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Impact of National Drug Pricing Policy 2018 on Access to Medicines in Lahore Division, Pakistan: A Pre-Post Survey Study Using WHO/HAI Methodology

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Impact of National Drug Pricing Policy 2018 on Access to Medicines in Lahore Division, Pakistan: A Pre-Post Survey Study Using WHO/HAI Methodology

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Abstract

Objective: To evaluate the impact of new national drug pricing policy (NDPP) 2018 on access to medicines in terms of prices, availability and affordability.

Design: Two cross-sectional surveys were undertaken before and after the launch of NDPP 2018, using a modified WHO/HAI methodology.

Setting: Four districts of Lahore division, Pakistan.

Participants: 16 public sector hospitals and 16 private sector retail pharmacies.

Measures: The pre and post survey data on price and availability of Lowest Price Generics (LPGs) and Originator Brands (OBs) of 50 medicines were obtained by visiting the same public and private sector health facilities (n=32). 46 out of 50 surveyed medicines were from National Essential Medicines List. Inflation-adjusted median unit prices (MUPs) and median price ratios (MPRs) from 2019 were used for price comparison. Affordability was calculated in terms of number of days' wages required to get a standard treatment by the lowest paid unskilled government worker.

Results: The overall mean percent availabilities remained poor in both years i.e. far less than 80%. In public sector, the mean percent availability of OBs improved from 6.8% to 33.1% whereas, in case of LPGs it was reduced from 35.1% to 9%. In private sector, the mean percent availability of both OBs and LPGs demonstrated slight improvements in 2019 i.e. 55.0% to 58.3% and 20.3% to 32.3%. The adjusted MUPs and MPRs of OBs significantly increased by a median of 4.29% (Wilcoxon test p=0.001, p=0.0001). Whereas, the adjusted MUPs and MPRs of LPGs were increased by a median of 15.7% (p=0.002, p=0.0002). Overall the affordability of many medicines for common ailments reduced significantly in 2019.

Conclusions: The availability of medicines has been slightly improved, except in the case of LPGs which was reduced at public sector. Although the main aim of the NDPP 2018 was to make the drugs affordable, but its implementation has led to increased drug prices which has made standard treatment for some of the most prevalent ailments, unaffordable. This policy needs to be improved further to have strict price control especially for the essential medicines, to improve their access.

Strengths

- This is the first study of its kind from Pakistan, where pre-post surveys were conducted and analyzed to estimate the impact of a national drug pricing policy, using the WHO/HAI methodology.
- The data was collected from the same health facilities in both years. So, the comparison is reliable. This study provides an objective evidence to the policy makers for improving the current pricing policies.

Limitations

- The study is limited to only one division of Pakistan, although the medicine prices are fixed centrally and are supposed to be same across the country – affecting generalizability of the findings.
- Moreover, this study is conducted after about a year from the launch of new drug pricing policy 2018, so the results do not reflect the long term impact of the policy.

Introduction

Access to quality assured and affordable essential medicines is considered as a key component of an effective healthcare system. It has also been pledged under Sustainable Development Goal (SDG) 3 by United Nations (UN) that the equitable access to affordable essential medicines will be ensured as a basic human right [1, 2]. Pakistani government, like many other Low and Middle Income Countries (LMICs), has been grappling with the issue of high medicine prices and poor availability of medicines that compromises the accessibility of medicines [1, 3-6]. The medicines are provided free of cost at public sector health facilities, while patient pays out of pocket to get medicines from private sector, in Pakistan [5]. In fact, the poor availability of medicines at public sector compels the patients to buy medicines from private sector that escalates the burden on patient's pocket, while 24.3% (in 2015) of the population is living below the national poverty line [3, 4, 7, 8]. Besides, medicine prices have increased up to 100%, both legally or illegally, in the past few years [3]. The ministry of National Health Services Regulation and Coordination (NHSRC) of Pakistan has been taking different policy measures to curb these issues through Drug Regulatory Authority of Pakistan (DRAP). The first ever National Drug Pricing Policy (NDPP) was launched in 2015 for making the pricing mechanism transparent but it had minimal impact on medicine prices, suitable for both patients and manufacturers as per media reports and available literature evidences [3, 9]. So, a new drug pricing policy was launched in 2018[10]. The objectives of this policy were to improve the access to essential medicines, to devise rational prices, to ensure a transparent mechanism for pricing of medicines and to discourage illegal price increases.

Many modifications have been made to the pricing strategies in the NDPP 2018 compared to NDPP 2015, the most important one is the inclusion of all drugs (n=414) from National Essential Medicines List (NEML) under scheduled drugs category where drugs are kept under strict price control as compared to other drugs. Whereas in NDPP 2015, only 160 drugs from NEML were enlisted in this category [9, 10]. In NDPP 2018, the annual adjustment in prices has been linked with the Consumer Price Index (CPI), the Maximum Retail Prices (MRPs) of scheduled drugs (all drugs from NEML) could be increased up to 70% of the CPI, whereas the MRPs of all other drugs could be increased equivalent to CPI of the immediate preceding year. This step seems to improve the affordability of essential medicines (EMs) for patients in Pakistan. If several generics are already available in the market then in NDPP 2015, the MRP of new entrant was fixed by taking the average of other generics, while in NDPP 2018, MRP will be fixed equivalent to the highest MRP of the available generics [9, 10]. However, this would lead to even higher priced generics in the market that could compromise patient's affordability. Some media reports are claiming that the current increase (up to 200%) in medicines prices is the highest in the last 40 years, while others are claiming that government is taking action against this illegal rise in medicine prices [11, 12]. But there is no objective evidence to prove or disapprove these claims. The NDPP 2018, allows the MRPs of the New Chemical Entities (NCEs) to be fixed while using External Reference Pricing (ERP) mechanism by considering India, Bangladesh, Indonesia, Sri Lanka, Philippines, Lebanon and Malaysia as reference countries. However, the reason behind using the MRPs of these countries as reference is not clear, though some of them practice free market economy model and don't impose any price control measures over the MRPs in community pharmacies that may lead to high prices. The NDPP 2018 also takes into account the wholesale or procurement prices

from British National Formulary, Australian Pharmaceutical Benefit Scheme and New Zealand Pharmaceutical Management Agency while fixing the MRPs of NCEs, whereas these may not be the true prices because as a common practice discounts and rebates are given while making the payments. So, these ambiguities in the policy necessitate the evaluation of actual impact of these policies on the access to medicines in Pakistan.

In this context, we designed a study to measure the impact of new NDPP 2018 on access to essential medicines in terms of their prices, availability and affordability in Lahore division Punjab. We undertook a survey after the implementation of NDPP 2018 and compared it with a similar survey performed before the launch of this policy in 2017. Considering the objectives of the NDPP 2018, we hypothesized that it will improve the availability and affordability while decrease the prices of EMs.

Methodology

Study Design

Two cross-sectional studies were conducted in 2016-17 and 2019 using a variant of World Health Organization/Health Action International (WHO/HAI) methodology in four districts of Lahore division, Pakistan [13]. Since, the focus of this study was to measure the impact of NDPP 2018 in terms of changes in medicines prices, availability and affordability after its implementation, thus, the data on these parameters was collected to evaluate the accessibility of medicines in both years [10]. The first survey was conducted from November 2016 to March 2017, while the second survey was from March-May 2019, representing two fiscal years of Pakistan. For optimal and reliable comparison, the list of medicines, survey region and survey outlets selected for the survey 2019 were similar to those selected for 2017. The details of survey region, medicine selection, sampling of medicine outlets and data collection are given elsewhere and are briefly described in this paper [7].

Survey Areas

Lahore is the largest division of Pakistan in terms of population i.e. 16.28 Million (2017) and estimated to be 19.4 Million as of 2018[14]. It consists of four districts named as Lahore, Kasur, Sheikhupura and Nankana Sahib which are further subdivided into 17 Tehsils. All the four districts were selected for the surveys.

Sampling of Medicine Outlets

Medicine outlets or health facilities from both public and private sectors were sampled systematically using WHO/HAI manual as a guiding principle in both the surveys [13]. Total 32 medicine outlets were surveyed (16 from public sector and 16 from private sector). From public sector, hospitals from all three tiers of healthcare system i.e. primary, secondary and tertiary were selected. One main hospital in each district was selected as a survey anchor along with additional three more hospitals selected randomly and situated within three hours' drive from the main hospital. In this way, 4 hospitals were selected in each district making up a total of 16 hospitals from Lahore division. From private sector, one registered pharmacy was selected situated within 10 kilometers range of each public sector hospital. So, a total of 16 pharmacies were selected from

Lahore division, i-e. 4 retail pharmacies from each district. It is important to note that each survey unit, one hospital and one nearby pharmacy, was located in different Tehsils, so out of 17 Tehsils of Lahore division, 16 were surveyed in both years.

Selection of Medicines

50 medicines were selected for survey as per WHO/HAI methodology, which included all 14 medicines from WHO core global list of medicines and 36 supplementary medicines. The criterion of selecting medicines for supplementary list was local disease burden and inclusion of medicines in NEML [15].

Data Collection

The data were collected using a data collection form by the trained data collectors. The data collectors visited the health facilities and physically checked the medicines prices and availability for both OBs and LPGs of each medicine and entered in to data collection forms. The data for each year were entered separately in to the WHO/HAI workbook by using double data entry process, to avoid any mistake [13]. The patient prices or the prices charged to patients were entered in to the forms for private sector only because in public sector, the medicines are provided free of charge in Pakistan. Thus, the availability of medicines was documented only for public sector facility.

Data Analysis

Data were analyzed by using WHO/HAI preprogrammed Excel workbook[13], IBM Statistical Package for the Social Sciences (SPSS) version 22.0 and R version 3.5.1 (codenamed "Feather Spray").

The availability was calculated as percentage of particular medicine available at each facility on the day of data collection. The mean percentage availabilities were also calculated and compared between different sectors (public and private), product types (OBs and LPGs) and among different groups (global medicines, supplementary medicines, medicines from NEML, medicines used to treat NCDs and IDs). Availability was documented as follows; Absent: 0% of facilities had surveyed enlisted medicines at the time of survey; Low: < 50% of facilities had the surveyed enlisted medicines; Fairly high: 50 -80% of facilities had surveyed enlisted medicines; High: > 80% of facilities, survey enlisted medicines were found in most of the facilities [16, 17].

Medicine prices were calculated as Median Unit Prices (MUPs) in Pakistani Rupees (PKR) and were also compared with International Reference Prices (IRPs) to calculate the Median Price Ratios (MPRs). The IRPs were obtained from Management Sciences for Health (MSH) drug price indicator guide 2015[18]. An MPR of greater than 1 for public sector and greater than 2 for private sector would lodge any medicine into high priced medicines category [7]. For comparing the prices between two years, the MUPs from 2019 were deflated by 3.33%, taking 2017 as base year. 70% of the CPI was used for calculating this deflation factor, because the medicine prices can be increased annually by 70% of the CPI as per NDPP 2018 [19]. Whereas MPR was calculated as follows:

$$Median\ Price\ Ratio(MPR) = Median\ local\ unit\ price / International\ reference\ unit\ price$$

Affordability for treatment of different common diseases with selected medicines was calculated and compared in terms of Number of Days Wages (NDWs) required for a lowest paid government employee to get the standard treatment courses. Whereas, if a patient had to spend more than one day of his wage for treatment with a specific medicine in a month, that medicine was considered unaffordable [13]. For affordability comparison, NDWs in two years, the prices in 2019 were not deflated because the salary has also been increased in 2019. So, the salary of the lowest paid unskilled government worker was taken as 14000PKR per month (2016-17) and 15000PKR per month (2018-19) [20].

Comparative analysis: Two patient prices were required to be included in the comparative analysis, one from 2017 and other from 2019. The difference in prices, availability and affordability were computed as percentage changes for each product. The mean availability and MUPs were also compared between different categories of medicines (NEML and non-NEML medicines; global and supplementary medicines; medicines for IDs and NCDs) across the years. We compared affordability in terms NDWs to get the standard treatment from the surveyed medicines. These were also compared among medicines for different disease groups (asthma, cardiovascular diseases, infectious diseases, brain disorders, diabetes, ulcer and arthritis; IDs and NCDs). To identify whether the difference between MUPs, MPRs and NDWs was significant across two years, we used Wilcoxon signed rank test. We took $p<0.01$ as an indicator of significant difference in all the statistical testing.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of this study.

Results

Availability of medicines

The overall availability of surveyed medicines was improved in 2019 when compared with 2017, except for LPGs in public sector, where it demonstrated reduction.

Availability in Public Sector: In public sector, the availability of both OBs and LPGs was poor in both years. None of the mean availabilities touched the benchmark of 80%. The mean percent availability of OBs improved from 6.8% to 33.1% whereas, in case of LPGs it reduced from 35.1% to 9%. The individual percent availabilities of each medicine (OB and LPG) are given in table S1. For better understanding of the data, we have used the data visualization tool in R and plotted a box plot of the data as shown in figure 1. The box plot showed distributional characteristics of the percent availability of medicines in two groups (OB and LPG) for the years 2017 and 2019. The mean percent availability is represented by the dot inside the box. In 2017, availabilities of 75% of the OBs in public sector were less than 11.2% as shown by the 3rd quartile or the upper bar of the 1st box plot. Whereas, in 2019, 75% of the OBs had availabilities higher than 6.3% which is almost equivalent to the mean percent availability (6.8%) in 2017. This indicates a substantial increase in the availability of OBs in public sector. In 2019, 75% of the LPGs had availability less than 12.5% (3rd quartile) whereas before the implementation of the

NDPP 2018, 75% of the LPGs had availabilities greater than 14.3% (1st quartile). This showed a remarkable decrease in the availability of LPGs in public sector in 2019.

Availability in private sector: In both years, the overall availability was better in private sector than the public sector. Mean percent availability of both OBs and LPGs were improved in 2019 i.e. 55.0% to 58.3% and 20.3% to 32.3%, respectively. Availability of LPGs was less than OBs in both years. For OBs, the mean percent availability improved slightly by 3.3% while data distribution remained almost the same across the years, as shown in the box plot (figure 1). For LPGs, a substantial increase in the availability was observed in terms of mean percent availability, maximum value and change in data distribution (figure 1). In 2017, the IQR (range between upper and lower bar of the box) for percentage availability of LPGs ranged from 6% to 31% whereas it got improved in 2019 and ranged from 6% to 50%.

Availability in different subgroups of medicines: When we compared availability of LPGs and OBs in different subgroups of medicines as shown in table 1, we found that mean percent availabilities of all global list medicines were higher than supplementary medicines in both years. Similarly, the availability of NEML medicines were higher than non-NEML medicines except for the non-NEML LPGs in public sector, which were higher than NEML LPGs (19.2% vs 8.1%). In 2017, in public sector, the availability of OBs for NCD medicines (6.7%) were lower than OBs for ID medicines (7.7%) whereas the availability of LPGs (35.9%) were better than LPGs of ID medicines (33%). Surprisingly, in 2019, the situation inversed completely for NCD medicines, increased and decreased availability of OBs (33.2%) and LPGs (33.1%), respectively, whereas, the availability decreased for LPGs (8.8%) and increased for OBs (9.5%) for ID medicines.

Table 1. Mean Percent Availabilities of Originator Brands (OBs) and Lowest Price Generics (LPGs) at both public and private sectors.

	Availability in 2017 (Mean, SD) ,%				**Availability in 2019 (Mean, SD) ,%**				**Change in mean percent availability (%)**			
	Public Sector		**Private Sector**		**Public Sector**		**Private Sector**		**Public Sector**		**Private Sector**	
	OBs	**LPGs**	**OBs**	**LPGs**	**OBs**	**LPGs**	**OBs**	**LPGs**	**OBs**	**LPGs**	**OBs**	**LPGs**
All medicines (n=50)	6.8 (10.4)	35.1 (23.6)	55 (31.1)	20.3 (14.4)	33.1 (27.8)	9 (14.9)	58.3 (32.3)	32.3 (26)	26.3	-26.1	3.3	12
Global Medicines (n=14)	11.2 (15.2)	50.1 (32.1)	64.3 (22.5)	25.9 (14.5)	48.4 (31.5)	14.3 (19.9)	66.5 (31.2)	43.8 (27.8)	37.2	-35.8	2.2	17.9
Supplementary medicines (n=36)	5 (7.0)	29.2 (21.4)	51.4 (33)	18.1 (14)	27.2 (24.1)	7 (12.1)	55 (32.6)	27.8 (24.1)	22.2	-22.3	3.6	9.7
NEML medicines (n=46)	7.2 (10.7)	35.5 (26)	55.3 (31)	20.7 (14.6)	33.9 (28.1)	8.1 (15.1)	58.4 (32.9)	33.3 (26.3)	26.7	-27	3.1	12.6
Non-NEML medicines (n=4)	1.8 (3.0)	35.5 (34)	51.6 (36)	15.6 (11)	24.8 (25)	19.2 (7)	56.3 (28)	20.3 (21)	23	-16	4.7	4.7

NCD medicines (n=36)	6.4 (9.2)	35.9 (25.5)	55.7 (28.8)	20 (14.3)	33.2 (27)	8.8 (14)	62.3 (29.3)	31.3 (25)	26.8	-27.1	6.6	11.1
ID medicines (n=14)	7.7 (13.3)	33 (29)	53.1 (37.3)	21 (15)	33.1 (30.5)	9.5 (17.4)	47.8 (38.1)	34.8 (29.2)	25.4	-23.5	-5.3	13.8

Availability at different levels of healthcare: When we compared the availability at different levels of public healthcare sectors i.e. primary, secondary and tertiary, the availability of OBs improved in 2019, while it was decreased for LPGs. The pattern of overall medicines availability remained almost the same as of 2017 i.e. tertiary care>secondary care>primary care as shown in table S2.

Medicine Prices

An overall increase was noted in all adjusted MUPs and adjusted MPRs between 2017 and 2019 for both OBs and LPGs as shown in Table 2. In 2019, for all 42 available OBs, the adjusted MUPs and MPRs significantly increased by a median of 4.3% (Wilcoxon test p=0.001, p=0.0001). Whereas in case of all 37 available LPGs, the adjusted MUPs and MPRs were increased by a median of 15.7% (p=0.002, p=0.0002). The MPRs of OBs ranged from 0.58 to 60.62 in 2017 and 0.73 to 77.59 in 2019. 63% of the OBs had MPR of more than 2 in 2017. Whereas, in 2019 almost 75% of the OBs had MPR greater than 2.The MPRs of LPGs ranged from 0.42 to 19.95 in 2017 and 0.39 to 19.89 in 2019. For LPGs in 2017, the median value of MPR was less than 2 (i.e. 1.36) while in 2019 this median value became greater than 2 (i.e. 2.26). Which means many LPGs which were previously affordable got shifted to the high priced medicines category in 2019. The MUPs and MPRs for all OBs is given in table S3 and for all LPGs is given in table S4.

Table 2. Median price ratios (MPRs) and median unit prices (MUPs) of originator brands (OBs) and lowest price generics (LPGs) in private sector among different subgroups across the years 2017 and 2019.

Originator Brands (OBs)					
	MPR-2017	**MPR-2019**	**MUP 2017 (PKR)**	**Adjusted MUP 2019 (PKR)**	**Median percent change in MUPs/MPR**
All medicines (n=42)	2.5	3.2	6.99	8.49	4.29%
Global Medicines (n=13)	2.8	3.2	7.66	8.22	3.35%
Supplementary medicines (n=29)	2.5	3.3	6.38	10.1	5.1%
NEML medicines (n=39)	2.4	3.3	6.38	8.51	5.1%
Non-NEML medicines (n=3)	3	3.2	7.66	8.22	1.93%
NCD medicines (n=36)	2.6	3.3	6.19	7.83	3.35%
CD medicines	2.3	2.9	24.3	31.2	7.36%

(n=10)					
Lowest Price Generics (LPGs)					
	MPR-2017	**MPR-2019**	**MUP 2017 (PKR)**	**Adjusted MUP 2019 (PKR)**	**Median percent change in MPR/MUP**
All medicines (n=37)	1.4	2.3	5.8	6.29	15.7%
Global Medicines (n=13)	1.6	2.7	5.8	6.56	19.2%
Supplementary medicines (n=24)	1.3	2.2	5.9	6.04	14.8%
NEML medicines (n=34)	1.4	2.2	5.4	6	15.8%
Non-NEML medicines (n=3)	2.5	2.7	6.5	6.7	3.97%
NCD medicines (n=26)	1.2	2.2	4.1	5.4	16.3%
CD medicines (n=11)	1.8	2.4	8.4	10.9	14.8%

The price data was also analyzed in different subgroups as shown in table 2. There was an increase in MUPs and MPRs for OBs of supplementary list of medicines compared to medicines from global list (5.5% vs 3.35%). However, it was inverse in case of LPGs, i.e. the prices of global medicines increased compared to supplementary medicines (19.2% vs 14.8%).Increment in prices of NEML medicines was more as compared to non-NEML medicines. Next, we compared medicines used for NCDs and IDs. Data suggested that the increase in the MUPs and MPRs of OBs for IDs was significant in comparison to NCDs (11.2% vs 7.36%). Whereas it was the opposite case for LPGs, where the increase was greater for NCD than ID medicines (16.3% vs 14.8%). It is also noteworthy that increase in prices for LPGs is more significant than OBs for all subgroups of medicines.

Affordability

Between 2017 and 2019, the median NDWs required for treatment with all OBs (n=36) increased from 1.05 to 2 and 0.5 to 0.7 for all LPGs (n=31), respectively. In 2019, the median percent increase in NDWs for LPGs (n=31) was much higher as compared to OBs (n=36) i.e. 12.5% (p=0.008) and 3% (p=0.081) respectively. So, an overall increase in NDWs for both OBs and LPGs was observed between 2017 and 2019. Similarly the Median Treatment Prices (MTPs) for OB and LPGs also increased significantly i.e. 464 PKR to 563 PKR (p<0.001) and 244 PKR to 350 PKR (p<0.001), respectively. The MTPs and NDWs for each medicine are given in tables S5 and S6. The medicines were categorized into seven disease groups to further analyze the changes in affordability between 2017 and 2019. In figure 2, a bar graph shows Median NDWs required for both OBs and LPGs in each disease group and the values above 1 are considered unaffordable. In 2017, the median NDWs of OBs to treat three types of diseases i.e. CVDs (1.2), diabetes (1.4) and ulcers (2.75) were more than 1. Whereas in 2019, medicines for one more

disease category made its place into this list i.e. the medicines for IDs (1.18). Compared to 2017, the median NDWs for all OBs increased in 2019 except for OBs acting on Central Nervous System (CNS) and OBs to treat ulcers. The treatment for ulcer remained highly unaffordable in both years. The median NDWs for LPGs increased in 2019 for the treatment of Arthritis, CNS disorders, CVDs and IDs, while the modest decrease in median NDWs for LPGs was observed for some diseases i.e. asthma, diabetes and ulcers as shown in figure 2.

