grant 1P30-DK092924].

Ethical approvals: The Brazilian National Ethics Committee, by the National School of Public Health – Fiocruz – Brazil and the WHO ERC, approved the ISAUM-Br project, which is the base for this paper.

This work was conducted in collaboration among the following institutions: Department of Medicines and Pharmaceutical Services Policies, Sergio Arouca, National School of Public Health, Fiocruz Brazil; Department of Epidemiology, University of Pelotas, Brazil; Department of Pharmaceutical Services / Office of Science Technology and Strategic Resources - Ministry of Health and the Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute.

Data sharing: No additional data are available.

Table 1. Patients participating in Brazil's "Farmácia Popular is Available Here" program, total and with two or more dispensings versus one dispensing, by gender, age and region, 2008 to 2012.

Table 2. Baseline level and trend in monthly number of dispensings (DISP)a per 100,000 for hypoglycemic and antihypertensive medicines, and changes in level and trend by stage of the "Farmácia Popular" program, Brazil, 2008 to 2012.

Table 3. Baseline median and trend in monthly Proportion of Days Covered (PDC) for hypoglycemic and antihypertensive medicines, and changes in level and trend by stage of the "Farmácia Popular" program, Brazil, 2008 to 2012.

Figure 1. Number of dispensings and 25th/Median/75th percentiles of Proportion of Days Covered, and predicted values from segmented regression models for oral hypoglycemic and oral antihypertensive medicines, by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

Appendix 1. Number of dispensings and unadjusted 25th/Median/75th percentiles of Proportion of Days Covered, glibenclamide 5mg, metformin 850mg, metformin 500mg and metformin slow release, by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

Appendix 2. Number of dispensings and unadjusted 25th/Median/75th percentiles of Proportion of Days Covered, atenolol 25mg, propranolol 40 mg, hydrochlorothiazide 25mg, captopril 25mg, enalapril 5mg and losartan 50 mg by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

References

1 Valor Econômico. Valor: Análise setorial: Farmácias e Drogarias. 2014.

2 Bermudez J. AZ, Oliveira MA, Luiza VL. Assistência Farmacêutica. In: Lígia Giovanella, Sarah Escorel, Lenaura de Vasconcelos Costa Lobato, *et al.*, eds. *Políticas e Sistema de Saúde no Brasil*. Rio de Janeiro: : Fiocruz 2012. 761–94.

3 Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. *Relação Nacional de Medicamentos Essenciais: RENAME 2014*. 9th ed. Brasília: : Ministério da Saúde 2014.

4 Emmerick ICM, do Nascimento JM, Pereira MA, *et al.* Farmacia Popular Program: changes in geographic accessibility of medicines during ten years of a medicine subsidy policy in Brazil. *J Pharm Policy Pract* 2015;**8**. doi:10.1186/s40545-015-0030-x

5 Santos-Pinto CDB, Miranda ES, Martins Emmerick IC, *et al.* Medicine prices and availability in the Brazilian popular pharmacy program [Preços e disponibilidade de medicamentos no Programa Farmácia Popular do Brasil]. *Rev Saude Publica* 2010;**44**:611–9.

6 Brasil. Ministério da Saúde. Sala de Apoio à Gestão Estratégica. Redes_e_Porgramas>Situação_de_Saúde>Gestão/Financiamento?Aqui_Tem_Farmácia_Popular. 2015. http://sage.saude.gov.br/ (accessed 29 Sep 2015).

7 Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Análise de Situação de Saúde. *Plano de ações estratégicas para o enfrentamento das doenças crônicas não transmissíveis (DCNT) no Brasil 2011-2022*. Brasília: : Ministério da Saúde 2011.

8 Sattler ELP, Lee JS, Perri M. Medication (Re)fill Adherence Measures Derived from Pharmacy Claims Data in Older Americans: A Review of the Literature. *Drugs Aging* 2013;**30**:383–99. doi:10.1007/s40266-013-0074-z

9 Andrade SE, Kahler KH, Frech F, *et al.* Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf* 2006;**15**:565–74. doi:10.1002/pds.1230

10 An J, Nichol MB. Multiple medication adherence and its effect on clinical outcomes among patients with comorbid type 2 diabetes and hypertension. *Med Care* 2013;**51**:879–887.

11 Athanasakis K, Skroumpelos AG, Tsiantou V, *et al.* Abolishing coinsurance for oral antihyperglycemic agents: Effects on social insurance budgets. 2011;**17**:130–5.

12 Hess LM, Raebel MA, Conner DA, *et al.* Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother* 2006;**40**:1280–8. doi:10.1345/aph.1H018

13 Maydeu-Olivares A. Goodness-of-Fit Testing. http://www.ub.edu/gdne/amaydeusp_archivos/encyclopedia_of_education10.pdf (accessed 10 Feb 2016).

14 Brasil. Ministério da Saúde, Secretaria de Vigilância em Saúde. *Vigitel Brasil 2013: vigilância de fatores de risco e proteção para doenças crônicas*. Brasília: : Ministério da Saúde 2014.

15 Araujo JLO, Pereira MD, de Sá Del Fiol F, *et al.* Access to Antihypertensive Agents in Brazil: Evaluation of the "Health Has No Price" Program. *Clin Ther* 2014;**36**:1191–5. doi:10.1016/j.clinthera.2014.06.003

16 Araujo JLO, Pereira MD, de Cássia Bergamaschi C, *et al.* Access to medicines for diabetes treatment in Brazil: evaluation of "health has no price" program. *Diabetol Metab Syndr* 2016;**8**. doi:10.1186/s13098-016-0150-8

17 Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol* 1997;**50**:105–16.

18 Franklin JM, Krumme AA, Shrank WH, *et al.* Predicting Adherence Trajectory Using Initial Patterns of Medication Filling. *Am J Manag Care* 2015;**21**.http://www.ajmc.com/journals/issue/2015/2015vol21n9/PredictingAdherenceTrajectoryUsingInitialPatternsofMedicationFilling?utm_source=Informz

19 Elhayany A, Vinker S. Addressing healthcare inequities in Israel by eliminating prescription drug copayments. *Am J Manag Care* 2011;**17**:e255-9.

20 Lynch WD, Pesa J, Melkonian AK, *et al.* Effect of Antihypertensive Medication Adherence Among Employees With Hypertension. *Am J Manag Care* 2009;**15**:871–80.

21 Nair KV, Miller K, Saseen J, *et al.* Prescription copay reduction program for diabetic employees: Impact on medication compliance and healthcare costs and utilization. 2009;**2**:14–24.

22 Asche C, LaFleur J, Conner C. A Review of Diabetes Treatment Adherence and the Association with Clinical and Economic Outcomes. *Clin Ther* 2011;**33**:74–109. doi:10.1016/j.clinthera.2011.01.019

23 Nichols GA, Rosales AG, Kimes TM, *et al.* Impact on glycated haemoglobin of a biological response-based measure of medication adherence. *Diabetes Obes Metab* Published Online First: 2015.http://onlinelibrary.wiley.com/doi/10.1111/dom.12476/full (accessed 28 Sep 2015).

24 Roebuck MC, Liberman JN, Gemmill-Toyama M, *et al.* Medication Adherence Leads To Lower Health Care Use And Costs Despite Increased Drug Spending. *Health Aff (Millwood)* 2011;**30**:91–9. doi:10.1377/hlthaff.2009.1087

25 Huber CA, Rapold R, Brüngger B, *et al.* One-year adherence to oral antihyperglycemic medication and risk prediction of patient outcomes for adults with diabetes mellitus: An observational study. *Medicine (Baltimore)* 2016;**95**:e3994. doi:10.1097/MD.0000000000003994

26 Cramer JA. A systematic review of adherence with medications for diabetes. *Diabetes Care* 2004;**27**:1218–1224.

27 Ho PM, Rumsfeld JS, Masoudi FA, *et al.* Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Arch Intern Med* 2006;**166**:1836–1841.

28 An J, Nichol MB. Multiple medication adherence and its effect on clinical outcomes among patients with comorbid type 2 diabetes and hypertension. *Med Care* 2013;**51**:879–887.

29 Luiza VL, Chaves LA, Silva RM, *et al.* Pharmaceutical policies: effects of cap and co-payment on rational use of medicines. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd 2015. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007017.pub2/abstract (accessed 12 May 2015).

30 Brasil, Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Atenção Básica. *Estratégias para o cuidado da pessoa com doença crônica: hipertensão arterial sistêmica [Strategies for the care of the person with chronic disease: systemic arterial hypertension]*. 1st ed. Brasília - DF: : Ministerio da Saúde, Brazil 2013. http://bvsms.saude.gov.br/bvs/publicacoes/estrategias_cuidado_pessoa_doenca_cronica.pdf

2 Bermudez J. AZ, Oliveira MA, Luiza VL. Assistência Farmacêutica. In: Lígia Giovanella, Sarah Escorel, Lenaura de Vasconcelos Costa Lobato, *et al.*, eds. *Políticas e Sistema de Saúde no Brasil*. Rio de Janeiro: : Fiocruz 2012. 761–94.

3 Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. *Relação Nacional de Medicamentos Essenciais: RENAME 2014*. 9th ed. Brasília: : Ministério da Saúde 2014.

4 Emmerick ICM, do Nascimento JM, Pereira MA, *et al.* Farmacia Popular Program: changes in geographic accessibility of medicines during ten years of a medicine subsidy policy in Brazil. *J Pharm Policy Pract* 2015;**8**. doi:10.1186/s40545-015-0030-x

5 Santos-Pinto CDB, Miranda ES, Martins Emmerick IC, *et al.* Medicine prices and availability in the Brazilian popular pharmacy program [Preços e disponibilidade de medicamentos no Programa Farmácia Popular do Brasil]. *Rev Saude Publica* 2010;**44**:611–9.

6 Brasil. Ministério da Saúde. Sala de Apoio à Gestão Estratégica. Redes_e_Porgramas>Situação_de_Saúde>Gestão/Financiamento?Aqui_Tem_Farmácia_Popular. 2015. http://sage.saude.gov.br/ (accessed 29 Sep2015).

7 Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Análise de Situação de Saúde. *Plano de ações estratégicas para o enfrentamento das doenças crônicas não transmissíveis (DCNT) no Brasil 2011-2022*. Brasília: : Ministério da Saúde 2011.

8 Sattler ELP, Lee JS, Perri M. Medication (Re)fill Adherence Measures Derived from Pharmacy Claims Data in Older Americans: A Review of the Literature. *Drugs Aging* 2013;**30**:383–99. doi:10.1007/s40266-013-0074-z

9 Andrade SE, Kahler KH, Frech F, *et al.* Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf* 2006;**15**:565–74. doi:10.1002/pds.1230

10 An J, Nichol MB. Multiple medication adherence and its effect on clinical outcomes among patients with comorbid type 2 diabetes and hypertension. *Med Care* 2013;**51**:879–887.

11 Athanasakis K, Skroumpelos AG, Tsiantou V, *et al.* Abolishing coinsurance for oral antihyperglycemic agents: Effects on social insurance budgets. 2011;**17**:130–5.

12 Hess LM, Raebel MA, Conner DA, *et al.* Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother* 2006;**40**:1280–8. doi:10.1345/aph.1H018

13 Maydeu-Olivares A. Goodness-of-Fit Testing. http://www.ub.edu/gdne/amaydeusp_archivos/encyclopedia_of_education10.pdf (accessed 10 Feb2016).

14 Brasil. Ministério da Saúde, Secretaria de Vigilância em Saúde. *Vigitel Brasil 2013: vigilância de fatores de risco e proteção para doenças crônicas*. Brasília: : Ministério da Saúde 2014.

15 Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol* 1997;**50**:105–16.

16 Franklin JM, Krumme AA, Shrank WH, *et al.* Predicting Adherence Trajectory Using Initial Patterns of Medication Filling. *Am J Manag Care* 2015;**21**.http://www.ajmc.com/journals/issue/2015/2015vol21n9/PredictingAdherenceTrajectoryUsingInitialPatternsofMedicationFilling?utm_source=Informz

17 Elhayany A, Vinker S. Addressing healthcare inequities in Israel by eliminating prescription drug copayments. *Am J Manag Care* 2011;**17**:e255-9.

18 Lynch WD, Pesa J, Melkonian AK, *et al.* Effect of Antihypertensive Medication Adherence Among Employees With Hypertension. *Am J Manag Care* 2009;**15**:871–80.

19 Nair KV, Miller K, Saseen J, *et al.* Prescription copay reduction program for diabetic employees: Impact on medication compliance and healthcare costs and utilization. 2009;**2**:14–24.

20 Asche C, LaFleur J, Conner C. A Review of Diabetes Treatment Adherence and the Association with Clinical and Economic Outcomes. *Clin Ther* 2011;**33**:74–109. doi:10.1016/j.clinthera.2011.01.019

21 Nichols GA, Rosales AG, Kimes TM, *et al.* Impact on glycated haemoglobin of a biological response-based measure of medication adherence. *Diabetes Obes Metab* Published Online First: 2015.http://onlinelibrary.wiley.com/doi/10.1111/dom.12476/full (accessed 28 Sep2015).

22 Roebuck MC, Liberman JN, Gemmill-Toyama M, *et al.* Medication Adherence Leads To Lower Health Care Use And Costs Despite Increased Drug Spending. *Health Aff (Millwood)* 2011;**30**:91–9. doi:10.1377/hlthaff.2009.1087

23 Huber CA, Rapold R, Brüngger B, *et al.* One-year adherence to oral antihyperglycemic medication and risk prediction of patient outcomes for adults with diabetes mellitus: An observational study. *Medicine (Baltimore)* 2016;**95**:e3994. doi:10.1097/MD.0000000000003994

24 Cramer JA. A systematic review of adherence with medications for diabetes. *Diabetes Care* 2004;**27**:1218–1224.

25 Ho PM, Rumsfeld JS, Masoudi FA, *et al.* Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Arch Intern Med* 2006;**166**:1836–1841.

26 An J, Nichol MB. Multiple medication adherence and its effect on clinical outcomes among patients with comorbid type 2 diabetes and hypertension. *Med Care* 2013;**51**:879–887.

27 Luiza VL, Chaves LA, Silva RM, *et al.* Pharmaceutical policies: effects of cap and co-payment on rational use of medicines. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd 2015. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007017.pub2/abstract (accessed 12 May2015).

28 Brasil, Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Atenção Básica. *Estratégias para o cuidado da pessoa com doença crônica: hipertensão arterial sistêmica [Strategies for the care of the person with chronic disease: systemic arterial hypertension]*. 1st ed. Brasília - DF: : Ministerio da Saúde, Brazil 2013.

http://bvsms.saude.gov.br/bvs/publicacoes/estrategias_cuidado_pessoa_doenca_cronica.pdf

29 Araujo JLO, Pereira MD, de Sá Del Fiol F, *et al.* Access to Antihypertensive Agents in Brazil: Evaluation of the "Health Has No Price" Program. *Clin Ther* 2014;**36**:1191–5. doi:10.1016/j.clinthera.2014.06.003

30 Araujo JLO, Pereira MD, de Cássia Bergamaschi C, *et al.* Access to medicines for diabetes treatment in Brazil: evaluation of "health has no price" program. *Diabetol Metab Syndr* 2016;**8**. doi:10.1186/s13098-016-0150-8

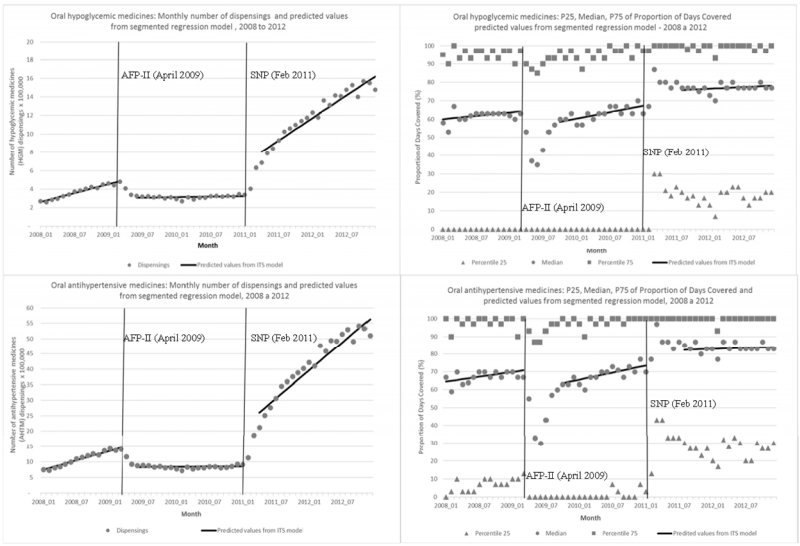
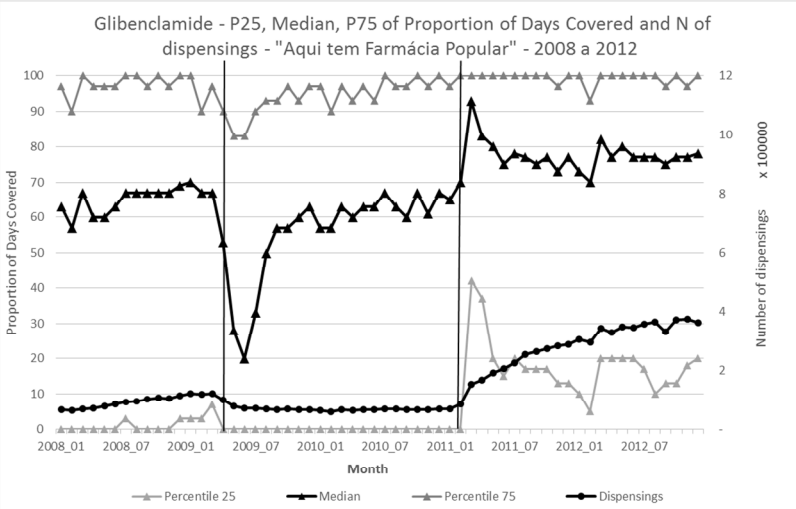
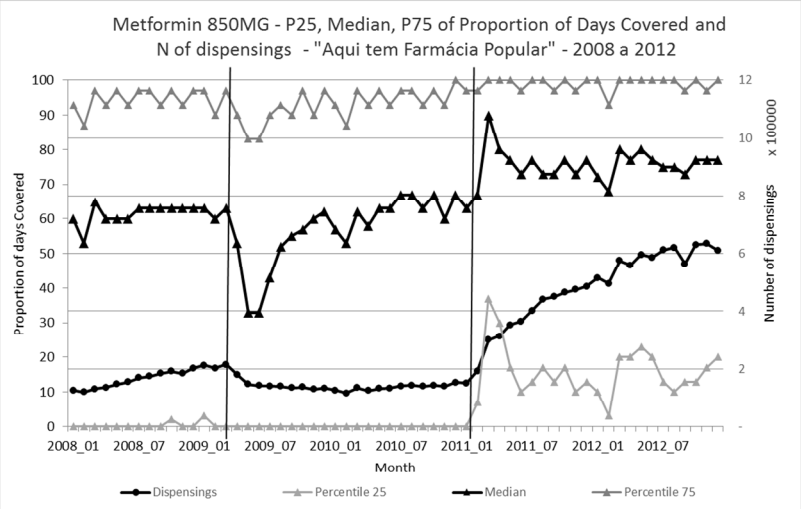


