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

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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

Pharmacy 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

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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

1
2
3 adjust for pre-existing trends in the period before the policy change. Segmented linear
4 regression models were constructed using the *prais* command in STATA v12.

5
6 ITS models included three segments, one per program period, with 15, 22, and 23 monthly
7 observations, respectively. The baseline segment was fit with an intercept and a variable
8 estimating trend. We estimate each policy effect by one variable representing the change in
9 level of the outcome immediately after the policy and a second representing the change in
10 trend of the post-policy segment. Patients experienced the changes in cost sharing only when
11 they presented to fill a prescription after the policy change. We thus defined a post-policy
12 implementation period of two months for participation and six months for PDC (to account for
13 the 120-day refill period); these periods were excluded in the ITS models so that we could
14 estimate stable post-intervention effects.

15
16 We retained all parameters in the models regardless of statistical significance. We highlight the
17 results with $p < 0.05$. We also tested logarithmic trend terms to accommodate possible non-
18 linear trends during each post-intervention segment, selecting the best model using the BIC and
19 AIC goodness of fitness criteria. [13] For the trends in metformin 500mg, atenolol 25mg, and
20 enalapril 5mg dispensing after the 2009 increase in cost sharing, the natural log of trend
21 represented a better model fit. We tested the adequacy of each model by residual analysis. To
22 create single number summaries of policy effects, we calculated estimates of the relative
23 changes in outcomes compared to expected values based on prior trends in April 2010 and
24 February 2012, about one year after the two cost sharing interventions.

30 Results

31
32 A total of 6,032,380 and 14,392,076 patients who received any OH or AH, respectively, from the
33 FP program comprised the dataset; of these, 3,611,512 (59.9%) and 9,534,333 (66.25%)
34 patients received two or more dispensings (Table 1). The mean age was 57 years for both
35 diabetes and hypertension patients, with females comprising about 60% of patients; the
36 Southeast region represented the majority of patients in the program. Patients with two or
37 more dispensings did not differ significantly from those with a single medication fill in age,
38 gender or region.

39
40 During the baseline period prior to the cost sharing changes, patients filled an average of 1.1
41 and 2.7 million dispensings per medicine per year for DM and HTN, respectively; dispensings
42 were growing at an average rate of 7.4 % per month for the medicines analyzed (Figure 1, Table
43 2). Metformin 850mg was the most widely used OH medicine and had the highest rate of
44 growth, while metformin slow release had the smallest monthly number of dispensings
45 (Appendix 1); enalapril was the most widely used AH medicine and propranolol the least widely
46 used, but utilization of all AH medicines was growing rapidly (Appendix 2).

47
48 Prior to the increased cost sharing, PDC levels for studied medicines were relatively stable; by
49 March 2009, one month before the AFP-II policy, median PDC levels for OH and AH medicines
50 were 64.2 and 70.4%, respectively. Median PDC levels varied across covered medicines from
51 63.3% (metformin slow release) to 78.7% (captopril 25mg) (Figure 1, Table 3, Appendix 1, and
52 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%

Trends in hypertension and diabetes medicines utilization

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

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)

1
2
3 After SNP, rates of monthly dispensing for most medicines followed similar patterns, varying
4 from an immediate increase in participation of 47,000 (metformin slow release) to 415,000
5 (hydrochlorothiazide 25mg) fills per month; increases in trend of monthly dispensing persisted
6 over time. By one year after the free medicines policy, in February 2012, significant relative
7 increases varied from 226% to 481% for metformin slow release and hydrochlorothiazide 25mg,
8 respectively. (Table 2)
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11 Losartan was added to the medicines reference list in October 2010; by the time of SNP
12 implementation four months later, there were only about 10 thousand dispensings. By one year
13 after medicines became free to patients, losartan dispensings had increased to more than 2
14 million dispensings. In comparison, its therapeutic competitors captopril and enalapril had only
15 700,000 and 1 million dispensings, respectively, in February 2012. (Appendix 2)
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18 After SNP and the substantial influx of patients, median monthly PDC increased for OH
19 medicines by 4.88% [0.37%, 9.39%] and for AH medicines by 4.87% [1.00%, 8.73%], and
20 remained relatively constant until the end of the study period (December 2012). (Table 3)
21 Changes in PDC varied by medicine; six of the nine medicines covered increased significantly by
22 5.3% (glibenclamide 5mg) to 14.8% (propranolol 40mg), but three experienced only small,
23 nonsignificant increases by the year after the free medicine policy. (Table 3).
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27 Discussion

28 Coverage policies in “Farmácia Popular”, a publicly-financed program designed to increase
29 access to essential medicines in Brazil, have evolved over time. Patient cost sharing increased
30 by 58% in 2009, resulting in immediate decreases in program participation and PDC. In contrast,
31 rapid increases in both outcomes followed implementation of a 2011 policy to make essential
32 medicines for diabetes and hypertension free to patients.
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35 Program participation for hypertension and diabetes follow the prevalence profile of these two
36 diseases in the country. [14] The majority of AFP patients are from the wealthier Southeast
37 region where there is a higher density of participating pharmacies; [4] this may imply increasing
38 socioeconomic disparities in access to treatment for diabetes and hypertension, especially now
39 that medicines are available for free. Other studies that have evaluated access to medicines for
40 hypertension[15] and diabetes[16] through the Health has No Price program have concluded
41 that the intervention contributed to increased access to these medicines in Brazil.
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44 PDC is usually used in the literature as a proxy for treatment adherence. [9,12,17] In this paper,
45 PDC measures consistency of filling in the AFP program. Since prescriptions can be filled in
46 either public or private FP pharmacies, available data is insufficient to determine the actual
47 level of prescription filling in the program; the observed PDC can be thought of as measuring a
48 minimum level of program adherence.
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51 In the literature, about half of patients treated for chronic disease become no adherent within a
52 year. [18] The consistency of prescription filling in the AFP program, particularly after medicines
53 for diabetes and hypertension were made free to patients, suggest that private sector outlets
54 are convenient and preferred by patients as a source of these free medicines.
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Trends in hypertension and diabetes medicines utilization

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3 The relationship between PDC levels and clinical outcomes is well-established in the literature.
4 [19,20] For example, adherence to hypoglycemic treatment measured through administrative
5 data has been found to be related to better glycemic control, fewer emergency department
6 visits, and lower rates of hospital admission. [21] [22] [23] Many studies consider patients with
7 PDC 80% or higher to be adherent to treatment; [21] lower adherence can lead to higher rates
8 of adverse events, poor long-term health outcomes, and higher healthcare costs. [24] After
9 SNP, rates of PDC were higher than 80% for well over half of patients taking OH and AH
10 medicines, levels likely to have positive impact on clinical outcomes. One study that have
11 analyzed the impact of full subsidy policies on medicines use have found similar effects on PDC
12 as in our study. [11,25–28]

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

21
22 Although losartan is not a first-line treatment in the Brazilian guideline to treat
23 hypertension, [30] it was included in the FP reimbursement list in 2010. Within a few months,
24 losartan had become the most widely dispensed AH medicine. Coverage decisions in
25 government subsidy programs should be consistent with treatment guidelines to encourage
26 appropriate choice of therapy and more cost-effective treatment.

