Evaluating the impact of the change in regulations related to Medicine Pricing and Pharmacy Ownership in the Private Pharmaceutical Sector of South Africa

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A dissertation submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in Pharmacy

School of Health Sciences

Opinions expressed and conclusions arrived at, are those of the author.

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A thesis submitted to the School of Health Sciences, College of Health Science, University of KwaZulu-Natal, Westville Campus, for the degree of Doctor of Philosophy (Pharmacy).

This is a thesis in which the chapters are written as a set of research papers (published or submitted), with an overall introduction, literature reviews, a final summary.

This is to certify that the content of this thesis is the original research work of Mr Rajatheran Moodley.

DECLARATION

I, Rajatheran Moodley declare that

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DEDICATION

To my dad, NS Moodley (1 June 1929 – 2 June 2019) who has been a guiding light, my moral compass and my role model. I dedicate this dissertation in your loving memory. Sadly, you did not live to see me complete it: I love and miss you, dad.

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ABSTRACT

One of the imperatives of the post-1994 government was to improve access to medicines and related pharmaceutical services to previously disadvantaged areas. The government implemented multiple strategies to achieve this goal.

The first was to ensure the availability of quality affordable medicines to all its citizens. In the public sector, the government controlled the purchases through a tender system and ensured the availability and affordability of medicines to the majority of the population free at the point of service. In 2004 the government introduced the Single Exit Price (SEP), a transparent pricing system in the private sector for all prescription medicines comprising of a fixed ex-factory price with a logistics fee component (and value-added tax) for medicines sold to all purchasers other than the State.

This study presents two papers that evaluated a basket of 50 originator medicines and its available generics using the WHO/HAI methodology. Data were obtained from community pharmacy and pharmacy software vendors and subjected to an Interrupted Time Series (ITS) evaluation, where the changes in slope and levels of the medicines before and after regulations were obtained.

A second strategy was to look at opening up ownership of pharmacies with the goal of improving access to medicines and services. On 23 October 1997, Minister Zuma introduced the amendment to the Pharmacy Bill that intended removing the restriction that 'only people registered as pharmacists may own a pharmacy.' The objective of the open ownership policy change was to increase public access to pharmaceutical services by increasing the number of pharmacies, especially in outlying areas. This amendment came into effect in 2003.

While no extensive studies have been performed in South Africa to examine this change in ownership impact, research has suggested that open ownership has contributed to the demise of community pharmacy in rural areas (Blignault, 2010; Lowe, 2009). However, a comprehensive longitudinal evaluation has not been undertaken to date. It is unclear whether South Africa benefited from this policy or repeated the same mistakes as other countries, that have deregulated ownership, have demonstrated.

The third paper examines the opening, transfer, and closing of all pharmaceutical licenses as per the South African Pharmacy Council register prior to the changes in regulation and post-regulations up to 2014. Each license was tracked over time and mapped at a municipal and district level. The investigation further allowed for a population overlay to determine changes in access, ownership categories, and urban-rural access over time, and in this way, examined the impact of the change in policy and whether its intended outcomes were achieved. It addressed the gap in research and evidence in terms of the policy on the deregulation of pharmacy ownership. The research contributed to lessons for low- and middle-income (LMIC) countries, especially those on the African continent.

Conclusions:

Using interrupted time series methodology, the research confirmed that substantial price reductions were achieved through the Single Exit Price regulations. This was true in both the originator and generic medicine where possible savings were experienced in the private sector. While the liberalisation of the ownership laws in South Africa may have increased the number of pharmacies in the country it did not result in increased access in previously disadvantaged and rural areas to any marked degree.

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LIST OF ABBREVIATIONS

ANC	African National Congress
ARIMA	Auto Regressive Integrated Moving Average
BPS	Banco de Prescos em Saude
CMS	Council for Medical Schemes
COMED	Coordinating Committee for Medicines Procurement
CPI	Consumer Price Index
EML	Essential Medicine List
ERP	External Reference Pricing
EU	European Union
FIP	International Pharmaceutical Federation
GNP	Gross National Product
HAI	Health Action International
IRP	Internal Reference Price
ITS	interrupted-time-series
LMIC	Low- and Middle-Income Countries
MCC	Medicine Control Council
MeSH	Medical Subject Headings
MMAP	Maximum Medical Aid Price
NAPPI	National Pharmaceutical Product Index
NDoH	National Department of Health
NDP	National Drug Policy
NHA	National Health Accounts
NHI	National Health Insurance
NHIF	National Health Insurance Fund

No-POS	Complementary Health Plan of Colombia
OBIG	Österreichisches Bundesinstitut für Gesundheitswesen
OECD	Organisation for Economic Co-operation and Development
POS	Compulsory Health Plan of Colombia
PPI	Producer Price Index
RP	Responsible Pharmacist
SAHPRA	South African Health Product Regulatory Authorities
SEP	Single Exit Price
STG	Standard Treatment Guidelines
UHC	Universal Health Coverage
VAT	Value Added Tax
WHO	World Health Organization
ZAR	South African Rand

CHAPTER 1. INTRODUCTION

In order to achieve the fundamental goal of making healthcare available to all its population in South Africa, the democratic government introduced several health policy reforms since 1994. Any policy effort to improve health system performance must, as a matter of monitoring and evaluation, measure the appropriateness of its outcomes. Political scientists as early as the 1970s recognised that public policies were rarely implemented as designed and that those policy outcomes were rarely achieved as desired[1]. It is imperative therefore, that any policy change that is implemented in a country, even though it may work well in another country must always be evaluated in context[2]. A perfect scenario is for evaluation of policy change to begin well before its implementation but because of a lack of data, scarce administrative and organisational resources most policymakers take strategic decisions with the hope that it will be effective and sustainable[2]. The more straightforward evaluation approach is a before-and-after comparison, where outcomes are examined over time as reforms are implemented.