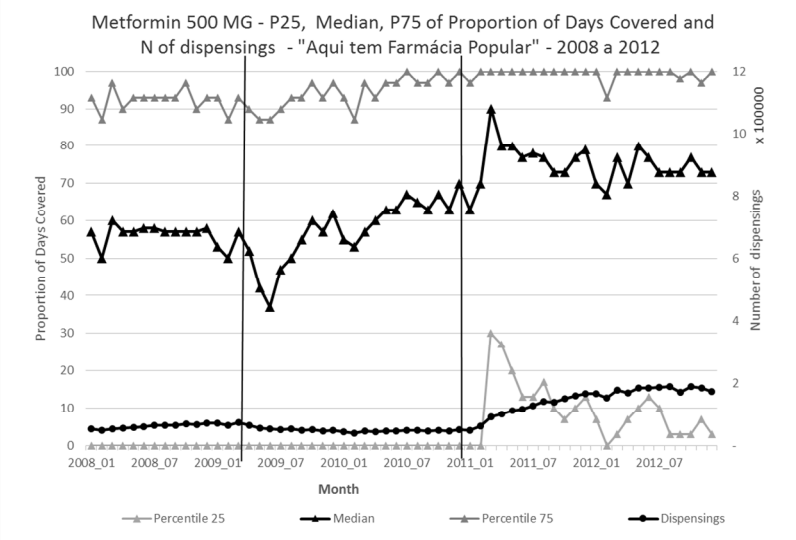
Figure 1. Number of dispensings and 25th/Median/75th percentiles of Proportion of Days Covered, and predicted values from segmented regression models for oral hypoglycemic and oral antihypertensive medicines, by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

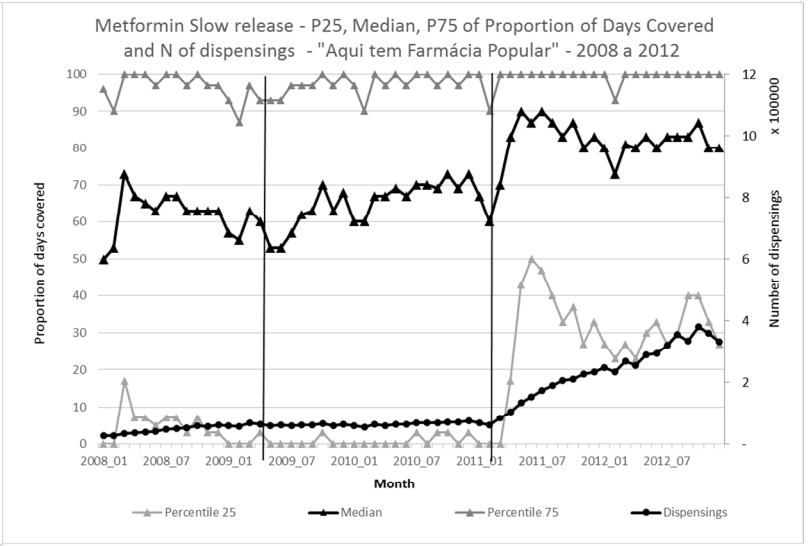
279x215mm (150 x 152 DPI)

Appendix 1. Number of dispensings and unadjusted 25th/Median/75th percentiles of Proportion of Days Covered, glibenclamide 5mg, metformin 850mg, metformin 500mg and metformin slow release, by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

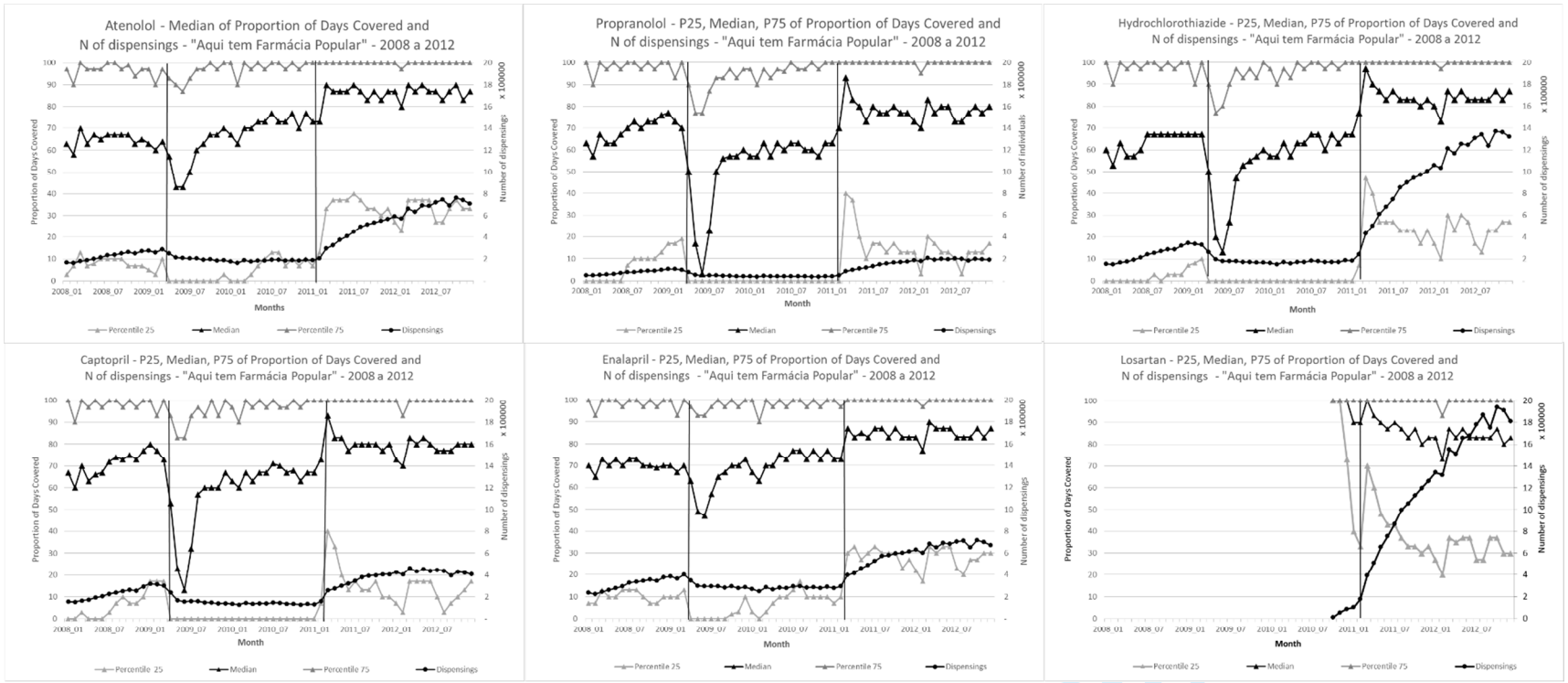








Appendix 2. Number of dispensings and unadjusted 25th/Median/75th percentiles of Proportion of Days Covered, atenolol 25mg, propranolol 40 mg, hydrochlorothiazide 25mg, captopril 25mg, enalapril 5mg and losartan 50 mg by stage of the Farmácia Popular program, Brazil, 2008 to 2012.



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Location in the Paper
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1 and 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract including Strengths and limitations of this study page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	describes changes in utilization and continuity of coverage for oral hypoglycemic (OH) and antihypertensive (AH) medicines following changes in patient cost sharing in the FP program. – pages 3, 4
Methods			
Study design	4	Present key elements of study design early in the paper	Methods - analysis and statistical methods – pages 5 and 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods – intervention and Data source and study population – pages 4 and 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods - Data source and study population – page 5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods – analysis – page 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods - Data source and study population – page 5
Bias	9	Describe any efforts to address potential sources of bias	We recognize as possible limitations on the discussion page 12
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods – analysis and statistical methods pages 5 and 6
Statistical methods	12	(*a*) Describe all statistical methods, including those	Methods – analysis and

		used to control for confounding	statistical methods pages 5 and 6
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	Methods – analysis and statistical methods pages 5 and 6
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results – page 6
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results page 6
		(b) Indicate number of participants with missing data for each variable of interest	In the methods is described how we handled the missing data – page 5
		(c) Summarise follow-up time (eg, average and total amount)	Results page 6
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results pages 6 to 11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results pages 6 to 11
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	We calculated the Percentage of change for specific periods in time – tables 2 and 3 pages 8 and 9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion – pages 11 and 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion – page 12

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion – pages 11 and 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	Not applicable
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Trends in hypertension and diabetes medicines utilization following changes in patient cost sharing in the "Farmácia Popular" program in Brazil

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017308.R1
Article Type:	Research
Date Submitted by the Author:	01-Aug-2017
Complete List of Authors:	Emmerick, Isabel; ENSP/Fiocruz, Nucleuos for Pharmaceutical Policies Campos, Monica; Fundacao Oswaldo Cruz, Luiza, Vera Lucia; National School of Public Health/ Oswaldo Cruz Foundation, Nucleus for Pharmaceutical Policies; Home, Chaves, Luisa; UFRJ Macaé, ; Escola Nacional de Saude Publica - Sergio Arouca, Bertoldi, Andrea D. Ross-Degnan, Dennis; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine
Primary Subject Heading:	Public health
Secondary Subject Heading:	Health services research, Health policy, Cardiovascular medicine, Diabetes and endocrinology
Keywords:	chronic illness, non-communicable diseases, health services, medicines utilization, patient cost sharing, medication adherence

Trends in hypertension and diabetes medicines utilization following changes in patient cost sharing in the "Farmácia Popular" program in Brazil

Isabel Cristina Martins Emmerick, ScD

Research Fellow, Pharmaceutical Policy Research Fellowship, Department of Population Medicine, Harvard Medical School & Harvard Pilgrim Health Care Institute. Landmark Center, 401 Park Drive Suite 401 Boston, MA 02215·

Mônica Rodrigues Campos, PhD

Department of Social Sciences, Sergio Arouca National School of Public Health, Oswaldo Cruz Foundation.1480 Rua Leopoldo Bulhões #905, Manguinhos, Rio de Janeiro 21041-210, Brazil

Vera Lucia Luiza, ScD

Department of Medicines and Pharmaceutical Services Policies, Sergio Arouca National School of Public Health, Oswaldo Cruz Foundation. 1480 Rua Leopoldo Bulhões #624, Manguinhos, Rio de Janeiro 21041-210, Brazil

Luisa Arueira Chaves, MSc

Phamacy Department, Federal University of Rio de Janeiro, Macaé Campus. Av. Aluizio da Silva Gomes, #50, Granja dos Cavaleiros, Macaé, 27930-560, Brazil - Rio de Janeiro Federal University – Macaé Campus.

Andréa Dâmaso Bertoldi, PhD

Postgraduate Program in Epidemiology, Federal University of Pelotas. Rua Marechal Deodoro 1160, 96020-220, Pelotas, Brazil.

Dennis Ross-Degnan, ScD

Department of Population Medicine, Drug Policy Research Group, Harvard Medical School & Harvard Pilgrim Health Care Institute. Landmark Center, 401 Park Drive Suite 401 Boston, MA 02215

Corresponding Author:
Isabel Emmerick, Research Fellow
Pharmaceutical Policy Research Fellowship
Department of Population Medicine
Harvard Medical School & Harvard Pilgrim Health Care Institute
Landmark Center, 401 Park Drive Suite 401 Boston, MA 02215
Phone: 1-617-509-9510, Fax: 1-617-859-8112
emmerick. isabel@gmail. com

Key words: chronic illness, non-communicable diseases, health services, patient cost sharing, medicines utilization, medication adherence

Running Title: Trends in hypertension and diabetes medicines utilization

Words and tables count

Number of tables: 03

Number of figures: 01

Words (Abstract): 239

Words (Text): 4061

Appendix: 03

Abstract

Objectives: "Farmácia Popular" (FP) program was launched in 2004, expanded in 2006 and changed the cost sharing for oral hypoglycemic (OH) and antihypertensive (AH) medicines in 2009 and in 2011. This paper describes patterns of utilization and continuity of coverage for OH and AH medicines following changes in patient cost sharing in the FP.

Study Design: Interrupted time series study using retrospective administrative data.

Methods: Monthly program participation (PP) and proportion of days covered (PDC) were the two outcome measures. The open cohort included all patients with two or more dispensings for a given study medicine in 2008-2012. The interventions were an increase in patient cost sharing in 2009 and zero patient cost sharing for key medicines in 2011.

Results: A total of 3.6 and 9.5 million patients receiving treatment for diabetes and hypertension, respectively, qualified for the study. Before the interventions, PP was growing by 7.3% per month; median PDC varied by medicine from 50-75%. After patient cost sharing increased in 2009, PP reduced by 56.5% and PDC decreased for most medicines (median 60.3%). After the 2011 free medicine program, PP surged by 121,000 new dispensings per month and PDC increased for all covered medicines (80.7%).

Conclusion: Cost sharing was found to be a barrier to continuity of treatment in Brazil's private sector FP program. Making essential medicines free to patients appear to increase participation and continuity of treatment to clinically beneficial levels (PDC greater than 80%).

Strengths and limitations of this study

- This paper contributes to our understanding of the impacts of sequential national policies in Brazil's *Farmácia Popular* (FP) program that were intended to improve access to medicines for non-communicable diseases in a middle-income country.
- Reduced program participation when patient cost sharing was increased and dramatic increases when key essential medicines were dispensed free of charge in private sector pharmacies provide important evidence about the impact of financial barriers on strategies to improve adherence to use of chronic medicines.
- The analysis uses the strongest quasi-experimental design - Interrupted Times Series (ITS) with segmented regression analysis - to evaluate policy impacts.
- The study is limited to patients treated under the FP program and not the entire population in Brazil. Overlaps between the FP program and other medicines provision mechanisms in the country including public sector health facilities could not be analyzed.
- The analyses of medicine utilization are based on dispensed amounts and enable us to evaluate average availability over time, but not actual adherence to treatment, overuse of medicines, or potential diversion outside of the program.

Background

Brazil has three main mechanisms by which individuals obtain access to medicines: out-of-pocket purchase in private pharmacies, provision in public health facilities, and the "Farmácia Popular" (FP) program. For out-of-pocket purchase, there are about 63,000 private pharmaceutical outlets all over the country, although the wealthier Southeast region was responsible for 51.9% of sales in 2013. [1] Medicines have been offered free-of-charge in all levels of public health care facilities since the 1970s. [2] The National Essential Medicines List, comprising 840 items in 2014, is the reference list for public coverage. [3]

FP, a new medicines subsidy program created in 2004,[4] has evolved in four phases. First, FP was implemented only in government-owned pharmacies to address persistent shortages of medicines in public health facilities. Medicines were sold at cost price plus operating cost, with selling prices 64-90% lower than the private market. [5] In the second phase, beginning in 2006 ("Aqui tem Farmácia Popular", AFP-I), a limited list of essential medicines (see complete list in each phase in Emmerick, 2015 [4]) swas authorized to be sold in private pharmacies contracted by the Ministry of Health. The government paid either 90% of a government-established reference price for each medicine or 90% of the selling price, whichever was less; patients paid the remaining value not covered by the government. In the third phase beginning in 2009 (AFP-II), administrative changes were introduced to improve accountability and reference prices were reduced for most medicines, resulting in increases in the patient's share. [4] In the fourth phase starting in February 2011 ("Saúde Não Tem Preço", SNP), hypoglycemic and antihypertensive medicines that were already in the program list began to be offered free-of-charge to patients in both government-owned and contracted private pharmacies, with the government paying a fixed negotiated price per medicine. In 2014, FP accounted for about 2.4 billion "reais" (1.09 billion USD) in government expenditures. [6]

Hypoglycemic (OH) and antihypertensive (AH) medicines present in the program's list were covered in all phases of FP program as part of broad ranging government initiatives to address these two non-communicable diseases. [7] One measure of private sector FP's contribution to control of these two illnesses is the proportion of days covered (PDC) by medicines dispensed by private FP pharmacies. PDC is a commonly-used refill-based measure of treatment adherence; [8–12] in this study, it refers to consistency of dispensing from the FP program, since there are other unobserved sources of medicines available to patients.

This paper aims to analyze changes in program participation and PDC for OH and AH medicines covered in the FP following changes in cost sharing during the AFP-II and SNP phases of the private sector FP program, using AFP data from January 2008 through December 2012. Comparable patient-level data are not available to evaluate changes in utilization of the public sector FP program.

Methods

Design

This study is a retrospective, quantitative, analytic study using interrupted time series based on administrative data and using an open cohort.