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29 Our study has several limitations. Patient-level utilization data are only available from private
30 AFP pharmacies and not from government-owned pharmacies in public sector facilities. Thus, it
31 is impossible to evaluate the impact of these two cost sharing interventions on utilization in the
32 FP program as a whole or on the actual proportion of days covered for patients who filled
33 prescriptions in both sectors. To make the estimates of PDC interpretable, we limited analysis
34 of program impacts to patients who filled more than one prescription of a medicine in the FP
35 private sector program; there were no relevant differences in characteristics between patients
36 who filled only one prescription and those who used it more regularly. Additionally, we have no
37 data on medicines that are not part of the program, so cannot evaluate the impact of FP
38 program policies on use of other medicines used to treat diabetes and hypertension. Finally, as
39 a result of the method chosen to calculate the PDC, [12] the possible overuse due to
40 overlapping dispensings was not evaluated.

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

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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.

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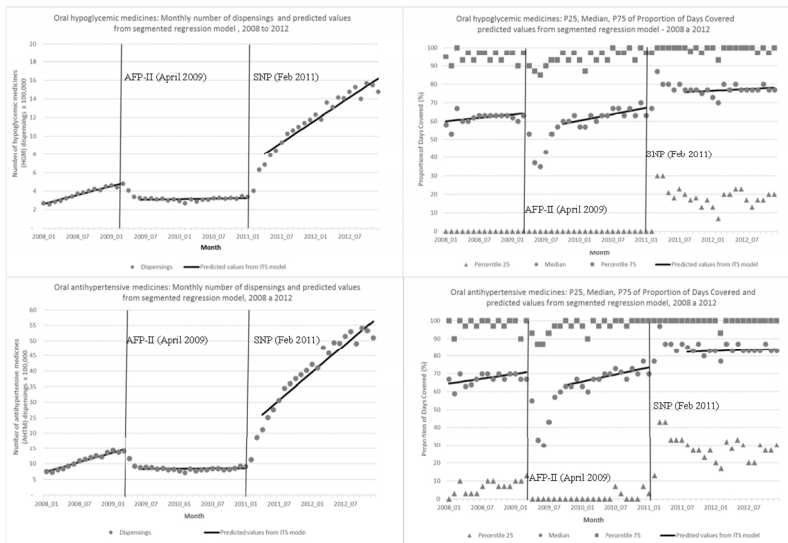
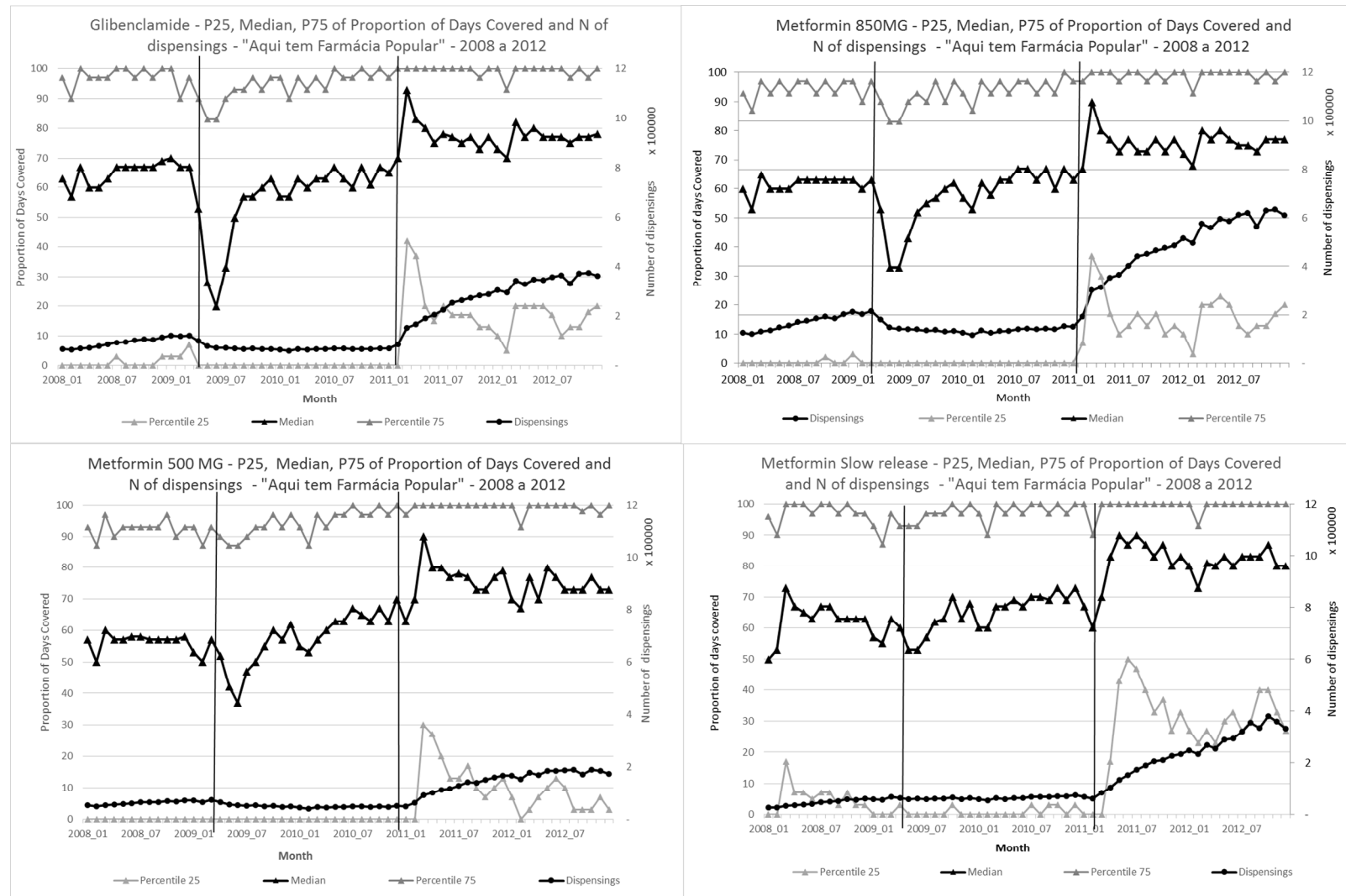


Figure 1. Number of dispensings and 25th/Median/75th percentiles of Proportion of Days Covered, and predicted values from segmented regression models for oral hypoglycemic and oral antihypertensive medicines, by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