Discussion

This study gives a conscionable insight in to the effects of NDPP 2018 associated changes on medicine prices, availability and affordability in both public and private healthcare sectors of Lahore division, Pakistan. The main objective of this refined policy was to improve the access to essential medicines (EMs) and improvise rational drug pricing. Our study has shown that the overall availability of medicines improved in 2019 in comparison to 2017 i.e. before the implementation of this policy, except for the LPGs in public sector, demonstrating reduction. Overall the medicine prices were increased significantly, making majority of the EMs used for the common ailments unaffordable, with much higher price increases for LPGs in comparison to OBs. The medicines used to treat ulcer, diabetes and CVDs remained most unaffordable in both years. Thus, it can fairly be assumed that the current pricing policy, to some extent, ensures the availability of medicines, nonetheless, significant policy refinements targeting essential medicines are pivotal to make medicine prices affordable to patients. Although, this study provides an objective evidence to the policy makers for improving the current pricing policies. Our study has some limitations as well. The study includes medicines with specific strengths and dosage forms to compare with IRPs. There might be other strengths/dosage forms of the surveyed medicines, available in the health facilities, so the availability of the medicines may be under estimated. Moreover, the affordability was calculated for single medicine for each disease, whereas patients are usually taking more than one drug at a time – under-estimating the extent of affordability of a specific treatment for a specific disease.

Despite improvements in the availability of medicines between 2017 and 2019, the availability of medicine remained below the optimal benchmark of 80% [13]. In public sector the availability of OBs improved remarkably probably be due to decentralization procurement of medicines in public sector. Before 2018, the medicines were procured centrally for all the public sector hospitals except for teaching hospitals, within a province. But after 2018, the medicines procurement was decentralized for public sector hospital to allow hospitals in each district a free choice to select desired manufactures, thus, ending up in the selection of more OBs than LPGs, possibly due to quality concerns about medicines. Another factor that improved medicines availability after 2018 was authorization of hospitals to acquire medicines directly without any delays. However, as practiced in the previous central supply system, the medicines were received centrally from the manufacturers before reaching the concerned hospital with considerable effect on timely availability of medicines. In both years, the mean percentage availabilities for all medicines were found higher in the private sector compared to the public sector, corroborating similar previous studies conducted in Bangladesh and Malawi in 2019 [21, 22]. The overall

availability of medicines from NEML was slightly better than non-NEML medicines in both public and private sectors. This might be attributed to the active role of DRAP in the revision and subsequent dissemination of the revised NEML i.e. NEML 2018 [15]. Furthermore, the public hospitals are encouraged to procure drugs from the latest NEML 2018 that has been standardized in line with WHO essential medicines model list 2017 [23]. Besides, a mobile application was launched in 2018 with user friendly interface to better disseminate the information on enlisted medicines [24]. So, the NDPP 2018, doesn't seem to be solely responsible for the availability of medicines.

Although we found some improvements in the availability of medicines, there was a substantial increase in medicine prices, making them inaccessible for most of the population. According to one estimate approximately 46 million people are living below the national poverty line in Pakistan (as per 2015) [8]. The increases in prices of both OBs and LPGs may fairly be attributable to the NDPP 2018, that allows an annual increase in the prices of scheduled drugs up to 70% of CPI compared to 50% of CPI as per NDPP 2015 [9, 10]. These changes in price calculations seems to accentuate the substantial impact on overall prices of medicines, thus, making them more expensive. The increase in LPGs prices were more significant as compared to OBs suggesting that with already expensive OBs, the price increase in LPGs would impoverish the overall access to medicines, imputable to the changes in formula for LPGs (new entrants) price calculation. According to NDPP 2018, the MRP of new entrant first generic should be fixed at 20% less than that of OB compared with 30% less than MRP of OB as per NDPP 2015. Another possible variable is the prior availability of generics in the market for price calculation, where, according to NDPP2018, the MRP of a new entrant (LPGs) was fixed equal to the highest MRP of the available generics in the market, while as per NDPP2015 practice, MRP was fixed by taking the average of other generics in the market. Therefore, these changes in price calculating mechanisms might have led to higher prices of many new LPGs in the market. Hence, contrary to NDPP 2018's price steerage objectives, the increase in medicine prices was more distinct for NEML medicines as compared to non-NEML medicines.

Data from further analysis on affordability of standard treatment by selected OBs and LPGs suggested that majority of the medicines have become more unaffordable in 2019. When the affordability was compared for medicines of different disease groups, the three top most unaffordable OBs were found for the treatment of ulcers, diabetes and CVDs. Additionally, the treatment for ulcers remained awfully unaffordable with OBs and LPGs in both years. Nevertheless, the treatment of CVDs and diabetes with LPGs remained affordable in 2017 but the NDWs for CVDs surpassed affordability threshold in 2019. Among the disease categories, NCDs harbor the top three unaffordable slots. It is noteworthy, that the burden of NCDs is increasing worldwide and is responsible for higher mortality rates than all other diseases combined [25-27]. The CVDs, diabetes, cancer and chronic respiratory diseases are responsible for about 80% of these deaths [28]. Pakistan is among top 10 countries where prevalence of diabetes is very high. Besides, one third of Pakistanis, above 45 years of age have hypertension [29-31]. Thus, the unaffordability of the essential medicines for NCDs, such as CVDs and diabetes, has worse bearing on affordability associated therapeutic outcomes that ultimately leads to increased morbidity and mortality due to un-controlled disease.

Additionally, we also compared the median drug prices in 2019 with the prices published/allowed by DRAP in its latest Statutory Regulatory Orders (SROs). DRAP revised and published the maximum retail prices (MRPs) of about 1084 drugs on December 31, 2018 through SRO-1608, SRO-1609 and SRO-1610 [32]. Eighteen OBs from our study sample were part of these price revisions (table 3). Surprisingly, after comparing the MUPs of 18 selected OBs with prices allowed by the government, we found that most of the OBs, 14 out of 18, were sold at higher prices than the allowable prices – with median percent increase of 29.37%. These data suggested that these intentional malpractices by the drug sellers might be driven by poor price control regulation by price enforcement authorities. Therefore, the current drug pricing policy NDPP 2018, is not the sole reason of price hike, probably main stakeholders in drug supply chain are also contributing towards medicine inflated prices. Thus, it's reasonable to deduce that these factors may interfere with measuring the direct impact of current pricing policy.

Table 3. Maximum retail unit prices (MRPs) of Originator Brands (OBs) allowed by the government versus median unit prices (MUPs) found in private sector pharmacies.

Medicine Name	Strength (Dosage form)	Allowed Unit Price (PKR)	MUP 2019 (PKR)	Percentage difference
Aciclovir	200mg (tab)	52.6	75	42.5%
Amlodipine	5mg (tab)	8.5	13	52.9%
Amoxicillin	250mg (cap)	3.75	3.75	0%
Amoxicillin	500mg (cap)	5.58	8.75	56.8%
Atorvastatin	20mg (cap)	141.37	203.5	43.9%
Bisoprolol	5mg (tab)	15.35	16.72	8.9%
Carbamezipine	200mg (tab)	4	5	25%
Ceftriaxone	1g (inj)	783	783	0%
Ciprofloxacin	500mg (tab)	39.25	52.5	33.7%
Digoxin	0.25mg (tab)	1.75	2.68	53.1%
Fluconazole	200mg (cap)	425	585	37.6%
Insulin N	100IU (vial)	88.47	75.88	-14.2%
Insulin R	100IU (vial)	93.88	75.88	-19.1%
Methyldopa	250mg (tab)	7.71	8.1	5.05%
Omeprazole	20mg (cap)	42.9	52.29	21.8%
Propranolol	40mg (tab)	1.1	3.16	187.2%
Pyremethamine+Sulfadoxime	(25+500)mg (tab)	12.01	12.02	0.08%
Simvastatin	20mg (cap)	47.01	68	44.6%
Medians		27.3	34.505	29.3%

There could be many policy implications having an impact on drug pricing, availability and affordability. The procurement of medicines should be strictly based on the NEML. Clear cut mechanism for NEML based procurement should be devised and implemented specially in the

public sector hospitals. Besides this, the hospital pharmacy and therapeutics committees must actively evaluate the safety, efficacy and cost-effectiveness of drugs before purchasing. Pharmaco-economic evaluations of drugs must be promoted by allocating research funds to experts. Not all drugs should be fully reimbursed in the hospitals, only essential medicines must be included in this list. So, the profits from other drugs can be used to purchase essential drugs when needed. Smooth functioning of the drug supply chain with proper quality control must be ensured. The current inflated prices would have a grave impact on the access to essential medicines, especially for the lower and middle income population in Pakistan. Thus, there is dire need to develop more clear, evidence based and stringent price control policy, especially for essential medicines. Exempting or reducing taxes and tariffs on EMs and promotion of local generic manufacture by providing subsidies on raw materials may improve both the availability and affordability of these medicines. While using the External Reference Pricing (ERP) mechanism, the reference countries should be chosen critically e.g. countries with similar pharmaceutical market and economic status. For costly medicines, regressive markups must be encouraged over progressive markups. The drug prices must be monitored on regular basis using a validated and well-designed scientific methodology and pricing policy must be revised based on such evidences. The essential medicines for most prevalent diseases such as diabetes and CVDs must be preferentially made affordable by devising some specific pricing strategies for these medicines. Besides, efforts must be made to enforce the pricing policy effectively by introducing reward and punishment system to induce a healthy competition among the drug manufacturers and sellers.

In Conclusion, the availability of medicines has been improved after the launch of a new drug pricing policy by Pakistani government but it is still poor, forcing the patients to buy medicines from private sector at their own expense. The prices of both LPGs and OBs of EMs have increased remarkably in 2019, when compared with 2017. The medicines to treat most prevalent non-communicable diseases (diabetes and CVDs) have become more expensive and unaffordable. The maximum retail prices of several originator brands have been illegally increased in the market, adding more burden on patients' pockets. The pricing policy needs to be improved further to bring a strict price control, especially on the EMs and on the medicines for most prevalent diseases.

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Contributions

AS, ZB and YF conceptualize the study. ZA, HS, AS and ZB designed methodology. ZS, HS, AS trained the data collectors and obtained the data. YF provided resources and supervised the project. ZS worked as survey area manager. MA, AH, NA, FK and MZ did data cleaning, validation and entry. AS, HS, CY, MJ analyzed the data. AS and HS wrote original draft. YF, ZB, ZS, CY and MJ, WJ reviewed and edited the manuscript.

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Competing Interests

None

Patient Consent for Publication

Not Required

Ethics Approval

Ethics approval was obtained from the Medical Ethics Committee of Xi'an Jiaotong University under study ID 2019-067.

Data availability statement

Data are available on reasonable request.

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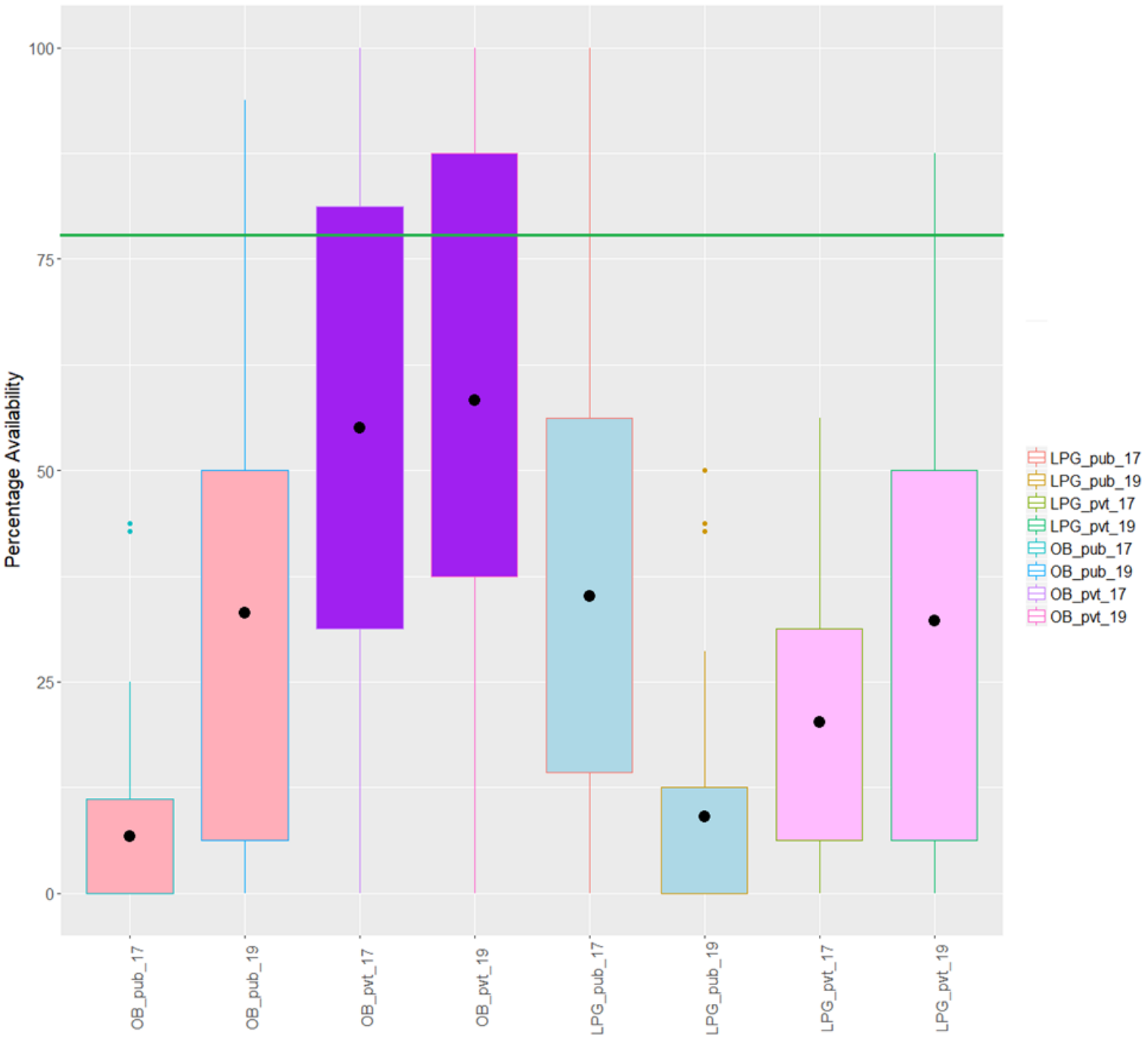
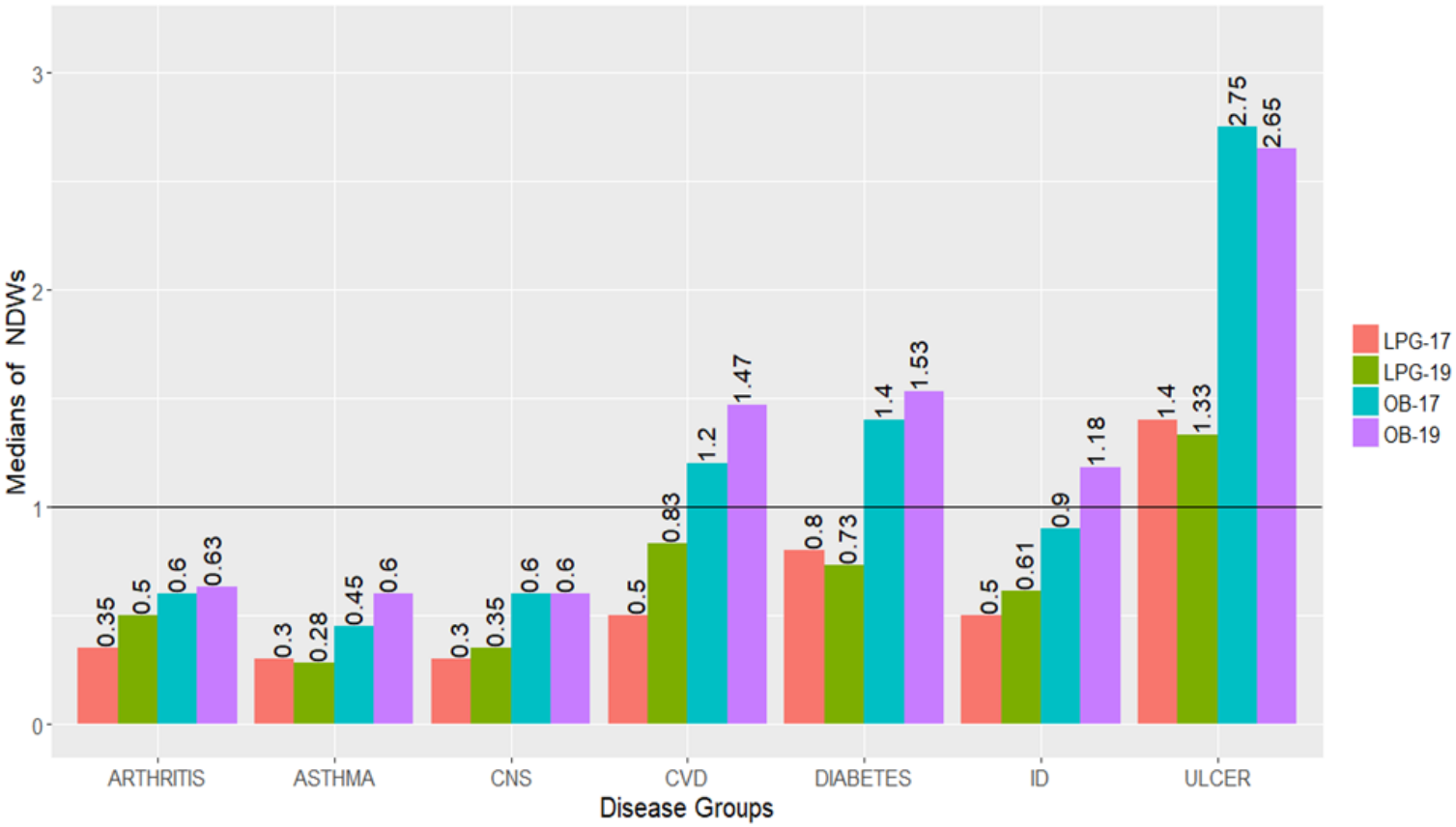
Figure 1. Box plot of percent availability of lowest price generics (LPGs) and originator brands (OBs) in both public (pub) and private (pvt) sectors in 2017 and 2019. This box plot shows the distributional characteristics of the percent availability of medicines in two groups (OB and LPG) for the years 2017 and 2019. The mean percent availability is represented by the dot inside the box.

Figure 2. Bar graph of affordability of originator brands (OBs) and lowest price generics (LPGs) for different diseases in both years i.e. 2017 and 2019.





Supplementary Tables

Table S1. Percent availabilities and of originator brands (OBs) and lowest price generics (LPGs) of all medicines in public and private sector in 2017 and 2019 (%)

Names of meds	OB (Public) 2017	OB (Pvt.) 2017	LPG (Public) 2017	LPG (Pvt.) 2017	OB (Public) 2019	OB (Pvt) 2019	LPG (Public) 2019	LPG (pvt.) 2019
Acetylsalicylic Acid	0.0	25.0	56.3	25.0	18.8	75.0	50.0	18.8
Aciclovir	0.0	50.0	25.0	37.5	6.3	18.8	0.0	50.0
Amiodarone	7.1	62.5	21.4	6.3	0.0	62.5	21.4	0.0
Amitriptyline	0.0	31.3	0.0	25.0	0.0	0.0	50.0	50.0
Amlodipine	6.3	75.0	62.5	31.3	37.5	93.8	12.5	56.3
Amoxicillin	43.8	93.8	18.8	25.0	93.8	68.8	0.0	37.5
Amoxicillin (250)	18.8	100.0	12.5	31.3	50.0	87.5	0.0	37.5
Atenolol	12.5	87.5	81.3	43.8	43.8	81.3	0.0	56.3
Atorvastatin	7.1	50.0	21.4	25.0	42.9	62.5	21.4	18.8
Azithromycin	0.0	25.0	25.0	31.3	31.3	25.0	25.0	75.0
Beclometasone inhaler	0.0	6.3	35.7	12.5	35.7	43.8	0.0	0.0
Bisoprolol	6.3	87.5	18.8	25.0	37.5	81.3	0.0	56.3
Captopril	0.0	81.3	85.7	25.0	50.0	93.8	28.6	50.0
Carbamazepine	12.5	87.5	56.3	25.0	25.0	31.3	0.0	56.3
Ceftriaxone injection	14.3	68.8	71.4	31.3	21.4	75.0	50.0	87.5
Ciprofloxacin	0.0	81.3	100.0	37.5	64.3	93.8	14.3	25.0
Clarithromycin	0.0	87.5	35.7	25.0	50.0	93.8	0.0	56.3
Co-trimoxazole suspension	6.3	31.3	62.5	6.3	6.3	6.3	43.8	6.3
Diazepam	6.3	62.5	12.5	0.0	43.8	68.8	0.0	0.0
Diclofenac	42.9	50.0	35.7	6.3	85.7	93.8	0.0	81.3
Digoxin	21.4	62.5	28.6	0.0	28.6	68.8	0.0	56.3
Enalapril	0.0	68.8	62.5	18.8	12.5	68.8	12.5	50.0
Fluconazole	0.0	37.5	18.8	25.0	43.8	43.8	0.0	50.0
Fluoxetine	0.0	43.8	12.5	43.8	6.3	62.5	6.3	62.5
Fluphenazine Decanoate	0.0	0.0	0.0	12.5	0.0	0.0	7.1	6.3
Furosemide	12.5	93.8	50.0	6.3	50.0	87.5	0.0	0.0
Glibenclamide	18.8	68.8	56.3	12.5	68.8	93.8	0.0	12.5
Gliclazide	0.0	75.0	0.0	18.8	7.1	75.0	0.0	31.3
Hydrochlorothiazide	0.0	0.0	0.0	12.5	18.8	0.0	0.0	0.0
Indinavir	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Insulin Isophane (NPH)	0.0	75.0	50.0	25.0	56.3	68.8	0.0	18.8
Insulin Neutral Soluble (Regular)	0.0	68.8	50.0	25.0	68.8	68.8	0.0	18.8
Losartan	7.1	43.8	14.3	43.8	0.0	43.8	42.9	43.8
Lovastatin	0.0	0.0	6.3	0.0	6.3	37.5	12.5	0.0

Metformin	25.0	81.3	56.3	31.3	68.8	93.8	0.0	50.0
Methyldopa	12.5	81.3	25.0	0.0	75.0	68.8	0.0	0.0
Metronidazole	25.0	93.8	56.3	37.5	75.0	87.5	0.0	56.3
Nevirapine	0.0	0.0	14.3	0.0	0.0	0.0	0.0	0.0
Nifedipine Retard	0.0	75.0	28.6	12.5	0.0	31.3	14.3	12.5
Omeprazole	6.3	56.3	75.0	37.5	62.5	62.5	6.3	50.0
Omeprazole (10)	0.0	12.5	43.8	18.8	18.8	0.0	12.5	31.3
Paracetamol suspension	6.3	68.8	87.5	25.0	81.3	87.5	0.0	81.3
Phenytoin	0.0	6.3	12.5	6.3	0.0	50.0	6.3	0.0
Propranolol	12.5	68.8	12.5	6.3	18.8	87.5	0.0	25.0
Pyrimethamine with sulfadoxine	0.0	75.0	21.4	6.3	21.4	68.8	0.0	6.3
Ranitidine	0.0	81.3	31.3	25.0	50.0	100.0	0.0	50.0
Salbutamol inhaler	0.0	81.3	56.3	31.3	62.5	68.8	0.0	12.5
Simvastatin	0.0	25.0	21.4	56.3	0.0	37.5	7.1	25.0
Spironolactone	6.3	62.5	25.0	0.0	12.5	93.8	6.3	43.8
Zidovudine	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Mean availabilities	6.8	55.0	35.1	20.3	33.1	58.3	9.0	32.3

Table (S2). Change in availability at different levels of healthcare (Public Sector).