Intervention

The study interventions are two changes in patient cost sharing in AFP. In April 2009, the government reduced reference prices for most FP medicines by an average of 24.5 %, resulting in an immediate increase in patient copayment from an average of 2.45 “reais” to 3.88 “reais” per 30 days dispensing, a relative increase of 58.4% (for complete information on prices for each medicine, see Appendix 1). In February 2011, the government made all covered medicines for hypertension and diabetes free to patients, reimbursing pharmacies according to a set of negotiated prices.

Data source and study population

There have been no changes in FP eligibility criteria during the program. To have a medicine dispensed at any FP private pharmacy, a patient must present a valid prescription and a national ID. Medicines were dispensed on a monthly basis, although prescriptions were valid for 120 days. Over time, the number of participating private sector pharmacies has expanded substantially, especially in some regions. [4]

Data are derived from an electronic point-of-sales dispensing program implemented in 2006 in FP retail pharmacies. Available data include patient and pharmacy identifiers, patient age and gender, facilities geographic location, date of dispensing, name and quantity of medicine dispensed, daily-prescribed dose, MoH reimbursement, and patient copayment. For this paper we use data on dispensings of hypertension and diabetes medicines from January 2008 to December 2012. Dispensing data are of good quality and relatively complete, with duplicate cases accounting for less than 0.005% and individual-level missing data at less than 0.05%. We excluded encounters with missing data from all analyses.

Patients are included only if they received two or more dispensings for a given medicine during the study period. We used an open cohort, which means that when a patient had a dispensing he enter the analysis and was kept in it for 120 days (maximum time that the prescription is valid in Brazil). If the patient did not have a “new dispensing” during the 120 days interval, the patient fall out of the analysis and it is not in the denominator anymore. Patients with a single dispensing were considered occasional buyers and, for that reason were excluded from the analysis.

Analysis

The primary outcome variables were the number of monthly dispensings of AFP program medicines and the monthly median proportion of days covered (PDC) for included patients. All dispensings were for 30-day supply. 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). The number of days covered by a dispensing was defined as the amount of medicines dispensed divided by the prescribed daily dose. Days of therapy remaining in hand from prior dispensings were used to extend the number of days covered; possible overuse due to overlapping dispensings was not evaluated. [12]

We calculated monthly PDC as the number of days of therapy available during a month divided by the number of days in the month, with PDC thus varying between 0% and 100%;[12] the calculation for the first month of treatment considered only the days after the first dispensing. The median, 25th and 75th percentile PDCs represent aggregate values across all patients who were in an episode of treatment with that medicine during the month.

Statistical methods

We used interrupted time series (ITS) segmented linear regression models to determine the effect of the FP policy changes on the two study outcomes. In estimating effects, ITS models adjust for pre-existing trends in the period before the policy change. Segmented linear regression models were constructed using the *prais* command in STATA v12.

ITS models included three segments, one per program period, with 15, 22, and 23 monthly observations, respectively. The baseline segment was fit with an intercept and a variable estimating trend. We estimate each policy effect by one variable representing the change in level of the outcome immediately after the policy and a second representing the change in trend of the post-policy segment. Patients experienced the changes in cost sharing only when they presented to fill a prescription after the policy change. We thus defined a post-policy implementation period of two months for participation and six months for PDC (to account for the 120-day refill period); these periods were excluded in the ITS models so that we could estimate stable post-intervention effects.

We retained all parameters in the models regardless of statistical significance. We highlight the results with $p<0.05$. We also tested logarithmic trend terms to accommodate possible non-linear trends during each post-intervention segment, selecting the best model using the BIC and AIC goodness of fitness criteria. [13] For the trends in metformin 500mg, atenolol 25mg, and enalapril 5mg dispensing after the 2009 increase in cost sharing, the natural log of trend represented a better model fit. We tested the adequacy of each model by residual analysis. To create single number summaries of policy effects, we calculated estimates of the relative changes in outcomes compared to expected values based on prior trends in April 2010 and February 2012, about one year after the two cost sharing interventions.

Results

A total of 6,032,380 and 14,392,076 patients who received any OH or AH, respectively, from the FP program comprised the dataset; of these, 3,611,512 (59.9%) and 9,534,333 (66.25%) patients received two or more dispensings (Table 1). The mean age was 57 years for both diabetes and hypertension patients, with females comprising about 60% of patients; the Southeast region represented the majority of patients in the program. Patients with two or more dispensings did not differ significantly from those with a single medication fill in age, gender or region.

During the baseline period prior to the cost sharing changes, patients filled an average of 1.1 and 2.7 million dispensings per medicine per year for DM and HTN, respectively; dispensings were growing at an average rate of 7.4 % per month for the medicines analyzed (Figure 1, Table 2). Metformin 850mg was the most widely used OH medicine and had the highest rate of

growth, while metformin slow release had the smallest monthly number of dispensings (Appendix 2); enalapril was the most widely used AH medicine and propranolol the least widely used, but utilization of all AH medicines was growing rapidly (Appendix 3).

Prior to the increased cost sharing, PDC levels for studied medicines were relatively stable; by March 2009, one month before the AFP-II policy, median PDC levels for OH and AH medicines were 64.2 and 70.4%, respectively. Median PDC levels varied across covered medicines from 63.3% (metformin slow release) to 78.7% (captopril 25mg) (Figure 1, Table 3, Appendix 2, and Appendix 3).

Table 1. Patients participating in Brazil's "Farmácia Popular is Available Here" program, total and with two or more dispensings versus one dispensing, by gender, age and region, 2008 to 2012.

		Total		Two or more dispensings		One dispensing only	
DIABETES							
Age (n; mean (SD))		6,026,058	55.5 (15.1)	3,608,677	56.8 (14.0)	2,417,381	53.6 (16.5)
Gender (n, %)	Female	3,602,944	59.7%	2,168,131	60.0%	1,434,813	59.3%
	Male	2,413,718	40.0%	1,433,895	39.7%	979,823	40.5%
Region (n, %)	North	169,330	2.8%	79,517	2.2%	89,813	3.7%
	Northeast	849,184	14.1%	444,653	12.3%	404,531	16.7%
	Southeast	3,769,151	62.5%	2,336,807	64.7%	1,432,344	59.2%
	South	885,391	14.7%	540,572	15.0%	344,819	14.2%
	West-Center	359,324	6.0%	209,963	5.8%	149,361	6.2%
Total		**6,032,380**	**100.0%**	**3,611,512**	**100.0%**	**2,420,868**	**100.0%**
HYPERTENSION							
Age (n; mean (SD))		14,374,244	55.8 (15.1)	9,525,183	56.7 (14.3)	4,849,061	53.97 (16.4)
Gender (n, %)	Female	8,636,053	60,0%	5,777,649	60.6%	2,858,404	58.8%
	Male	5,714,487	39,7%	3,728,721	39.1%	1,985,766	40.9%
Region (n, %)	North	469,739	3,3%	232,250	2.4%	237,489	4.9%
	Northeast	2,121,308	14,7%	1,201,133	12.6%	920,175	18.9%
	Southeast	8,290,832	57,6%	5,714,243	59.9%	2,576,589	53.0%
	South	2,562,095	17,8%	1,780,678	18.7%	781,417	16.1%
	West-Center	948,102	6,6%	606,029	6.4%	342,073	7.0%
Total		**14,392,076**	**100,0%**	**9,534,333**	**100.0%**	**4,857,743**	**100.0%**

Table 2. Baseline level and trend in monthly number of dispensings (DISP)[a] per 100,000 for hypoglycemic and antihypertensive medicines, and changes in level and trend by stage of the "Farmácia Popular" program, Brazil, 2008 to 2012.

	Baseline		AFP-II (April 2009)					SNP (February 2011)		
	Level (DISP)	Trend	DISP (March 2009)	Level AFPII (April 2009)	Trend AFPII	%relative Change (AFPII) (April 2010)	DISP (Jan 2011)	Level SNP (Feb 2011)	Trend SNP	%relative change (SNP) (Feb2012)
Oral Hypoglycemic	2.45	0.16	4.85	**-2.12 (-3.13;-1.1)**	**-0.15 (-0.24;-0.06)**	**-54.5**	3.23	**4.39 (3.47;5.31)**	**0.40 (0.33;0.47)**	**262.0**
Glibenclamide 5mg	0.58	0.04	1.25	**-0.67 (-0.99;-0.35)**	**-0.05 (-0.07;-0.02)**	**-63.7**	0.66	**1.22 (0.93;1.52)**	**0.10 (0.07;0.12)**	**350.2**
Metformin 850mg	1.14	0.07	2.19	**-1.01 (-1.43;-0.59)**	**-0.06 (-0.1;-0.03)**	**-55.4**	1.43	**1.98 (1.6;2.36)**	**0.15 (0.12;0.18)**	**239.8**
Metformin 500mg	0.51	0.02	0.73	**-0.26 (-0.48;-0.05)**	-0.02 (-0.04;0.00)	**-48.7**	0.46	**0.68 (0.48;0.88)**	**0.04 (0.03;0.06)**	**258.9**
Metformin slow release	0.23	0.03	0.67	-0.16 (-0.38;0.06)	-0.02 (-0.04;0.00)	**-39.2**	0.69	**0.47 (0.27;0.66)**	**0.12 (0.1;0.13)**	**226.5**
Oral Antihypertensive	6.94	0.51	14.58	**-7.28 (-12.1;-2.45)**	**-0.5 (-0.93;-0.06)**	**-60.1**	8.56	**15.91 (11.45;20.37)**	**1.5 (1.16;1.84)**	**371.9**
Atenolol 25mg	1.59	0.09	2.90	**-1.1 (-1.68;-0.52)**	**-0.1 (-0.15;-0.04)**	**-53.3**	1.81	**1.87 (1.34;2.4)**	**0.21 (0.17;0.25)**	**242.4**
Propranolol 40mg	0.45	0.04	1.03	**-0.64 (-0.99;-0.29)**	**-0.04 (-0.07;-0.01)**	**-72.8**	0.37	**0.76 (0.43;1.1)**	**0.05 (0.03;0.07)**	424.7
Hydrochlorothiazide 25mg	1.31	0.14	3.46	**-2.05 (-3.14;-0.97)**	**-0.14 (-0.24;-0.04)**	**-67.6**	1.75	**4.15 (3.16;5.14)**	**0.4 (0.33;0.48)**	**481.1**
Captopril 25mg	1.42	0.11	3.12	**-1.8 (-2.42;-1.17)**	**-0.13 (-0.18;-0.07)**	**-69.3**	1.29	**1.92 (1.34;2.51)**	**0.08 (0.03;0.12)**	**244.3**
Enalapril 5mg	2.18	0.12	4.04	**-1.42 (-2.04;-0.8)**	**-0.13 (-0.18;-0.07)**	**-50.0**	2.78	**1.93 (1.36;2.5)**	**0.13 (0.09;0.17)**	**123.1**

significant values p<0.05 are highlighted in bold
NA - no applicable

[a] DISP – number of dispensings. The number of dispensings was divided by 100,000.

Table 3. Baseline median and trend in monthly Proportion of Days Covered (PDC) for hypoglycemic and antihypertensive medicines, and changes in level and trend by stage of the "Farmácia Popular" program, Brazil, 2008 to 2012.

	Baseline			AFP II (April 2009)				SNP (February 2011)		
	Level (PDC)	Trend	PDC (Mar 2009)	Level AFP II (Change at the intervention)	Trend AFP II	% relative change (AFP II) (April 2010)	PDC (Jan 2011)	Level SNP (Change at the intervention)	Trend SNP	% relative change (SNP) (Feb 2012)
Oral Hypoglycemic	59.67	0.30	64.22	**-8.1 (-12.85;-3.36)**	0.28 (-0.12;0.67)	**-9.0**	67.21	**4.88 (0.37;9.39)**	**-0.43 (-0.79;-0.07)**	2.5
Glibenclamide 5mg	61.40	0.56	69.75	**-15.23 (-19.65;-10.81)**	-0.07 (-0.43;0.3)	**-20.4**	65.73	**6.23 (2.03;10.42)**	**-0.35 (-0.68;-0.01)**	**5.3**
Metformin 850mg	59.02	0.38	64.74	**-10.41 (-15.3;-5.52)**	0.21 (-0.2;0.62)	**-12.8**	66.08	**3.84 (-0.81;8.49)**	**-0.37 (-0.74;-0.01)**	1.7
*Metformin 500mg	56.24	0.05	57.04	-1.75 (-7.23;3.73)	**2.87 (0.07;5.67)**	6.7	64.41	**8.56 (2.9;14.22)**	-0.15 (-0.77;0.46)	**11.2**
Metformin slow release	61.09	0.15	63.29	0.61 (-10.35;11.57)	0.16 (-0.75;1.06)	2.6	69.67	**11.09 (0.61;21.56)**	-0.43 (-1.25;0.4)	11.0
Oral Antihypertensive	63.98	0.45	70.74	**-10.63 (-14.7;-6.55)**	0.22 (-0.12;0.55)	**-11.9**	73.48	**4.87 (1;8.73)**	**-0.57 (-0.88;-0.27)**	1.0
*Atenolol 25mg	64.88	0.02	65.15	-0.70 (-5.53;4.13)	**3.4 (1.03;5.78)**	9.1	74.27	**10.63 (6.6;14.67)**	-0.14 (-0.49;0.21)	**12.6**
Propranolol 40 mg	61.34	1.07	77.40	**-26.21 (-32.49;-19.93)**	**-0.73 (-1.25;-0.21)**	**-34.3**	63.00	**11.63 (5.66;17.6)**	-0.23 (-0.71;0.24)	**14.8**
Hydrochlorothiazide 25mg	56.88	0.82	69.22	**-18.17 (-22.91;-13.43)**	-0.12 (-0.51;0.28)	**-23.8**	67.25	**10.1 (5.6;14.6)**	**-0.53 (-0.89;-0.17)**	**8.4**
Captopril 25mg	63.81	0.99	78.66	**-23.07 (-28.85;-17.29)**	**-0.52 (-1;-0.04)**	**-29.2**	69.11	**5.86 (0.37;11.35)**	-0.38 (-0.82;0.06)	4.2
*Enalapril 5mg	70.16	0.02	70.39	-2.91 (-7.74;1.93)	**2.56 (0.18;4.95)**	3.0	74.93	**7.79 (3.75;11.83)**	-0.02 (-0.37;0.34)	**10.0**

significant values p<0.05 are highlighted in bold
NA - no applicable
*it was used the Log of the AFP II trend

Cost sharing increases (AFP-II) April 2009

After patient copayments increased, OH dispensings declined immediately by -2.12 per 100,000 (95% CI [-3.13, -1.10]) compared to 4.85 per 100,000 in March 2009, immediately before the policy (Table 2). In addition, the previous upward monthly trend in participation flattened to nearly zero (slope change -0.15 per month, [-0.24, -0.06]). By one year after the policy, dispensings had declined by 54.5% [-65.9%,-43.0%] compared to where they would have been had baseline trends continued. Similarly, dispensings of AH medicines declined by -7.8 per 100,000 [-12.1,-2.45] from their level of 14.6 per 100,000 immediately before the AFP-II policy. As with OH medicines, the previous monthly increase in participation of 0.51 declined by -0.5 [-0.93, -0.06]. After one year, participation was 60.1% [-76.1, -44.2] lower than expected based on prior trends. (Table 2)

After AFP-II, rates of monthly dispensing for most studied medicines followed similar patterns. Dispensing had been increasing by 1,600 (metformin 500mg) to 14,000 (hydrochlorothiazide 25mg) fills per month prior to the increased cost sharing. After AFP-II implementation, there were immediate reductions in participation and flattened rates of dispensing that persisted over time. By one year after the intervention, in April 2010, all medicines had experienced significant relative decreases varying from 39.2% for metformin slow release to 72.8% for propranolol 40mg. (Table 2)

After patient copayments increased and substantial numbers of patients left the program, median PDC declined for OH medicines by 8.11% [-12.85%, -3.36%] and for AH medicines by 10.61% [-14.7%, -6.55%]. While the AFP policy remained in effect (until December 2010), median monthly PDC tended to increase slightly among participating patients (OH medicines: 0.28 per month [-0.12, 0.67]; AH medicines: 0.22 [-12, 0.55]). By one year after the policy, median PDC had declined for OH medicines by 9.0% [-18.0%, -5.8 %] and for AH medicines by 11.9% [-26.3,-14.4] relative to where they would have been had baseline trends continued. (Table 3)

Changes in PDC following increased cost sharing varied across medicines. PDC for five of the nine medicines covered decreased by 12.8% (metformin 850mg) to 34.3% (propranolol 40mg). However, four medicines actually experienced small nonsignificant increases in PDC for patients remaining in the program by a year after the cost sharing increase. (Table 3)

Availability of free medicines (SNP) – February 2011

After the SNP implementation, dispensings of OH medicines increased by 4.39 per 100,000 [3.47, -5.31] compared to 3.23 per 100,000 in January 2011, immediately before the policy (Table 2). Additionally, there was an upward monthly trend in dispensings of 0.40 per month [0.33, 0.47] contrasting with the previous flattened trend. By a year after the policy, dispensings had increased by 262% [130.7, 393.3] compared to where they would have been had previous trends continued. AH medicines followed the same pattern; dispensings increased by 15.9 per 100,000 [11.45, 20.37] from their level of 8.6 per 100,000 immediately before the SNP policy. Participation increased by 1.5 [1.16, 1.84] per 100,000 per month. After one year, participation was 372% (57.2, 686.6) higher than expected based on prior trend. (Table 2)

After SNP, rates of monthly dispensing for most medicines followed similar patterns, varying from an immediate increase in participation of 47,000 (metformin slow release) to 415,000 (hydrochlorothiazide 25mg) fills per month; increases in trend of monthly dispensing persisted over time. By one year after the free medicines policy, in February 2012, significant relative increases varied from 226% to 481% for metformin slow release and hydrochlorothiazide 25mg, respectively. (Table 2)

Losartan was added to the medicines reference list in October 2010; by the time of SNP implementation four months later, there were only about 10 thousand dispensings. By one year after medicines became free to patients, losartan dispensings had increased to more than 2 million dispensings. In comparison, its therapeutic competitors captopril and enalapril had only 700,000 and 1 million dispensings, respectively, in February 2012. (Appendix 2)

After SNP and the substantial influx of patients, median monthly PDC increased for OH medicines by 4.88% [0.37%, 9.39%] and for AH medicines by 4.87% [1.00%, 8.73%], and remained relatively constant until the end of the study period (December 2012). (Table 3) Changes in PDC varied by medicine; six of the nine medicines covered increased significantly by 5.3% (glibenclamide 5mg) to 14.8% (propranolol 40mg), but three experienced only small, nonsignificant increases by the year after the free medicine policy. (Table 3).