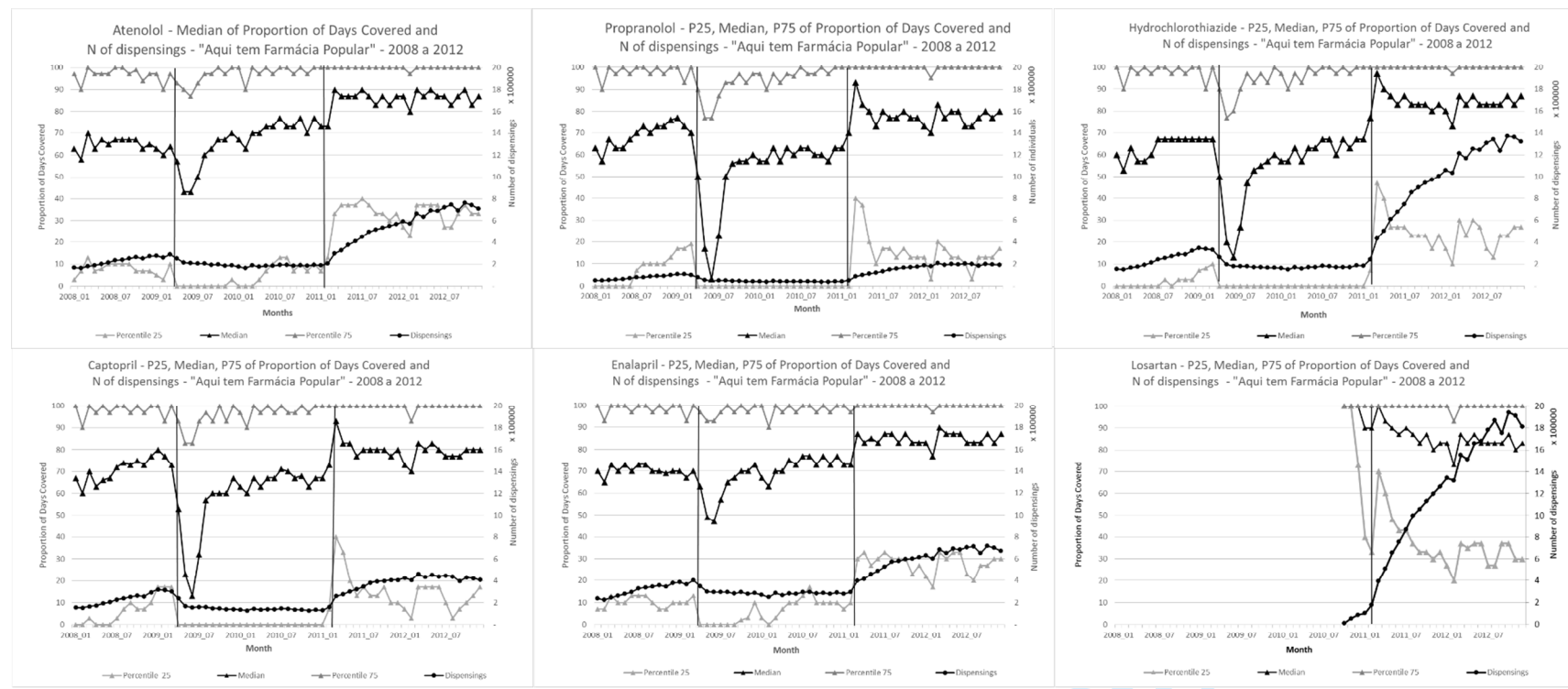
279x215mm (150 x 152 DPI)

Trends in hypertension and diabetes medicines utilization

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.



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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

1		used to control for confounding	statistical methods pages
2			5 and 6
3		(b) Describe any methods used to examine subgroups	Not applicable
4		and interactions	
5		(c) Explain how missing data were addressed	Methods – analysis and
6			statistical methods pages
7			5 and 6
8		(d) If applicable, explain how loss to follow-up was	Not applicable
9		addressed	
10		(e) Describe any sensitivity analyses	Not applicable
11			
12			
13			
14		Results	
15	Participants	13* (a) Report numbers of individuals at each stage of	Results – page 6
16		study—eg numbers potentially eligible, examined for	
17		eligibility, confirmed eligible, included in the study,	
18		completing follow-up, and analysed	
19		(b) Give reasons for non-participation at each stage	Not applicable
20		(c) Consider use of a flow diagram	Not applicable
21			
22	Descriptive data	14* (a) Give characteristics of study participants (eg	Results page 6
23		demographic, clinical, social) and information on	
24		exposures and potential confounders	
25		(b) Indicate number of participants with missing data	In the methods is
26		for each variable of interest	described how we
27			handled the missing data
28			– page 5
29		(c) Summarise follow-up time (eg, average and total	Results page 6
30		amount)	
31			
32			
33	Outcome data	15* Report numbers of outcome events or summary	Results pages 6 to 11
34		measures over time	
35			
36	Main results	16 (a) Give unadjusted estimates and, if applicable,	Results pages 6 to 11
37		confounder-adjusted estimates and their precision	
38		(eg, 95% confidence interval). Make clear which	
39		confounders were adjusted for and why they were	
40		included	
41		(b) Report category boundaries when continuous	Not applicable
42		variables were categorized	
43		(c) If relevant, consider translating estimates of	We calculated the
44		relative risk into absolute risk for a meaningful time	Percentage of change for
45		period	specific periods in time –
46			tables 2 and 3 pages 8 and
47			9
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49			
50	Other analyses	17 Report other analyses done—eg analyses of	Not applicable
51		subgroups and interactions, and sensitivity analyses	
52			
53		Discussion	
54	Key results	18 Summarise key results with reference to study	Discussion – pages 11 and
55		objectives	12
56			
57	Limitations	19 Discuss limitations of the study, taking into account	Discussion – page 12
58		sources of potential bias or imprecision. Discuss both	
59		direction and magnitude of any potential bias	
60			

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

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15 *Give information separately for exposed and unexposed groups.

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

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

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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

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

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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.

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15

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

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17
18
19

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

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25

Luisa Arueira Chaves, MSc

Pharmacy 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.

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Andréa Dâmaso Bertoldi, PhD

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

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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

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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

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Trends in hypertension and diabetes medicines utilization

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

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Number of figures: 01

Words (Abstract): 239

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Appendix: 03

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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]) 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 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

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3 growth, while metformin slow release had the smallest monthly number of dispensings
4 (Appendix 2); enalapril was the most widely used AH medicine and propranolol the least widely
5 used, but utilization of all AH medicines was growing rapidly (Appendix 3).
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8 Prior to the increased cost sharing, PDC levels for studied medicines were relatively stable; by
9 March 2009, one month before the AFP-II policy, median PDC levels for OH and AH medicines
10 were 64.2 and 70.4%, respectively. Median PDC levels varied across covered medicines from
11 63.3% (metformin slow release) to 78.7% (captopril 25mg) (Figure 1, Table 3, Appendix 2, and
12 Appendix 3).
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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.