	Primary level (n=2 outlets)		**Secondary level (n=13 outlets)**		**Tertiary level (n=1 outlet)**	
	All medicines (n=50)		**All medicines (n=50)**		**All medicines (n=50)**	
	OB	**LPG**	**OB**	**LPG**	**OB**	**LPG**
Mean Availability 2017 (SD),%	0.0 (0.0)	25.8 (44.5)	7.1 (11.2)	35.2 (27.5)	12.0 (32.8)	50.0 (50.5)
Mean Availability 2019 (SD) ,%	21.0 (31.0)	3.2 (18)	32.3 (29.1)	7.4 (13.4)	68.0 (47.1)	22.0 (41.8)
Change in mean percent availability,%	21.0	-22.6	25.2	-27.8	56.0	-28.0

Table S3. Change in median unit prices (MUPs) and median price ratios (MPRs) of the Originator Brands (OBs) at private sector.

Sr. no.	Medicines (OB)	MUPs 2017 (PKR)	MPR 2017	Adjusted MUP in 2019	MPR 2019	Percentage change in MUPs/MPRs
1	Acetylsalicylic Acid	1.16	0.8	1.12	0.7	-3.41%
2	Aciclovir	70	20	72.5	21	3.48%
3	Amiodarone	17.78	2.2	17.4	2.2	-2.15%
4	Amlodipine	11.93	7.3	12.6	7.7	5.1%
5	Amoxicillin	8.616	2.8	8.46	2.7	-1.83%
6	Amoxicillin (250)	3.56	2.1	3.63	2.2	1.83%
7	Atenolol	6.19	5.6	6.14	5.5	-0.81%
8	Atorvastatin	201.9	18	197	18	-2.6%
9	Azithromycin	40	1.7	118	5	66.2%
10	Beclometasone inhaler	1.25	1.2	1.84	1.8	32%
11	Bisoprolol	11.28	1.2	16.2	1.7	30.2%
12	Captopril	7.66	3	8.22	3.2	6.81%
13	Carbamazepine	4.91	2.6	4.84	2.5	-1.55%
14	Ceftriaxone injection	672	16	757	18	11.2%
15	Ciprofloxacin	50.4	13	50.8	13	0.72%
16	Clarithromycin	65.7	2.5	76.4	2.9	14%
17	Co-trimoxazole suspension	0.29	0.6	0.44	0.9	33.4%
18	Diazepam	2	2	1.93	1.9	-3.41%
19	Diclofenac	5.625	12	5.61	12	-0.29%
20	Digoxin	2.52	2.4	2.59	2.5	2.76%
21	Enalapril	5.85	5.4	6	5.6	2.43%
22	Fluconazole	442	61	566	78	21.9%
23	Fluoxetine	43.42	9.7	43	9.6	-0.9%
24	Furosemide	1.89	3	2.34	3.7	19.2%
25	Glibenclamide	1.69	2.9	2.09	3.5	19.1%
26	Gliclazide	7.6	1.5	16.4	3.3	53.8%
27	Insulin Isophane (NPH)	64.5	1.1	73.4	1.3	12.1%
28	Insulin Neutral Soluble (Regular)	64.5	1.1	73.4	1.2	12.1%
29	Losartan	51.67	4.3	50.3	4.2	-2.76%
30	Metformin	1.54	1	1.62	1	5.21%
31	Methyldopa	6.38	1.9	7.83	2.3	18.5%
32	Metronidazole	1.57	1.3	1.52	1.2	-3.41%
33	Nifedipine Retard	5.69	2.7	5.8	2.8	1.93%
34	Omeprazole	49.78	34	50.6	35	1.55%
35	Paracetamol suspension	0.85	1.6	2.2	4.1	61.4%
36	Phenytoin	5.2	4.8	23.2	22	77.6%
37	Propranolol	1.55	2.2	3.06	4.3	49.3%

38	Pyrimethamine with sulfadoxine	5.83	1.4	11.6	2.8	49.8%
39	Ranitidine	8.8	3.7	8.51	3.6	-3.41%
40	Salbutamol inhaler	1	1	1.03	1.1	3.35%
41	Simvastatin	67.13	12	65.8	12	-2.09%
42	Spironolactone	8.6	0.8	10.1	1	14.5%
Medians		6.99	2.5	8.49	3.2	4.29%

Table S4. Change in median unit prices (MUPs) and median price ratios (MPRs) of the lowest price generics (LPGs) in private sector.

Sr. no.	**Medicines**	**MUPs 2017 (PKR)**	**MPR 2017**	**Adjusted MUP in 2019**	**MPR 2019**	**Percentage change in MUPs/ MPRs**
1	Acetylsalicylic Acid	1.015	0.7	1.06	0.7	4.58
2	Aciclovir	12.4	3.6	13.5	3.9	8.41
3	Amitriptyline	1.19	1.4	1.24	1.4	3.86
4	Amlodipine	1.8	1.1	6.29	3.8	71.4
5	Amoxicillin	5.8	1.9	8.32	2.7	30.3
6	Amoxicillin (250)	3	1.8	3.48	2.1	13.8
7	Atenolol	2.05	1.8	2.47	2.2	16.9
8	Atorvastatin	37.5	3.4	35.8	3.2	-4.8
9	Azithromycin	40	1.7	19.3	0.8	-107
10	Bisoprolol	6.55	0.7	6.56	0.7	0.1
11	Captopril	6.5	2.5	6.77	2.7	3.97
12	Carbamazepine	3.3	1.7	4.35	2.3	24.2
13	Ceftriaxone injection	280	6.8	290	7	3.48
14	Ciprofloxacin	11	2.8	24.2	6.2	54.5
15	Clarithromycin	36	1.4	42.7	1.6	15.8
16	Co-trimoxazole suspension	0.21	0.4	2.32	4.7	91
17	Diclofenac	3.5	7.5	4.79	10	26.9
18	Enalapril	2.05	1.9	2.84	2.6	27.8
19	Fluconazole	145.5	20	145	20	-0.3
20	Fluoxetine	13.8	3.1	13.5	3	-1.9
21	Fluphenazine Decanoate	90.5	1	93.8	1.1	3.5
22	Glibenclamide	1.57	2.7	1.42	2.4	-10
23	Gliclazide	4.75	0.9	5.8	1.1	18.1

24	Insulin Isophane (NPH)	48	0.8	62.3	1.1	22.9
25	Insulin Neutral Soluble (Regular)	48	0.8	62.3	1	22.9
26	Losartan	11	0.9	13.1	1.1	15.7
27	Metformin	1.5	1	1.86	1.2	19.2
28	Metronidazole	1.5	1.2	1.93	1.6	22.4
29	Nifedipine Retard	2.65	1.3	5.14	2.4	48.4
30	Omeprazole	15.35	10	11.4	7.8	-35
31	Omeprazole (10)	12.14	0.9	5.13	0.4	-137
32	Paracetamol suspension	0.47	0.9	1.02	1.9	53.7
33	Propranolol	0.66	0.9	2.03	2.8	67.5
34	Pyrimethamine with sulfadoxine	5	1.2	4.84	1.2	-3.4
35	Ranitidine	6.93	2.9	7.78	3.3	11
36	Salbutamol inhaler	0.64	0.7	0.68	0.7	5.45
37	Simvastatin	8.5	1.6	16.6	3	48.7
	Medians	**5.8**	**1.4**	**6.29**	**2.3**	**15.7**

Table S5. Affordability of originator brands (OBs) for different diseases in 2017 and 2019, in private sector.

Disease	Medicine	Strength	Dosage form	No. of units needed per treatment	Duration of treatment	MTP 2017 (PKR)	NDWs 2017	MTP 2019 (PKR)	NDWs 2019
ASTHMA	Salbutamol Inhaler	100mcg/ dose	Inhaler	200	As needed	200	0.4	214	0.4
	Beclomethasone	50mcg/dose	inhaler	200	As needed	250	0.5	380	0.8
Cardiovascular Diseases	Bisoprolol	5mg	tab	60	30	676.8	1.5	1003	2
	Atenolol	50mg	tab	30	30	185.7	0.4	190.5	0.4
	Captopril	25mg	tab	60	30	459.6	1	510	1
	Amlodipine	5mg	tab	60	30	715.8	1.5	780	1.6
	Amiodarone	200mg	tab	60	30	1066.8	2.3	1080	2.2
	Losartan	50mg	tab	60	30	3100.2	6.6	3120	6.2
	methyldopa	250mg	tab	90	30	574.2	1.2	729	1.5
	Nifedipine retard	20mg	tab	90	30	512.1	1.1	540	1.1

	Spironolactone	100mg	tab	30	30	258	0.5	312	0.6
	Propranolol	40mg	tab	90	30	139.5	0.3	284.4	0.6
	Acetylsalicylic acid	75mg	tab	30	30	34.8	0.1	34.8	0.1
Anti hyperlipidemics	Simvastatin	20mg	Cap/tab	30	30	2013.9	4.3	2040	4.1
	Atorvastatin	20mg	Cap/tab	30	30	6057	13	6105	12
Infections-Adult respiratory tract infection	Ceftriaxone Injection	1g/vial	Inj.	1	1	672	1.4	783	1.6
	Ciprofloxacin	500mg	tab	14	7	705.6	1.5	735	1.5
	Azithromycin	500mg	tab	3	3	120	0.3	367	0.7
	clarithromycin	500mg	tab	28	14	1839.6	3.9	2212	4.4
	Amoxicillin	500mg	cap	42	14	361.87	0.8	367.5	0.7
	Amoxicillin	250mg	cap	84	14	299.04	0.6	315	0.6
Fungal Infection	Fluconazole	200mg	cap	1	1	442	0.9	585	1.2
Viral Infection	aciclovir	200mg	tab	25	5	1750	3.8	1875	3.8
Amoebiasis	metronidazole	400mg	tab	21	7	32.97	0.1	32.97	0.1
CNS Drugs-Anti epileptics	Carbamezipine	200mg	tab	60	30	294.6	0.6	300	0.6
	Phenytoin	100mg	tab	90	30	468	1	2160	4.3
Anxiety	diazepam	5mg	tab	90	30	180	0.4	180	0.4
Anti Diabetics	Metformin	500mg	tab	90	30	138.6	0.3	151.2	0.3
	Glibenclamide	5mg	tab	90	30	152	0.3	194.4	0.4
	Gliclazide	80mg	tab	60	30	456	1.5	1020	2
	Insulin Isophane (NPH)	100IU/ml	vial	10	30	645	1.4	758.8	1.5
	Insulin Neutral Soluble (Regular)	100IU/ml	vial	10	30	645	1.4	758.8	1.5
Ulcer Treatment	Omeprazole	20mg	cap	30	30	1493.4	3.2	1569	3.1
	ranitidine	150mg	tab	120	30	1056	2.3	1056	2.1
Pain/Inflammation	Paracetamol	24mg/ml	susp	45	3	38.25	0.1	102.6	0.2
Arthritis	Diclofenac	50mg	tab	90	30	506.25	1.1	522	1

Where, MTP: Median treatment price, NDWs: Number of days' wages

Table S6. Affordability of lowest price generics (LPGs) for different diseases in 2017 and 2019, in private sector.

Disease/Condition	Medicine	Strength	Dosage form	No. of units needed per treatment	Duration of treatment	MTP 2017 (PKR)	NDWs 2017	MTP 2019 (PKR)	NDWs 2019
ASTHMA	Salbutamol Inhaler	100mcg/dose	Inhaler	200	As needed	128	0.3	140	0.3
Cardiovascular Diseases/ Anti Hypertensives	Bisoprolol	5mg	tab	60	30	393	0.8	406.8	0.8
	Atenolol	50mg	tab	30	30	61.5	0.1	76.5	0.2
	Captopril	25mg	tab	60	30	390	0.8	420	0.8
	Amlodipine	5mg	tab	60	30	108	0.2	390	0.8
	Losartan	50mg	tab	60	30	660	1.4	810	1.6
	Nifedipine retard	20mg	tab	90	30	238.5	0.5	478.4	1
	Propranolol	40mg	tab	90	30	59.4	0.1	189	0.4
	Acetylsalicylic acid	75mg	tab	30	30	30.45	0.1	33	0.1
Anti hyperlipidemics	Simvastatin	20mg	Cap/tab	30	30	255	0.5	513.8	1
	Atorvastatin	20mg	Cap/tab	30	30	1125	2.4	1110	2.2
Infections- Adult respiratory tract infection	Ceftriaxone Injection	1g/vial	Inj.	1	1	280	0.6	300	0.6
	Ciprofloxacin	500mg	tab	14	7	154	0.3	350	0.7
	Azithromycin	500mg	tab	3	3	120	0.3	60	0.1
	clarithromycin	500mg	tab	28	14	1008	2.2	1238	2.5
	Amoxicillin	500mg	cap	42	14	243.6	0.5	361.2	0.7
	Amoxicillin	250mg	cap	84	14	252	0.5	302.4	0.6
Fungal Infection	Fluconazole	200mg	cap	1	1	145.5	0.3	150	0.3
Viral Infection	aciclovir	200mg	tab	25	5	310	0.7	350	0.7
Amoebiasis	metronidazole	400mg	tab	21	7	31.5	0.1	42	0.1
CNS Drugs- Anti epileptics	Carbamezipine	200mg	tab	60	30	198	0.4	270	0.5
Depression	Amitriptyline	25mg	tab	60	30	71.4	0.2	76.8	0.2

Anti Diabetics	Metformin	500mg	tab	90	30	135	0.3	180	0.4
	Glibenclamide	5mg	tab	90	30	141	0	132.3	0.3
	Gliclazide	80mg	tab	60	30	285	0.8	360	0.7
	Insulin Isophane (NPH)	100IU/ml	vial	10	30	480	1	644	1.3
	Insulin Neutral Soluble (Regular)	100IU/ml	vial	10	30	480	1	644	1.3
Ulcer Treatment	Omeprazole	20mg	cap	30	30	460.5	1	353.7	0.7
	ranitidine	150mg	tab	120	30	831.6	1.8	966	1.9
Pain/Inflammation	Paracetamol	24mg/ml	susp	45	3	21.15	0	47.25	0.1
Arthritis	Diclofenac	50mg	tab	90	30	315	0.7	445.5	0.9

Research Checklist

Dear editor,

We submit the manuscript entitled **"Impact of National Drug Pricing Policy 2018 on Access to Medicines in Lahore Division, Pakistan: A Pre-Post Survey Study Using WHO/HAI Methodology"**, for your consideration to be published in ***BMJ Open.*** And we confirm that we have prepared submission materials according to the guideline.

And our main document has covered everything required, which including the following:

Title page

Abstract

Introduction

Methods

Results

Discussion

Other Information

Funding

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Contributorship Statement

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Impact of National Drug Pricing Policy 2018 on Access to Medicines in Lahore Division, Pakistan: A Pre-Post Survey Study Using WHO/HAI Methodology

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Abstract

Objective: To evaluate the impact of new national drug pricing policy (NDPP) 2018 on access to medicines in terms of prices, availability and affordability.

Design: Two cross-sectional surveys were undertaken before and after the launch of NDPP 2018, using a modified WHO/HAI methodology.

Setting: Four districts of Lahore division, Pakistan.

Participants: 16 public sector hospitals and 16 private sector retail pharmacies.

Measures: The pre and post survey data on prices and availability of Lowest Price Generics (LPGs) and Originator Brands (OBs) of 50 medicines were obtained by visiting the same public and private sector health facilities (n=32). 46 out of 50 surveyed medicines were from National Essential Medicines List (NEML). Inflation-adjusted median unit prices (MUPs) and median price ratios (MPRs) from 2019 were used for price comparison. Affordability was calculated in terms of number of days' wages required to get a standard treatment by the lowest paid unskilled government worker.

Results: The overall mean percent availabilities remained poor in both years i.e. far less than 80%. In public sector, the mean percent availability of OBs improved from 6.8% to 33.1% whereas, in case of LPGs it was reduced from 35.1% to 9%. In private sector, the mean percent availability of both OBs and LPGs demonstrated slight improvements in 2019 i.e. 55.0% to 58.3% and 20.3% to 32.3%. The adjusted MUPs and MPRs of OBs significantly increased by a median of 4.29% (Wilcoxon test p=0.001, p=0.0001). Whereas, the adjusted MUPs and MPRs of LPGs were increased by a median of 15.7% (p=0.002, p=0.0002). Overall the affordability of many medicines for common ailments reduced significantly in 2019.

Conclusions: The availability of medicines slightly improved, except in the case of LPGs which was reduced at public sector. Although the main aim of NDPP 2018 was to make the drugs affordable, but its implementation led to increased drug prices thereby making standard treatment for some of the most prevalent ailments, unaffordable. This policy needs to be improved further to have strict price control especially for essential medicines, in order to improve their access.

Strengths

- This is the first study of its kind from Pakistan, where pre-post surveys were conducted and analyzed to estimate the impact of a national drug pricing policy, using the WHO/HAI methodology.
- The data was collected from the same health facilities in both years. So, the comparison is reliable. This study provides an objective evidence to the policy makers for improving the current pricing policies.

Limitations

- The study is limited to only one division of Pakistan, although the medicine prices are fixed centrally and are supposed to be same across the country – affecting generalizability of the findings.
- Moreover, this study is conducted after about a year from the launch of new drug pricing policy 2018, so the results do not reflect the long term impact of the policy.

Introduction

Access to affordable and quality assured essential medicines is considered as a key component of an effective healthcare system. It has also been pledged under Sustainable Development Goal (SDG) 3 by United Nations (UN) that the equitable access to affordable essential medicines will be ensured as a basic human right [1, 2]. Pakistani government, like many other Low and Middle Income Countries (LMICs), has been grappling with the issue of high medicine prices and poor availability of medicines that compromises the accessibility of medicines [1, 3-6]. The medicines are provided free of cost at public sector health facilities, while patient pays out of pocket to get medicines from private sector, in Pakistan [5]. In fact, the poor availability of medicines at public sector compels the patients to buy medicines from the private sector that escalates the burden on patient's pocket, as 24.3% (in 2015) of the population is living below the national poverty line [3, 4, 7, 8]. Besides, medicine prices have increased up to 100%, both legally or illegally, in the past few years [3]. The drug prices are fixed by the federal government and the National Health Services Regulation and Coordination (NHSRC). The regional drug inspectors (DIs) are responsible for monitoring of drug prices in the pharmacies of their area. The NHSRC has been taking different policy measures to curb these issues through Drug Regulatory Authority of Pakistan (DRAP). The first ever National Drug Pricing Policy (NDPP) was launched in 2015 for making the pricing mechanism transparent but it had minimal impact on medicine prices, suitable for both patients and manufacturers as per media reports and available literature evidences [3, 9]. So, a new drug pricing policy was launched in 2018[10]. The objectives of this policy were to improve the access to essential medicines, devise rational prices, ensure a transparent mechanism for medicine pricing and to discourage illegal increase in drug prices.

Many modifications have been made to the pricing strategies in the NDPP 2018 compared to NDPP 2015, the most important one is the inclusion of all drugs (n=414) from National Essential Medicines List (NEML) under scheduled drugs category where drugs are kept under strict price control as compared to other drugs. Whereas in NDPP 2015, only 160 drugs from NEML were enlisted in this category [9, 10]. In NDPP 2018, the annual adjustment in prices has been linked with the Consumer Price Index (CPI), the Maximum Retail Prices (MRPs) of scheduled drugs (all drugs from NEML) could be increased up to 70% of the CPI, whereas the MRPs of all other drugs could be increased equivalent to CPI of the immediate preceding year. This step seems to improve the affordability of essential medicines (EMs) for patients in Pakistan. If several generics are already available in the market then in NDPP 2015, the MRP of new entrant was fixed by taking the average of other generics, while in NDPP 2018, MRP will be fixed equivalent to the highest MRP of the available generics [9, 10]. However, this would lead to even higher priced generics in the market that could compromise patient's affordability. Some media reports are claiming that the current increase (up to 200%) in medicines prices is the highest in the last 40 years, while others are claiming that government is taking action against this illegal rise in medicine prices [11, 12]. But there is no objective evidence to prove or disapprove these claims. The NDPP 2018, allows the MRPs of the New Chemical Entities (NCEs) to be fixed by using the External Reference Pricing (ERP) mechanism by considering India, Bangladesh, Indonesia, Sri Lanka, Philippines, Lebanon and Malaysia as reference countries. However, the reason behind using the MRPs of these countries as reference is not clear, though some of them practice free market economy model

and don't impose any price control measures over the MRPs in community pharmacies that may lead to high prices. The NDPP 2018 also takes into account the wholesale or procurement prices from British National Formulary, Australian Pharmaceutical Benefit Scheme and New Zealand Pharmaceutical Management Agency while fixing the MRPs of NCEs, however these may not be the true prices because discounts and rebates are given as a common practice, while making the payments. So, these ambiguities in the policy necessitate the evaluation of actual impact of these policies on the access to medicines in Pakistan.

In this context, we designed a study to measure the impact of new NDPP 2018 on access to essential medicines in terms of their prices, availability and affordability in Lahore division Punjab. We undertook a survey after the implementation of NDPP 2018 and compared it with a similar survey performed before the launch of this policy in 2017. Considering the objectives of the NDPP 2018, we hypothesized that it will improve the availability and affordability, meanwhile decrease the prices of EMs.

Methodology

Study Design

Two cross-sectional studies were conducted in 2016-17 and 2019 using a variant of World Health Organization/Health Action International (WHO/HAI) methodology in four districts of Lahore division, Pakistan [13]. Since, the focus of this study was to measure the impact of NDPP 2018 in terms of changes in medicines prices, availability and affordability after its implementation, thus, the data on these parameters was collected to evaluate the accessibility of medicines in both years [10]. The first survey was conducted from November 2016 to March 2017, while the second survey was from March-May 2019, representing two fiscal years of Pakistan. For optimal and reliable comparison, the list of medicines, survey region and survey outlets selected for the survey 2019 were similar to those selected for 2017. The details of survey region, medicine selection, sampling of medicine outlets and data collection are given elsewhere and are briefly described in this paper [7].

Survey Areas

Lahore is the largest division of Pakistan in terms of population i.e. 16.28 Million (2017) and estimated to be 19.4 Million as of 2018[14]. It consists of four districts named as Lahore, Kasur, Sheikhupura and Nankana Sahib which are further subdivided into 17 Tehsils. All the four districts were selected for the surveys.

Sampling of Medicine Outlets

Medicine outlets or health facilities from both public and private sectors were sampled systematically using WHO/HAI manual as a guiding principle in both the surveys [13]. Total 32 medicine outlets were surveyed (16 from public sector and 16 from private sector). From public sector, hospitals from all three tiers of healthcare system i.e. primary, secondary and tertiary were selected. One main hospital in each district was selected as a survey anchor along with additional three more hospitals selected randomly and situated within three hours' drive from the main

hospital. In this way, 4 hospitals were selected in each district making up a total of 16 hospitals from Lahore division. From private sector, one registered pharmacy was selected situated within 10 kilometers range of each public sector hospital. So, a total of 16 pharmacies were selected from Lahore division, i-e. 4 retail pharmacies from each district. It is important to note that each survey unit, one hospital and one nearby pharmacy, was located in different Tehsils, so out of 17 Tehsils of Lahore division, 16 were surveyed in both years.

Selection of Medicines

50 medicines were selected for survey as per WHO/HAI methodology, which included all 14 medicines from WHO core global list of medicines and 36 supplementary medicines. The criterion of selecting medicines for supplementary list was local disease burden and inclusion of medicines in NEML [15].