Discussion

Coverage policies in "Farmácia Popular", a publicly-financed program designed to increase access to essential medicines in Brazil, have evolved over time. Patient cost sharing increased by 58% in 2009, resulting in immediate decreases in program participation and PDC. In contrast, rapid increases in both outcomes followed implementation of a 2011 policy to make essential medicines for diabetes and hypertension free to patients.

Program participation for hypertension and diabetes follow the prevalence profile of these two diseases in the country. [14] The majority of AFP patients are from the wealthier Southeast region where there is a higher density of participating pharmacies; [4] this may imply increasing socioeconomic disparities in access to treatment for diabetes and hypertension, especially now that medicines are available for free. Other studies that have evaluated access to medicines for hypertension[15] and diabetes[16] through the Health has No Price program have concluded that the intervention contributed to increased access to these medicines in Brazil.

The impact of cost-sharing interventions on the use of medicines has been addressed in the literature[17]. It may be expressed in terms of the amount used, measured as sales volume or prescriptions filled, of expenditures or sales, healthcare utilization or health outcomes.

PDC is usually used in the literature as a proxy for treatment adherence. [9,12,18] Therefore, it is a measure of use of medicines with a closer link to health outcomes. 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.

In the literature, about half of patients treated for chronic disease become no adherent within a year. [19] The consistency of prescription filling in the AFP program, particularly after medicines for diabetes and hypertension were made free to patients, suggest that private sector outlets are convenient and preferred by patients as a source of these free medicines.

The relationship between PDC levels and clinical outcomes is well-established in the literature. [20,21] For example, adherence to hypoglycemic treatment measured through administrative data has been found to be related to better glycemic control, fewer emergency department visits, and lower rates of hospital admission. [22] [23] [24] Many studies consider patients with PDC 80% or higher to be adherent to treatment;[22] lower adherence can lead to higher rates of adverse events, poor long-term health outcomes, and higher healthcare costs. [25] After SNP, rates of PDC were higher than 80% for well over half of patients taking OH and AH medicines, levels likely to have positive impact on clinical outcomes. One study that analyzed the impact of full subsidy policies on medicines use have found similar effects on PDC as in our study. [11,26–29]

The relation between cost sharing and medication adherence has been widely studied. [17] In our study, all medicines with increased copayments in April 2009 experienced decreases in rates of dispensing and PDC. After SNP, we observed the opposite response; when patients had no cost sharing, program participation and PDC increased dramatically.

Although losartan is not a first-line treatment in the Brazilian guideline to treat hypertension,[30] it was included in the FP reimbursement list in 2010. Within a few months, losartan had become the most widely dispensed AH medicine. Coverage decisions in government subsidy programs should be consistent with treatment guidelines to encourage appropriate choice of therapy and more cost-effective treatment.

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]. We have the issue that there are other sources for medicines to patients. However, we did not intend to use PDC as adherence to treatment measure, but as 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. Then, we think that these potential treats to internal validity have negligible impact on our findings. To make the estimates of PDC interpretable, we limited analysis of program impacts to patients who filled more than one prescription of a medicine in the FP private sector; there were no relevant differences in characteristics between patients who filled only one prescription and those who used it more regularly. We have no data on medicines that are not part of the program, so cannot evaluate the impact of FP program policies on use of other medicines used to treat diabetes and hypertension. Since patients could have switched treatment among the medicines covered (e.g. change from captopril to enalapril), we may have underestimated PDC because we did not evaluate this possible change. That way, the median PDC would be lower when actually the patient was changing the therapy and using other medicine. Finally, as a result of the method

chosen to calculate the PDC,[12] the possible overuse due to overlapping dispensings was not evaluated.

In conclusion, participation in the "Farmácia Popular" private sector program evolved in response to two cost sharing interventions implemented between 2008 and 2012. Increased patient cost sharing reduced participation, while full subsidy of key medicines in private pharmacies substantially increased participation; patients in the program achieved PDC levels that have been shown to improve health outcomes. Risks to rational use of medicines, especially overuse, can be minimized through controlling mechanisms, such as the requirement of prescription, validity of prescriptions and maximum dispensing amounts. Policy makers should consider reducing or removing cost sharing for essential medicines to treat chronic illness, while aligning subsidies to encourage greater use of first-line therapies.

Acknowledgements: The authors thank the Ministry of Health in Brazil for providing the data used in this study. Dr. Isabel Emmerick was supported by CNPQ process number 202246/2012-4 and the Pyle Fellowship of Harvard Pilgrim Health Care Institute.

Author contributions: All authors made substantial contribution to study conception, ICME MRC, DRD made substantial contribution to study design. ICME, VLL, MRC, LAC, ADB were responsible for data acquisition. ICME, MRC and DRD were responsible for data analysis. All authors contributed to interpretation of data. ICME drafted the article and is guarantor. All authors provided critical revisions for important intellectual content and approved the final version.

Conflicts of interest: Dr. Emmerick, principal investigator, reports grants from World Health Organization Access to Medicines Research Network, during the conduct of the study. Dr. Campos, Dr. Luiza, Dr. Chaves, Dr. Bertoldi and Dr. Ross-Degnan report personal fees from World Health Organization Access to Medicines Research Network, during the conduct of the study; Dr. Luiza also reports personal fees from Oswaldo Cruz Foundation (Fiocruz), outside the submitted work.

Funding: Research grant from the World Health Organization Alliance for Health Policy and Systems Research. Dr. Emmerick is supported by the Pyle Fellowship of Harvard Pilgrim Health Care Institute. Dr. Ross-Degnan is supported in part by the Health Delivery Systems Center for Diabetes Translational Research (HDS-CDTR) [NIDDK grant 1P30-DK092924].

Ethical approvals: The Brazilian National Ethics Committee, by the National School of Public Health – Fiocruz – Brazil and the WHO ERC, approved the ISAUM-Br project, which is the base for this paper.

This work was conducted in collaboration among the following institutions: Department of Medicines and Pharmaceutical Services Policies, Sergio Arouca, National School of Public Health, Fiocruz Brazil; Department of Epidemiology, University of Pelotas, Brazil; Department of Pharmaceutical Services / Office of Science Technology and Strategic Resources - Ministry of Health and the Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute.

Data sharing: No additional data are available.

Table 1. Patients participating in Brazil's "Farmácia Popular is Available Here" program, total and with two or more dispensings versus one dispensing, by gender, age and region, 2008 to 2012.

Table 2. Baseline level and trend in monthly number of dispensings (DISP)a per 100,000 for hypoglycemic and antihypertensive medicines, and changes in level and trend by stage of the "Farmácia Popular" program, Brazil, 2008 to 2012.

Table 3. Baseline median and trend in monthly Proportion of Days Covered (PDC) for hypoglycemic and antihypertensive medicines, and changes in level and trend by stage of the "Farmácia Popular" program, Brazil, 2008 to 2012.

Figure 1. Number of dispensings and 25th/Median/75th percentiles of Proportion of Days Covered, and predicted values from segmented regression models for oral hypoglycemic and oral antihypertensive medicines, by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

Appendix 1. Medicines average unit price in local currency (reais), and average price treatment for 30 days' supply for glibenclamide 5mg, metformin 850mg, metformin 500mg, metformin slow release, losartan 50 mg, atenolol 25mg, propranolol 40 mg , hydrochlorothiazide 25mg, captopril 25mg, enalapril 5mg by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

Appendix 2. Number of dispensings and unadjusted 25th/Median/75th percentiles of Proportion of Days Covered, glibenclamide 5mg, metformin 850mg, metformin 500mg and metformin slow release, by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

Appendix 3. Number of dispensings and unadjusted 25th/Median/75th percentiles of Proportion of Days Covered, atenolol 25mg, propranolol 40 mg, hydrochlorothiazide 25mg, captopril 25mg, enalapril 5mg and losartan 50 mg by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

References

1 Valor Econômico. Valor: Análise setorial: Farmácias e Drogarias. 2014.

2 Bermudez J. AZ, Oliveira MA, Luiza VL. Assistência Farmacêutica. In: Lígia Giovanella, Sarah Escorel, Lenaura de Vasconcelos Costa Lobato, *et al.*, eds. *Políticas e Sistema de Saúde no Brasil*. Rio de Janeiro: : Fiocruz 2012. 761–94.

3 Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. *Relação Nacional de Medicamentos Essenciais: RENAME 2014*. 9th ed. Brasília: : Ministério da Saúde 2014.

4 Emmerick ICM, do Nascimento JM, Pereira MA, *et al.* Farmacia Popular Program: changes in geographic accessibility of medicines during ten years of a medicine subsidy policy in Brazil. *J Pharm Policy Pract* 2015;**8**. doi:10.1186/s40545-015-0030-x

5 Santos-Pinto CDB, Miranda ES, Martins Emmerick IC, *et al.* Medicine prices and availability in the Brazilian popular pharmacy program [Preços e disponibilidade de medicamentos no Programa Farmácia Popular do Brasil]. *Rev Saude Publica* 2010;**44**:611–9.

6 Brasil. Ministério da Saúde. Sala de Apoio à Gestão Estratégica. Redes_e_Porgramas>Situação_de_Saúde>Gestão/Financiamento?Aqui_Tem_Farmácia_Popular. 2015. http://sage.saude.gov.br/ (accessed 29 Sep 2015).

7 Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Análise de Situação de Saúde. *Plano de ações estratégicas para o enfrentamento das doenças crônicas não transmissíveis (DCNT) no Brasil 2011-2022*. Brasília: : Ministério da Saúde 2011.

8 Sattler ELP, Lee JS, Perri M. Medication (Re)fill Adherence Measures Derived from Pharmacy Claims Data in Older Americans: A Review of the Literature. *Drugs Aging* 2013;**30**:383–99. doi:10.1007/s40266-013-0074-z

9 Andrade SE, Kahler KH, Frech F, *et al.* Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf* 2006;**15**:565–74. doi:10.1002/pds.1230

10 An J, Nichol MB. Multiple medication adherence and its effect on clinical outcomes among patients with comorbid type 2 diabetes and hypertension. *Med Care* 2013;**51**:879–887.

11 Athanasakis K, Skroumpelos AG, Tsiantou V, *et al.* Abolishing coinsurance for oral antihyperglycemic agents: Effects on social insurance budgets. 2011;**17**:130–5.

12 Hess LM, Raebel MA, Conner DA, *et al.* Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother* 2006;**40**:1280–8. doi:10.1345/aph.1H018

13 Maydeu-Olivares A. Goodness-of-Fit Testing. http://www.ub.edu/gdne/amaydeusp_archivos/encyclopedia_of_education10.pdf (accessed 10 Feb 2016).

14 Brasil. Ministério da Saúde, Secretaria de Vigilância em Saúde. *Vigitel Brasil 2013: vigilância de fatores de risco e proteção para doenças crônicas*. Brasília: : Ministério da Saúde 2014.

15 Araujo JLO, Pereira MD, de Sá Del Fiol F, *et al.* Access to Antihypertensive Agents in Brazil: Evaluation of the "Health Has No Price" Program. *Clin Ther* 2014;**36**:1191–5. doi:10.1016/j.clinthera.2014.06.003

16 Araujo JLO, Pereira MD, de Cássia Bergamaschi C, *et al.* Access to medicines for diabetes treatment in Brazil: evaluation of "health has no price" program. *Diabetol Metab Syndr* 2016;**8**. doi:10.1186/s13098-016-0150-8

17 Luiza VL, Chaves LA, Silva RM, *et al.* Pharmaceutical policies: effects of cap and co-payment on rational use of medicines. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd 2015. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007017.pub2/abstract (accessed 12 May 2015).

18 Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol* 1997;**50**:105–16.

19 Franklin JM, Krumme AA, Shrank WH, *et al.* Predicting Adherence Trajectory Using Initial Patterns of Medication Filling. *Am J Manag Care* 2015;**21**.http://www.ajmc.com/journals/issue/2015/2015vol21n9/PredictingAdherenceTrajectoryUsingInitialPatternsofMedicationFilling?utm_source=Informz

20 Elhayany A, Vinker S. Addressing healthcare inequities in Israel by eliminating prescription drug copayments. *Am J Manag Care* 2011;**17**:e255-9.

21 Lynch WD, Pesa J, Melkonian AK, *et al.* Effect of Antihypertensive Medication Adherence Among Employees With Hypertension. *Am J Manag Care* 2009;**15**:871–80.

22 Nair KV, Miller K, Saseen J, *et al.* Prescription copay reduction program for diabetic employees: Impact on medication compliance and healthcare costs and utilization. 2009;**2**:14–24.

23 Asche C, LaFleur J, Conner C. A Review of Diabetes Treatment Adherence and the Association with Clinical and Economic Outcomes. *Clin Ther* 2011;**33**:74–109. doi:10.1016/j.clinthera.2011.01.019

24 Nichols GA, Rosales AG, Kimes TM, *et al.* Impact on glycated haemoglobin of a biological response-based measure of medication adherence. *Diabetes Obes Metab* Published Online

First: 2015.http://onlinelibrary.wiley.com/doi/10.1111/dom.12476/full (accessed 28 Sep 2015).

25 Roebuck MC, Liberman JN, Gemmill-Toyama M, *et al.* Medication Adherence Leads To Lower Health Care Use And Costs Despite Increased Drug Spending. *Health Aff (Millwood)* 2011;**30**:91–9. doi:10.1377/hlthaff.2009.1087

26 Huber CA, Rapold R, Brüngger B, *et al.* One-year adherence to oral antihyperglycemic medication and risk prediction of patient outcomes for adults with diabetes mellitus: An observational study. *Medicine (Baltimore)* 2016;**95**:e3994. doi:10.1097/MD.0000000000003994

27 Cramer JA. A systematic review of adherence with medications for diabetes. *Diabetes Care* 2004;**27**:1218–1224.

28 Ho PM, Rumsfeld JS, Masoudi FA, *et al.* Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Arch Intern Med* 2006;**166**:1836–1841.

29 An J, Nichol MB. Multiple medication adherence and its effect on clinical outcomes among patients with comorbid type 2 diabetes and hypertension. *Med Care* 2013;**51**:879–887.

30 Brasil, Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Atenção Básica. *Estratégias para o cuidado da pessoa com doença crônica: hipertensão arterial sistêmica [Strategies for the care of the person with chronic disease: systemic arterial hypertension]*. 1st ed. Brasília - DF: : Ministerio da Saúde, Brazil 2013. http://bvsms.saude.gov.br/bvs/publicacoes/estrategias_cuidado_pessoa_doenca_cronica.pdf

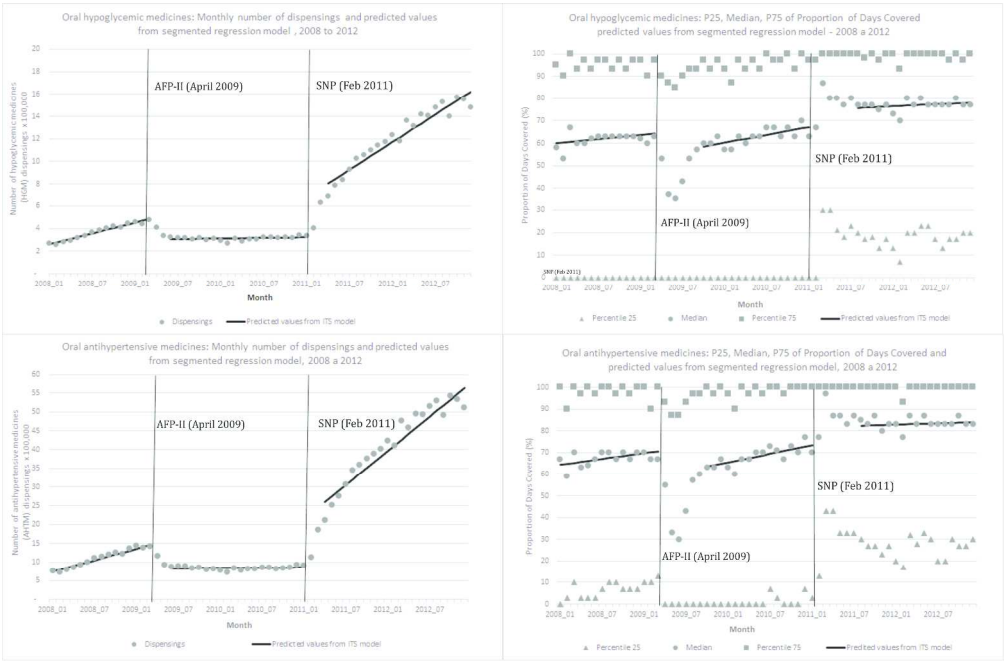


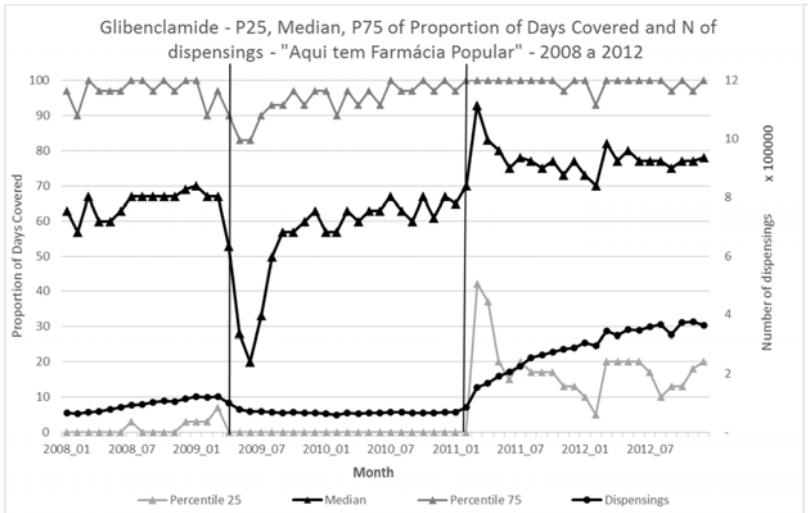
Figure 1. Number of dispensings and 25th/Median/75th percentiles of Proportion of Days Covered, and predicted values from segmented regression models for oral hypoglycemic and oral antihypertensive medicines, by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