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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				-8.1	0.28			4.88	-0.43	
	59.67	0.30	64.22	(-12.85;-3.36)	(-0.12;0.67)	-9.0	67.21	(0.37;9.39)	(-0.79;-0.07)	2.5
Glibenclamide 5mg	61.40	0.56	69.75	(-19.65;-10.81)	(-0.43;0.3)	-20.4	65.73	(2.03;10.42)	(-0.68;-0.01)	5.3
Metformin 850mg	59.02	0.38	64.74	(-10.41)	0.21			3.84	-0.37	
*Metformin 500mg	56.24	0.05	57.04	(-15.3;-5.52)	(-0.2;0.62)	-12.8	66.08	(-0.81;8.49)	(-0.74;-0.01)	1.7
Metformin slow release				-1.75	2.87	6.7	64.41	8.56	-0.15	11.2
	61.09	0.15	63.29	(-7.23;3.73)	(0.07;5.67)		69.67	(2.9;14.22)	(-0.77;0.46)	
				0.61	0.16	2.6		11.09	-0.43	11.0
				(-10.35;11.57)	(-0.75;1.06)			(0.61;21.56)	(-1.25;0.4)	
Oral Antihypertensive				-10.63	0.22			4.87	-0.57	
	63.98	0.45	70.74	(-14.7;-6.55)	(-0.12;0.55)	-11.9	73.48	(1;8.73)	(-0.88;-0.27)	1.0
*Atenolol 25mg	64.88	0.02	65.15	-0.70	3.4	9.1	74.27	10.63	-0.14	12.6
Propranolol 40 mg	61.34	1.07	77.40	(-5.53;4.13)	(1.03;5.78)	-34.3	63.00	(6.6;14.67)	(-0.49;0.21)	
Hydrochlorothiazide				-26.21	-0.73			11.63	-0.23	14.8
25mg	56.88	0.82	69.22	(-32.49;-19.93)	(-1.25;-0.21)		67.25	(5.66;17.6)	(-0.71;0.24)	
Captopril 25mg	63.81	0.99	78.66	(-18.17)	-0.12	-23.8	69.11	10.1	(-0.89;-0.17)	8.4
*Enalapril 5mg				(-22.91;-13.43)	(-0.51;0.28)			(5.6;14.6)	(-0.82;0.06)	
	70.16	0.02	70.39	(-23.07)	-0.52		74.93	5.86	-0.38	
				(-28.85;-17.29)	(-1;-0.04)			(3.7;11.35)	(-0.37;0.34)	10.0
				-2.91	2.56	3.0		7.79	-0.02	
				(-7.74;1.93)	(0.18;4.95)			(3.75;11.83)		

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)

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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.

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3 In the literature, about half of patients treated for chronic disease become no adherent within a
4 year. [19] The consistency of prescription filling in the AFP program, particularly after medicines
5 for diabetes and hypertension were made free to patients, suggest that private sector outlets
6 are convenient and preferred by patients as a source of these free medicines.
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9 The relationship between PDC levels and clinical outcomes is well-established in the literature.
10 [20,21] For example, adherence to hypoglycemic treatment measured through administrative
11 data has been found to be related to better glycemic control, fewer emergency department
12 visits, and lower rates of hospital admission. [22] [23] [24] Many studies consider patients with
13 PDC 80% or higher to be adherent to treatment; [22] lower adherence can lead to higher rates
14 of adverse events, poor long-term health outcomes, and higher healthcare costs. [25] After
15 SNP, rates of PDC were higher than 80% for well over half of patients taking OH and AH
16 medicines, levels likely to have positive impact on clinical outcomes. One study that analyzed
17 the impact of full subsidy policies on medicines use have found similar effects on PDC as in our
18 study. [11,26–29]
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22 The relation between cost sharing and medication adherence has been widely studied. [17] In
23 our study, all medicines with increased copayments in April 2009 experienced decreases in
24 rates of dispensing and PDC. After SNP, we observed the opposite response; when patients had
25 no cost sharing, program participation and PDC increased dramatically.
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27 Although losartan is not a first-line treatment in the Brazilian guideline to treat
28 hypertension, [30] it was included in the FP reimbursement list in 2010. Within a few months,
29 losartan had become the most widely dispensed AH medicine. Coverage decisions in
30 government subsidy programs should be consistent with treatment guidelines to encourage
31 appropriate choice of therapy and more cost-effective treatment.
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34 The limitations of this study comprises that the patient-level utilization data are only available
35 from private AFP pharmacies and not from government-owned pharmacies. Thus, this study
36 does not evaluate the impact of these two cost-sharing interventions on utilization in the FP
37 program as a whole or on the actual proportion of days covered for patients who filled
38 prescriptions in both sectors. Nevertheless, the public arm accounts for about 2.2% of FP
39 dispensing facilities [4]. We have the issue that there are other sources for medicines to
40 patients. However, we did not intend to use PDC as adherence to treatment measure, but as
41 adherence to the program instead. The dispensings in FP program are monthly, for 30 days'
42 supply, so no stockpiling is possible due the program rules. Then, we think that these potential
43 treats to internal validity have negligible impact on our findings. To make the estimates of PDC
44 interpretable, we limited analysis of program impacts to patients who filled more than one
45 prescription of a medicine in the FP private sector; there were no relevant differences in
46 characteristics between patients who filled only one prescription and those who used it more
47 regularly. We have no data on medicines that are not part of the program, so cannot evaluate
48 the impact of FP program policies on use of other medicines used to treat diabetes and
49 hypertension. Since patients could have switched treatment among the medicines covered (e.g.
50 change from captopril to enalapril), we may have underestimated PDC because we did not
51 evaluate this possible change. That way, the median PDC would be lower when actually the
52 patient was changing the therapy and using other medicine. Finally, as a result of the method
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3 chosen to calculate the PDC,[12] the possible overuse due to overlapping dispensings was not
4 evaluated.
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7 In conclusion, participation in the “Farmácia Popular” private sector program evolved in
8 response to two cost sharing interventions implemented between 2008 and 2012. Increased
9 patient cost sharing reduced participation, while full subsidy of key medicines in private
10 pharmacies substantially increased participation; patients in the program achieved PDC levels
11 that have been shown to improve health outcomes. Risks to rational use of medicines,
12 especially overuse, can be minimized through controlling mechanisms, such as the requirement
13 of prescription, validity of prescriptions and maximum dispensing amounts. Policy makers
14 should consider reducing or removing cost sharing for essential medicines to treat chronic
15 illness, while aligning subsidies to encourage greater use of first-line therapies.
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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.

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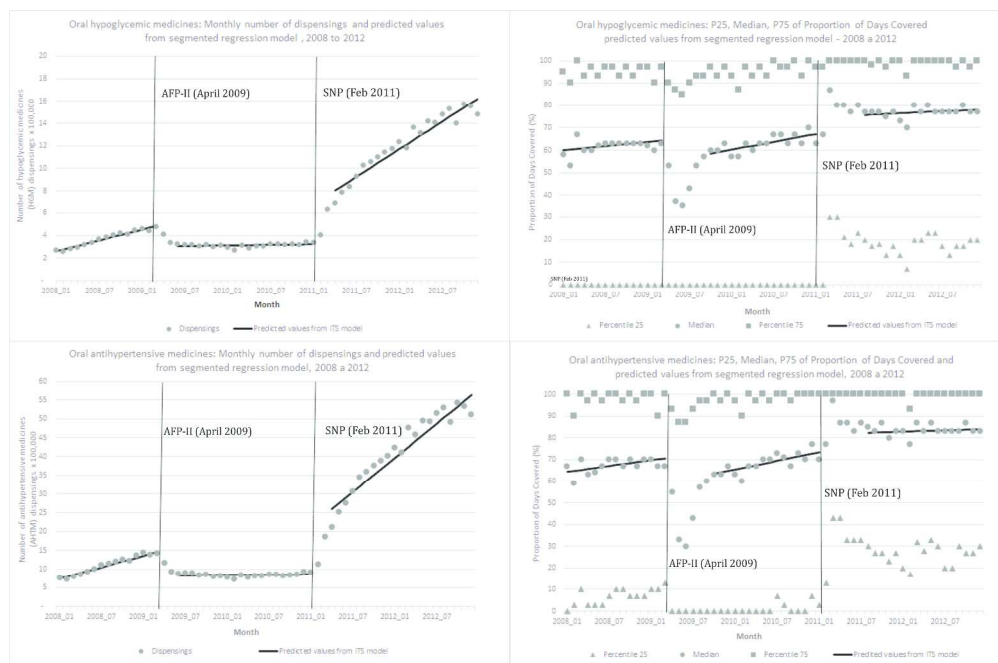