Data Collection

The data were collected using a data collection form by the trained data collectors. The data collectors visited the health facilities and physically checked the medicines prices and availability for both OBs and LPGs of each medicine and entered it into data collection forms. The data for each year were entered separately in to the WHO/HAI workbook by using double data entry process, to avoid any mistake [13]. The patient prices or the prices charged to patients were entered into the forms for private sector only, since the medicines are provided free of charge in public sector, in Pakistan. Thus, the availability of medicines was documented only for public sector facility.

Data Analysis

Data were analyzed by using WHO/HAI preprogrammed Excel workbook [13], IBM Statistical Package for the Social Sciences (SPSS) version 22.0 and R version 3.5.1 (codenamed "Feather Spray").

The availability was calculated as percentage of particular medicine available at each facility on the day of data collection. The mean percentage availabilities were also calculated and compared between different sectors (public and private), product types (OBs and LPGs) and among different groups (global medicines, supplementary medicines, medicines from NEML, medicines used to treat NCDs and IDs). Availability was documented as follows; absent: 0% of facilities had surveyed enlisted medicines at the time of survey; Low: < 50% of facilities had the surveyed enlisted medicines; fairly high: 50 -80% of facilities had surveyed enlisted medicines; High: > 80% of facilities, survey enlisted medicines were found in most of the facilities [16, 17].

Medicine prices were calculated as Median Unit Prices (MUPs) in Pakistani Rupees (PKR) and were also compared with International Reference Prices (IRPs) to calculate the Median Price Ratios (MPRs). The IRPs were obtained from Management Sciences for Health (MSH) drug price indicator guide 2015[18]. An MPR of greater than 1 for public sector and greater than 2 for private sector would lodge any medicine into high priced medicines category [7]. For comparing the prices between two years, the MUPs from 2019 were deflated by 3.33%, taking 2017 as base year. 70% of the CPI was used for calculating this deflation factor, because the medicine prices can be

increased annually by 70% of the CPI as per NDPP 2018 [19]. Whereas MPR was calculated as follows:

$$Median\ Price\ Ratio(MPR) = Median\ local\ unit\ price / International\ reference\ unit\ price$$

Affordability for treatment of different common diseases with selected medicines was calculated and compared in terms of Number of Days Wages (NDWs) required for a lowest paid government employee to get the standard treatment courses. Whereas, if a patient had to spend more than one day of his wage for treatment with a specific medicine in a month, that medicine was considered unaffordable [13]. For affordability comparison, NDWs in two years, the prices in 2019 were not deflated because the salary has also been increased in 2019. So, the salary of the lowest paid unskilled government worker was taken as 14000PKR per month (2016-17) and 15000PKR per month (2018-19) [20].

Comparative analysis: Two patient prices were required to be included in the comparative analysis, one from 2017 and other from 2019. The difference in prices, availability and affordability were computed as percentage changes for each product. The mean availability and MUPs were also compared between different categories of medicines (NEML and non-NEML medicines; global and supplementary medicines; medicines for IDs and NCDs) across the years. We compared affordability in terms NDWs to get the standard treatment from the surveyed medicines. These were also compared among medicines for different disease groups (asthma, cardiovascular diseases, infectious diseases, brain disorders, diabetes, ulcer and arthritis; IDs and NCDs). To identify whether the difference between MUPs, MPRs and NDWs was significant across two years, we used Wilcoxon signed rank test. We took $p<0.01$ as an indicator of significant difference in all the statistical testing.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of this study.

Results

Availability of medicines

The overall availability of surveyed medicines was improved in 2019 when compared with 2017, except for LPGs in public sector, where it demonstrated reduction.

Availability in Public Sector: In public sector, the availability of both OBs and LPGs was poor in both years. None of the mean availabilities touched the benchmark of 80%. The mean percent availability of OBs improved from 6.8% to 33.1% whereas, in case of LPGs it reduced from 35.1% to 9%. The individual percent availabilities of each medicine (OB and LPG) are given in table S1. For better understanding of the data, we have used the data visualization tool in R and plotted a box plot of the data as shown in figure 1. The box plot showed distributional characteristics of the percent availability of medicines in two groups (OB and LPG) for the years 2017 and 2019. The mean percent availability is represented by the dot inside the box. In 2017, availabilities of 75% of the OBs in public sector were less than 11.2% as shown by the 3rd quartile

or the upper bar of the 1st box plot. Whereas, in 2019, 75% of the OBs had availabilities higher than 6.3% which is almost equivalent to the mean percent availability (6.8%) in 2017. This indicates a substantial increase in the availability of OBs in public sector. In 2019, 75% of the LPGs had availability less than 12.5% (3rd quartile) whereas before the implementation of the NDPP 2018, 75% of the LPGs had availabilities greater than 14.3% (1st quartile). This showed a remarkable decrease in the availability of LPGs in public sector in 2019.

Availability in private sector: In both years, the overall availability was better in private sector than the public sector. Mean percent availability of both OBs and LPGs were improved in 2019 i.e. 55.0% to 58.3% and 20.3% to 32.3%, respectively. Availability of LPGs was less than OBs in both years. For OBs, the mean percent availability improved slightly by 3.3% while data distribution remained almost the same across the years, as shown in the box plot (figure 1). For LPGs, a substantial increase in the availability was observed in terms of mean percent availability, maximum value and change in data distribution (figure 1). In 2017, the IQR (range between upper and lower bar of the box) for percentage availability of LPGs ranged from 6% to 31% whereas it got improved in 2019 and ranged from 6% to 50%.

Availability in different subgroups of medicines: When we compared availability of LPGs and OBs in different subgroups of medicines as shown in table 1, we found that mean percent availabilities of all global list medicines were higher than supplementary medicines in both years. Similarly, the availability of NEML medicines were higher than non-NEML medicines except for the non-NEML LPGs in public sector, which were higher than NEML LPGs (19.2% vs 8.1%). In 2017, in public sector, the availability of OBs for NCD medicines (6.7%) were lower than OBs for ID medicines (7.7%) whereas the availability of LPGs (35.9%) were better than LPGs of ID medicines (33%). Surprisingly, in 2019, the situation inversed completely for NCD medicines, increased and decreased availability of OBs (33.2%) and LPGs (33.1%), respectively, whereas, the availability decreased for LPGs (8.8%) and increased for OBs (9.5%) for ID medicines.

Table 1. Mean Percent Availabilities of Originator Brands (OBs) and Lowest Price Generics (LPGs) at both public and private sectors.

	Availability in 2017 (Mean, SD) ,%				**Availability in 2019 (Mean, SD) ,%**				**Change in mean percent availability (%)**			
	Public Sector		**Private Sector**		**Public Sector**		**Private Sector**		**Public Sector**		**Private Sector**	
	OBs	**LPGs**	**OBs**	**LPGs**	**OBs**	**LPGs**	**OBs**	**LPGs**	**OBs**	**LPGs**	**OBs**	**LPGs**
All medicines (n=50)	6.8 (10.4)	35.1 (23.6)	55 (31.1)	20.3 (14.4)	33.1 (27.8)	9 (14.9)	58.3 (32.3)	32.3 (26)	26.3	-26.1	3.3	12
Global Medicines (n=14)	11.2 (15.2)	50.1 (32.1)	64.3 (22.5)	25.9 (14.5)	48.4 (31.5)	14.3 (19.9)	66.5 (31.2)	43.8 (27.8)	37.2	-35.8	2.2	17.9
Supplementary medicines (n=36)	5 (7.0)	29.2 (21.4)	51.4 (33)	18.1 (14)	27.2 (24.1)	7 (12.1)	55 (32.6)	27.8 (24.1)	22.2	-22.3	3.6	9.7

NEML medicines (n=46)	7.2 (10.7)	35.5 (26)	55.3 (31)	20.7 (14.6)	33.9 (28.1)	8.1 (15.1)	58.4 (32.9)	33.3 (26.3)	26.7	-27	3.1	12.6
Non-NEML medicines (n=4)	1.8 (3.0)	35.5 (34)	51.6 (36)	15.6 (11)	24.8 (25)	19.2 (7)	56.3 (28)	20.3 (21)	23	-16	4.7	4.7
NCD medicines (n=36)	6.4 (9.2)	35.9 (25.5)	55.7 (28.8)	20 (14.3)	33.2 (27)	8.8 (14)	62.3 (29.3)	31.3 (25)	26.8	-27.1	6.6	11.1
ID medicines (n=14)	7.7 (13.3)	33 (29)	53.1 (37.3)	21 (15)	33.1 (30.5)	9.5 (17.4)	47.8 (38.1)	34.8 (29.2)	25.4	-23.5	-5.3	13.8

Where, SD refers to Standard deviation, NEML refers to National Essential Medicine List, NCD refers to Non Communicable Diseases and ID refers to Infectious Diseases.

Availability at different levels of healthcare: When we compared the availability at different levels of public healthcare sectors i.e. primary, secondary and tertiary, the availability of OBs improved in 2019, while it was decreased for LPGs. The pattern of overall medicines availability remained almost the same as of 2017 i.e. tertiary care>secondary care>primary care as shown in table S2.

Medicine Prices

An overall increase was noted in all adjusted MUPs and adjusted MPRs between 2017 and 2019 for both OBs and LPGs as shown in Table 2. In 2019, for all 42 available OBs, the adjusted MUPs and MPRs significantly increased by a median of 4.3% (Wilcoxon test p=0.001, p=0.0001). Whereas in case of all 37 available LPGs, the adjusted MUPs and MPRs were increased by a median of 15.7% (p=0.002, p=0.0002). The MPRs of OBs ranged from 0.58 to 60.62 in 2017 and 0.73 to 77.59 in 2019. 63% of the OBs had MPR of more than 2 in 2017. Whereas, in 2019 almost 75% of the OBs had MPR greater than 2.The MPRs of LPGs ranged from 0.42 to 19.95 in 2017 and 0.39 to 19.89 in 2019. For LPGs in 2017, the median value of MPR was less than 2 (i.e. 1.36) while in 2019 this median value became greater than 2 (i.e. 2.26). Which means many LPGs which were previously affordable got shifted to the high priced medicines category in 2019. The MUPs and MPRs for all OBs is given in table S3 and for all LPGs is given in table S4.

Table 2. Median price ratios (MPRs) and median unit prices (MUPs) of originator brands (OBs) and lowest price generics (LPGs) in private sector among different subgroups across the years 2017 and 2019.

Originator Brands (OBs)					
	MPR-2017	**MPR-2019**	**MUP 2017 (PKR)**	**Adjusted MUP 2019 (PKR)**	**Median percent change in MUPs/MPR**
All medicines (n=42)	2.5	3.2	6.99	8.49	4.29%
Global Medicines (n=13)	2.8	3.2	7.66	8.22	3.35%
Supplementary medicines (n=29)	2.5	3.3	6.38	10.1	5.1%

NEML medicines (n=39)	2.4	3.3	6.38	8.51	5.1%
Non-NEML medicines (n=3)	3	3.2	7.66	8.22	1.93%
NCD medicines (n=36)	2.6	3.3	6.19	7.83	3.35%
CD medicines (n=10)	2.3	2.9	24.3	31.2	7.36%
Lowest Price Generics (LPGs)					
	MPR-2017	**MPR-2019**	**MUP 2017 (PKR)**	**Adjusted MUP 2019 (PKR)**	**Median percent change in MPR/MUP**
All medicines (n=37)	1.4	2.3	5.8	6.29	15.7%
Global Medicines (n=13)	1.6	2.7	5.8	6.56	19.2%
Supplementary medicines (n=24)	1.3	2.2	5.9	6.04	14.8%
NEML medicines (n=34)	1.4	2.2	5.4	6	15.8%
Non-NEML medicines (n=3)	2.5	2.7	6.5	6.7	3.97%
NCD medicines (n=26)	1.2	2.2	4.1	5.4	16.3%
CD medicines (n=11)	1.8	2.4	8.4	10.9	14.8%

Where PKR is Pakistani Rupee.

The price data was also analyzed in different subgroups as shown in table 2. There was an increase in MUPs and MPRs for OBs of supplementary list of medicines compared to medicines from global list (5.5% vs 3.35%). However, it was inverse in case of LPGs, i.e. the prices of global medicines increased compared to supplementary medicines (19.2% vs 14.8%).Increment in prices of NEML medicines was more as compared to non-NEML medicines. Next, we compared medicines used for NCDs and IDs. Data suggested that the increase in the MUPs and MPRs of OBs for IDs was significant in comparison to NCDs (11.2% vs 7.36%). Whereas it was the opposite case for LPGs, where the increase was greater for NCD than ID medicines (16.3% vs 14.8%). It is also noteworthy that increase in prices for LPGs is more significant than OBs for all subgroups of medicines.

Affordability

Between 2017 and 2019, the median NDWs required for treatment with all OBs (n=36) increased from 1.05 to 2 and 0.5 to 0.7 for all LPGs (n=31), respectively. In 2019, the median percent increase in NDWs for LPGs (n=31) was much higher as compared to OBs (n=36) i.e. 12.5% (p=0.008) and 3% (p=0.081) respectively. So, an overall increase in NDWs for both OBs and LPGs was observed between 2017 and 2019. Similarly the Median Treatment Prices (MTPs) for OB and LPGs also increased significantly i.e. 464 PKR to 563 PKR (p<0.001) and 244 PKR

to 350 PKR ($p<0.001$), respectively. The MTPs and NDWs for each medicine are given in supplementary tables S5 and S6. The medicines were categorized into seven disease groups to further analyze the changes in affordability between 2017 and 2019. In figure 2, a bar graph shows Median NDWs required for both OBs and LPGs in each disease group and the values above 1 are considered unaffordable. In 2017, the median NDWs of OBs to treat three types of diseases i.e. CVDs (1.2), diabetes (1.4) and ulcers (2.75) were more than 1. Whereas in 2019, medicines for one more disease category made its place into this list i.e. the medicines for IDs (1.18). Compared to 2017, the median NDWs for all OBs increased in 2019 except for OBs acting on Central Nervous System (CNS) and OBs to treat ulcers. The treatment for ulcer remained highly unaffordable in both years. The median NDWs for LPGs increased in 2019 for the treatment of Arthritis, CNS disorders, CVDs and IDs, while the modest decrease in median NDWs for LPGs was observed for some diseases i.e. asthma, diabetes and ulcers as shown in figure 2.

Discussion

This study gives a conscionable insight in to the effects of NDPP 2018 associated changes on medicine prices, availability and affordability in both public and private healthcare sectors of Lahore division, Pakistan. The main objective of this refined policy was to improve the access to essential medicines (EMs) and improvise rational drug pricing. Our study has shown that the overall availability of medicines improved in 2019 in comparison to 2017 i.e. before the implementation of this policy, except for the LPGs in public sector, demonstrating reduction. Overall the medicine prices were increased significantly, making majority of the EMs used for the common ailments unaffordable, with a much higher price increases for LPGs in comparison to OBs. The medicines used to treat ulcers, diabetes and CVDs remained most unaffordable in both years. Thus, it can fairly be assumed that the current pricing policy, to some extent, ensures the availability of medicines, nonetheless, significant policy refinements targeting essential medicines are pivotal in making medicine prices affordable to patients.

Despite improvements in the availability of medicines between 2017 and 2019, the availability of medicine remained below the optimal benchmark of 80% [13]. In public sector the availability of OBs improved remarkably probably be due to decentralization procurement of medicines in public sector. Before 2018, the medicines were procured centrally for all the public sector hospitals except for teaching hospitals, within a province. But after 2018, the medicines procurement was decentralized for public sector hospital to allow hospitals in each district a free choice to select desired manufactures, thus, ending up in the selection of more OBs than LPGs, possibly due to quality concerns about medicines. Another factor that improved medicines availability after 2018 was authorization of hospitals to acquire medicines directly without any delays. However, as practiced in the previous central supply system, the medicines were received centrally from the manufacturers before reaching the concerned hospital with considerable effect on timely availability of medicines. In both years, the mean percentage availabilities for all medicines were found higher in the private sector compared to the public sector, corroborating similar previous studies conducted in Bangladesh and Malawi in 2019 [21, 22]. The overall availability of medicines from NEML was slightly better than non-NEML medicines in both public

and private sectors. This might be attributed to the active role of DRAP in the revision and subsequent dissemination of the revised NEML i.e. NEML 2018 [15]. Furthermore, the public hospitals are encouraged to procure drugs from the latest NEML 2018 that has been standardized in line with WHO essential medicines model list 2017 [23]. Besides, a mobile application was launched in 2018 with user friendly interface to better disseminate the information on enlisted medicines [24]. So, the NDPP 2018, doesn't seem to be solely responsible for the availability of medicines.

Although we found some improvements in the availability of medicines, there was a substantial increase in medicine prices, making them inaccessible for most of the population. According to one estimate approximately 46 million people are living below the national poverty line in Pakistan (as per 2015) [8]. The increases in prices of both OBs and LPGs may fairly be attributable to the NDPP 2018, that allows an annual increase in the prices of scheduled drugs up to 70% of CPI compared to 50% of CPI as per NDPP 2015 [9, 10]. These changes in price calculations seems to accentuate the substantial impact on overall prices of medicines, thus, making them more expensive. The increase in LPGs prices were more significant as compared to OBs suggesting that with already expensive OBs, the price increase in LPGs would impoverish the overall access to medicines, imputable to the changes in formula for LPGs (new entrants) price calculation. According to NDPP 2018, the MRP of new entrant first generic should be fixed at 20% less than that of OB compared with 30% less than MRP of OB as per NDPP 2015. Another possible variable is the prior availability of generics in the market for price calculation, where, according to NDPP2018, the MRP of a new entrant (LPGs) was fixed equal to the highest MRP of the available generics in the market, while as per NDPP2015 practice, MRP was fixed by taking the average of other generics in the market. Therefore, these changes in price calculating mechanisms might have led to higher prices of many new LPGs in the market. Hence, contrary to NDPP 2018's price steerage objectives, the increase in medicine prices was more distinct for NEML medicines as compared to non-NEML medicines.

Data from further analysis on affordability of standard treatment by selected OBs and LPGs suggested that majority of the medicines have become more unaffordable in 2019. When the affordability was compared for medicines of different disease groups, the three foremost unaffordable OBs were ones for treatment of ulcers, diabetes and CVDs. Additionally, the treatment for ulcers remained exceptionally unaffordable with OBs and LPGs in both years. Nevertheless, the treatment of CVDs and diabetes with LPGs remained affordable in 2017 but the NDWs for CVDs surpassed affordability threshold in 2019. Among the disease categories, NCDs harbor the top three unaffordable slots. It is noteworthy, that the burden of NCDs is increasing worldwide and is responsible for higher mortality rates than all other diseases combined [25-27]. The CVDs, diabetes, cancer and chronic respiratory diseases are responsible for about 80% of these deaths [28]. Pakistan is among top 10 countries where prevalence of diabetes is very high. Besides, one third of Pakistanis, above 45 years of age have hypertension [29-31]. Thus, the unaffordability of the essential medicines for NCDs, such as CVDs and diabetes, has worse bearing on affordability associated therapeutic outcomes that ultimately leads to increased morbidity and mortality due to un-controlled disease.

Additionally, we also compared the median drug prices in 2019 with the prices published/allowed by DRAP in its latest Statutory Regulatory Orders (SROs). DRAP revised and published the maximum retail prices (MRPs) of about 1084 drugs on December 31, 2018 through SRO-1608, SRO-1609 and SRO-1610 [32]. Eighteen OBs from our study sample were part of these price revisions (table 3). Surprisingly, after comparing the MUPs of 18 selected OBs with prices allowed by the government, we found that most of the OBs, 14 out of 18, were sold at higher prices than the allowable prices – with median percent increase of 29.37%. These data suggested that these intentional malpractices by the drug sellers might be driven by poor price control regulation by price enforcement authorities. Therefore, the current drug pricing policy NDPP 2018, is not the sole reason for the price hike. Most probably main stakeholders in the drug supply chain are also contributing towards medicine inflated prices. Thus, it's reasonable to deduce that these factors may interfere with measuring the direct impact of current pricing policy.

Table 3. Maximum retail unit prices (MRPs) of Originator Brands (OBs) allowed by the government versus median unit prices (MUPs) found in private sector pharmacies.

Medicine Name	Strength (Dosage form)	Allowed Unit Price (PKR)	MUP 2019 (PKR)	Percentage difference
Aciclovir	200mg (tab)	52.6	75	42.5%
Amlodipine	5mg (tab)	8.5	13	52.9%
Amoxicillin	250mg (cap)	3.75	3.75	0%
Amoxicillin	500mg (cap)	5.58	8.75	56.8%
Atorvastatin	20mg (cap)	141.37	203.5	43.9%
Bisoprolol	5mg (tab)	15.35	16.72	8.9%
Carbamezipine	200mg (tab)	4	5	25%
Ceftriaxone	1g (inj)	783	783	0%
Ciprofloxacin	500mg (tab)	39.25	52.5	33.7%
Digoxin	0.25mg (tab)	1.75	2.68	53.1%
Fluconazole	200mg (cap)	425	585	37.6%
Insulin N	100IU (vial)	88.47	75.88	-14.2%
Insulin R	100IU (vial)	93.88	75.88	-19.1%
Methyldopa	250mg (tab)	7.71	8.1	5.05%
Omeprazole	20mg (cap)	42.9	52.29	21.8%
Propranolol	40mg (tab)	1.1	3.16	187.2%
Pyremethamine+Sulfadoxime	(25+500)mg (tab)	12.01	12.02	0.08%
Simvastatin	20mg (cap)	47.01	68	44.6%
Medians		27.3	34.505	29.3%

Although the formation of a national scale pricing policy is laudable but it seems to be a collection of drug price calculation formulas only. It could also include the mechanism for price monitoring, an aspect which seems to be one of the major reasons behind failure to achieve the

goals of NDPP 2018. Inclusion of WHO/HAI based surveys on regular basis could also be an option, in this case. The WHO has developed a mobile application named "WHO Essential Medicines and Health Products Price and Availability Monitoring (WHO EMP MedMon)", which can be used to collect and analyze price and availability data from health care outlets. This application is based on standard WHO/HAI methodology and it can be used both online and offline, make it both time saving and cost effective [33]. The drug inspectors or a third party can be given this responsibility to monitor and report the prices using WHO EMP MedMon on a regular basis, ensuring the compliance by drug manufacturers and sellers to NDPP. There could be many other policy implications having an impact on drug pricing, availability and affordability. The procurement of medicines should be strictly based on the NEML. Clear cut mechanism for NEML based procurement should be devised and implemented specially in the public sector hospitals. Besides this, the hospital pharmacy and therapeutics committees must actively evaluate the safety, efficacy and cost-effectiveness of drugs before purchasing. Pharmaco-economic evaluations of drugs must be promoted by allocating research funds to experts. Not all drugs should be fully reimbursed in the hospitals, only essential medicines must be included in this list. Hence, the profits from other drugs can be used to purchase essential drugs when needed. Smooth functioning of the drug supply chain with proper quality control must be ensured. The current inflated prices would have a grave impact on the access to essential medicines, especially for the lower and middle income population in Pakistan. Thus, there is dire need to develop clearer evidence based and stringent price control policy, especially for essential medicines. Exempting or reducing taxes and tariffs on EMs and promotion of local generic manufacture by providing subsidies on raw materials may improve both the availability and affordability of these medicines. While using the External Reference Pricing (ERP) mechanism, the reference countries should be chosen critically e.g. countries with similar pharmaceutical market and economic status. For costly medicines, regressive markups must be encouraged over progressive markups. The drug prices must be monitored on regular basis using a validated and well-designed scientific methodology and pricing policy must be revised based on such evidences. The essential medicines for most prevalent diseases such as diabetes and CVDs must be preferentially made affordable by devising some specific pricing strategies for these medicines. Besides, efforts must be made to enforce the pricing policy effectively by introducing reward and punishment system to induce a healthy competition among the drug manufacturers and sellers.