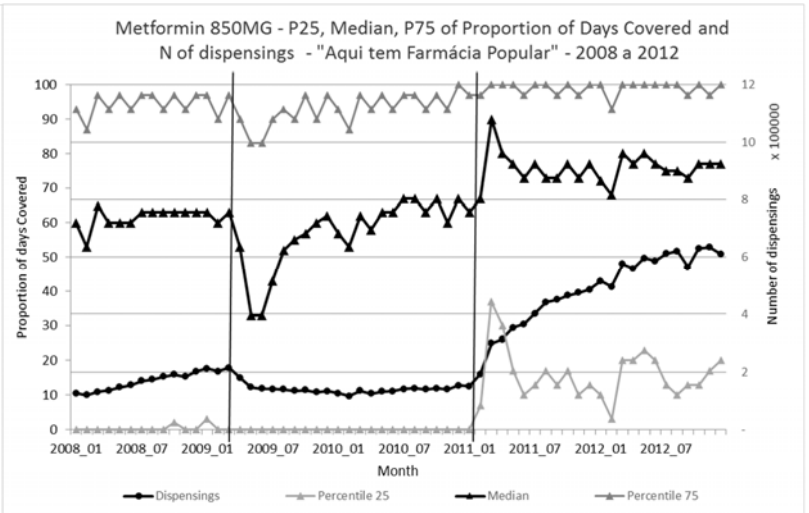
512x337mm (300 x 300 DPI)

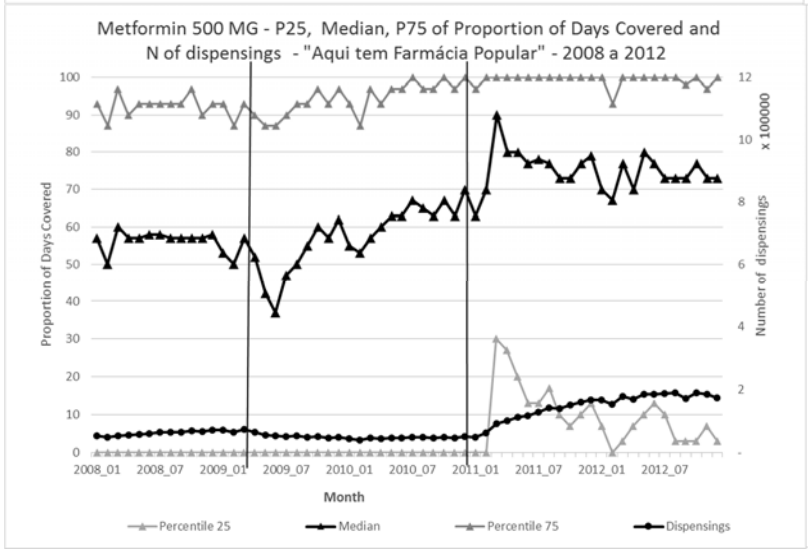
Appendix 1. Medicines average unit price in local currency (reais), and average price treatment for 30 days' supply for glibenclamide 5mg, metformin 850mg, metformin 500mg, metformin slow release, losartan 50 mg, atenolol 25mg, propranolol 40 mg , hydrochlorothiazide 25mg, captopril 25mg, enalapril 5mg by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

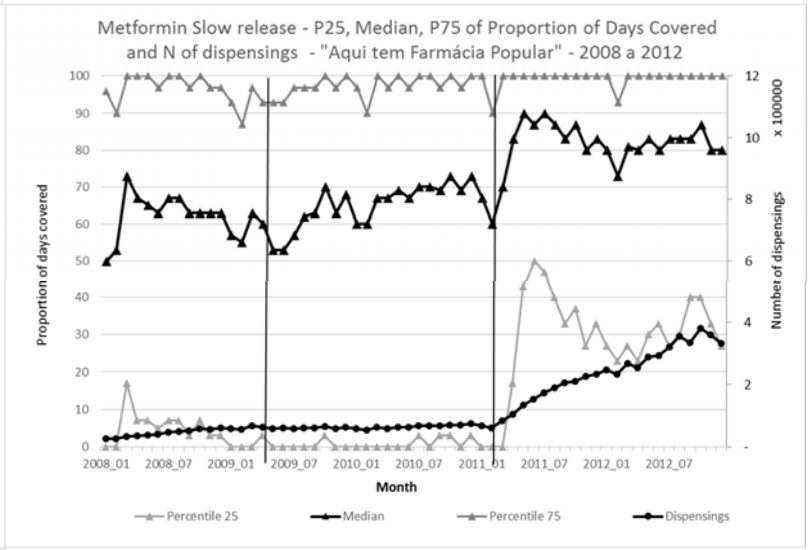
	Baseline Average Price (Jan 2008 to March 2009)			AFP II Average Price (April 2009 to Jan 2011)					SNP Average Price (Feb 2011 to Dec 2012)			
	Total	Patient	MoH	Total	Patient	MoH	Absolute change	Relative Change	Total	MoH	Absolute change	Relative Change
UNIT PRICE												
Hypoglycemic												
Glibenclamide 5mg	0.24	0.04	0.20	0.21	0.06	0.15	0.02	39.0	0.13	0.13	-0.02	-100
Metformin 850mg	0.37	0.07	0.30	0.33	0.10	0.23	0.04	53.9	0.17	0.17	-0.04	-100
Metformin 500mg	0.26	0.06	0.20	0.25	0.08	0.17	0.01	24.1	0.14	0.14	-0.01	-100
Metformin slow release	0.45	0.25	0.19	0.45	0.29	0.15	0.04	16.8	0.19	0.19	-0.04	-100
Antihypertensive												
Losartan 50 mg	-	-	-	0.75	0.34	0.41	0.34	NA	0.34	0.34	-0.34	-100
Atenolol 25mg	0.32	0.05	0.27	0.30	0.08	0.22	0.03	54.4	0.20	0.20	-0.03	-100
Propranolol 40 mg	0.17	0.04	0.13	0.15	0.05	0.10	0.01	32.76	0.09	0.08	-0.01	-100
Hydrochlorothiazide 25mg	0.19	0.03	0.16	0.15	0.05	0.10	0.02	80.12	0.08	0.08	-0.02	-100
Captopril 25mg	0.53	0.09	0.44	0.43	0.11	0.33	0.02	23.17	0.30	0.29	-0.02	-100
Enalapril 5mg	0.71	0.11	0.60	0.59	0.14	0.46	0.03	26.18	0.41	0.41	-0.03	-100
TREATMENT PRICE												
Hypoglycemic												
Glibenclamide 5mg	7.27	1.33	5.94	6.38	1.86	4.53	0.52	39.0	3.83	3.81	-0.52	-100
Metformin 850mg	10.99	2.00	8.99	9.83	3.07	6.75	1.08	53.9	5.12	5.09	-1.08	-100
Metformin 500mg	7.67	1.82	5.85	7.44	2.26	5.18	0.44	24.1	4.16	4.13	-0.44	-100
Metformin slow release	13.39	7.57	5.83	13.63	8.84	4.53	1.27	16.8	5.71	5.56	-1.27	-100
Antihypertensive												
Losartan 50 mg	-	-	-	22.39	10.22	12.17	10.22	NA	10.27	10.19	10.22	NA
Atenolol 25mg	9.60	1.46	8.14	8.98	2.25	6.73	0.79	54.4	6.04	6.01	-0.79	-100
Propranolol 40 mg	4.97	1.13	3.83	4.44	1.50	2.93	0.37	32.7	2.56	2.54	-0.37	-100
Hydrochlorothiazide 25mg	5.67	0.82	4.85	4.46	1.47	2.98	0.66	80.1	2.55	2.53	-0.66	-100
Captopril 25mg	15.78	2.61	13.17	13.04	3.22	9.82	0.61	23.1	8.86	8.82	-0.61	-100
Enalapril 5mg	21.15	3.29	17.87	17.83	4.15	13.68	0.86	26.1	12.34	12.29	-0.86	-100

Appendix 2. Number of dispensings and unadjusted 25th/Median/75th percentiles of Proportion of Days Covered, glibenclamide 5mg, metformin 850mg, metformin 500mg and metformin slow release, by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

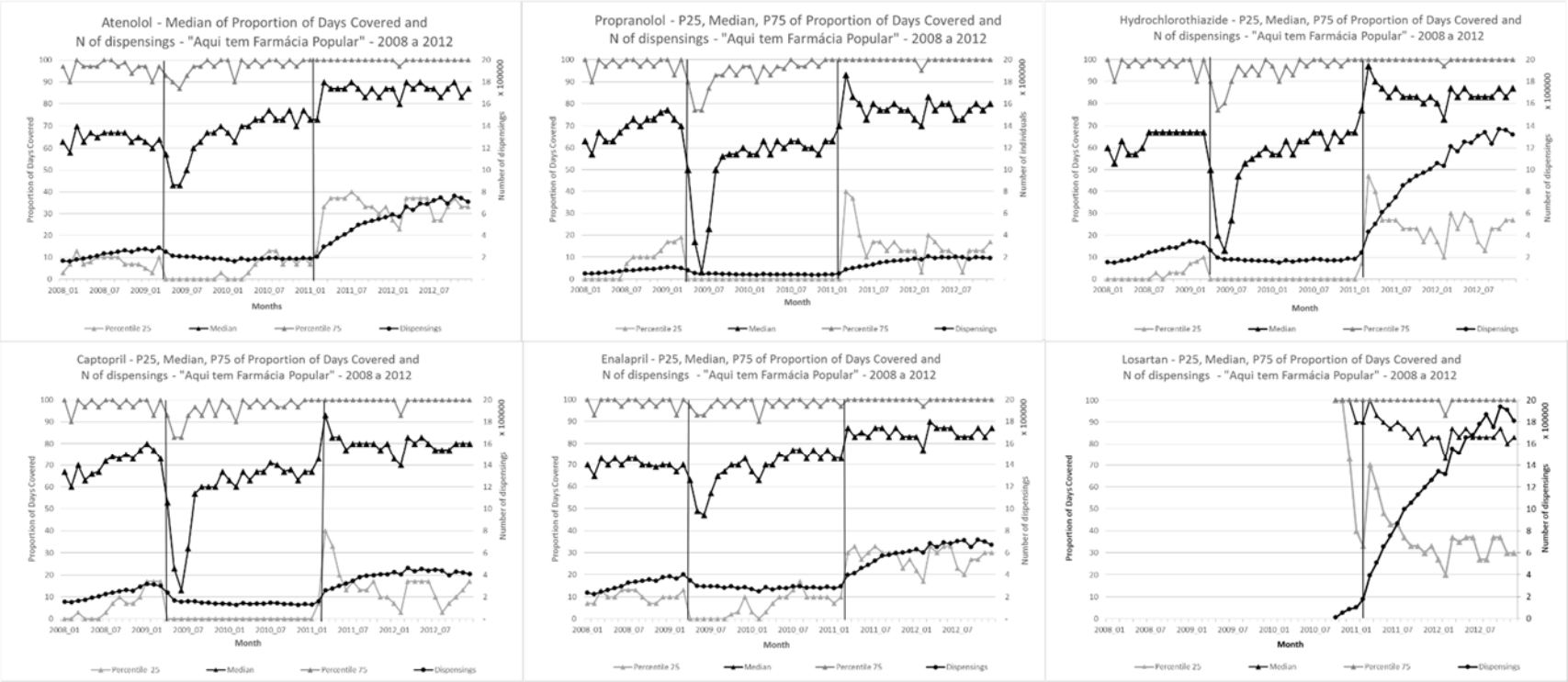








Appendix 3. Number of dispensings and unadjusted 25th/Median/75th percentiles of Proportion of Days Covered, atenolol 25mg, propranolol 40 mg, hydrochlorothiazide 25mg, captopril 25mg, enalapril 5mg and losartan 50 mg by stage of the Farmácia Popular program, Brazil, 2008 to 2012.



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Location in the Paper
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1 and 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract including Strengths and limitations of this study page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	describes changes in utilization and continuity of coverage for oral hypoglycemic (OH) and antihypertensive (AH) medicines following changes in patient cost sharing in the FP program. – pages 3, 4
Methods			
Study design	4	Present key elements of study design early in the paper	Methods – study design analysis and statistical methods – pages 4, 5 and 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods – intervention and Data source and study population – pages 4 and 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods - Data source and study population – page 5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods – analysis – page 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods - Data source and study population – page 5
Bias	9	Describe any efforts to address potential sources of bias	We recognize as possible limitations on the discussion page 12
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods – analysis and statistical methods pages 5 and 6

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods – analysis and statistical methods pages 5 and 6
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	Methods – analysis and statistical methods pages 5 and 6
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results – page 6
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results page 6
		(b) Indicate number of participants with missing data for each variable of interest	In the methods is described how we handled the missing data – page 5
		(c) Summarise follow-up time (eg, average and total amount)	Results page 6
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results pages 6 to 11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results pages 6 to 11
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	We calculated the Percentage of change for specific periods in time – tables 2 and 3 pages 8 and 9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion – pages 11 and 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both	Discussion – page 12

		direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion – pages 11 and 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	Not applicable
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Retrospective interrupted time series examining hypertension and diabetes medicines utilization following changes in patient cost sharing in the "Farmácia Popular" program in Brazil

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017308.R2
Article Type:	Research
Date Submitted by the Author:	29-Aug-2017
Complete List of Authors:	Emmerick, Isabel; ENSP/Fiocruz, Nucleuos for Pharmaceutical Policies Campos, Monica; Fundacao Oswaldo Cruz, Luiza, Vera Lucia; National School of Public Health/ Oswaldo Cruz Foundation, Nucleus for Pharmaceutical Policies; Home, Chaves, Luisa; UFRJ Macaé, ; Escola Nacional de Saude Publica - Sergio Arouca, Bertoldi, Andrea D. Ross-Degnan, Dennis; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine
Primary Subject Heading:	Public health
Secondary Subject Heading:	Health services research, Health policy, Cardiovascular medicine, Diabetes and endocrinology
Keywords:	chronic illness, non-communicable diseases, health services, medicines utilization, patient cost sharing, medication adherence

Retrospective Interrupted time series examining hypertension and diabetes medicines utilization following changes in patient cost sharing in the "Farmácia Popular" program in Brazil

Isabel Cristina Martins Emmerick, ScD

Research Fellow, Pharmaceutical Policy Research Fellowship, Department of Population Medicine, Harvard Medical School & Harvard Pilgrim Health Care Institute. Landmark Center, 401 Park Drive Suite 401 Boston, MA 02215·

Mônica Rodrigues Campos, PhD

Department of Social Sciences, Sergio Arouca National School of Public Health, Oswaldo Cruz Foundation.1480 Rua Leopoldo Bulhões #905, Manguinhos, Rio de Janeiro 21041-210, Brazil

Vera Lucia Luiza, ScD

Department of Medicines and Pharmaceutical Services Policies, Sergio Arouca National School of Public Health, Oswaldo Cruz Foundation. 1480 Rua Leopoldo Bulhões #624, Manguinhos, Rio de Janeiro 21041-210, Brazil

Luisa Arueira Chaves, MSc

Phamacy Department, Federal University of Rio de Janeiro, Macaé Campus. Av. Aluizio da Silva Gomes, #50, Granja dos Cavaleiros, Macaé, 27930-560, Brazil - Rio de Janeiro Federal University – Macaé Campus.

Andréa Dâmaso Bertoldi, PhD

Postgraduate Program in Epidemiology, Federal University of Pelotas. Rua Marechal Deodoro 1160, 96020-220, Pelotas, Brazil.

Dennis Ross-Degnan, ScD

Department of Population Medicine, Drug Policy Research Group, Harvard Medical School & Harvard Pilgrim Health Care Institute. Landmark Center, 401 Park Drive Suite 401 Boston, MA 02215

Corresponding Author:
Isabel Emmerick, Research Fellow
Pharmaceutical Policy Research Fellowship
Department of Population Medicine
Harvard Medical School & Harvard Pilgrim Health Care Institute
Landmark Center, 401 Park Drive Suite 401 Boston, MA 02215
Phone: 1-617-509-9510, Fax: 1-617-859-8112
emmerick. isabel@gmail. com

Key words: chronic illness, non-communicable diseases, health services, patient cost sharing, medicines utilization, medication adherence

Running Title: Trends in hypertension and diabetes medicines utilization

Words and tables count

Number of tables: 03

Number of figures: 01

Words (Abstract): 239

Words (Text): 4061

Appendix: 03

Abstract

Objectives: "Farmácia Popular" (FP) program was launched in 2004, expanded in 2006 and changed the cost sharing for oral hypoglycemic (OH) and antihypertensive (AH) medicines in 2009 and in 2011. This paper describes patterns of utilization and continuity of coverage for OH and AH medicines following changes in patient cost sharing in the FP.

Study Design: Interrupted time series study using retrospective administrative data.

Methods: Monthly program participation (PP) and proportion of days covered (PDC) were the two outcome measures. The open cohort included all patients with two or more dispensings for a given study medicine in 2008-2012. The interventions were an increase in patient cost sharing in 2009 and zero patient cost sharing for key medicines in 2011.