Figure 1. Number of dispensings and 25th/Median/75th percentiles of Proportion of Days Covered, and predicted values from segmented regression models for oral hypoglycemic and oral antihypertensive medicines, by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

512x337mm (300 x 300 DPI)

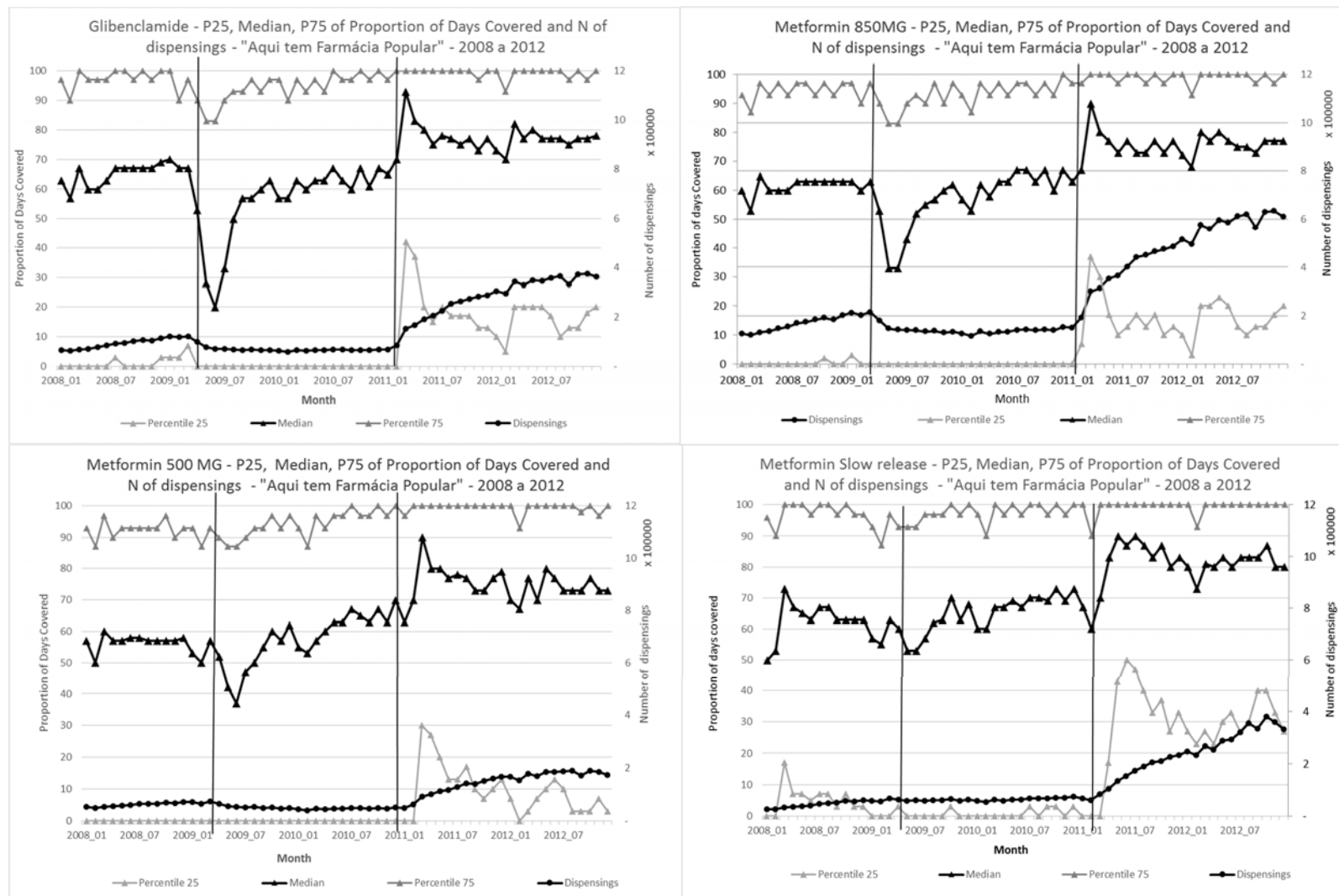
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Appendix 1. Medicines average unit price in local currency (reais), and average price treatment for 30 days' supply for glibenclamide 5mg, metformin 850mg, metformin 500mg, metformin slow release, losartan 50 mg, atenolol 25mg, propranolol 40 mg, hydrochlorothiazide 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

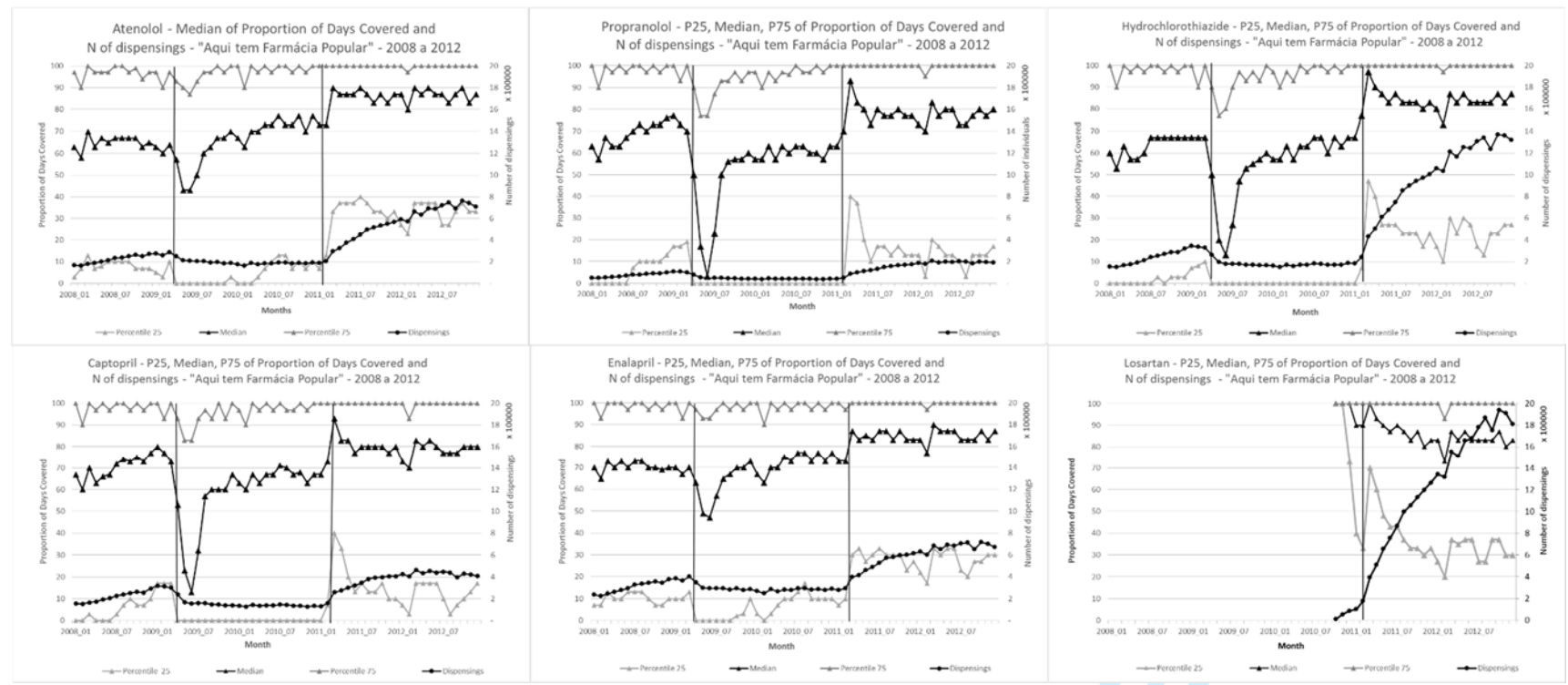
Trends in hypertension and diabetes medicines utilization