Although, this study provides an objective evidence to the policy makers for improving the current pricing policies. It has some limitations as well. The study includes medicines with specific strengths and dosage forms to compare with IRPs. There might be other strengths/dosage forms of the surveyed medicines, available in the health facilities, so the availability of the medicines may be under estimated. The affordability was calculated for single medicine for each disease, whereas patients are usually taking more than one drug at a time – under-estimating the extent of affordability of a specific treatment for a specific disease. Moreover, the post survey was conducted after about a year from the launch of new drug pricing policy 2018, so the results do not reflect the long term impact of the policy. Further surveys could be conducted in future to gauge the long term effects of the policy as it was done by Fang et al in two such surveys conducted after the health reform in China [17].

In Conclusion, the availability of medicines has been improved after the launch of a new drug pricing policy by Pakistani government but it is still poor, forcing the patients to buy medicines from private sector at their own expense. The prices of both LPGs and OBs of EMs have increased remarkably in 2019, when compared with 2017. The medicines to treat most prevalent non-communicable diseases (diabetes and CVDs) have become more expensive and unaffordable. The maximum retail prices of several originator brands have been illegally increased in the market, adding more burden on patients' pockets. The pricing policy needs to be improved further to bring a strict price control, especially on the EMs and on the medicines for most prevalent diseases.

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Contributions

AS, ZB and YF conceptualize the study. ZS, HS, AS and ZB designed methodology. ZS, HS, AS trained the data collectors and obtained the data. YF provided resources and supervised the project. ZS worked as survey area manager. MA, AHG, NA, FK and MZ did data cleaning, validation and entry. AS, HS, CY, MJ analyzed the data. AS and HS wrote original draft. YF, ZB, ZS, CY and MJ, WJ reviewed and edited the manuscript.

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Competing Interests

None

Patient Consent for Publication

Not Required

Ethics Approval

Ethics approval was obtained from the Medical Ethics Committee of Xi'an Jiaotong University under study ID 2019-067.

Data availability statement

Further data will be available upon reasonable request from the first author (https://orcid.org/0000-0002-4144-9272).

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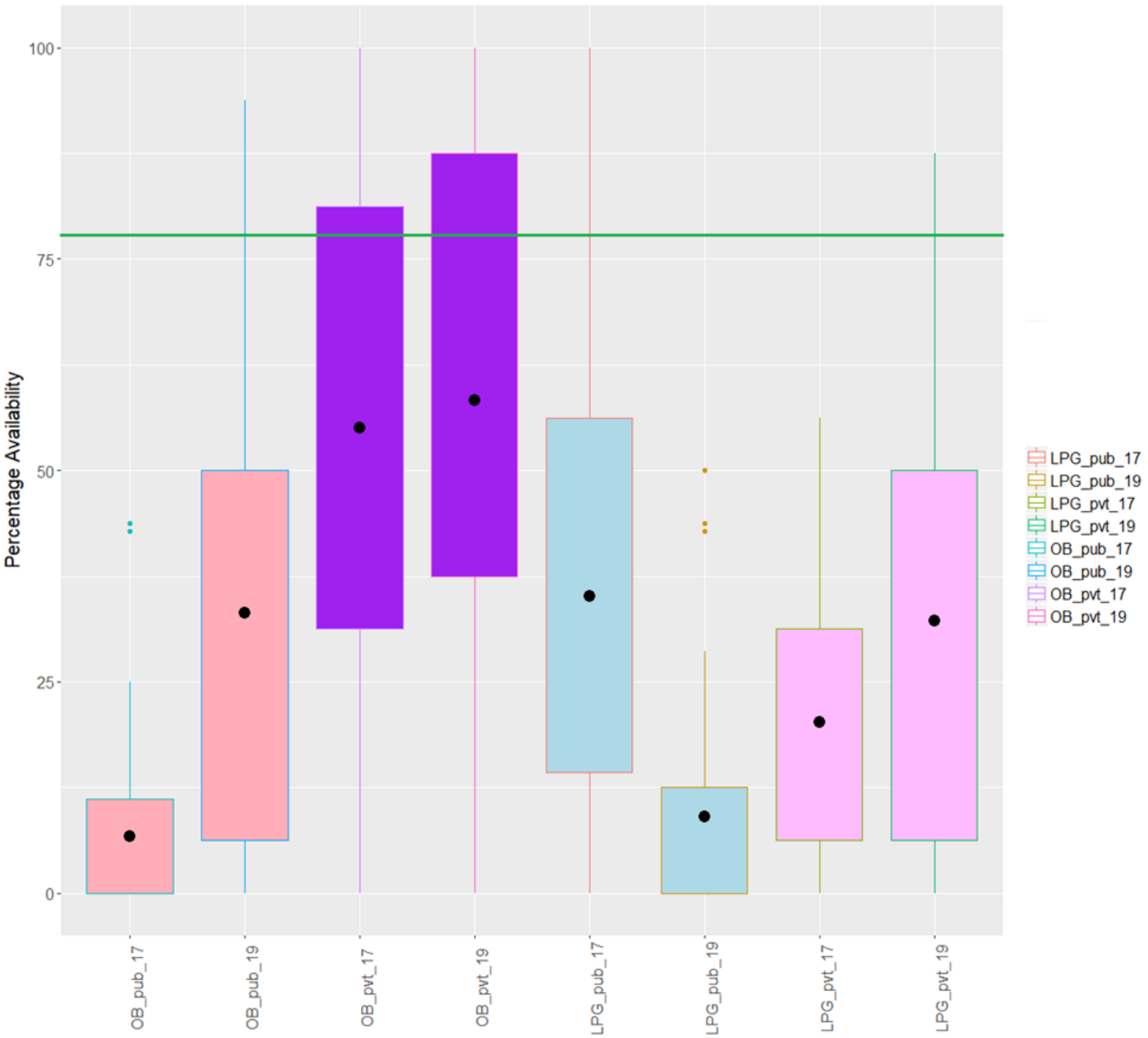
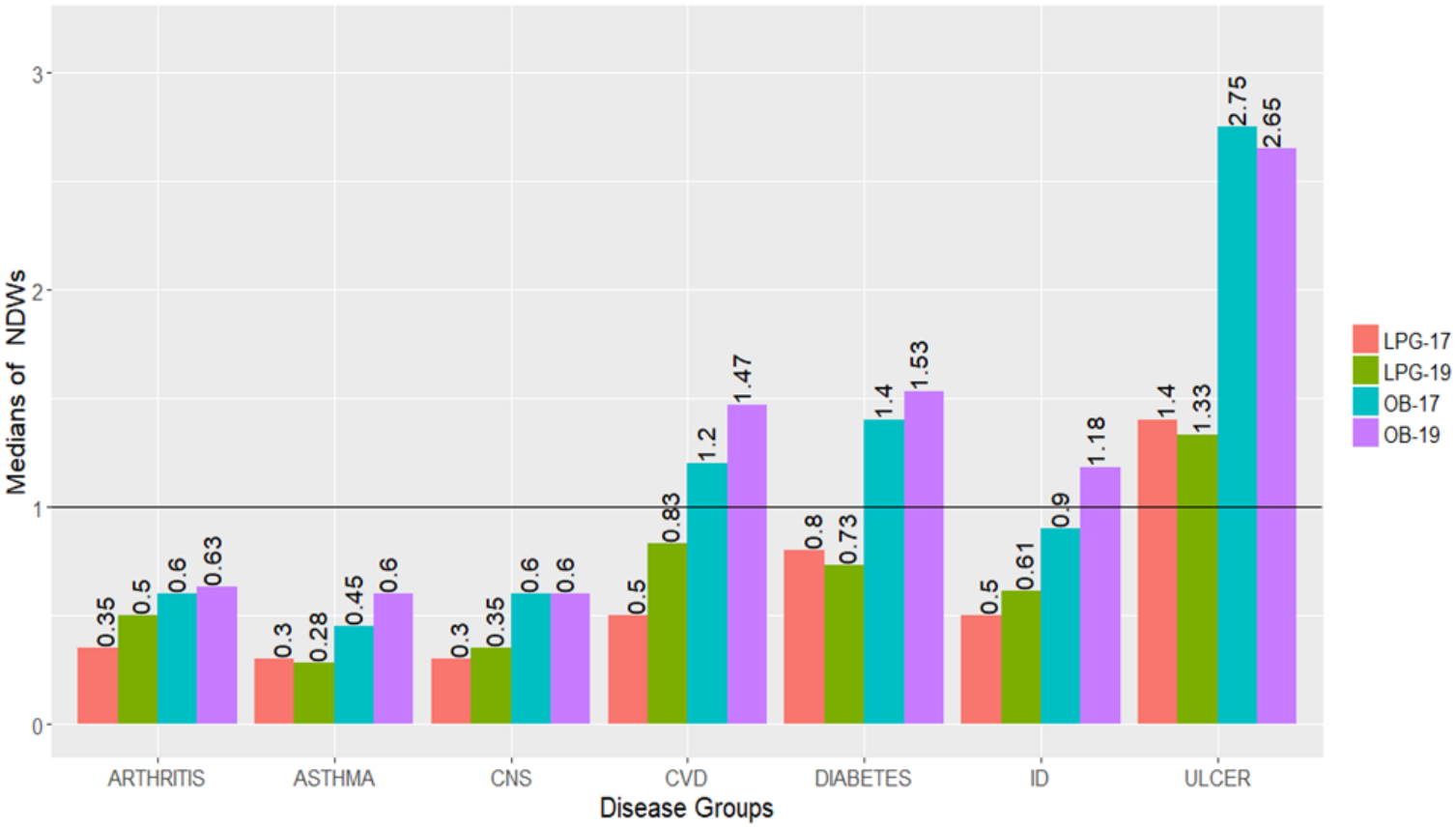
Figure 1. Box plot of percent availability of lowest price generics (LPGs) and originator brands (OBs) in both public (pub) and private (pvt) sectors in 2017 and 2019. This box plot shows the distributional characteristics of the percent availability of medicines in two groups (OB and LPG) for the years 2017 and 2019. The mean percent availability is represented by the dot inside the box.

Figure 2. Bar graph of affordability of originator brands (OBs) and lowest price generics (LPGs) for different diseases in both years i.e. 2017 and 2019.





Supplementary Tables

Table S1. Percent availabilities and of originator brands (OBs) and lowest price generics (LPGs) of all medicines in public and private sector in 2017 and 2019 (%)

Names of meds	OB (Public) 2017	OB (Pvt.) 2017	LPG (Public) 2017	LPG (Pvt.) 2017	OB (Public) 2019	OB (Pvt) 2019	LPG (Public) 2019	LPG (pvt.) 2019
Acetylsalicylic Acid	0.0	25.0	56.3	25.0	18.8	75.0	50.0	18.8
Aciclovir	0.0	50.0	25.0	37.5	6.3	18.8	0.0	50.0
Amiodarone	7.1	62.5	21.4	6.3	0.0	62.5	21.4	0.0
Amitriptyline	0.0	31.3	0.0	25.0	0.0	0.0	50.0	50.0
Amlodipine	6.3	75.0	62.5	31.3	37.5	93.8	12.5	56.3
Amoxicillin	43.8	93.8	18.8	25.0	93.8	68.8	0.0	37.5
Amoxicillin (250)	18.8	100.0	12.5	31.3	50.0	87.5	0.0	37.5
Atenolol	12.5	87.5	81.3	43.8	43.8	81.3	0.0	56.3
Atorvastatin	7.1	50.0	21.4	25.0	42.9	62.5	21.4	18.8
Azithromycin	0.0	25.0	25.0	31.3	31.3	25.0	25.0	75.0
Beclometasone inhaler	0.0	6.3	35.7	12.5	35.7	43.8	0.0	0.0
Bisoprolol	6.3	87.5	18.8	25.0	37.5	81.3	0.0	56.3
Captopril	0.0	81.3	85.7	25.0	50.0	93.8	28.6	50.0
Carbamazepine	12.5	87.5	56.3	25.0	25.0	31.3	0.0	56.3
Ceftriaxone injection	14.3	68.8	71.4	31.3	21.4	75.0	50.0	87.5
Ciprofloxacin	0.0	81.3	100.0	37.5	64.3	93.8	14.3	25.0
Clarithromycin	0.0	87.5	35.7	25.0	50.0	93.8	0.0	56.3
Co-trimoxazole suspension	6.3	31.3	62.5	6.3	6.3	6.3	43.8	6.3
Diazepam	6.3	62.5	12.5	0.0	43.8	68.8	0.0	0.0
Diclofenac	42.9	50.0	35.7	6.3	85.7	93.8	0.0	81.3
Digoxin	21.4	62.5	28.6	0.0	28.6	68.8	0.0	56.3
Enalapril	0.0	68.8	62.5	18.8	12.5	68.8	12.5	50.0
Fluconazole	0.0	37.5	18.8	25.0	43.8	43.8	0.0	50.0
Fluoxetine	0.0	43.8	12.5	43.8	6.3	62.5	6.3	62.5
Fluphenazine Decanoate	0.0	0.0	0.0	12.5	0.0	0.0	7.1	6.3
Furosemide	12.5	93.8	50.0	6.3	50.0	87.5	0.0	0.0
Glibenclamide	18.8	68.8	56.3	12.5	68.8	93.8	0.0	12.5
Gliclazide	0.0	75.0	0.0	18.8	7.1	75.0	0.0	31.3
Hydrochlorothiazide	0.0	0.0	0.0	12.5	18.8	0.0	0.0	0.0
Indinavir	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Insulin Isophane (NPH)	0.0	75.0	50.0	25.0	56.3	68.8	0.0	18.8
Insulin Neutral Soluble (Regular)	0.0	68.8	50.0	25.0	68.8	68.8	0.0	18.8
Losartan	7.1	43.8	14.3	43.8	0.0	43.8	42.9	43.8
Lovastatin	0.0	0.0	6.3	0.0	6.3	37.5	12.5	0.0

Metformin	25.0	81.3	56.3	31.3	68.8	93.8	0.0	50.0
Methyldopa	12.5	81.3	25.0	0.0	75.0	68.8	0.0	0.0
Metronidazole	25.0	93.8	56.3	37.5	75.0	87.5	0.0	56.3
Nevirapine	0.0	0.0	14.3	0.0	0.0	0.0	0.0	0.0
Nifedipine Retard	0.0	75.0	28.6	12.5	0.0	31.3	14.3	12.5
Omeprazole	6.3	56.3	75.0	37.5	62.5	62.5	6.3	50.0
Omeprazole (10)	0.0	12.5	43.8	18.8	18.8	0.0	12.5	31.3
Paracetamol suspension	6.3	68.8	87.5	25.0	81.3	87.5	0.0	81.3
Phenytoin	0.0	6.3	12.5	6.3	0.0	50.0	6.3	0.0
Propranolol	12.5	68.8	12.5	6.3	18.8	87.5	0.0	25.0
Pyrimethamine with sulfadoxine	0.0	75.0	21.4	6.3	21.4	68.8	0.0	6.3
Ranitidine	0.0	81.3	31.3	25.0	50.0	100.0	0.0	50.0
Salbutamol inhaler	0.0	81.3	56.3	31.3	62.5	68.8	0.0	12.5
Simvastatin	0.0	25.0	21.4	56.3	0.0	37.5	7.1	25.0
Spironolactone	6.3	62.5	25.0	0.0	12.5	93.8	6.3	43.8
Zidovudine	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Mean availabilities	6.8	55.0	35.1	20.3	33.1	58.3	9.0	32.3

Table (S2). Change in availability at different levels of healthcare (Public Sector).

	Primary level (n=2 outlets)		**Secondary level (n=13 outlets)**		**Tertiary level (n=1 outlet)**	
	All medicines (n=50)		**All medicines (n=50)**		**All medicines (n=50)**	
	OB	**LPG**	**OB**	**LPG**	**OB**	**LPG**
Mean Availability 2017 (SD),%	0.0 (0.0)	25.8 (44.5)	7.1 (11.2)	35.2 (27.5)	12.0 (32.8)	50.0 (50.5)
Mean Availability 2019 (SD) ,%	21.0 (31.0)	3.2 (18)	32.3 (29.1)	7.4 (13.4)	68.0 (47.1)	22.0 (41.8)
Change in mean percent availability,%	21.0	-22.6	25.2	-27.8	56.0	-28.0

Table S3. Change in median unit prices (MUPs) and median price ratios (MPRs) of the Originator Brands (OBs) at private sector.

Sr. no.	Medicines (OB)	MUPs 2017 (PKR)	MPR 2017	Adjusted MUP in 2019	MPR 2019	Percentage change in MUPs/MPRs
1	Acetylsalicylic Acid	1.16	0.8	1.12	0.7	-3.41%
2	Aciclovir	70	20	72.5	21	3.48%
3	Amiodarone	17.78	2.2	17.4	2.2	-2.15%
4	Amlodipine	11.93	7.3	12.6	7.7	5.1%
5	Amoxicillin	8.616	2.8	8.46	2.7	-1.83%
6	Amoxicillin (250)	3.56	2.1	3.63	2.2	1.83%
7	Atenolol	6.19	5.6	6.14	5.5	-0.81%
8	Atorvastatin	201.9	18	197	18	-2.6%
9	Azithromycin	40	1.7	118	5	66.2%
10	Beclometasone inhaler	1.25	1.2	1.84	1.8	32%
11	Bisoprolol	11.28	1.2	16.2	1.7	30.2%
12	Captopril	7.66	3	8.22	3.2	6.81%
13	Carbamazepine	4.91	2.6	4.84	2.5	-1.55%
14	Ceftriaxone injection	672	16	757	18	11.2%
15	Ciprofloxacin	50.4	13	50.8	13	0.72%
16	Clarithromycin	65.7	2.5	76.4	2.9	14%
17	Co-trimoxazole suspension	0.29	0.6	0.44	0.9	33.4%
18	Diazepam	2	2	1.93	1.9	-3.41%
19	Diclofenac	5.625	12	5.61	12	-0.29%
20	Digoxin	2.52	2.4	2.59	2.5	2.76%
21	Enalapril	5.85	5.4	6	5.6	2.43%
22	Fluconazole	442	61	566	78	21.9%
23	Fluoxetine	43.42	9.7	43	9.6	-0.9%
24	Furosemide	1.89	3	2.34	3.7	19.2%
25	Glibenclamide	1.69	2.9	2.09	3.5	19.1%
26	Gliclazide	7.6	1.5	16.4	3.3	53.8%
27	Insulin Isophane (NPH)	64.5	1.1	73.4	1.3	12.1%
28	Insulin Neutral Soluble (Regular)	64.5	1.1	73.4	1.2	12.1%
29	Losartan	51.67	4.3	50.3	4.2	-2.76%
30	Metformin	1.54	1	1.62	1	5.21%
31	Methyldopa	6.38	1.9	7.83	2.3	18.5%
32	Metronidazole	1.57	1.3	1.52	1.2	-3.41%
33	Nifedipine Retard	5.69	2.7	5.8	2.8	1.93%
34	Omeprazole	49.78	34	50.6	35	1.55%
35	Paracetamol suspension	0.85	1.6	2.2	4.1	61.4%
36	Phenytoin	5.2	4.8	23.2	22	77.6%
37	Propranolol	1.55	2.2	3.06	4.3	49.3%

38	Pyrimethamine with sulfadoxine	5.83	1.4	11.6	2.8	49.8%
39	Ranitidine	8.8	3.7	8.51	3.6	-3.41%
40	Salbutamol inhaler	1	1	1.03	1.1	3.35%
41	Simvastatin	67.13	12	65.8	12	-2.09%
42	Spironolactone	8.6	0.8	10.1	1	14.5%
Medians		6.99	2.5	8.49	3.2	4.29%

Table S4. Change in median unit prices (MUPs) and median price ratios (MPRs) of the lowest price generics (LPGs) in private sector.

Sr. no.	**Medicines**	**MUPs 2017 (PKR)**	**MPR 2017**	**Adjusted MUP in 2019**	**MPR 2019**	**Percentage change in MUPs/ MPRs**
1	Acetylsalicylic Acid	1.015	0.7	1.06	0.7	4.58
2	Aciclovir	12.4	3.6	13.5	3.9	8.41
3	Amitriptyline	1.19	1.4	1.24	1.4	3.86
4	Amlodipine	1.8	1.1	6.29	3.8	71.4
5	Amoxicillin	5.8	1.9	8.32	2.7	30.3
6	Amoxicillin (250)	3	1.8	3.48	2.1	13.8
7	Atenolol	2.05	1.8	2.47	2.2	16.9
8	Atorvastatin	37.5	3.4	35.8	3.2	-4.8
9	Azithromycin	40	1.7	19.3	0.8	-107
10	Bisoprolol	6.55	0.7	6.56	0.7	0.1
11	Captopril	6.5	2.5	6.77	2.7	3.97
12	Carbamazepine	3.3	1.7	4.35	2.3	24.2
13	Ceftriaxone injection	280	6.8	290	7	3.48
14	Ciprofloxacin	11	2.8	24.2	6.2	54.5
15	Clarithromycin	36	1.4	42.7	1.6	15.8
16	Co-trimoxazole suspension	0.21	0.4	2.32	4.7	91
17	Diclofenac	3.5	7.5	4.79	10	26.9
18	Enalapril	2.05	1.9	2.84	2.6	27.8
19	Fluconazole	145.5	20	145	20	-0.3
20	Fluoxetine	13.8	3.1	13.5	3	-1.9
21	Fluphenazine Decanoate	90.5	1	93.8	1.1	3.5
22	Glibenclamide	1.57	2.7	1.42	2.4	-10
23	Gliclazide	4.75	0.9	5.8	1.1	18.1

24	Insulin Isophane (NPH)	48	0.8	62.3	1.1	22.9
25	Insulin Neutral Soluble (Regular)	48	0.8	62.3	1	22.9
26	Losartan	11	0.9	13.1	1.1	15.7
27	Metformin	1.5	1	1.86	1.2	19.2
28	Metronidazole	1.5	1.2	1.93	1.6	22.4
29	Nifedipine Retard	2.65	1.3	5.14	2.4	48.4
30	Omeprazole	15.35	10	11.4	7.8	-35
31	Omeprazole (10)	12.14	0.9	5.13	0.4	-137
32	Paracetamol suspension	0.47	0.9	1.02	1.9	53.7
33	Propranolol	0.66	0.9	2.03	2.8	67.5
34	Pyrimethamine with sulfadoxine	5	1.2	4.84	1.2	-3.4
35	Ranitidine	6.93	2.9	7.78	3.3	11
36	Salbutamol inhaler	0.64	0.7	0.68	0.7	5.45
37	Simvastatin	8.5	1.6	16.6	3	48.7
	Medians	**5.8**	**1.4**	**6.29**	**2.3**	**15.7**

Table S5. Affordability of originator brands (OBs) for different diseases in 2017 and 2019, in private sector.