Results: A total of 3.6 and 9.5 million patients receiving treatment for diabetes and hypertension, respectively, qualified for the study. Before the interventions, PP was growing by 7.3% per month; median PDC varied by medicine from 50-75%. After patient cost sharing increased in 2009, PP reduced by 56.5% and PDC decreased for most medicines (median 60.3%). After the 2011 free medicine program, PP surged by 121,000 new dispensings per month and PDC increased for all covered medicines (80.7%).

Conclusion: Cost sharing was found to be a barrier to continuity of treatment in Brazil's private sector FP program. Making essential medicines free to patients appear to increase participation and continuity of treatment to clinically beneficial levels (PDC greater than 80%).

Strengths and limitations of this study

- This paper contributes to our understanding of the impacts of sequential national policies in Brazil's *Farmácia Popular* (FP) program that were intended to improve access to medicines for non-communicable diseases in a middle-income country.
- Reduced program participation when patient cost sharing was increased and dramatic increases when key essential medicines were dispensed free of charge in private sector pharmacies provide important evidence about the impact of financial barriers on strategies to improve adherence to use of chronic medicines.
- The analysis uses the strongest quasi-experimental design - Interrupted Times Series (ITS) with segmented regression analysis - to evaluate policy impacts.
- The study is limited to patients treated under the FP program and not the entire population in Brazil. Overlaps between the FP program and other medicines provision mechanisms in the country including public sector health facilities could not be analyzed.
- The analyses of medicine utilization are based on dispensed amounts and enable us to evaluate average availability over time, but not actual adherence to treatment, overuse of medicines, or potential diversion outside of the program.

Background

Brazil has three main mechanisms by which individuals obtain access to medicines: out-of-pocket purchase in private pharmacies, provision in public health facilities, and the "Farmácia Popular" (FP) program. For out-of-pocket purchase, there are about 63,000 private pharmaceutical outlets all over the country, although the wealthier Southeast region was responsible for 51.9% of sales in 2013. [1] Medicines have been offered free-of-charge in all levels of public health care facilities since the 1970s. [2] The National Essential Medicines List, comprising 840 items in 2014, is the reference list for public coverage. [3]

FP, a new medicines subsidy program created in 2004,[4] has evolved in four phases. First, FP was implemented only in government-owned pharmacies to address persistent shortages of medicines in public health facilities. Medicines were sold at cost price plus operating cost, with selling prices 64-90% lower than the private market. [5] In the second phase, beginning in 2006 ("Aqui tem Farmácia Popular", AFP-I), a limited list of essential medicines (see complete list in each phase in Emmerick, 2015 [4]) swas authorized to be sold in private pharmacies contracted by the Ministry of Health. The government paid either 90% of a government-established reference price for each medicine or 90% of the selling price, whichever was less; patients paid the remaining value not covered by the government. In the third phase beginning in 2009 (AFP-II), administrative changes were introduced to improve accountability and reference prices were reduced for most medicines, resulting in increases in the patient's share. [4] In the fourth phase starting in February 2011 ("Saúde Não Tem Preço", SNP), hypoglycemic and antihypertensive medicines that were already in the program list began to be offered free-of-charge to patients in both government-owned and contracted private pharmacies, with the government paying a fixed negotiated price per medicine. In 2014, FP accounted for about 2.4 billion "reais" (1.09 billion USD) in government expenditures. [6]

Hypoglycemic (OH) and antihypertensive (AH) medicines present in the program's list were covered in all phases of FP program as part of broad ranging government initiatives to address these two non-communicable diseases. [7] One measure of private sector FP's contribution to control of these two illnesses is the proportion of days covered (PDC) by medicines dispensed by private FP pharmacies. PDC is a commonly-used refill-based measure of treatment adherence; [8–12] in this study, it refers to consistency of dispensing from the FP program, since there are other unobserved sources of medicines available to patients.

This paper aims to analyze changes in program participation and PDC for OH and AH medicines covered in the FP following changes in cost sharing during the AFP-II and SNP phases of the private sector FP program, using AFP data from January 2008 through December 2012. Comparable patient-level data are not available to evaluate changes in utilization of the public sector FP program.

Methods

Design

This study is a retrospective, quantitative, analytic study using interrupted time series based on administrative data and using an open cohort.

Intervention

The study interventions are two changes in patient cost sharing in AFP. In April 2009, the government reduced reference prices for most FP medicines by an average of 24.5 %, resulting in an immediate increase in patient copayment from an average of 2.45 “reais” to 3.88 “reais” per 30 days dispensing, a relative increase of 58.4% (for complete information on prices for each medicine, see Appendix 1). In February 2011, the government made all covered medicines for hypertension and diabetes free to patients, reimbursing pharmacies according to a set of negotiated prices.

Data source and study population

There have been no changes in FP eligibility criteria during the program. To have a medicine dispensed at any FP private pharmacy, a patient must present a valid prescription and a national ID. Medicines were dispensed on a monthly basis, although prescriptions were valid for 120 days. Over time, the number of participating private sector pharmacies has expanded substantially, especially in some regions. [4]

Data are derived from an electronic point-of-sales dispensing program implemented in 2006 in FP retail pharmacies. Available data include patient and pharmacy identifiers, patient age and gender, facilities geographic location, date of dispensing, name and quantity of medicine dispensed, daily-prescribed dose, MoH reimbursement, and patient copayment. For this paper we use data on dispensings of hypertension and diabetes medicines from January 2008 to December 2012. Dispensing data are of good quality and relatively complete, with duplicate cases accounting for less than 0.005% and individual-level missing data at less than 0.05%. We excluded encounters with missing data from all analyses.

Patients are included only if they received two or more dispensings for a given medicine during the study period. We used an open cohort, which means that when a patient had a dispensing he enter the analysis and was kept in it for 120 days (maximum time that the prescription is valid in Brazil). If the patient did not have a “new dispensing” during the 120 days interval, the patient fall out of the analysis and it is not in the denominator anymore. Patients with a single dispensing were considered occasional buyers and, for that reason were excluded from the analysis.

Analysis

The primary outcome variables were the number of monthly dispensings of AFP program medicines and the monthly median proportion of days covered (PDC) for included patients. All dispensings were for 30-day supply. 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). The number of days covered by a dispensing was defined as the amount of medicines dispensed divided by the prescribed daily dose. Days of therapy remaining in hand from prior dispensings were used to extend the number of days covered; possible overuse due to overlapping dispensings was not evaluated. [12]

We calculated monthly PDC as the number of days of therapy available during a month divided by the number of days in the month, with PDC thus varying between 0% and 100%;[12] the calculation for the first month of treatment considered only the days after the first dispensing. The median, 25th and 75th percentile PDCs represent aggregate values across all patients who were in an episode of treatment with that medicine during the month.

Statistical methods

We used interrupted time series (ITS) segmented linear regression models to determine the effect of the FP policy changes on the two study outcomes. In estimating effects, ITS models adjust for pre-existing trends in the period before the policy change. Segmented linear regression models were constructed using the *prais* command in STATA v12.

ITS models included three segments, one per program period, with 15, 22, and 23 monthly observations, respectively. The baseline segment was fit with an intercept and a variable estimating trend. We estimate each policy effect by one variable representing the change in level of the outcome immediately after the policy and a second representing the change in trend of the post-policy segment. Patients experienced the changes in cost sharing only when they presented to fill a prescription after the policy change. We thus defined a post-policy implementation period of two months for participation and six months for PDC (to account for the 120-day refill period); these periods were excluded in the ITS models so that we could estimate stable post-intervention effects.

We retained all parameters in the models regardless of statistical significance. We highlight the results with $p<0.05$. We also tested logarithmic trend terms to accommodate possible non-linear trends during each post-intervention segment, selecting the best model using the BIC and AIC goodness of fitness criteria. [13] For the trends in metformin 500mg, atenolol 25mg, and enalapril 5mg dispensing after the 2009 increase in cost sharing, the natural log of trend represented a better model fit. We tested the adequacy of each model by residual analysis. To create single number summaries of policy effects, we calculated estimates of the relative changes in outcomes compared to expected values based on prior trends in April 2010 and February 2012, about one year after the two cost sharing interventions.

Results

A total of 6,032,380 and 14,392,076 patients who received any OH or AH, respectively, from the FP program comprised the dataset; of these, 3,611,512 (59.9%) and 9,534,333 (66.25%) patients received two or more dispensings (Table 1). The mean age was 57 years for both diabetes and hypertension patients, with females comprising about 60% of patients; the Southeast region represented the majority of patients in the program. Patients with two or more dispensings did not differ significantly from those with a single medication fill in age, gender or region.

During the baseline period prior to the cost sharing changes, patients filled an average of 1.1 and 2.7 million dispensings per medicine per year for DM and HTN, respectively; dispensings were growing at an average rate of 7.4 % per month for the medicines analyzed (Figure 1, Table 2). Metformin 850mg was the most widely used OH medicine and had the highest rate of

growth, while metformin slow release had the smallest monthly number of dispensings (Appendix 2); enalapril was the most widely used AH medicine and propranolol the least widely used, but utilization of all AH medicines was growing rapidly (Appendix 3).

Prior to the increased cost sharing, PDC levels for studied medicines were relatively stable; by March 2009, one month before the AFP-II policy, median PDC levels for OH and AH medicines were 64.2 and 70.4%, respectively. Median PDC levels varied across covered medicines from 63.3% (metformin slow release) to 78.7% (captopril 25mg) (Figure 1, Table 3, Appendix 2, and Appendix 3).

Table 1. Patients participating in Brazil's "Farmácia Popular is Available Here" program, total and with two or more dispensings versus one dispensing, by gender, age and region, 2008 to 2012.

		Total		Two or more dispensings		One dispensing only	
DIABETES							
Age (n; mean (SD))		6,026,058	55.5 (15.1)	3,608,677	56.8 (14.0)	2,417,381	53.6 (16.5)
Gender (n, %)	Female	3,602,944	59.7%	2,168,131	60.0%	1,434,813	59.3%
	Male	2,413,718	40.0%	1,433,895	39.7%	979,823	40.5%
Region (n, %)	North	169,330	2.8%	79,517	2.2%	89,813	3.7%
	Northeast	849,184	14.1%	444,653	12.3%	404,531	16.7%
	Southeast	3,769,151	62.5%	2,336,807	64.7%	1,432,344	59.2%
	South	885,391	14.7%	540,572	15.0%	344,819	14.2%
	West-Center	359,324	6.0%	209,963	5.8%	149,361	6.2%
Total		**6,032,380**	**100.0%**	**3,611,512**	**100.0%**	**2,420,868**	**100.0%**
HYPERTENSION							
Age (n; mean (SD))		14,374,244	55.8 (15.1)	9,525,183	56.7 (14.3)	4,849,061	53.97 (16.4)
Gender (n, %)	Female	8,636,053	60,0%	5,777,649	60.6%	2,858,404	58.8%
	Male	5,714,487	39,7%	3,728,721	39.1%	1,985,766	40.9%
Region (n, %)	North	469,739	3,3%	232,250	2.4%	237,489	4.9%
	Northeast	2,121,308	14,7%	1,201,133	12.6%	920,175	18.9%
	Southeast	8,290,832	57,6%	5,714,243	59.9%	2,576,589	53.0%
	South	2,562,095	17,8%	1,780,678	18.7%	781,417	16.1%
	West-Center	948,102	6,6%	606,029	6.4%	342,073	7.0%
Total		**14,392,076**	**100,0%**	**9,534,333**	**100.0%**	**4,857,743**	**100.0%**

Table 2. Baseline level and trend in monthly number of dispensings (DISP)[a] per 100,000 for hypoglycemic and antihypertensive medicines, and changes in level and trend by stage of the "Farmácia Popular" program, Brazil, 2008 to 2012.

	Baseline		AFP-II (April 2009)					SNP (February 2011)		
	Level (DISP)	Trend	DISP (March 2009)	Level AFPII (April 2009)	Trend AFPII	%relative Change (AFPII) (April 2010)	DISP (Jan 2011)	Level SNP (Feb 2011)	Trend SNP	%relative change (SNP) (Feb2012)
Oral Hypoglycemic	2.45	0.16	4.85	**-2.12 (-3.13;-1.1)**	**-0.15 (-0.24;-0.06)**	**-54.5**	3.23	**4.39 (3.47;5.31)**	**0.40 (0.33;0.47)**	**262.0**
Glibenclamide 5mg	0.58	0.04	1.25	**-0.67 (-0.99;-0.35)**	**-0.05 (-0.07;-0.02)**	**-63.7**	0.66	**1.22 (0.93;1.52)**	**0.10 (0.07;0.12)**	**350.2**
Metformin 850mg	1.14	0.07	2.19	**-1.01 (-1.43;-0.59)**	**-0.06 (-0.1;-0.03)**	**-55.4**	1.43	**1.98 (1.6;2.36)**	**0.15 (0.12;0.18)**	**239.8**
Metformin 500mg	0.51	0.02	0.73	**-0.26 (-0.48;-0.05)**	-0.02 (-0.04;0.00)	**-48.7**	0.46	**0.68 (0.48;0.88)**	**0.04 (0.03;0.06)**	**258.9**
Metformin slow release	0.23	0.03	0.67	-0.16 (-0.38;0.06)	-0.02 (-0.04;0.00)	**-39.2**	0.69	**0.47 (0.27;0.66)**	**0.12 (0.1;0.13)**	**226.5**
Oral Antihypertensive	6.94	0.51	14.58	**-7.28 (-12.1;-2.45)**	**-0.5 (-0.93;-0.06)**	**-60.1**	8.56	**15.91 (11.45;20.37)**	**1.5 (1.16;1.84)**	**371.9**
Atenolol 25mg	1.59	0.09	2.90	**-1.1 (-1.68;-0.52)**	**-0.1 (-0.15;-0.04)**	**-53.3**	1.81	**1.87 (1.34;2.4)**	**0.21 (0.17;0.25)**	**242.4**
Propranolol 40mg	0.45	0.04	1.03	**-0.64 (-0.99;-0.29)**	**-0.04 (-0.07;-0.01)**	**-72.8**	0.37	**0.76 (0.43;1.1)**	**0.05 (0.03;0.07)**	424.7
Hydrochlorothiazide 25mg	1.31	0.14	3.46	**-2.05 (-3.14;-0.97)**	**-0.14 (-0.24;-0.04)**	**-67.6**	1.75	**4.15 (3.16;5.14)**	**0.4 (0.33;0.48)**	**481.1**
Captopril 25mg	1.42	0.11	3.12	**-1.8 (-2.42;-1.17)**	**-0.13 (-0.18;-0.07)**	**-69.3**	1.29	**1.92 (1.34;2.51)**	**0.08 (0.03;0.12)**	**244.3**
Enalapril 5mg	2.18	0.12	4.04	**-1.42 (-2.04;-0.8)**	**-0.13 (-0.18;-0.07)**	**-50.0**	2.78	**1.93 (1.36;2.5)**	**0.13 (0.09;0.17)**	**123.1**

significant values p<0.05 are highlighted in bold
NA - no applicable

[a] DISP – number of dispensings. The number of dispensings was divided by 100,000.

Table 3. Baseline median and trend in monthly Proportion of Days Covered (PDC) for hypoglycemic and antihypertensive medicines, and changes in level and trend by stage of the "Farmácia Popular" program, Brazil, 2008 to 2012.

	Baseline			AFP II (April 2009)				SNP (February 2011)		
	Level (PDC)	Trend	PDC (Mar 2009)	Level AFP II (Change at the intervention)	Trend AFP II	% relative change (AFP II) (April 2010)	PDC (Jan 2011)	Level SNP (Change at the intervention)	Trend SNP	% relative change (SNP) (Feb 2012)
Oral Hypoglycemic	59.67	0.30	64.22	**-8.1 (-12.85;-3.36)**	0.28 (-0.12;0.67)	**-9.0**	67.21	**4.88 (0.37;9.39)**	**-0.43 (-0.79;-0.07)**	2.5
Glibenclamide 5mg	61.40	0.56	69.75	**-15.23 (-19.65;-10.81)**	-0.07 (-0.43;0.3)	**-20.4**	65.73	**6.23 (2.03;10.42)**	**-0.35 (-0.68;-0.01)**	**5.3**
Metformin 850mg	59.02	0.38	64.74	**-10.41 (-15.3;-5.52)**	0.21 (-0.2;0.62)	**-12.8**	66.08	**3.84 (-0.81;8.49)**	**-0.37 (-0.74;-0.01)**	1.7
*Metformin 500mg	56.24	0.05	57.04	-1.75 (-7.23;3.73)	**2.87 (0.07;5.67)**	6.7	64.41	**8.56 (2.9;14.22)**	-0.15 (-0.77;0.46)	**11.2**
Metformin slow release	61.09	0.15	63.29	0.61 (-10.35;11.57)	0.16 (-0.75;1.06)	2.6	69.67	**11.09 (0.61;21.56)**	-0.43 (-1.25;0.4)	11.0
Oral Antihypertensive	63.98	0.45	70.74	**-10.63 (-14.7;-6.55)**	0.22 (-0.12;0.55)	**-11.9**	73.48	**4.87 (1;8.73)**	**-0.57 (-0.88;-0.27)**	1.0
*Atenolol 25mg	64.88	0.02	65.15	-0.70 (-5.53;4.13)	**3.4 (1.03;5.78)**	9.1	74.27	**10.63 (6.6;14.67)**	-0.14 (-0.49;0.21)	**12.6**
Propranolol 40 mg	61.34	1.07	77.40	**-26.21 (-32.49;-19.93)**	**-0.73 (-1.25;-0.21)**	**-34.3**	63.00	**11.63 (5.66;17.6)**	-0.23 (-0.71;0.24)	**14.8**
Hydrochlorothiazide 25mg	56.88	0.82	69.22	**-18.17 (-22.91;-13.43)**	-0.12 (-0.51;0.28)	**-23.8**	67.25	**10.1 (5.6;14.6)**	**-0.53 (-0.89;-0.17)**	**8.4**
Captopril 25mg	63.81	0.99	78.66	**-23.07 (-28.85;-17.29)**	**-0.52 (-1;-0.04)**	**-29.2**	69.11	**5.86 (0.37;11.35)**	-0.38 (-0.82;0.06)	4.2
*Enalapril 5mg	70.16	0.02	70.39	-2.91 (-7.74;1.93)	**2.56 (0.18;4.95)**	3.0	74.93	**7.79 (3.75;11.83)**	-0.02 (-0.37;0.34)	**10.0**

significant values p<0.05 are highlighted in bold
NA - no applicable
*it was used the Log of the AFP II trend