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.



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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

1	Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods – analysis and statistical methods pages 5 and 6
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3				
4			(b) Describe any methods used to examine subgroups and interactions	Not applicable
5				
6				
7			(c) Explain how missing data were addressed	Methods – analysis and statistical methods pages 5 and 6
8				
9				
10				
11			(d) If applicable, explain how loss to follow-up was addressed	Not applicable
12				
13			(e) Describe any sensitivity analyses	Not applicable
14				
15	Results			
16	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
17				
18			(b) Give reasons for non-participation at each stage	Not applicable
19				
20			(c) Consider use of a flow diagram	Not applicable
21				
22	Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results page 6
23				
24			(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
25				
26				
27			(c) Summarise follow-up time (eg, average and total amount)	Results page 6
28				
29	Outcome data	15*	Report numbers of outcome events or summary measures over time	Results pages 6 to 11
30				
31	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
32				
33			(b) Report category boundaries when continuous variables were categorized	Not applicable
34				
35			(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
36				
37	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
38				
39	Discussion			
40	Key results	18	Summarise key results with reference to study objectives	Discussion – pages 11 and 12
41				
42	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both	Discussion – page 12
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		direction and magnitude of any potential bias	
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2	Interpretation	20	Give a cautious overall interpretation of results
3			Discussion – pages 11 and
4			12
5			
6			
7	Generalisability	21	Discuss the generalisability (external validity) of the
8			study results
9			
10	Other information		
11	Funding	22	Give the source of funding and the role of the funders
12			Page 13
13			for the present study and, if applicable, for the
14			original study on which the present article is based
15			

*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:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017308.R2
Article Type:	Research
Date Submitted by the Author:	29-Aug-2017
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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

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Manuscripts

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3 **Retrospective Interrupted time series examining hypertension and diabetes medicines**
4 **utilization following changes in patient cost sharing in the “Farmácia Popular” program in**
5 **Brazil**
6

7
8 **Isabel Cristina Martins Emmerick, ScD**

9
10 Research Fellow, Pharmaceutical Policy Research Fellowship, Department of Population
11 Medicine, Harvard Medical School & Harvard Pilgrim Health Care Institute. Landmark Center,
12 401 Park Drive Suite 401 Boston, MA 02215.

13
14 **Mônica Rodrigues Campos, PhD**

15
16 Department of Social Sciences, Sergio Arouca National School of Public Health, Oswaldo Cruz
17 Foundation.1480 Rua Leopoldo Bulhões #905, Manguinhos, Rio de Janeiro 21041-210, Brazil

18
19 **Vera Lucia Luiza, ScD**

20
21 Department of Medicines and Pharmaceutical Services Policies, Sergio Arouca National School
22 of Public Health, Oswaldo Cruz Foundation. 1480 Rua Leopoldo Bulhões #624, Manguinhos, Rio
23 de Janeiro 21041-210, Brazil

24
25 **Luisa Arueira Chaves, MSc**

26
27 Pharmacy Department, Federal University of Rio de Janeiro, Macaé Campus. Av. Aluizio da Silva
28 Gomes, #50, Granja dos Cavaleiros, Macaé, 27930-560, Brazil - Rio de Janeiro Federal University
29 – Macaé Campus.

30
31 **Andréa Dâmaso Bertoldi, PhD**

32
33 Postgraduate Program in Epidemiology, Federal University of Pelotas. Rua Marechal Deodoro
34 1160, 96020-220, Pelotas, Brazil.

35
36 **Dennis Ross-Degnan, ScD**

37
38 Department of Population Medicine, Drug Policy Research Group, Harvard Medical School &
39 Harvard Pilgrim Health Care Institute. Landmark Center, 401 Park Drive Suite 401 Boston, MA
40 02215

41
42
43 Corresponding Author:

44 Isabel Emmerick, Research Fellow

45 Pharmaceutical Policy Research Fellowship

46 Department of Population Medicine

47 Harvard Medical School & Harvard Pilgrim Health Care Institute

48 Landmark Center, 401 Park Drive Suite 401 Boston, MA 02215

49 Phone: 1-617-509-9510, Fax: 1-617-859-8112

50 emmerick.isabel@gmail.com
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54
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Trends in hypertension and diabetes medicines utilization

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

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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]) 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 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

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3 growth, while metformin slow release had the smallest monthly number of dispensings
4 (Appendix 2); enalapril was the most widely used AH medicine and propranolol the least widely
5 used, but utilization of all AH medicines was growing rapidly (Appendix 3).
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8 Prior to the increased cost sharing, PDC levels for studied medicines were relatively stable; by
9 March 2009, one month before the AFP-II policy, median PDC levels for OH and AH medicines
10 were 64.2 and 70.4%, respectively. Median PDC levels varied across covered medicines from
11 63.3% (metformin slow release) to 78.7% (captopril 25mg) (Figure 1, Table 3, Appendix 2, and
12 Appendix 3).
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Trends in hypertension and diabetes medicines utilization

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.

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

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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.