Disease	Medicine	Strength	Dosage form	No. of units needed per treatment	Duration of treatment	MTP 2017 (PKR)	NDWs 2017	MTP 2019 (PKR)	NDWs 2019
ASTHMA	Salbutamol Inhaler	100mcg/ dose	Inhaler	200	As needed	200	0.4	214	0.4
	Beclomethasone	50mcg/dose	inhaler	200	As needed	250	0.5	380	0.8
Cardiovascular Diseases	Bisoprolol	5mg	tab	60	30	676.8	1.5	1003	2
	Atenolol	50mg	tab	30	30	185.7	0.4	190.5	0.4
	Captopril	25mg	tab	60	30	459.6	1	510	1
	Amlodipine	5mg	tab	60	30	715.8	1.5	780	1.6
	Amiodarone	200mg	tab	60	30	1066.8	2.3	1080	2.2
	Losartan	50mg	tab	60	30	3100.2	6.6	3120	6.2
	methyldopa	250mg	tab	90	30	574.2	1.2	729	1.5
	Nifedipine retard	20mg	tab	90	30	512.1	1.1	540	1.1

	Spironolactone	100mg	tab	30	30	258	0.5	312	0.6
	Propranolol	40mg	tab	90	30	139.5	0.3	284.4	0.6
	Acetylsalicylic acid	75mg	tab	30	30	34.8	0.1	34.8	0.1
Anti hyperlipidemics	Simvastatin	20mg	Cap/tab	30	30	2013.9	4.3	2040	4.1
	Atorvastatin	20mg	Cap/tab	30	30	6057	13	6105	12
Infections-Adult respiratory tract infection	Ceftriaxone Injection	1g/vial	Inj.	1	1	672	1.4	783	1.6
	Ciprofloxacin	500mg	tab	14	7	705.6	1.5	735	1.5
	Azithromycin	500mg	tab	3	3	120	0.3	367	0.7
	clarithromycin	500mg	tab	28	14	1839.6	3.9	2212	4.4
	Amoxicillin	500mg	cap	42	14	361.87	0.8	367.5	0.7
	Amoxicillin	250mg	cap	84	14	299.04	0.6	315	0.6
Fungal Infection	Fluconazole	200mg	cap	1	1	442	0.9	585	1.2
Viral Infection	aciclovir	200mg	tab	25	5	1750	3.8	1875	3.8
Amoebiasis	metronidazole	400mg	tab	21	7	32.97	0.1	32.97	0.1
CNS Drugs-Anti epileptics	Carbamezipine	200mg	tab	60	30	294.6	0.6	300	0.6
	Phenytoin	100mg	tab	90	30	468	1	2160	4.3
Anxiety	diazepam	5mg	tab	90	30	180	0.4	180	0.4
Anti Diabetics	Metformin	500mg	tab	90	30	138.6	0.3	151.2	0.3
	Glibenclamide	5mg	tab	90	30	152	0.3	194.4	0.4
	Gliclazide	80mg	tab	60	30	456	1.5	1020	2
	Insulin Isophane (NPH)	100IU/ml	vial	10	30	645	1.4	758.8	1.5
	Insulin Neutral Soluble (Regular)	100IU/ml	vial	10	30	645	1.4	758.8	1.5
Ulcer Treatment	Omeprazole	20mg	cap	30	30	1493.4	3.2	1569	3.1
	ranitidine	150mg	tab	120	30	1056	2.3	1056	2.1
Pain/Inflammation	Paracetamol	24mg/ml	susp	45	3	38.25	0.1	102.6	0.2
Arthritis	Diclofenac	50mg	tab	90	30	506.25	1.1	522	1

Where, MTP: Median treatment price, NDWs: Number of days' wages

Table S6. Affordability of lowest price generics (LPGs) for different diseases in 2017 and 2019, in private sector.

Disease/Condition	Medicine	Strength	Dosage form	No. of units needed per treatment	Duration of treatment	MTP 2017 (PKR)	NDWs 2017	MTP 2019 (PKR)	NDWs 2019
ASTHMA	Salbutamol Inhaler	100mcg/dose	Inhaler	200	As needed	128	0.3	140	0.3
Cardiovascular Diseases/ Anti Hypertensives	Bisoprolol	5mg	tab	60	30	393	0.8	406.8	0.8
	Atenolol	50mg	tab	30	30	61.5	0.1	76.5	0.2
	Captopril	25mg	tab	60	30	390	0.8	420	0.8
	Amlodipine	5mg	tab	60	30	108	0.2	390	0.8
	Losartan	50mg	tab	60	30	660	1.4	810	1.6
	Nifedipine retard	20mg	tab	90	30	238.5	0.5	478.4	1
	Propranolol	40mg	tab	90	30	59.4	0.1	189	0.4
	Acetylsalicylic acid	75mg	tab	30	30	30.45	0.1	33	0.1
Anti hyperlipidemics	Simvastatin	20mg	Cap/tab	30	30	255	0.5	513.8	1
	Atorvastatin	20mg	Cap/tab	30	30	1125	2.4	1110	2.2
Infections- Adult respiratory tract infection	Ceftriaxone Injection	1g/vial	Inj.	1	1	280	0.6	300	0.6
	Ciprofloxacin	500mg	tab	14	7	154	0.3	350	0.7
	Azithromycin	500mg	tab	3	3	120	0.3	60	0.1
	clarithromycin	500mg	tab	28	14	1008	2.2	1238	2.5
	Amoxicillin	500mg	cap	42	14	243.6	0.5	361.2	0.7
	Amoxicillin	250mg	cap	84	14	252	0.5	302.4	0.6
Fungal Infection	Fluconazole	200mg	cap	1	1	145.5	0.3	150	0.3
Viral Infection	aciclovir	200mg	tab	25	5	310	0.7	350	0.7
Amoebiasis	metronidazole	400mg	tab	21	7	31.5	0.1	42	0.1
CNS Drugs- Anti epileptics	Carbamezipine	200mg	tab	60	30	198	0.4	270	0.5
Depression	Amitriptyline	25mg	tab	60	30	71.4	0.2	76.8	0.2

Anti Diabetics	Metformin	500mg	tab	90	30	135	0.3	180	0.4
	Glibenclamide	5mg	tab	90	30	141	0	132.3	0.3
	Gliclazide	80mg	tab	60	30	285	0.8	360	0.7
	Insulin Isophane (NPH)	100IU/ml	vial	10	30	480	1	644	1.3
	Insulin Neutral Soluble (Regular)	100IU/ml	vial	10	30	480	1	644	1.3
Ulcer Treatment	Omeprazole	20mg	cap	30	30	460.5	1	353.7	0.7
	ranitidine	150mg	tab	120	30	831.6	1.8	966	1.9
Pain/Inflammation	Paracetamol	24mg/ml	susp	45	3	21.15	0	47.25	0.1
Arthritis	Diclofenac	50mg	tab	90	30	315	0.7	445.5	0.9

Research Checklist

Dear editor,

We submit the manuscript entitled **"Impact of National Drug Pricing Policy 2018 on Access to Medicines in Lahore Division, Pakistan: A Pre-Post Survey Study Using WHO/HAI Methodology"**, for your consideration to be published in ***BMJ Open.*** And we confirm that we have prepared submission materials according to the guideline.

And our main document has covered everything required, which including the following:

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Impact of National Drug Pricing Policy 2018 on Access to Medicines in Lahore Division, Pakistan: A Pre-Post Survey Study Using WHO/HAI Methodology

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Impact of National Drug Pricing Policy 2018 on Access to Medicines in Lahore Division, Pakistan: A Pre-Post Survey Study Using WHO/HAI Methodology

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Abstract

Objective: To evaluate the impact of new national drug pricing policy (NDPP) 2018 on the access to medicines in terms of prices, availability and affordability.

Design: Two cross-sectional surveys were undertaken before and after the launch of NDPP 2018, using a modified WHO/HAI methodology.

Setting: Four districts of Lahore division, Pakistan.

Participants: 16 public sector hospitals and 16 private sector retail pharmacies.

Measures: The pre and post survey data on prices and availability of Lowest Price Generics (LPGs) and Originator Brands (OBs) of 50 medicines were obtained by visiting the same public and private sector health facilities (n=32). Out of 50, 46 surveyed medicines were from National Essential Medicines List (NEML). Inflation-adjusted median unit prices (MUPs) and median price ratios (MPRs) from 2019 were used for price comparison. Affordability was calculated in terms of number of days' wages required to get a standard treatment by the lowest paid unskilled government worker.

Results: The overall mean percent availabilities remained poor in both years i.e. far less than 80%. In public sector, the mean percent availability of OBs improved from 6.8% to 33.1% whereas, in case of LPGs it was reduced from 35.1% to 9%. In private sector, the mean percent availability of both OBs and LPGs demonstrated slight improvements in 2019 i.e. 55.0% to 58.3% and 20.3% to 32.3%. The adjusted MUPs and MPRs of OBs significantly increased by a median of 4.29% (Wilcoxon test p=0.001, p=0.0001). Whereas, the adjusted MUPs and MPRs of LPGs were increased by a median of 15.7% (p=0.002, p=0.0002). Overall the affordability of many medicines for common ailments reduced significantly in 2019.

Conclusions: The availability of medicines slightly improved, except in the case of LPGs which was reduced at public sector. The implementation of NDPP 2018 led to increase in drug prices, making the standard treatment for some of the most prevalent ailments unaffordable. So verily, the drug pricing policy must be reviewed to ensure the access to essential medicines.

Strengths and limitations of this study

- This study is the first attempt to estimate the impact of a drug pricing policy, on the prices of essential medicines in four districts of Lahore division, Pakistan using validated WHO/HAI methodology.
- The data were collected from the same health facilities in both years to make the comparison of results reliable.
- This study provides an objective evidence to the policy makers, in terms of impact of NDPP 2018 on access to medicines, for improving the current pricing policies.
- The study is limited to only one division of Pakistan, although the medicine prices are fixed centrally and are supposed to be the same across the country – affecting generalizability of the findings.
- The cross-sectional design of the study might not reflect the long term impact of NDPP 2018 - the average monthly, quarterly or yearly availability of medicines at individual outlets.

Introduction

Access to affordable and quality assured essential medicines is considered as a key component of an effective healthcare system. It has also been pledged under Sustainable Development Goal (SDG) 3 by United Nations (UN) that the equitable access to affordable essential medicines will be ensured as a basic human right [1, 2]. Pakistani government, like many other Low and Middle Income Countries (LMICs), has been grappling with the issue of high medicine prices and poor availability of medicines that compromises the accessibility of medicines [1, 3-6]. In Pakistan, the medicines are provided free of cost at public sector health facilities, while patient pays out of pocket to get medicines from private sector [5]. In fact, the poor availability of medicines at public sector compels the patients to buy medicines from the private sector that escalates the burden on patient's pocket, as 24.3% (in 2015) of the population is living below the national poverty line [3, 4, 7, 8]. Besides, medicine prices have increased up to 100%, both legally or illegally, in the past few years [3]. The drug prices are fixed by the federal government and the National Health Services Regulation and Coordination (NHSRC). The regional drug inspectors (DIs) are responsible for monitoring of drug prices in the pharmacies of their area. The NHSRC has been taking different policy measures to curb these issues through Drug Regulatory Authority of Pakistan (DRAP). The first ever National Drug Pricing Policy (NDPP) was launched in 2015 for making the pricing mechanism transparent but it had minimal impact on medicine prices, suitable for both patients and manufacturers as per media reports and available literature evidences [3, 9]. So, a new drug pricing policy was launched in 2018[10]. The objectives of this policy were to improve the access to essential medicines, devise rational prices, ensure a transparent mechanism for medicine pricing and to discourage illegal increase in drug prices.

Many modifications have been made to the pricing strategies in the NDPP 2018 compared to NDPP 2015, importantly the inclusion of all drugs (n=414) from National Essential Medicines List (NEML) under scheduled drugs category where the drugs are kept under strict price control as compared to other drugs. Whereas in NDPP 2015, only 160 drugs from NEML were enlisted in this category [9, 10]. In NDPP 2018, the annual adjustment in prices has been linked with the Consumer Price Index (CPI), the Maximum Retail Prices (MRPs) of scheduled drugs (all drugs from NEML) could be increased up to 70% of the CPI, whereas the MRPs of all other drugs could be increased equivalent to CPI of the immediate preceding year. This step seems to improve the affordability of essential medicines (EMs) for patients in Pakistan. If several generics are already available in the market then in NDPP 2015, the MRP of new entrant was fixed by taking the average of other generics, while in NDPP 2018, MRP will be fixed equivalent to the highest MRP of the available generics [9, 10]. However, this would lead to even higher priced generics in the market that could compromise patient's affordability. Some media reports are claiming that the current increase (up to 200%) in medicines prices is the highest in the last 40 years, while others are claiming that government is taking action against this illegal rise in medicine prices [11, 12]. But there is no objective evidence to prove or disapprove these claims. The NDPP 2018, allows the MRPs of the New Chemical Entities (NCEs) to be fixed by using the External Reference Pricing (ERP) mechanism by considering India, Bangladesh, Indonesia, Sri Lanka, Philippines, Lebanon and Malaysia as reference countries. However, the reason behind using the MRPs of these countries as reference is not clear, though some of them practice free market economy model

and don't impose any price control measures over the MRPs in community pharmacies that may lead to high prices. The NDPP 2018 also takes into account the wholesale or procurement prices from British National Formulary, Australian Pharmaceutical Benefit Scheme and New Zealand Pharmaceutical Management Agency while fixing the MRPs of NCEs, however these may not be the true prices because discounts and rebates are given as a common practice, while making the payments. So, these ambiguities in the policy necessitate the evaluation of actual impact of these policies on the access to medicines in Pakistan.

In this context, we designed a study to measure the impact of new NDPP 2018 on access to essential medicines in terms of their prices, availability and affordability in Lahore division Punjab. We undertook a survey after the implementation of NDPP 2018 and compared it with a similar survey performed before the launch of this policy in 2017. Considering the objectives of the NDPP 2018, we hypothesized that it will improve the availability and affordability, meanwhile decrease the prices of EMs.

Methodology

Study Design

Two cross-sectional studies were conducted in 2016-17 and 2019 using a variant of World Health Organization/Health Action International (WHO/HAI) methodology in four districts of Lahore division, Pakistan [13]. Since, the focus of this study was to measure the impact of NDPP 2018 in terms of changes in medicines prices, availability and affordability after its implementation, therefore, the data on these parameters was collected to evaluate the accessibility of medicines in both years [10]. The first survey was conducted from November 2016 to March 2017, while the second survey was from March-May 2019, representing two fiscal years of Pakistan. For optimal and reliable comparison, the list of medicines, survey region and survey outlets selected for the survey 2019 were similar to those selected for 2017. The details of survey region, medicine selection, sampling of medicine outlets and data collection are given elsewhere and are briefly described in this paper [7].

Survey Areas

Pakistan consists of four provinces which are sub-divided into several administrative units called "divisions", each division is further sub-divided into districts, and districts into tehsils. Lahore is the largest division of Pakistan in terms of population i.e. 16.28 Million (2017) and estimated to be 19.4 Million as of 2018 [14]. It consists of four districts named as Lahore, Kasur, Sheikhupura and Nankana Sahib and 17 Tehsils. All the four districts were selected for the surveys.

Sampling of Medicine Outlets

Medicine outlets or health facilities from both public and private sectors were sampled systematically using WHO/HAI manual as a guiding principle in both the surveys [13]. Total 32 medicine outlets were surveyed (16 from public sector and 16 from private sector). From public sector, hospitals from all three tiers of healthcare system i.e. primary, secondary and tertiary were selected. One main hospital in each district was selected as a survey anchor along with additional

three more hospitals selected randomly and situated within three hours' drive from the main hospital. In this way, 4 hospitals were selected in each district making up a total of 16 hospitals from Lahore division. From private sector, one registered pharmacy was selected situated within 10 kilometers range of each public sector hospital. So, a total of 16 pharmacies were selected from Lahore division, i-e. 4 retail pharmacies from each district. It is important to note that each survey unit, one hospital and one nearby pharmacy, was located in different Tehsils, so out of 17 Tehsils of Lahore division, 16 were surveyed in both years.

Selection of Medicines

50 medicines were selected for survey as per WHO/HAI methodology, which included all 14 medicines from WHO core global list of medicines and 36 supplementary medicines. The criterion of selecting medicines for supplementary list was local disease burden and inclusion of medicines in NEML [15].

Data Collection

The data were collected using a data collection form by the trained data collectors. The data collectors visited the health facilities and physically checked the medicines prices and availability for both OBs and LPGs of each medicine and entered it into data collection forms. The data for each year were entered separately in to the WHO/HAI workbook by using double data entry process, to avoid any mistake [13]. The patient prices or the prices charged to patients were entered into the forms for private sector only, since the medicines are provided free of charge in public sector, in Pakistan. Thus, the availability of medicines was documented only for public sector facility.

Data Analysis

Data were analyzed by using WHO/HAI preprogrammed Excel workbook [13], IBM Statistical Package for the Social Sciences (SPSS) version 22.0 and R version 3.5.1 (codenamed "Feather Spray").

The availability was calculated as percentage of particular medicine available at each facility on the day of data collection. The mean percentage availabilities were also calculated and compared between different sectors (public and private), product types (OBs and LPGs) and among different groups (global medicines, supplementary medicines, medicines from NEML, medicines used to treat NCDs and IDs). Availability was documented as follows; absent: 0% of facilities had surveyed enlisted medicines at the time of survey; Low: < 50% of facilities had the surveyed enlisted medicines; fairly high: 50 -80% of facilities had the surveyed enlisted medicines; High: > 80% of facilities, survey enlisted medicines were found in most of the facilities [16, 17].

Medicine prices were calculated as Median Unit Prices (MUPs) in Pakistani Rupees (PKR) and were also compared with International Reference Prices (IRPs) to calculate the Median Price Ratios (MPRs). The IRPs were obtained from Management Sciences for Health (MSH) drug price indicator guide 2015[18]. An MPR of greater than 1 for public sector and greater than 2 for private sector would lodge any medicine into high priced medicines category [7]. For comparing the prices between two years, the MUPs from 2019 were deflated by 3.33%, taking 2017 as base year. 70%

of the CPI was used for calculating this deflation factor, because the medicine prices can be increased annually by 70% of the CPI as per NDPP 2018 [19]. Whereas MPR was calculated as follows:

$$Median\ Price\ Ratio(MPR) = Median\ local\ unit\ price / International\ reference\ unit\ price$$

Affordability for treatment of different common diseases with selected medicines was calculated and compared in terms of Number of Days Wages (NDWs) required for a lowest paid government employee to get the standard treatment courses. Whereas, if a patient had to spend more than one day of his wage for treatment with a specific medicine in a month, that medicine was considered unaffordable [13]. For affordability comparison, NDWs in two years, the prices in 2019 were not deflated because the salary has also been increased in 2019. So, the salary of the lowest paid unskilled government worker was taken as 14000PKR per month (2016-17) and 15000PKR per month (2018-19) [20].

Comparative analysis: Two patient prices were required to be included in the comparative analysis, one from 2017 and other from 2019. The difference in prices, availability and affordability were computed as percentage changes for each product. The mean availability and MUPs were also compared between different categories of medicines (NEML and non-NEML medicines; global and supplementary medicines; medicines for IDs and NCDs) across the years. We compared affordability in terms NDWs to get the standard treatment from the surveyed medicines. These were also compared among medicines for different disease groups (asthma, cardiovascular diseases, infectious diseases, brain disorders, diabetes, ulcer and arthritis; IDs and NCDs). To identify whether the difference between MUPs, MPRs and NDWs was significant across two years, we used Wilcoxon signed rank test. We took $p<0.01$ as an indicator of significant difference in all the statistical testing.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of this study.

Results

Availability of medicines

The overall availability of surveyed medicines was improved in 2019 when compared with 2017, except for LPGs in public sector, where it demonstrated reduction.

Availability in Public Sector: In public sector, the availability of both OBs and LPGs was poor in both years. None of the mean availabilities touched the benchmark of 80%. The mean percent availability of OBs improved from 6.8% to 33.1%, whereas, in case of LPGs it reduced from 35.1% to 9%. The individual percent availabilities of each medicine (OB and LPG) are given in table S1. For better understanding of the data, we have used the data visualization tool in R and plotted a box plot of the data as shown in figure 1. The box plot showed distributional characteristics of the percent availability of medicines in two groups (OB and LPG) for the years 2017 and 2019. The mean percent availability is represented by the dot inside the box. In 2017,

availabilities of 75% of the OBs in public sector were less than 11.2% as shown by the 3rd quartile or the upper bar of the 1st box plot. Whereas, in 2019, 75% of the OBs had availabilities higher than 6.3% which is almost equivalent to the mean percent availability (6.8%) in 2017. This indicates a substantial increase in the availability of OBs in public sector. In 2019, 75% of the LPGs had the availability of less than 12.5% (3rd quartile) whereas before the implementation of the NDPP 2018, 75% of the LPGs had availabilities of more than 14.3% (1st quartile). This showed a remarkable decrease in the availability of LPGs in public sector in 2019.

Availability in private sector: In both years, the overall availability was better in private sector than the public sector. Mean percent availability of both OBs and LPGs were improved in 2019 i.e. 55.0% to 58.3% and 20.3% to 32.3%, respectively. Availability of LPGs was less than OBs in both years. For OBs, the mean percent availability improved slightly by 3.3% while data distribution remained almost the same across the years, as shown in the box plot (figure 1). For LPGs, a substantial increase in the availability was observed in terms of mean percent availability, maximum value and change in data distribution (figure 1). In 2017, the IQR (range between upper and lower bar of the box) for percentage availability of LPGs ranged from 6% to 31% whereas it got improved in 2019 and ranged from 6% to 50%.

Availability in different subgroups of medicines: When we compared availability of LPGs and OBs in different subgroups of medicines as shown in table 1, we found that mean percent availabilities of all global list medicines were higher than supplementary medicines in both years. Similarly, the availability of NEML medicines were higher than non-NEML medicines except for the non-NEML LPGs in public sector, which were higher than NEML LPGs (19.2% vs 8.1%). In 2017, in public sector, the availability of OBs for NCD medicines (6.7%) were lower than OBs for ID medicines (7.7%), whereas the availability of LPGs (35.9%) were better than LPGs of ID medicines (33%). Surprisingly, in 2019, the situation inversed completely for NCD medicines, increased and decreased availability of OBs (33.2%) and LPGs (33.1%), respectively, whereas, the availability decreased for LPGs (8.8%) and increased for OBs (9.5%) for ID medicines.

Table 1. Mean Percent Availabilities of Originator Brands (OBs) and Lowest Price Generics (LPGs) at both public and private sectors.

	Availability in 2017 (Mean, SD) ,%				**Availability in 2019 (Mean, SD) ,%**				**Change in mean percent availability (%)**			
	Public Sector		**Private Sector**		**Public Sector**		**Private Sector**		**Public Sector**		**Private Sector**	
	OBs	**LPGs**	**OBs**	**LPGs**	**OBs**	**LPGs**	**OBs**	**LPGs**	**OBs**	**LPGs**	**OBs**	**LPGs**
All medicines (n=50)	6.8 (10.4)	35.1 (23.6)	55 (31.1)	20.3 (14.4)	33.1 (27.8)	9 (14.9)	58.3 (32.3)	32.3 (26)	26.3	-26.1	3.3	12
Global Medicines (n=14)	11.2 (15.2)	50.1 (32.1)	64.3 (22.5)	25.9 (14.5)	48.4 (31.5)	14.3 (19.9)	66.5 (31.2)	43.8 (27.8)	37.2	-35.8	2.2	17.9
Supplementary medicines (n=36)	5 (7.0)	29.2 (21.4)	51.4 (33)	18.1 (14)	27.2 (24.1)	7 (12.1)	55 (32.6)	27.8 (24.1)	22.2	-22.3	3.6	9.7

NEML medicines (n=46)	7.2 (10.7)	35.5 (26)	55.3 (31)	20.7 (14.6)	33.9 (28.1)	8.1 (15.1)	58.4 (32.9)	33.3 (26.3)	26.7	-27	3.1	12.6
Non-NEML medicines (n=4)	1.8 (3.0)	35.5 (34)	51.6 (36)	15.6 (11)	24.8 (25)	19.2 (7)	56.3 (28)	20.3 (21)	23	-16	4.7	4.7
NCD medicines (n=36)	6.4 (9.2)	35.9 (25.5)	55.7 (28.8)	20 (14.3)	33.2 (27)	8.8 (14)	62.3 (29.3)	31.3 (25)	26.8	-27.1	6.6	11.1
ID medicines (n=14)	7.7 (13.3)	33 (29)	53.1 (37.3)	21 (15)	33.1 (30.5)	9.5 (17.4)	47.8 (38.1)	34.8 (29.2)	25.4	-23.5	-5.3	13.8

Where, SD refers to Standard deviation, NEML refers to National Essential Medicine List, NCD refers to Non Communicable Diseases and ID refers to Infectious Diseases.