Cost sharing increases (AFP-II) April 2009

After patient copayments increased, OH dispensings declined immediately by -2.12 per 100,000 (95% CI [-3.13, -1.10]) compared to 4.85 per 100,000 in March 2009, immediately before the policy (Table 2). In addition, the previous upward monthly trend in participation flattened to nearly zero (slope change -0.15 per month, [-0.24, -0.06]). By one year after the policy, dispensings had declined by 54.5% [-65.9%,-43.0%] compared to where they would have been had baseline trends continued. Similarly, dispensings of AH medicines declined by -7.8 per 100,000 [-12.1,-2.45] from their level of 14.6 per 100,000 immediately before the AFP-II policy. As with OH medicines, the previous monthly increase in participation of 0.51 declined by -0.5 [-0.93, -0.06]. After one year, participation was 60.1% [-76.1, -44.2] lower than expected based on prior trends. (Table 2)

After AFP-II, rates of monthly dispensing for most studied medicines followed similar patterns. Dispensing had been increasing by 1,600 (metformin 500mg) to 14,000 (hydrochlorothiazide 25mg) fills per month prior to the increased cost sharing. After AFP-II implementation, there were immediate reductions in participation and flattened rates of dispensing that persisted over time. By one year after the intervention, in April 2010, all medicines had experienced significant relative decreases varying from 39.2% for metformin slow release to 72.8% for propranolol 40mg. (Table 2)

After patient copayments increased and substantial numbers of patients left the program, median PDC declined for OH medicines by 8.11% [-12.85%, -3.36%] and for AH medicines by 10.61% [-14.7%, -6.55%]. While the AFP policy remained in effect (until December 2010), median monthly PDC tended to increase slightly among participating patients (OH medicines: 0.28 per month [-0.12, 0.67]; AH medicines: 0.22 [-12, 0.55]). By one year after the policy, median PDC had declined for OH medicines by 9.0% [-18.0%, -5.8 %] and for AH medicines by 11.9% [-26.3,-14.4] relative to where they would have been had baseline trends continued. (Table 3)

Changes in PDC following increased cost sharing varied across medicines. PDC for five of the nine medicines covered decreased by 12.8% (metformin 850mg) to 34.3% (propranolol 40mg). However, four medicines actually experienced small nonsignificant increases in PDC for patients remaining in the program by a year after the cost sharing increase. (Table 3)

Availability of free medicines (SNP) – February 2011

After the SNP implementation, dispensings of OH medicines increased by 4.39 per 100,000 [3.47, -5.31] compared to 3.23 per 100,000 in January 2011, immediately before the policy (Table 2). Additionally, there was an upward monthly trend in dispensings of 0.40 per month [0.33, 0.47] contrasting with the previous flattened trend. By a year after the policy, dispensings had increased by 262% [130.7, 393.3] compared to where they would have been had previous trends continued. AH medicines followed the same pattern; dispensings increased by 15.9 per 100,000 [11.45, 20.37] from their level of 8.6 per 100,000 immediately before the SNP policy. Participation increased by 1.5 [1.16, 1.84] per 100,000 per month. After one year, participation was 372% (57.2, 686.6) higher than expected based on prior trend. (Table 2)

After SNP, rates of monthly dispensing for most medicines followed similar patterns, varying from an immediate increase in participation of 47,000 (metformin slow release) to 415,000 (hydrochlorothiazide 25mg) fills per month; increases in trend of monthly dispensing persisted over time. By one year after the free medicines policy, in February 2012, significant relative increases varied from 226% to 481% for metformin slow release and hydrochlorothiazide 25mg, respectively. (Table 2)

Losartan was added to the medicines reference list in October 2010; by the time of SNP implementation four months later, there were only about 10 thousand dispensings. By one year after medicines became free to patients, losartan dispensings had increased to more than 2 million dispensings. In comparison, its therapeutic competitors captopril and enalapril had only 700,000 and 1 million dispensings, respectively, in February 2012. (Appendix 2)

After SNP and the substantial influx of patients, median monthly PDC increased for OH medicines by 4.88% [0.37%, 9.39%] and for AH medicines by 4.87% [1.00%, 8.73%], and remained relatively constant until the end of the study period (December 2012). (Table 3) Changes in PDC varied by medicine; six of the nine medicines covered increased significantly by 5.3% (glibenclamide 5mg) to 14.8% (propranolol 40mg), but three experienced only small, nonsignificant increases by the year after the free medicine policy. (Table 3).

Discussion

Coverage policies in "Farmácia Popular", a publicly-financed program designed to increase access to essential medicines in Brazil, have evolved over time. Patient cost sharing increased by 58% in 2009, resulting in immediate decreases in program participation and PDC. In contrast, rapid increases in both outcomes followed implementation of a 2011 policy to make essential medicines for diabetes and hypertension free to patients.

Program participation for hypertension and diabetes follow the prevalence profile of these two diseases in the country. [14] The majority of AFP patients are from the wealthier Southeast region where there is a higher density of participating pharmacies; [4] this may imply increasing socioeconomic disparities in access to treatment for diabetes and hypertension, especially now that medicines are available for free. Other studies that have evaluated access to medicines for hypertension[15] and diabetes[16] through the Health has No Price program have concluded that the intervention contributed to increased access to these medicines in Brazil.

The impact of cost-sharing interventions on the use of medicines has been addressed in the literature[17]. It may be expressed in terms of the amount used, measured as sales volume or prescriptions filled, of expenditures or sales, healthcare utilization or health outcomes.

PDC is usually used in the literature as a proxy for treatment adherence. [9,12,18] Therefore, it is a measure of use of medicines with a closer link to health outcomes. 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.

In the literature, about half of patients treated for chronic disease become no adherent within a year. [19] The consistency of prescription filling in the AFP program, particularly after medicines for diabetes and hypertension were made free to patients, suggest that private sector outlets are convenient and preferred by patients as a source of these free medicines.

The relationship between PDC levels and clinical outcomes is well-established in the literature. [20,21] For example, adherence to hypoglycemic treatment measured through administrative data has been found to be related to better glycemic control, fewer emergency department visits, and lower rates of hospital admission. [22] [23] [24] Many studies consider patients with PDC 80% or higher to be adherent to treatment;[22] lower adherence can lead to higher rates of adverse events, poor long-term health outcomes, and higher healthcare costs. [25] After SNP, rates of PDC were higher than 80% for well over half of patients taking OH and AH medicines, levels likely to have positive impact on clinical outcomes. One study that analyzed the impact of full subsidy policies on medicines use have found similar effects on PDC as in our study. [11,26–29]

The relation between cost sharing and medication adherence has been widely studied. [17] In our study, all medicines with increased copayments in April 2009 experienced decreases in rates of dispensing and PDC. After SNP, we observed the opposite response; when patients had no cost sharing, program participation and PDC increased dramatically.

Although losartan is not a first-line treatment in the Brazilian guideline to treat hypertension,[30] it was included in the FP reimbursement list in 2010. Within a few months, losartan had become the most widely dispensed AH medicine. Coverage decisions in government subsidy programs should be consistent with treatment guidelines to encourage appropriate choice of therapy and more cost-effective treatment.

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]. We have the issue that there are other sources for medicines to patients. However, we did not intend to use PDC as adherence to treatment measure, but as 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. Then, we think that these potential treats to internal validity have negligible impact on our findings. To make the estimates of PDC interpretable, we limited analysis of program impacts to patients who filled more than one prescription of a medicine in the FP private sector; there were no relevant differences in characteristics between patients who filled only one prescription and those who used it more regularly. We have no data on medicines that are not part of the program, so cannot evaluate the impact of FP program policies on use of other medicines used to treat diabetes and hypertension. Since patients could have switched treatment among the medicines covered (e.g. change from captopril to enalapril), we may have underestimated PDC because we did not evaluate this possible change. That way, the median PDC would be lower when actually the patient was changing the therapy and using other medicine. Finally, as a result of the method

chosen to calculate the PDC,[12] the possible overuse due to overlapping dispensings was not evaluated.

In conclusion, participation in the "Farmácia Popular" private sector program evolved in response to two cost sharing interventions implemented between 2008 and 2012. Increased patient cost sharing reduced participation, while full subsidy of key medicines in private pharmacies substantially increased participation; patients in the program achieved PDC levels that have been shown to improve health outcomes. Risks to rational use of medicines, especially overuse, can be minimized through controlling mechanisms, such as the requirement of prescription, validity of prescriptions and maximum dispensing amounts. Policy makers should consider reducing or removing cost sharing for essential medicines to treat chronic illness, while aligning subsidies to encourage greater use of first-line therapies.

Acknowledgements: The authors thank the Ministry of Health in Brazil for providing the data used in this study. Dr. Isabel Emmerick was supported by CNPQ process number 202246/2012-4 and the Pyle Fellowship of Harvard Pilgrim Health Care Institute.

Author contributions: All authors made substantial contribution to study conception, ICME MRC, DRD made substantial contribution to study design. ICME, VLL, MRC, LAC, ADB were responsible for data acquisition. ICME, MRC and DRD were responsible for data analysis. All authors contributed to interpretation of data. ICME drafted the article and is guarantor. All authors provided critical revisions for important intellectual content and approved the final version.

Conflicts of interest: Dr. Emmerick, principal investigator, reports grants from World Health Organization Access to Medicines Research Network, during the conduct of the study. Dr. Campos, Dr. Luiza, Dr. Chaves, Dr. Bertoldi and Dr. Ross-Degnan report personal fees from World Health Organization Access to Medicines Research Network, during the conduct of the study; Dr. Luiza also reports personal fees from Oswaldo Cruz Foundation (Fiocruz), outside the submitted work.

Funding: Research grant from the World Health Organization Alliance for Health Policy and Systems Research. Dr. Emmerick is supported by the Pyle Fellowship of Harvard Pilgrim Health Care Institute. Dr. Ross-Degnan is supported in part by the Health Delivery Systems Center for Diabetes Translational Research (HDS-CDTR) [NIDDK grant 1P30-DK092924].

Ethical approvals: The Brazilian National Ethics Committee, by the National School of Public Health – Fiocruz – Brazil and the WHO ERC, approved the ISAUM-Br project, which is the base for this paper.

This work was conducted in collaboration among the following institutions: Department of Medicines and Pharmaceutical Services Policies, Sergio Arouca, National School of Public Health, Fiocruz Brazil; Department of Epidemiology, University of Pelotas, Brazil; Department of Pharmaceutical Services / Office of Science Technology and Strategic Resources - Ministry of Health and the Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute.

Data sharing: No additional data are available.

Table 1. Patients participating in Brazil's "Farmácia Popular is Available Here" program, total and with two or more dispensings versus one dispensing, by gender, age and region, 2008 to 2012.

Table 2. Baseline level and trend in monthly number of dispensings (DISP)a per 100,000 for hypoglycemic and antihypertensive medicines, and changes in level and trend by stage of the "Farmácia Popular" program, Brazil, 2008 to 2012.

Table 3. Baseline median and trend in monthly Proportion of Days Covered (PDC) for hypoglycemic and antihypertensive medicines, and changes in level and trend by stage of the "Farmácia Popular" program, Brazil, 2008 to 2012.

Figure 1. Number of dispensings and 25th/Median/75th percentiles of Proportion of Days Covered, and predicted values from segmented regression models for oral hypoglycemic and oral antihypertensive medicines, by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

Appendix 1. Medicines average unit price in local currency (reais), and average price treatment for 30 days' supply for glibenclamide 5mg, metformin 850mg, metformin 500mg, metformin slow release, losartan 50 mg, atenolol 25mg, propranolol 40 mg , hydrochlorothiazide 25mg, captopril 25mg, enalapril 5mg by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

Appendix 2. Number of dispensings and unadjusted 25th/Median/75th percentiles of Proportion of Days Covered, glibenclamide 5mg, metformin 850mg, metformin 500mg and metformin slow release, by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

Appendix 3. Number of dispensings and unadjusted 25th/Median/75th percentiles of Proportion of Days Covered, atenolol 25mg, propranolol 40 mg, hydrochlorothiazide 25mg, captopril 25mg, enalapril 5mg and losartan 50 mg by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

References

1 Valor Econômico. Valor: Análise setorial: Farmácias e Drogarias. 2014.

2 Bermudez J. AZ, Oliveira MA, Luiza VL. Assistência Farmacêutica. In: Lígia Giovanella, Sarah Escorel, Lenaura de Vasconcelos Costa Lobato, *et al.*, eds. *Políticas e Sistema de Saúde no Brasil*. Rio de Janeiro: : Fiocruz 2012. 761–94.

3 Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. *Relação Nacional de Medicamentos Essenciais: RENAME 2014*. 9th ed. Brasília: : Ministério da Saúde 2014.

4 Emmerick ICM, do Nascimento JM, Pereira MA, *et al.* Farmacia Popular Program: changes in geographic accessibility of medicines during ten years of a medicine subsidy policy in Brazil. *J Pharm Policy Pract* 2015;**8**. doi:10.1186/s40545-015-0030-x

5 Santos-Pinto CDB, Miranda ES, Martins Emmerick IC, *et al.* Medicine prices and availability in the Brazilian popular pharmacy program [Preços e disponibilidade de medicamentos no Programa Farmácia Popular do Brasil]. *Rev Saude Publica* 2010;**44**:611–9.

6 Brasil. Ministério da Saúde. Sala de Apoio à Gestão Estratégica. Redes_e_Porgramas>Situação_de_Saúde>Gestão/Financiamento?Aqui_Tem_Farmácia_Popular. 2015. http://sage.saude.gov.br/ (accessed 29 Sep 2015).

7 Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Análise de Situação de Saúde. *Plano de ações estratégicas para o enfrentamento das doenças crônicas não transmissíveis (DCNT) no Brasil 2011-2022*. Brasília: : Ministério da Saúde 2011.

8 Sattler ELP, Lee JS, Perri M. Medication (Re)fill Adherence Measures Derived from Pharmacy Claims Data in Older Americans: A Review of the Literature. *Drugs Aging* 2013;**30**:383–99. doi:10.1007/s40266-013-0074-z

9 Andrade SE, Kahler KH, Frech F, *et al.* Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf* 2006;**15**:565–74. doi:10.1002/pds.1230

10 An J, Nichol MB. Multiple medication adherence and its effect on clinical outcomes among patients with comorbid type 2 diabetes and hypertension. *Med Care* 2013;**51**:879–887.

11 Athanasakis K, Skroumpelos AG, Tsiantou V, *et al.* Abolishing coinsurance for oral antihyperglycemic agents: Effects on social insurance budgets. 2011;**17**:130–5.

12 Hess LM, Raebel MA, Conner DA, *et al.* Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother* 2006;**40**:1280–8. doi:10.1345/aph.1H018

13 Maydeu-Olivares A. Goodness-of-Fit Testing. http://www.ub.edu/gdne/amaydeusp_archivos/encyclopedia_of_education10.pdf (accessed 10 Feb 2016).

14 Brasil. Ministério da Saúde, Secretaria de Vigilância em Saúde. *Vigitel Brasil 2013: vigilância de fatores de risco e proteção para doenças crônicas*. Brasília: : Ministério da Saúde 2014.

15 Araujo JLO, Pereira MD, de Sá Del Fiol F, *et al.* Access to Antihypertensive Agents in Brazil: Evaluation of the "Health Has No Price" Program. *Clin Ther* 2014;**36**:1191–5. doi:10.1016/j.clinthera.2014.06.003

16 Araujo JLO, Pereira MD, de Cássia Bergamaschi C, *et al.* Access to medicines for diabetes treatment in Brazil: evaluation of "health has no price" program. *Diabetol Metab Syndr* 2016;**8**. doi:10.1186/s13098-016-0150-8

17 Luiza VL, Chaves LA, Silva RM, *et al.* Pharmaceutical policies: effects of cap and co-payment on rational use of medicines. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd 2015. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007017.pub2/abstract (accessed 12 May 2015).

18 Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol* 1997;**50**:105–16.

19 Franklin JM, Krumme AA, Shrank WH, *et al.* Predicting Adherence Trajectory Using Initial Patterns of Medication Filling. *Am J Manag Care* 2015;**21**.http://www.ajmc.com/journals/issue/2015/2015vol21n9/PredictingAdherenceTrajectoryUsingInitialPatternsofMedicationFilling?utm_source=Informz

20 Elhayany A, Vinker S. Addressing healthcare inequities in Israel by eliminating prescription drug copayments. *Am J Manag Care* 2011;**17**:e255-9.

21 Lynch WD, Pesa J, Melkonian AK, *et al.* Effect of Antihypertensive Medication Adherence Among Employees With Hypertension. *Am J Manag Care* 2009;**15**:871–80.

22 Nair KV, Miller K, Saseen J, *et al.* Prescription copay reduction program for diabetic employees: Impact on medication compliance and healthcare costs and utilization. 2009;**2**:14–24.

23 Asche C, LaFleur J, Conner C. A Review of Diabetes Treatment Adherence and the Association with Clinical and Economic Outcomes. *Clin Ther* 2011;**33**:74–109. doi:10.1016/j.clinthera.2011.01.019

24 Nichols GA, Rosales AG, Kimes TM, *et al.* Impact on glycated haemoglobin of a biological response-based measure of medication adherence. *Diabetes Obes Metab* Published Online

First: 2015.http://onlinelibrary.wiley.com/doi/10.1111/dom.12476/full (accessed 28 Sep 2015).