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3 In the literature, about half of patients treated for chronic disease become no adherent within a
4 year. [19] The consistency of prescription filling in the AFP program, particularly after medicines
5 for diabetes and hypertension were made free to patients, suggest that private sector outlets
6 are convenient and preferred by patients as a source of these free medicines.
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9 The relationship between PDC levels and clinical outcomes is well-established in the literature.
10 [20,21] For example, adherence to hypoglycemic treatment measured through administrative
11 data has been found to be related to better glycemic control, fewer emergency department
12 visits, and lower rates of hospital admission. [22] [23] [24] Many studies consider patients with
13 PDC 80% or higher to be adherent to treatment; [22] lower adherence can lead to higher rates
14 of adverse events, poor long-term health outcomes, and higher healthcare costs. [25] After
15 SNP, rates of PDC were higher than 80% for well over half of patients taking OH and AH
16 medicines, levels likely to have positive impact on clinical outcomes. One study that analyzed
17 the impact of full subsidy policies on medicines use have found similar effects on PDC as in our
18 study. [11,26–29]
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22 The relation between cost sharing and medication adherence has been widely studied. [17] In
23 our study, all medicines with increased copayments in April 2009 experienced decreases in
24 rates of dispensing and PDC. After SNP, we observed the opposite response; when patients had
25 no cost sharing, program participation and PDC increased dramatically.
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27 Although losartan is not a first-line treatment in the Brazilian guideline to treat
28 hypertension, [30] it was included in the FP reimbursement list in 2010. Within a few months,
29 losartan had become the most widely dispensed AH medicine. Coverage decisions in
30 government subsidy programs should be consistent with treatment guidelines to encourage
31 appropriate choice of therapy and more cost-effective treatment.
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34 The limitations of this study comprises that the patient-level utilization data are only available
35 from private AFP pharmacies and not from government-owned pharmacies. Thus, this study
36 does not evaluate the impact of these two cost-sharing interventions on utilization in the FP
37 program as a whole or on the actual proportion of days covered for patients who filled
38 prescriptions in both sectors. Nevertheless, the public arm accounts for about 2.2% of FP
39 dispensing facilities [4]. We have the issue that there are other sources for medicines to
40 patients. However, we did not intend to use PDC as adherence to treatment measure, but as
41 adherence to the program instead. The dispensings in FP program are monthly, for 30 days'
42 supply, so no stockpiling is possible due the program rules. Then, we think that these potential
43 treats to internal validity have negligible impact on our findings. To make the estimates of PDC
44 interpretable, we limited analysis of program impacts to patients who filled more than one
45 prescription of a medicine in the FP private sector; there were no relevant differences in
46 characteristics between patients who filled only one prescription and those who used it more
47 regularly. We have no data on medicines that are not part of the program, so cannot evaluate
48 the impact of FP program policies on use of other medicines used to treat diabetes and
49 hypertension. Since patients could have switched treatment among the medicines covered (e.g.
50 change from captopril to enalapril), we may have underestimated PDC because we did not
51 evaluate this possible change. That way, the median PDC would be lower when actually the
52 patient was changing the therapy and using other medicine. Finally, as a result of the method
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3 chosen to calculate the PDC,[12] the possible overuse due to overlapping dispensings was not
4 evaluated.
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7 In conclusion, participation in the “Farmácia Popular” private sector program evolved in
8 response to two cost sharing interventions implemented between 2008 and 2012. Increased
9 patient cost sharing reduced participation, while full subsidy of key medicines in private
10 pharmacies substantially increased participation; patients in the program achieved PDC levels
11 that have been shown to improve health outcomes. Risks to rational use of medicines,
12 especially overuse, can be minimized through controlling mechanisms, such as the requirement
13 of prescription, validity of prescriptions and maximum dispensing amounts. Policy makers
14 should consider reducing or removing cost sharing for essential medicines to treat chronic
15 illness, while aligning subsidies to encourage greater use of first-line therapies.
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Data sharing: No additional data are available.

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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.

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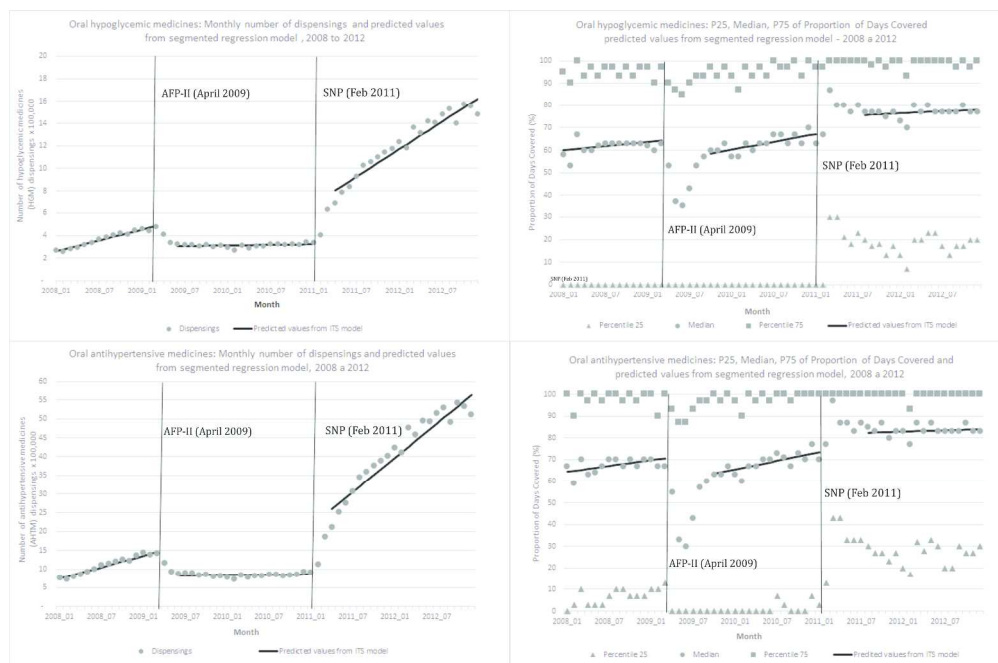


Figure 1. Number of dispensings and 25th/Median/75th percentiles of Proportion of Days Covered, and predicted values from segmented regression models for oral hypoglycemic and oral antihypertensive medicines, by stage of the Farmácia Popular program, Brazil, 2008 to 2012.