Availability at different levels of healthcare: When we compared the availability at different levels of public healthcare sectors i.e. primary, secondary and tertiary, the availability of OBs improved in 2019, while it was decreased for LPGs. The pattern of overall medicines availability remained almost the same as of 2017 i.e. tertiary care>secondary care>primary care as shown in table S2.

Medicine Prices

An overall increase was noted in all adjusted MUPs and adjusted MPRs between 2017 and 2019 for both OBs and LPGs as shown in Table 2. In 2019, for all 42 available OBs, the adjusted MUPs and MPRs significantly increased by a median of 4.3% (Wilcoxon test p=0.001, p=0.0001). Whereas in case of all 37 available LPGs, the adjusted MUPs and MPRs were increased by a median of 15.7% (p=0.002, p=0.0002). In 2017, the MPRs of OBs ranged from 0.58 to 60.62 in 2017 and 0.73 to 77.59 in 2019. 63% of the OBs had MPR of more than 2. Whereas, in 2019 almost 75% of the OBs had MPR greater than 2.The MPRs of LPGs ranged from 0.42 to 19.95 in 2017 and 0.39 to 19.89 in 2019. In 2017, for LPGs, the median value of MPR was less than 2 (i.e. 1.36) while in 2019 this median value became greater than 2 (i.e. 2.26). This means that many LPGs which were previously affordable got shifted to the high priced medicines category in 2019. The MUPs and MPRs for all OBs is given in table S3 and for all LPGs is given in table S4.

Table 2. Median price ratios (MPRs) and median unit prices (MUPs) of originator brands (OBs) and lowest price generics (LPGs) in private sector among different subgroups across the years 2017 and 2019.

Originator Brands (OBs)					
	MPR-2017	**MPR-2019**	**MUP 2017 (PKR)**	**Adjusted MUP 2019 (PKR)**	**Median percent change in MUPs/MPR**
All medicines (n=42)	2.5	3.2	6.99	8.49	4.29%
Global Medicines (n=13)	2.8	3.2	7.66	8.22	3.35%
Supplementary medicines (n=29)	2.5	3.3	6.38	10.1	5.1%
NEML medicines	2.4	3.3	6.38	8.51	5.1%

(n=39)					
Non-NEML medicines (n=3)	3	3.2	7.66	8.22	1.93%
NCD medicines (n=36)	2.6	3.3	6.19	7.83	3.35%
CD medicines (n=10)	2.3	2.9	24.3	31.2	7.36%
Lowest Price Generics (LPGs)					
	MPR-2017	**MPR-2019**	**MUP 2017 (PKR)**	**Adjusted MUP 2019 (PKR)**	**Median percent change in MPR/MUP**
All medicines (n=37)	1.4	2.3	5.8	6.29	15.7%
Global Medicines (n=13)	1.6	2.7	5.8	6.56	19.2%
Supplementary medicines (n=24)	1.3	2.2	5.9	6.04	14.8%
NEML medicines (n=34)	1.4	2.2	5.4	6	15.8%
Non-NEML medicines (n=3)	2.5	2.7	6.5	6.7	3.97%
NCD medicines (n=26)	1.2	2.2	4.1	5.4	16.3%
CD medicines (n=11)	1.8	2.4	8.4	10.9	14.8%

Where PKR is Pakistani Rupee.

The price data was also analyzed in different subgroups as shown in table 2. There was an increase in MUPs and MPRs for OBs of supplementary list of medicines compared to medicines from global list (5.5% vs 3.35%). However, it was inverse in case of LPGs, i.e. the prices of global medicines increased compared to supplementary medicines (19.2% vs 14.8%).Increment in the prices of NEML medicines was more as compared to non-NEML medicines. Next, we compared the medicines used for NCDs and IDs. Data suggested that the increase in the MUPs and MPRs of OBs for IDs was significant in comparison to NCDs (11.2% vs 7.36%). Whereas it was completely opposite in the case of LPGs, where the increase was greater for NCD than ID medicines (16.3% vs 14.8%). It is also noteworthy that increase in prices for LPGs is more significant than OBs for all subgroups of medicines.

Affordability

Between 2017 and 2019, the median NDWs required for treatment with all OBs (n=36) increased from 1.05 to 2 and 0.5 to 0.7 for all LPGs (n=31), respectively. In 2019, the median percent increase in NDWs for LPGs (n=31) was much higher as compared to OBs (n=36) i.e. 12.5% (p=0.008) and 3% (p=0.081) respectively. So, an overall increase in NDWs for both OBs and LPGs was observed between 2017 and 2019. Similarly the Median Treatment Prices (MTPs) for OB and LPGs also increased significantly i.e. 464 PKR to 563 PKR (p<0.001) and 244 PKR to 350 PKR (p<0.001), respectively. The MTPs and NDWs for each medicine are given in

supplementary tables S5 and S6. The medicines were categorized into seven disease groups to further analyze changes in the affordability between 2017 and 2019. In figure 2, a bar graph shows Median NDWs required for both OBs and LPGs in each disease group, where the values above 1 were considered unaffordable. In 2017, the median NDWs of OBs to treat three types of diseases i.e. CVDs (1.2), diabetes (1.4) and ulcers (2.75) were more than 1. Whereas in 2019, medicines for another disease category made its place into this list i.e. the medicines for IDs (1.18). Compared to 2017, the median NDWs for all OBs increased in 2019 except for OBs acting on Central Nervous System (CNS) and OBs to treat ulcers. The treatment for ulcer remained highly unaffordable in both years. The median NDWs for LPGs increased in 2019 for the treatment of Arthritis, CNS disorders, CVDs and IDs, while the modest decrease in median NDWs for LPGs was observed for some diseases i.e. asthma, diabetes and ulcers as shown in figure 2.

Discussion

This study provides a valuable insight in to the effects of NDPP 2018 associated changes on medicine prices, availability and affordability in both public and private healthcare sectors of Lahore division, Pakistan. The main objective of this updated policy was to improve the access to essential medicines (EMs) and improvise rational drug pricing. Our study has shown that the overall availability of medicines improved in 2019 in comparison to 2017 i.e. before the implementation of this policy, except for the LPGs in public sector, demonstrating reduction. Overall the medicine prices were increased significantly, making majority of the EMs used for the common ailments unaffordable, with a much higher price increases for LPGs in comparison to OBs. The medicines used to treat ulcers, diabetes and CVDs remained most unaffordable in both years. Despite the modest improvements in the availability of surveyed medicines after NDPP 2018, the increased unaffordability of the surveyed medicines earnestly require significant revisions and improvements in the current pricing policy to ensure the affordability of surveyed medicines to the patients.

Despite improvements in the availability of medicines between 2017 and 2019, the availability of medicine remained below the optimal benchmark of 80% [13]. In public sector the availability of OBs improved remarkably probably be due to decentralization procurement of medicines in public sector. Before 2018, the medicines were procured centrally for all the public sector hospitals except for teaching hospitals, within a province. But after 2018, the medicines procurement was decentralized for public sector hospital to allow hospitals in each district a free choice to select desired manufactures, thus, ending up in the selection of more OBs than LPGs, possibly due to quality concerns about medicines. Another factor that improved medicines availability after 2018 was authorization of hospitals to acquire medicines directly without any delays. However, as practiced in the previous central supply system, the medicines were received centrally from the manufacturers before reaching the concerned hospital with considerable effect on timely availability of medicines. In both years, the mean percentage availabilities for all medicines were found higher in the private sector compared to the public sector, corroborating similar previous studies conducted in Bangladesh and Malawi in 2019 [21, 22]. The overall availability of medicines from NEML was slightly better than non-NEML medicines in both public and private sectors. This might be attributed to the active role of DRAP in the revision and

subsequent dissemination of the revised NEML i.e. NEML 2018 [15]. Furthermore, the public hospitals are encouraged to procure drugs from the latest NEML 2018 that has been standardized in line with WHO essential medicines model list 2017 [23]. Besides, a mobile application was launched in 2018 with user friendly interface to better disseminate the information on enlisted medicines [24]. So, the NDPP 2018, doesn't seem to be solely responsible for the availability of medicines.

Although we found some improvements in the availability of medicines, there was a substantial increase in medicine prices, making them inaccessible for most of the population. According to one estimate approximately 46 million people are living below the national poverty line in Pakistan (as per 2015) [8]. The increases in prices of both OBs and LPGs may fairly be attributable to the NDPP 2018, that allows an annual increase in the prices of scheduled drugs up to 70% of CPI compared to 50% of CPI as per NDPP 2015 [9, 10]. These changes in price calculations seems to accentuate the substantial impact on overall prices of medicines, thus, making them more expensive. The increase in LPGs prices were more significant as compared to OBs suggesting that with already expensive OBs, the price increase in LPGs would impoverish the overall access to medicines, imputable to the changes in formula for LPGs (new entrants) price calculation. According to NDPP 2018, the MRP of new entrant first generic should be fixed at 20% less than that of OB compared to NDPP2015, where it was 30% less than MRP of OB. Another possible variable is the prior availability of generics in the market for price calculation, where, according to NDPP2018, the MRP of a new entrant (LPGs) was fixed equal to the highest MRP of the available generics in the market, while as per NDPP2015 practice, MRP was fixed by taking the average of other generics in the market. Therefore, these changes in price calculating mechanisms might have led to higher prices of many new LPGs in the market. Hence, contrary to NDPP 2018's price steerage objectives, the increase in medicine prices was more distinct for NEML medicines as compared to non-NEML medicines.

Data from further analysis on affordability of standard treatment by selected OBs and LPGs suggested that majority of the medicines have become more unaffordable in 2019. When the affordability was compared for medicines of different disease groups, the three foremost unaffordable OBs were ones for treatment of ulcers, diabetes and CVDs. Additionally, the treatment for ulcers remained exceptionally unaffordable with OBs and LPGs in both years. Nevertheless, the treatment of CVDs and diabetes with LPGs remained affordable in 2017 but the NDWs for CVDs surpassed affordability threshold in 2019. Among the disease categories, NCDs harbor the top three unaffordable slots. It is noteworthy, that the burden of NCDs is increasing worldwide and is responsible for higher mortality rates than all other diseases combined [25-27]. The CVDs, diabetes, cancer and chronic respiratory diseases are responsible for about 80% of these deaths [28]. Pakistan is among top 10 countries where prevalence of diabetes is very high. Besides, one third of Pakistanis, above 45 years of age have hypertension [29-31]. Thus, the unaffordability of the essential medicines for NCDs, such as CVDs and diabetes, has worse bearing on affordability associated therapeutic outcomes that ultimately leads to increased morbidity and mortality due to un-controlled disease.

Additionally, we also compared the median drug prices in 2019 with the prices published/allowed by DRAP in its latest Statutory Regulatory Orders (SROs). On December 31, 2018, the DRAP revised and published the maximum retail prices (MRPs) of about 1084 drugs through SRO-1608, SRO-1609 and SRO-1610 [32]. Eighteen OBs from our study sample were part of these price revisions (table 3). Surprisingly, after comparing the MUPs of 18 selected OBs with prices allowed by the government, we found that most of the OBs, 14 out of 18, were sold at higher prices than the allowable prices – with median percent increase of 29.37%. These data suggested that these intentional malpractices by the drug sellers might be driven by poor price control regulation by price enforcement authorities. Therefore, the current drug pricing policy NDPP 2018, is not the sole reason for the price hike. Most probably main stakeholders in the drug supply chain are also contributing towards medicine inflated prices. Thus, it's reasonable to deduce that these factors may interfere with measuring the direct impact of current pricing policy.

Table 3. Maximum retail unit prices (MRPs) of Originator Brands (OBs) allowed by the government versus median unit prices (MUPs) found in private sector pharmacies.

Medicine Name	Strength (Dosage form)	Allowed Unit Price (PKR)	MUP 2019 (PKR)	Percentage difference
Aciclovir	200mg (tab)	52.6	75	42.5%
Amlodipine	5mg (tab)	8.5	13	52.9%
Amoxicillin	250mg (cap)	3.75	3.75	0%
Amoxicillin	500mg (cap)	5.58	8.75	56.8%
Atorvastatin	20mg (cap)	141.37	203.5	43.9%
Bisoprolol	5mg (tab)	15.35	16.72	8.9%
Carbamezipine	200mg (tab)	4	5	25%
Ceftriaxone	1g (inj)	783	783	0%
Ciprofloxacin	500mg (tab)	39.25	52.5	33.7%
Digoxin	0.25mg (tab)	1.75	2.68	53.1%
Fluconazole	200mg (cap)	425	585	37.6%
Insulin N	100IU (vial)	88.47	75.88	-14.2%
Insulin R	100IU (vial)	93.88	75.88	-19.1%
Methyldopa	250mg (tab)	7.71	8.1	5.05%
Omeprazole	20mg (cap)	42.9	52.29	21.8%
Propranolol	40mg (tab)	1.1	3.16	187.2%
Pyremethamine+Sulfadoxime	(25+500)mg (tab)	12.01	12.02	0.08%
Simvastatin	20mg (cap)	47.01	68	44.6%
Medians		27.3	34.505	29.3%

Although the formation of a national scale pricing policy is laudable but it seems to be a collection of drug price calculation formulas only. It should also include the mechanism for price monitoring, an aspect which seems to be one of the major reasons behind failure to achieve the goals of NDPP 2018. Inclusion of WHO/HAI based surveys on regular basis could also be an option, in this case. The WHO has developed a mobile application named "WHO Essential

Medicines and Health Products Price and Availability Monitoring (WHO EMP MedMon)", which can be used to collect and analyze price and availability data from health care outlets. This application is based on standard WHO/HAI methodology and it can be used both online and offline, making it both time saving and cost effective [33]. The drug inspectors or a third party can be given this responsibility to monitor and report the prices using WHO EMP MedMon on a regular basis, ensuring the compliance by drug manufacturers and sellers to NDPP. There could be many other policy implications having an impact on drug pricing, availability and affordability. The procurement of medicines should be strictly based on the NEML. Clear cut mechanism for NEML based procurement should be devised and implemented specially in the public sector hospitals. Besides, the hospital pharmacy and therapeutics committees must actively evaluate the safety, efficacy and cost-effectiveness of drugs before purchasing. Pharmaco-economic evaluations of drugs must be promoted by allocating research funds to experts. Not all drugs should be fully reimbursed in the hospitals, only essential medicines must be included in this list. Hence, the profits from other drugs can be used to purchase essential drugs when needed. Smooth functioning of the drug supply chain with proper quality control must be ensured. The current inflated prices would have a grave impact on the access to essential medicines, especially for the low and middle income population of Pakistan. Thus, there is dire need to develop clearer evidence based and stringent price control policy, especially for essential medicines. Exempting or reducing taxes and tariffs on EMs and promotion of local generic manufacture by providing subsidies on raw materials may improve both the availability and affordability of these medicines. While using the External Reference Pricing (ERP) mechanism, the reference countries should be chosen critically e.g. countries with similar pharmaceutical market and economic status. For costly medicines, regressive markups must be encouraged over progressive markups. The drug prices must be monitored on regular basis using a validated and well-designed scientific methodology and pricing policy must be revised based on such evidences. The essential medicines for most prevalent diseases such as diabetes and CVDs must be preferentially made affordable by devising some specific pricing strategies for these medicines. Besides, efforts must be made to enforce the pricing policy effectively by introducing reward and punishment system to induce a healthy competition among the drug manufacturers and sellers.

Although, this study provides an objective evidence to the policy makers for improving the current pricing policies. It has some limitations as well. The study includes medicines with specific strengths and dosage forms to compare with IRPs. There might be other strengths/dosage forms of the surveyed medicines, available in the health facilities, so the availability of the medicines may be underestimated. The affordability was calculated for single medicine for each disease, whereas patients are usually taking more than one drug at a time – under-estimating the extent of affordability of a specific treatment for a specific disease. Moreover, the post survey was conducted after about a year from the launch of new drug pricing policy 2018, so the results do not reflect the long term impact of the policy. Further surveys could be conducted in future to gauge the long term effects of the policy as it was done by Fang et al in two such surveys conducted after the health reform in China [17].

In Conclusion, the availability of medicines has been improved after the launch of a new drug pricing policy by Pakistani government but it still below the benchmark, thus, forcing the patients

to buy medicines from private sector at their own expense. The prices of both LPGs and OBs of EMs have increased remarkably in 2019, when compared with 2017. The medicines to treat most prevalent non-communicable diseases (diabetes and CVDs) have become more expensive and unaffordable. The maximum retail prices of several OBs have been illegally increased in the market, adding more burden on patients' pockets. Thus, the pricing policy should be improved with strict price control measures, especially for the EMs, such as ensuring transparency on the costs of drug development process and distribution, NEML based procurement, and reduction in the taxes and tariffs on local production of EMs.

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Contributions

AS, ZB and YF conceptualize the study. ZS, HS, AS and ZB designed methodology. ZS, HS, AS trained the data collectors and obtained the data. YF provided resources and supervised the project. ZS worked as survey area manager. MA, AHG, NA, FK and MZ did data cleaning, validation and entry. AS, HS, CY, MJ analyzed the data. AS and HS wrote original draft. YF, ZB, ZS, CY and MJ, WJ reviewed and edited the manuscript.

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Competing Interests

None

Patient Consent for Publication

Not Required

Ethics Approval

Ethics approval was obtained from the Medical Ethics Committee of Xi'an Jiaotong University under study ID 2019-067.

Data availability statement

Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi:10.5061/dryad.tqjq2bvwq

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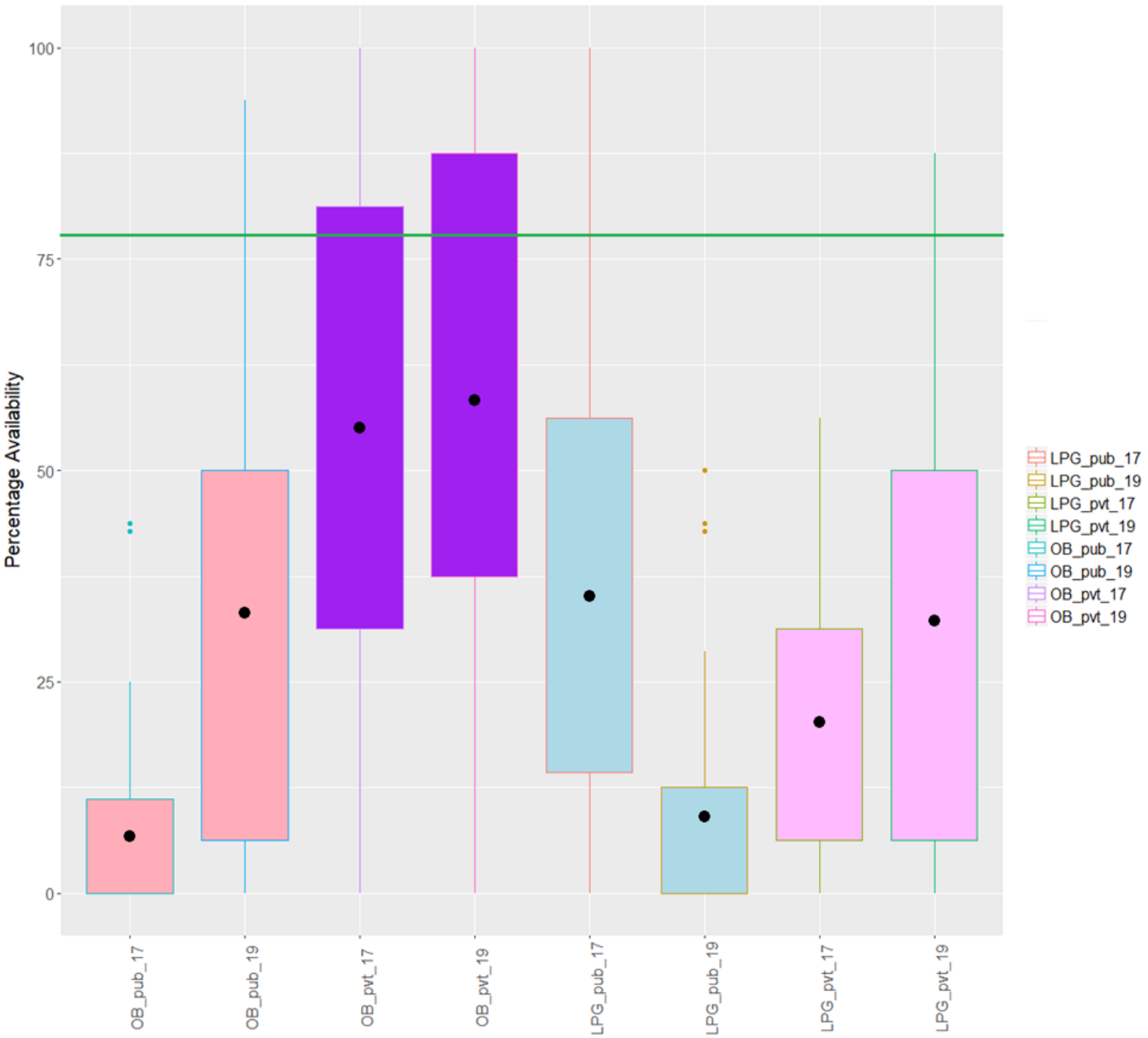
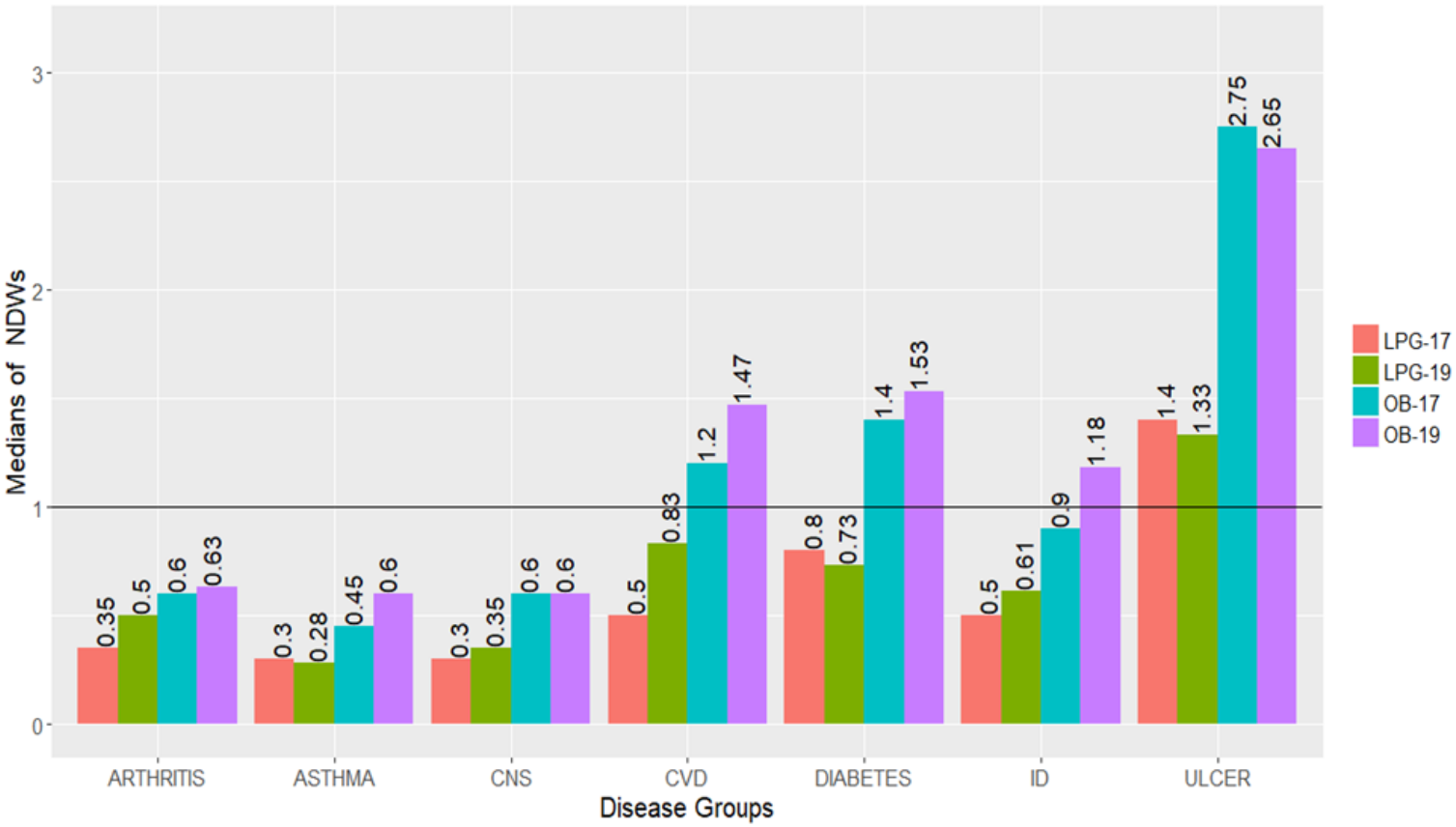
Figure 1. Box plot of percent availability of lowest price generics (LPGs) and originator brands (OBs) in both public (pub) and private (pvt) sectors in 2017 and 2019. This box plot shows the distributional characteristics of the percent availability of medicines in two groups (OB and LPG) for the years 2017 and 2019. The mean percent availability is represented by the dot inside the box.