25 Roebuck MC, Liberman JN, Gemmill-Toyama M, *et al.* Medication Adherence Leads To Lower Health Care Use And Costs Despite Increased Drug Spending. *Health Aff (Millwood)* 2011;**30**:91–9. doi:10.1377/hlthaff.2009.1087

26 Huber CA, Rapold R, Brüngger B, *et al.* One-year adherence to oral antihyperglycemic medication and risk prediction of patient outcomes for adults with diabetes mellitus: An observational study. *Medicine (Baltimore)* 2016;**95**:e3994. doi:10.1097/MD.0000000000003994

27 Cramer JA. A systematic review of adherence with medications for diabetes. *Diabetes Care* 2004;**27**:1218–1224.

28 Ho PM, Rumsfeld JS, Masoudi FA, *et al.* Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Arch Intern Med* 2006;**166**:1836–1841.

29 An J, Nichol MB. Multiple medication adherence and its effect on clinical outcomes among patients with comorbid type 2 diabetes and hypertension. *Med Care* 2013;**51**:879–887.

30 Brasil, Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Atenção Básica. *Estratégias para o cuidado da pessoa com doença crônica: hipertensão arterial sistêmica [Strategies for the care of the person with chronic disease: systemic arterial hypertension]*. 1st ed. Brasília - DF: : Ministerio da Saúde, Brazil 2013. http://bvsms.saude.gov.br/bvs/publicacoes/estrategias_cuidado_pessoa_doenca_cronica.pdf

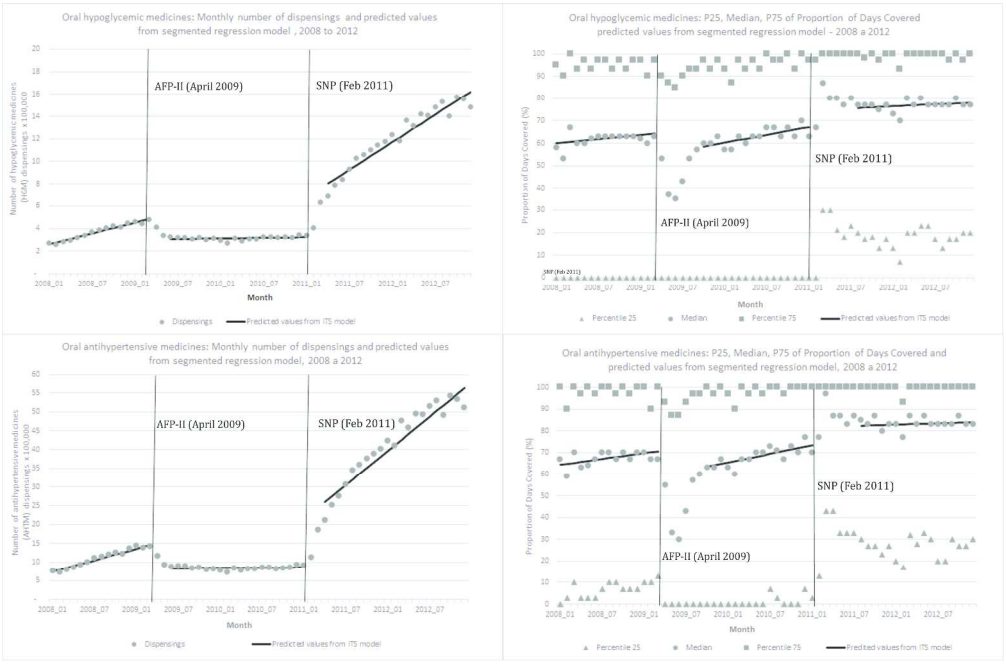


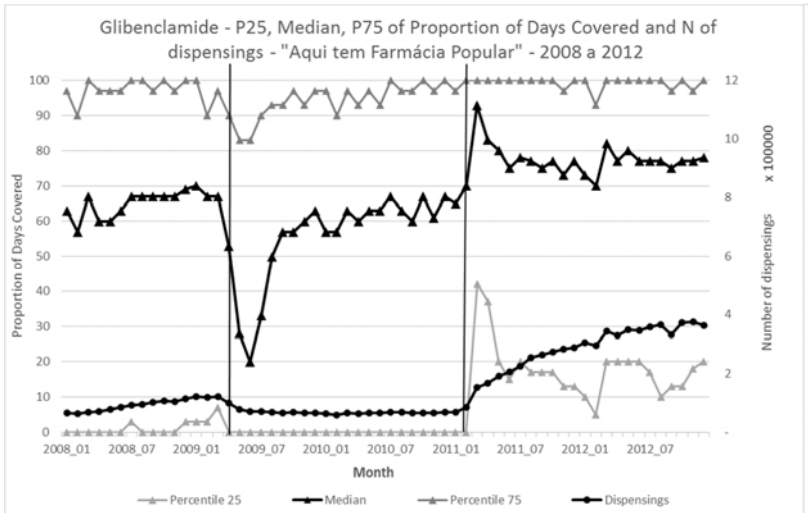
Figure 1. Number of dispensings and 25th/Median/75th percentiles of Proportion of Days Covered, and predicted values from segmented regression models for oral hypoglycemic and oral antihypertensive medicines, by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

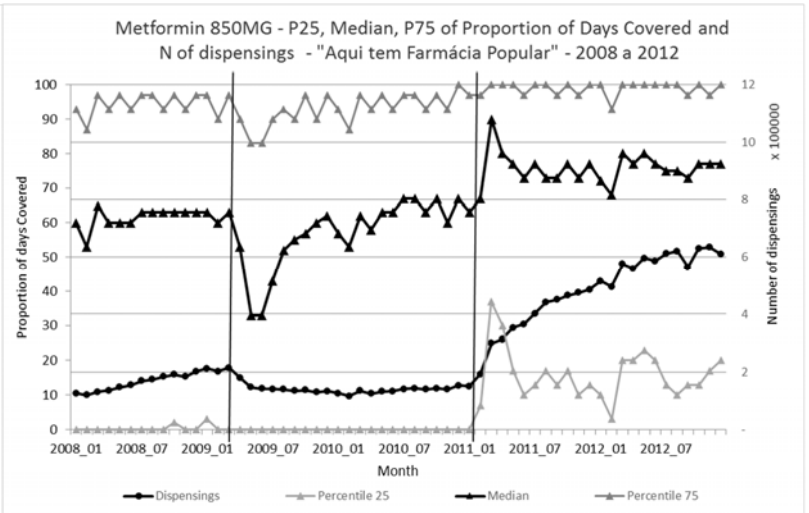
512x337mm (300 x 300 DPI)

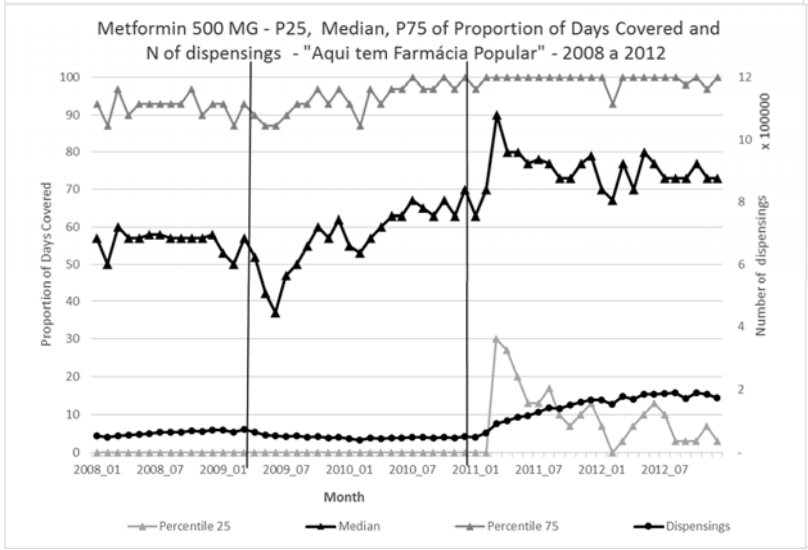
Appendix 1. Medicines average unit price in local currency (reais), and average price treatment for 30 days' supply for glibenclamide 5mg, metformin 850mg, metformin 500mg, metformin slow release, losartan 50 mg, atenolol 25mg, propranolol 40 mg , hydrochlorothiazide 25mg, captopril 25mg, enalapril 5mg by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

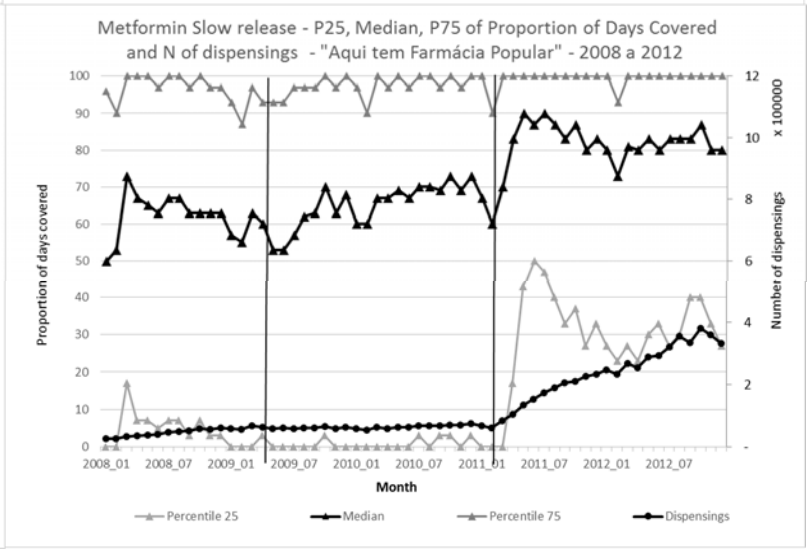
	Baseline Average Price (Jan 2008 to March 2009)			AFP II Average Price (April 2009 to Jan 2011)					SNP Average Price (Feb 2011 to Dec 2012)			
	Total	Patient	MoH	Total	Patient	MoH	Absolute change	Relative Change	Total	MoH	Absolute change	Relative Change
UNIT PRICE												
Hypoglycemic												
Glibenclamide 5mg	0.24	0.04	0.20	0.21	0.06	0.15	0.02	39.0	0.13	0.13	-0.02	-100
Metformin 850mg	0.37	0.07	0.30	0.33	0.10	0.23	0.04	53.9	0.17	0.17	-0.04	-100
Metformin 500mg	0.26	0.06	0.20	0.25	0.08	0.17	0.01	24.1	0.14	0.14	-0.01	-100
Metformin slow release	0.45	0.25	0.19	0.45	0.29	0.15	0.04	16.8	0.19	0.19	-0.04	-100
Antihypertensive												
Losartan 50 mg	-	-	-	0.75	0.34	0.41	0.34	NA	0.34	0.34	-0.34	-100
Atenolol 25mg	0.32	0.05	0.27	0.30	0.08	0.22	0.03	54.4	0.20	0.20	-0.03	-100
Propranolol 40 mg	0.17	0.04	0.13	0.15	0.05	0.10	0.01	32.76	0.09	0.08	-0.01	-100
Hydrochlorothiazide 25mg	0.19	0.03	0.16	0.15	0.05	0.10	0.02	80.12	0.08	0.08	-0.02	-100
Captopril 25mg	0.53	0.09	0.44	0.43	0.11	0.33	0.02	23.17	0.30	0.29	-0.02	-100
Enalapril 5mg	0.71	0.11	0.60	0.59	0.14	0.46	0.03	26.18	0.41	0.41	-0.03	-100
TREATMENT PRICE												
Hypoglycemic												
Glibenclamide 5mg	7.27	1.33	5.94	6.38	1.86	4.53	0.52	39.0	3.83	3.81	-0.52	-100
Metformin 850mg	10.99	2.00	8.99	9.83	3.07	6.75	1.08	53.9	5.12	5.09	-1.08	-100
Metformin 500mg	7.67	1.82	5.85	7.44	2.26	5.18	0.44	24.1	4.16	4.13	-0.44	-100
Metformin slow release	13.39	7.57	5.83	13.63	8.84	4.53	1.27	16.8	5.71	5.56	-1.27	-100
Antihypertensive												
Losartan 50 mg	-	-	-	22.39	10.22	12.17	10.22	NA	10.27	10.19	10.22	NA
Atenolol 25mg	9.60	1.46	8.14	8.98	2.25	6.73	0.79	54.4	6.04	6.01	-0.79	-100
Propranolol 40 mg	4.97	1.13	3.83	4.44	1.50	2.93	0.37	32.7	2.56	2.54	-0.37	-100
Hydrochlorothiazide 25mg	5.67	0.82	4.85	4.46	1.47	2.98	0.66	80.1	2.55	2.53	-0.66	-100
Captopril 25mg	15.78	2.61	13.17	13.04	3.22	9.82	0.61	23.1	8.86	8.82	-0.61	-100
Enalapril 5mg	21.15	3.29	17.87	17.83	4.15	13.68	0.86	26.1	12.34	12.29	-0.86	-100

Appendix 2. Number of dispensings and unadjusted 25th/Median/75th percentiles of Proportion of Days Covered, glibenclamide 5mg, metformin 850mg, metformin 500mg and metformin slow release, by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

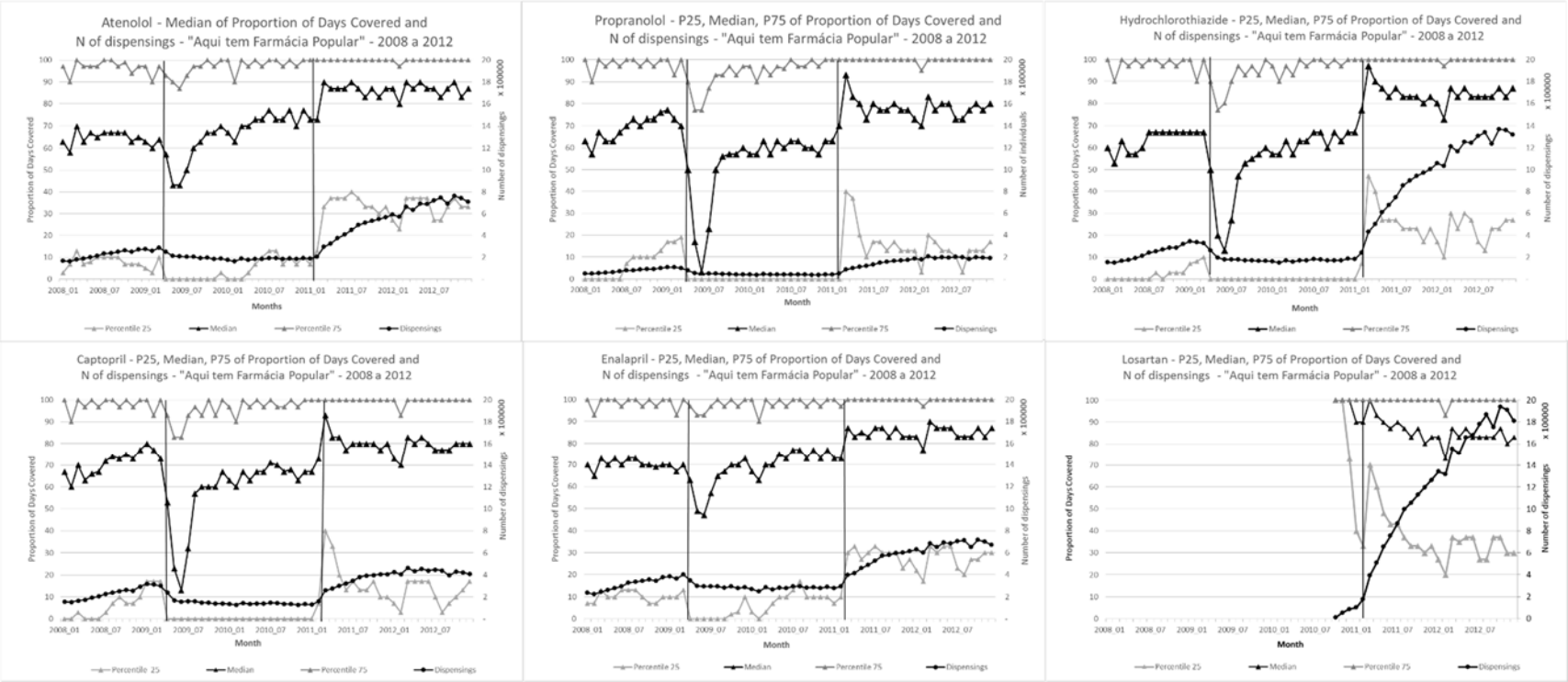








Appendix 3. Number of dispensings and unadjusted 25th/Median/75th percentiles of Proportion of Days Covered, atenolol 25mg, propranolol 40 mg, hydrochlorothiazide 25mg, captopril 25mg, enalapril 5mg and losartan 50 mg by stage of the Farmácia Popular program, Brazil, 2008 to 2012.



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Location in the Paper
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1 and 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract including Strengths and limitations of this study page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	describes changes in utilization and continuity of coverage for oral hypoglycemic (OH) and antihypertensive (AH) medicines following changes in patient cost sharing in the FP program. – pages 3, 4
Methods			
Study design	4	Present key elements of study design early in the paper	Methods – study design analysis and statistical methods – pages 4, 5 and 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods – intervention and Data source and study population – pages 4 and 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods - Data source and study population – page 5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods – analysis – page 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods - Data source and study population – page 5
Bias	9	Describe any efforts to address potential sources of bias	We recognize as possible limitations on the discussion page 12
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods – analysis and statistical methods pages 5 and 6

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods – analysis and statistical methods pages 5 and 6
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	Methods – analysis and statistical methods pages 5 and 6
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results – page 6
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results page 6
		(b) Indicate number of participants with missing data for each variable of interest	In the methods is described how we handled the missing data – page 5
		(c) Summarise follow-up time (eg, average and total amount)	Results page 6
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results pages 6 to 11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results pages 6 to 11
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	We calculated the Percentage of change for specific periods in time – tables 2 and 3 pages 8 and 9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion – pages 11 and 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both	Discussion – page 12

		direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion – pages 11 and 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	Not applicable
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.