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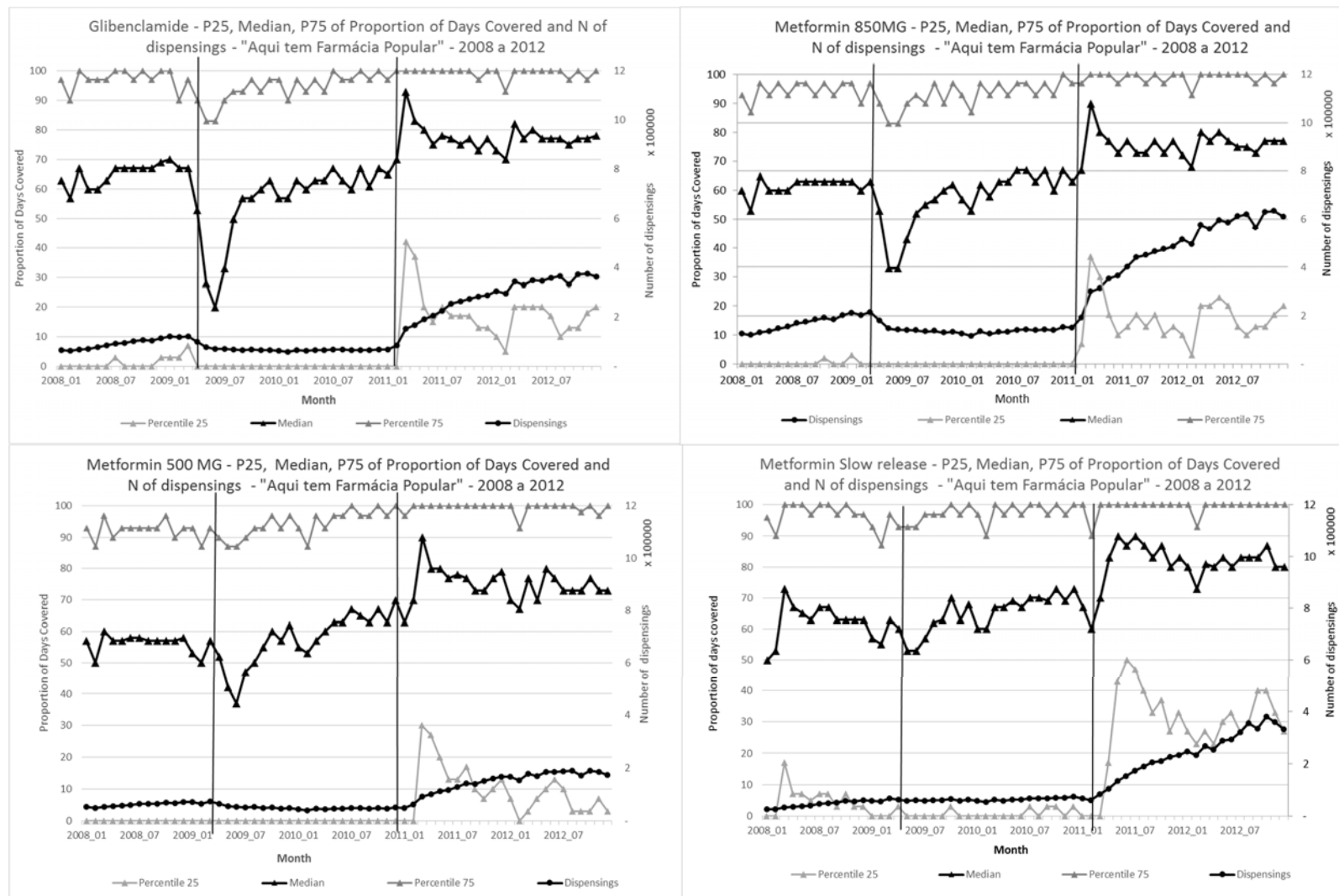
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Appendix 1. Medicines average unit price in local currency (reais), and average price treatment for 30 days' supply for glibenclamide 5mg, metformin 850mg, metformin 500mg, metformin slow release, losartan 50 mg, atenolol 25mg, propranolol 40 mg , 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

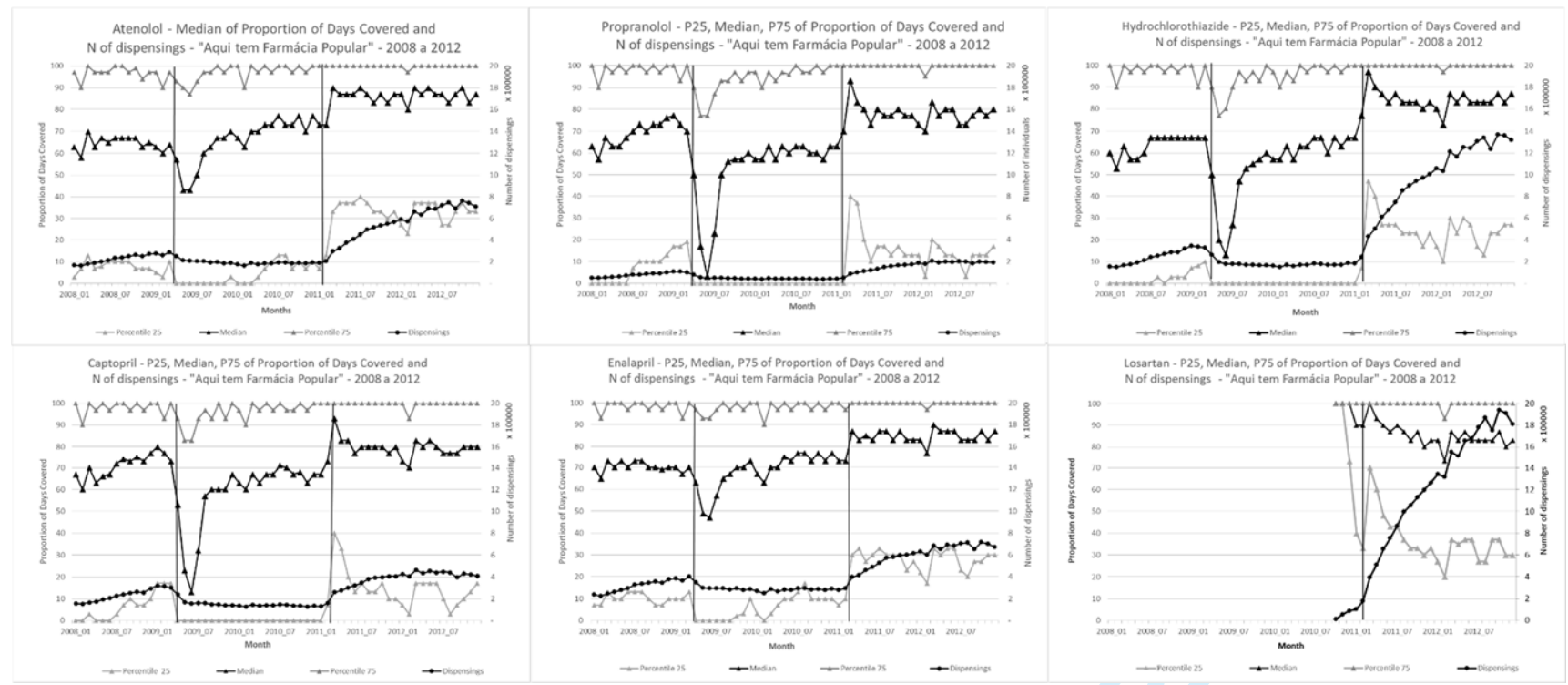
Trends in hypertension and diabetes medicines utilization

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.



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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

1	Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods – analysis and statistical methods pages 5 and 6
2			(b) Describe any methods used to examine subgroups and interactions	Not applicable
3			(c) Explain how missing data were addressed	Methods – analysis and statistical methods pages 5 and 6
4			(d) If applicable, explain how loss to follow-up was addressed	Not applicable
5			(e) Describe any sensitivity analyses	Not applicable
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15	Results			
16	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
17			(b) Give reasons for non-participation at each stage	Not applicable
18			(c) Consider use of a flow diagram	Not applicable
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23	Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results page 6
24			(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
25			(c) Summarise follow-up time (eg, average and total amount)	Results page 6
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34	Outcome data	15*	Report numbers of outcome events or summary measures over time	Results pages 6 to 11
35				
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37	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
38			(b) Report category boundaries when continuous variables were categorized	Not applicable
39			(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
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51	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
52				
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54	Discussion			
55	Key results	18	Summarise key results with reference to study objectives	Discussion – pages 11 and 12
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58	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both	Discussion – page 12
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		direction and magnitude of any potential bias	
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2	Interpretation	20	Give a cautious overall interpretation of results
3			Discussion – pages 11 and
4			12
5			considering objectives, limitations, multiplicity of
6			analyses, results from similar studies, and other
7			relevant evidence
8	Generalisability	21	Discuss the generalisability (external validity) of the
9			study results
10	Other information		
11	Funding	22	Give the source of funding and the role of the funders
12			Page 13
13			for the present study and, if applicable, for the
14			original study on which the present article is based

*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>.