Figure 2. Bar graph of affordability of originator brands (OBs) and lowest price generics (LPGs) for different diseases in both years i.e. 2017 and 2019.





Supplementary Tables

Table S1. Percent availabilities and of originator brands (OBs) and lowest price generics (LPGs) of all medicines in public and private sector in 2017 and 2019 (%)

Names of meds	OB (Public) 2017	OB (Pvt.) 2017	LPG (Public) 2017	LPG (Pvt.) 2017	OB (Public) 2019	OB (Pvt) 2019	LPG (Public) 2019	LPG (pvt.) 2019
Acetylsalicylic Acid	0.0	25.0	56.3	25.0	18.8	75.0	50.0	18.8
Aciclovir	0.0	50.0	25.0	37.5	6.3	18.8	0.0	50.0
Amiodarone	7.1	62.5	21.4	6.3	0.0	62.5	21.4	0.0
Amitriptyline	0.0	31.3	0.0	25.0	0.0	0.0	50.0	50.0
Amlodipine	6.3	75.0	62.5	31.3	37.5	93.8	12.5	56.3
Amoxicillin	43.8	93.8	18.8	25.0	93.8	68.8	0.0	37.5
Amoxicillin (250)	18.8	100.0	12.5	31.3	50.0	87.5	0.0	37.5
Atenolol	12.5	87.5	81.3	43.8	43.8	81.3	0.0	56.3
Atorvastatin	7.1	50.0	21.4	25.0	42.9	62.5	21.4	18.8
Azithromycin	0.0	25.0	25.0	31.3	31.3	25.0	25.0	75.0
Beclometasone inhaler	0.0	6.3	35.7	12.5	35.7	43.8	0.0	0.0
Bisoprolol	6.3	87.5	18.8	25.0	37.5	81.3	0.0	56.3
Captopril	0.0	81.3	85.7	25.0	50.0	93.8	28.6	50.0
Carbamazepine	12.5	87.5	56.3	25.0	25.0	31.3	0.0	56.3
Ceftriaxone injection	14.3	68.8	71.4	31.3	21.4	75.0	50.0	87.5
Ciprofloxacin	0.0	81.3	100.0	37.5	64.3	93.8	14.3	25.0
Clarithromycin	0.0	87.5	35.7	25.0	50.0	93.8	0.0	56.3
Co-trimoxazole suspension	6.3	31.3	62.5	6.3	6.3	6.3	43.8	6.3
Diazepam	6.3	62.5	12.5	0.0	43.8	68.8	0.0	0.0
Diclofenac	42.9	50.0	35.7	6.3	85.7	93.8	0.0	81.3
Digoxin	21.4	62.5	28.6	0.0	28.6	68.8	0.0	56.3
Enalapril	0.0	68.8	62.5	18.8	12.5	68.8	12.5	50.0
Fluconazole	0.0	37.5	18.8	25.0	43.8	43.8	0.0	50.0
Fluoxetine	0.0	43.8	12.5	43.8	6.3	62.5	6.3	62.5
Fluphenazine Decanoate	0.0	0.0	0.0	12.5	0.0	0.0	7.1	6.3
Furosemide	12.5	93.8	50.0	6.3	50.0	87.5	0.0	0.0
Glibenclamide	18.8	68.8	56.3	12.5	68.8	93.8	0.0	12.5
Gliclazide	0.0	75.0	0.0	18.8	7.1	75.0	0.0	31.3
Hydrochlorothiazide	0.0	0.0	0.0	12.5	18.8	0.0	0.0	0.0
Indinavir	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Insulin Isophane (NPH)	0.0	75.0	50.0	25.0	56.3	68.8	0.0	18.8
Insulin Neutral Soluble (Regular)	0.0	68.8	50.0	25.0	68.8	68.8	0.0	18.8
Losartan	7.1	43.8	14.3	43.8	0.0	43.8	42.9	43.8
Lovastatin	0.0	0.0	6.3	0.0	6.3	37.5	12.5	0.0

Metformin	25.0	81.3	56.3	31.3	68.8	93.8	0.0	50.0
Methyldopa	12.5	81.3	25.0	0.0	75.0	68.8	0.0	0.0
Metronidazole	25.0	93.8	56.3	37.5	75.0	87.5	0.0	56.3
Nevirapine	0.0	0.0	14.3	0.0	0.0	0.0	0.0	0.0
Nifedipine Retard	0.0	75.0	28.6	12.5	0.0	31.3	14.3	12.5
Omeprazole	6.3	56.3	75.0	37.5	62.5	62.5	6.3	50.0
Omeprazole (10)	0.0	12.5	43.8	18.8	18.8	0.0	12.5	31.3
Paracetamol suspension	6.3	68.8	87.5	25.0	81.3	87.5	0.0	81.3
Phenytoin	0.0	6.3	12.5	6.3	0.0	50.0	6.3	0.0
Propranolol	12.5	68.8	12.5	6.3	18.8	87.5	0.0	25.0
Pyrimethamine with sulfadoxine	0.0	75.0	21.4	6.3	21.4	68.8	0.0	6.3
Ranitidine	0.0	81.3	31.3	25.0	50.0	100.0	0.0	50.0
Salbutamol inhaler	0.0	81.3	56.3	31.3	62.5	68.8	0.0	12.5
Simvastatin	0.0	25.0	21.4	56.3	0.0	37.5	7.1	25.0
Spironolactone	6.3	62.5	25.0	0.0	12.5	93.8	6.3	43.8
Zidovudine	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Mean availabilities	6.8	55.0	35.1	20.3	33.1	58.3	9.0	32.3

Table (S2). Change in availability at different levels of healthcare (Public Sector).

	Primary level (n=2 outlets)		**Secondary level (n=13 outlets)**		**Tertiary level (n=1 outlet)**	
	All medicines (n=50)		**All medicines (n=50)**		**All medicines (n=50)**	
	OB	**LPG**	**OB**	**LPG**	**OB**	**LPG**
Mean Availability 2017 (SD),%	0.0 (0.0)	25.8 (44.5)	7.1 (11.2)	35.2 (27.5)	12.0 (32.8)	50.0 (50.5)
Mean Availability 2019 (SD) ,%	21.0 (31.0)	3.2 (18)	32.3 (29.1)	7.4 (13.4)	68.0 (47.1)	22.0 (41.8)
Change in mean percent availability,%	21.0	-22.6	25.2	-27.8	56.0	-28.0

Table S3. Change in median unit prices (MUPs) and median price ratios (MPRs) of the Originator Brands (OBs) at private sector.

Sr. no.	Medicines (OB)	MUPs 2017 (PKR)	MPR 2017	Adjusted MUP in 2019	MPR 2019	Percentage change in MUPs/MPRs
1	Acetylsalicylic Acid	1.16	0.8	1.12	0.7	-3.41%
2	Aciclovir	70	20	72.5	21	3.48%
3	Amiodarone	17.78	2.2	17.4	2.2	-2.15%
4	Amlodipine	11.93	7.3	12.6	7.7	5.1%
5	Amoxicillin	8.616	2.8	8.46	2.7	-1.83%
6	Amoxicillin (250)	3.56	2.1	3.63	2.2	1.83%
7	Atenolol	6.19	5.6	6.14	5.5	-0.81%
8	Atorvastatin	201.9	18	197	18	-2.6%
9	Azithromycin	40	1.7	118	5	66.2%
10	Beclometasone inhaler	1.25	1.2	1.84	1.8	32%
11	Bisoprolol	11.28	1.2	16.2	1.7	30.2%
12	Captopril	7.66	3	8.22	3.2	6.81%
13	Carbamazepine	4.91	2.6	4.84	2.5	-1.55%
14	Ceftriaxone injection	672	16	757	18	11.2%
15	Ciprofloxacin	50.4	13	50.8	13	0.72%
16	Clarithromycin	65.7	2.5	76.4	2.9	14%
17	Co-trimoxazole suspension	0.29	0.6	0.44	0.9	33.4%
18	Diazepam	2	2	1.93	1.9	-3.41%
19	Diclofenac	5.625	12	5.61	12	-0.29%
20	Digoxin	2.52	2.4	2.59	2.5	2.76%
21	Enalapril	5.85	5.4	6	5.6	2.43%
22	Fluconazole	442	61	566	78	21.9%
23	Fluoxetine	43.42	9.7	43	9.6	-0.9%
24	Furosemide	1.89	3	2.34	3.7	19.2%
25	Glibenclamide	1.69	2.9	2.09	3.5	19.1%
26	Gliclazide	7.6	1.5	16.4	3.3	53.8%
27	Insulin Isophane (NPH)	64.5	1.1	73.4	1.3	12.1%
28	Insulin Neutral Soluble (Regular)	64.5	1.1	73.4	1.2	12.1%
29	Losartan	51.67	4.3	50.3	4.2	-2.76%
30	Metformin	1.54	1	1.62	1	5.21%
31	Methyldopa	6.38	1.9	7.83	2.3	18.5%
32	Metronidazole	1.57	1.3	1.52	1.2	-3.41%
33	Nifedipine Retard	5.69	2.7	5.8	2.8	1.93%
34	Omeprazole	49.78	34	50.6	35	1.55%
35	Paracetamol suspension	0.85	1.6	2.2	4.1	61.4%
36	Phenytoin	5.2	4.8	23.2	22	77.6%
37	Propranolol	1.55	2.2	3.06	4.3	49.3%

38	Pyrimethamine with sulfadoxine	5.83	1.4	11.6	2.8	49.8%
39	Ranitidine	8.8	3.7	8.51	3.6	-3.41%
40	Salbutamol inhaler	1	1	1.03	1.1	3.35%
41	Simvastatin	67.13	12	65.8	12	-2.09%
42	Spironolactone	8.6	0.8	10.1	1	14.5%
Medians		6.99	2.5	8.49	3.2	4.29%

Table S4. Change in median unit prices (MUPs) and median price ratios (MPRs) of the lowest price generics (LPGs) in private sector.

Sr. no.	**Medicines**	**MUPs 2017 (PKR)**	**MPR 2017**	**Adjusted MUP in 2019**	**MPR 2019**	**Percentage change in MUPs/ MPRs**
1	Acetylsalicylic Acid	1.015	0.7	1.06	0.7	4.58
2	Aciclovir	12.4	3.6	13.5	3.9	8.41
3	Amitriptyline	1.19	1.4	1.24	1.4	3.86
4	Amlodipine	1.8	1.1	6.29	3.8	71.4
5	Amoxicillin	5.8	1.9	8.32	2.7	30.3
6	Amoxicillin (250)	3	1.8	3.48	2.1	13.8
7	Atenolol	2.05	1.8	2.47	2.2	16.9
8	Atorvastatin	37.5	3.4	35.8	3.2	-4.8
9	Azithromycin	40	1.7	19.3	0.8	-107
10	Bisoprolol	6.55	0.7	6.56	0.7	0.1
11	Captopril	6.5	2.5	6.77	2.7	3.97
12	Carbamazepine	3.3	1.7	4.35	2.3	24.2
13	Ceftriaxone injection	280	6.8	290	7	3.48
14	Ciprofloxacin	11	2.8	24.2	6.2	54.5
15	Clarithromycin	36	1.4	42.7	1.6	15.8
16	Co-trimoxazole suspension	0.21	0.4	2.32	4.7	91
17	Diclofenac	3.5	7.5	4.79	10	26.9
18	Enalapril	2.05	1.9	2.84	2.6	27.8
19	Fluconazole	145.5	20	145	20	-0.3
20	Fluoxetine	13.8	3.1	13.5	3	-1.9
21	Fluphenazine Decanoate	90.5	1	93.8	1.1	3.5
22	Glibenclamide	1.57	2.7	1.42	2.4	-10
23	Gliclazide	4.75	0.9	5.8	1.1	18.1

24	Insulin Isophane (NPH)	48	0.8	62.3	1.1	22.9
25	Insulin Neutral Soluble (Regular)	48	0.8	62.3	1	22.9
26	Losartan	11	0.9	13.1	1.1	15.7
27	Metformin	1.5	1	1.86	1.2	19.2
28	Metronidazole	1.5	1.2	1.93	1.6	22.4
29	Nifedipine Retard	2.65	1.3	5.14	2.4	48.4
30	Omeprazole	15.35	10	11.4	7.8	-35
31	Omeprazole (10)	12.14	0.9	5.13	0.4	-137
32	Paracetamol suspension	0.47	0.9	1.02	1.9	53.7
33	Propranolol	0.66	0.9	2.03	2.8	67.5
34	Pyrimethamine with sulfadoxine	5	1.2	4.84	1.2	-3.4
35	Ranitidine	6.93	2.9	7.78	3.3	11
36	Salbutamol inhaler	0.64	0.7	0.68	0.7	5.45
37	Simvastatin	8.5	1.6	16.6	3	48.7
	Medians	**5.8**	**1.4**	**6.29**	**2.3**	**15.7**

Table S5. Affordability of originator brands (OBs) for different diseases in 2017 and 2019, in private sector.

Disease	Medicine	Strength	Dosage form	No. of units needed per treatment	Duration of treatment	MTP 2017 (PKR)	NDWs 2017	MTP 2019 (PKR)	NDWs 2019
ASTHMA	Salbutamol Inhaler	100mcg/ dose	Inhaler	200	As needed	200	0.4	214	0.4
	Beclomethasone	50mcg/dose	inhaler	200	As needed	250	0.5	380	0.8
Cardiovascular Diseases	Bisoprolol	5mg	tab	60	30	676.8	1.5	1003	2
	Atenolol	50mg	tab	30	30	185.7	0.4	190.5	0.4
	Captopril	25mg	tab	60	30	459.6	1	510	1
	Amlodipine	5mg	tab	60	30	715.8	1.5	780	1.6
	Amiodarone	200mg	tab	60	30	1066.8	2.3	1080	2.2
	Losartan	50mg	tab	60	30	3100.2	6.6	3120	6.2
	methyldopa	250mg	tab	90	30	574.2	1.2	729	1.5
	Nifedipine retard	20mg	tab	90	30	512.1	1.1	540	1.1

	Spironolactone	100mg	tab	30	30	258	0.5	312	0.6
	Propranolol	40mg	tab	90	30	139.5	0.3	284.4	0.6
	Acetylsalicylic acid	75mg	tab	30	30	34.8	0.1	34.8	0.1
Anti hyperlipidemics	Simvastatin	20mg	Cap/tab	30	30	2013.9	4.3	2040	4.1
	Atorvastatin	20mg	Cap/tab	30	30	6057	13	6105	12
Infections-Adult respiratory tract infection	Ceftriaxone Injection	1g/vial	Inj.	1	1	672	1.4	783	1.6
	Ciprofloxacin	500mg	tab	14	7	705.6	1.5	735	1.5
	Azithromycin	500mg	tab	3	3	120	0.3	367	0.7
	clarithromycin	500mg	tab	28	14	1839.6	3.9	2212	4.4
	Amoxicillin	500mg	cap	42	14	361.87	0.8	367.5	0.7
	Amoxicillin	250mg	cap	84	14	299.04	0.6	315	0.6
Fungal Infection	Fluconazole	200mg	cap	1	1	442	0.9	585	1.2
Viral Infection	aciclovir	200mg	tab	25	5	1750	3.8	1875	3.8
Amoebiasis	metronidazole	400mg	tab	21	7	32.97	0.1	32.97	0.1
CNS Drugs-Anti epileptics	Carbamezipine	200mg	tab	60	30	294.6	0.6	300	0.6
	Phenytoin	100mg	tab	90	30	468	1	2160	4.3
Anxiety	diazepam	5mg	tab	90	30	180	0.4	180	0.4
Anti Diabetics	Metformin	500mg	tab	90	30	138.6	0.3	151.2	0.3
	Glibenclamide	5mg	tab	90	30	152	0.3	194.4	0.4
	Gliclazide	80mg	tab	60	30	456	1.5	1020	2
	Insulin Isophane (NPH)	100IU/ml	vial	10	30	645	1.4	758.8	1.5
	Insulin Neutral Soluble (Regular)	100IU/ml	vial	10	30	645	1.4	758.8	1.5
Ulcer Treatment	Omeprazole	20mg	cap	30	30	1493.4	3.2	1569	3.1
	ranitidine	150mg	tab	120	30	1056	2.3	1056	2.1
Pain/Inflammation	Paracetamol	24mg/ml	susp	45	3	38.25	0.1	102.6	0.2
Arthritis	Diclofenac	50mg	tab	90	30	506.25	1.1	522	1

Where, MTP: Median treatment price, NDWs: Number of days' wages

Table S6. Affordability of lowest price generics (LPGs) for different diseases in 2017 and 2019, in private sector.

Disease/Condition	Medicine	Strength	Dosage form	No. of units needed per treatment	Duration of treatment	MTP 2017 (PKR)	NDWs 2017	MTP 2019 (PKR)	NDWs 2019
ASTHMA	Salbutamol Inhaler	100mcg/dose	Inhaler	200	As needed	128	0.3	140	0.3
Cardiovascular Diseases/ Anti Hypertensives	Bisoprolol	5mg	tab	60	30	393	0.8	406.8	0.8
	Atenolol	50mg	tab	30	30	61.5	0.1	76.5	0.2
	Captopril	25mg	tab	60	30	390	0.8	420	0.8
	Amlodipine	5mg	tab	60	30	108	0.2	390	0.8
	Losartan	50mg	tab	60	30	660	1.4	810	1.6
	Nifedipine retard	20mg	tab	90	30	238.5	0.5	478.4	1
	Propranolol	40mg	tab	90	30	59.4	0.1	189	0.4
	Acetylsalicylic acid	75mg	tab	30	30	30.45	0.1	33	0.1
Anti hyperlipidemics	Simvastatin	20mg	Cap/tab	30	30	255	0.5	513.8	1
	Atorvastatin	20mg	Cap/tab	30	30	1125	2.4	1110	2.2
Infections- Adult respiratory tract infection	Ceftriaxone Injection	1g/vial	Inj.	1	1	280	0.6	300	0.6
	Ciprofloxacin	500mg	tab	14	7	154	0.3	350	0.7
	Azithromycin	500mg	tab	3	3	120	0.3	60	0.1
	clarithromycin	500mg	tab	28	14	1008	2.2	1238	2.5
	Amoxicillin	500mg	cap	42	14	243.6	0.5	361.2	0.7
	Amoxicillin	250mg	cap	84	14	252	0.5	302.4	0.6
Fungal Infection	Fluconazole	200mg	cap	1	1	145.5	0.3	150	0.3
Viral Infection	aciclovir	200mg	tab	25	5	310	0.7	350	0.7
Amoebiasis	metronidazole	400mg	tab	21	7	31.5	0.1	42	0.1
CNS Drugs- Anti epileptics	Carbamezipine	200mg	tab	60	30	198	0.4	270	0.5
Depression	Amitriptyline	25mg	tab	60	30	71.4	0.2	76.8	0.2

Anti Diabetics	Metformin	500mg	tab	90	30	135	0.3	180	0.4
	Glibenclamide	5mg	tab	90	30	141	0	132.3	0.3
	Gliclazide	80mg	tab	60	30	285	0.8	360	0.7
	Insulin Isophane (NPH)	100IU/ml	vial	10	30	480	1	644	1.3
	Insulin Neutral Soluble (Regular)	100IU/ml	vial	10	30	480	1	644	1.3
Ulcer Treatment	Omeprazole	20mg	cap	30	30	460.5	1	353.7	0.7
	ranitidine	150mg	tab	120	30	831.6	1.8	966	1.9
Pain/Inflammation	Paracetamol	24mg/ml	susp	45	3	21.15	0	47.25	0.1
Arthritis	Diclofenac	50mg	tab	90	30	315	0.7	445.5	0.9

STROBE—checklist

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	Cross-sectional
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	
Objectives	3	State specific objectives, including any prespecified hypotheses	5	
Methods				
Study design	4	Present key elements of study design early in the paper	5	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6	WHO/HAI methodology
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		N.A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7	
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	*5,6,7*	
Bias	9	Describe any efforts to address potential sources of bias	5,6,7,	WHO/HAI validated methodology
Study size	10	Explain how the study size was arrived at	5,6,7	

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7	
		(*b*) Describe any methods used to examine subgroups and interactions	N.A	
		(*c*) Explain how missing data were addressed	N.A	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N.A	
		(*e*) Describe any sensitivity analyses		N.A
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N.A	
		(b) Give reasons for non-participation at each stage		
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N.A	
		(b) Indicate number of participants with missing data for each variable of interest	N.A	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N.A	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*N.A*	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*N.A*	
		Cross-sectional study—Report numbers of outcome events or summary measures	*7-9*	
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	7,8,9,10	Main results
		(*b*) Report category boundaries when continuous variables were categorized	N.A	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		N.A

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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15