The thesis focuses on policy changes that may impact on both access and availability of medicines in the South African private market. In particular, it examines the implementation of the Single Exit Price (SEP) of medicines in 2004 and the introduction of open ownership regulation of community pharmacies in the same period. The literature research is accompanied by empirical studies that examined the price of a basket of medicines (originator and generic) from 1994 to 2014 and traces pharmacy licenses during the same period. The findings evaluate the success and failures of the new policies and assists in making recommendations towards the implementation of the National Health Insurance (NHI) and Universal Health Coverage (UHC). To achieve equitable pharmaceutical care, access within easy reach of patients, quality of care, affordability, and availability are critical elements required for success.

1.1. Background and Rationale for the Study

In 1994 the South African Government was faced with increasing medicine costs, a feature of the previous healthcare system where medicine expenditure was the main cost driver in the 1980 and early 1990's[3] with medicine expenditure reaching a 31.8% high of the total private market spend. This was in keeping with the several international reports in low- and middle - income countries (LMICs) where spending on medicines accounted for between 20-60% of healthcare budgets[4,5]. South Africa had the added problem[6] of the great racial divide in a two-

tiered healthcare system, the unequal distribution of resources both in infrastructure and healthcare professionals between urban and rural, and the high burden of disease that impacted the majority black population. The Government experienced the added burden of rectifying the wrongs of the past and finding solutions to the health crisis they found themselves in. The initiation phase of the generalised Human Immunodeficiency Virus (HIV) epidemic from 1989 to 1996 and the very rapid spread of the virus through 1996 to 2002[7] was a massive setback to the health plans as envisaged in the health charter. The health system inherited by the government in 1994 faced a quadruple burden[8] including HIV, Tuberculosis (TB), and Acquired immunodeficiency syndrome (AIDS); maternal, neonatal, infant and child mortality and morbidity; noncommunicable diseases; and trauma and injury. In 1992/93, South Africa spent 6.66% of its Gross National Product (GNP) on healthcare, with 3.44% being spent in the private sector. The private sector was responsible for 80% of the country's total expenditure[8] on medicines in 1990.

Medicine in healthcare systems forms an integral part of improving healthcare in this century including the increase in life expectancy[9]. Regulating medicine pricing is a challenging and complex exercise but leaving a market unregulated contributes to medicine price inflation and lack of pricing transparency and uniformity[10,11]. Price control is also said to be an important policy instrument but very controversial[12]. South Africa was faced with discounts, rebates, medicine bonusing and price discrimination. The State alleged that these perverse incentives added at least 50% to the final price of the medicine[12].

The National Drug Policy (NDP) was introduced in 1996[13]. The intention of the Government was to establish a pricing committee to regulate medicine prices, create transparency in the pricing structure from the manufacturer, wholesaler, distributor and providers of service, as well as to ensure a non-discriminatory pricing system through policy. The Medicines and Related Substance Control Amendment Act 90 of 1997, implemented on 2 May 2003, banned the offer of discounts and rebates to patients and healthcare providers (bonusing section 18G) and establishing a pricing committee (section 22G)[14] moving the private sector from a free market[15] to a regulated environment with the introduction of the Single Exit Price (SEP). The components of the single exit price include the ex-manufacturer price combined with the logistics fee (as determined by the manufacturer) and Value Added Tax (VAT)[16]. The SEP for each medicine in the market in 2004 was a mandatory declaration of the weighted average of all 2003 sales after taking into account all discounts and off-invoice rebates[17]. Further, the 1997 amendments to the Medicines and Related Substances Act in terms of section 18A, prevented

pharmaceutical manufacturers from offering discounts and or rebates[15]. The SEP is the only price available in the private sector across the country before the addition of the regulated dispensing fee to the end-user or patient. There is an annual regulated adjustment, and the regulation applies to all registered medicines and schedule substances as per the Medicines Act except those classified in the Schedule zero category which has been specifically exempted by the Minister of Health from the pricing regulations[14,16]. The SEP regulation excludes the Government or public sector where a tender process applies.

1.2. Significance of the Study

Sound pharmaceutical policies contribute to a country's socio-economic development, and the country needs economic growth for healthcare systems to perform well[18]. Policy further requires long-term strategic planning, effective regulations to ensure minimizing inefficiencies and unnecessary mark-ups in the supply chain and best possible pricing models to ensure access. Government interference in medicine pricing is opposed by market economist[19] who feel that markets should be left to its own devices, but medicine prices can determine the quality of life, especially for the most vulnerable.

In attempting to regulate the market in South Africa, the government implemented various strategies. It is critical to look at each of these strategies to assess its impact on the intention of the regulator but also for any unintended consequences that may result from the various strategies. Pammolli et al. (2001)[20] suggested that pricing mechanisms since 1990 may have contributed to the decline of medicine production. The implementation of the Chinese Medicine Policy may have resulted in a decrease of essential medicines in both the public and private sector between 2010 and 2012[21]. Some countries regulate prices on the assumption that competition is weak in this industry[22]. Danzon and Chao (2000) in their study of seven countries found that generic competition is significant in unregulated markets (United States (US), United Kingdom (UK), Canada, and Germany) and that regulations undermine generic competition in strict regulated systems (France, Italy, Japan)[22] and is counterproductive. They also concluded that in countries with strict regulatory systems, potential budgetary savings from post-patent competition are not fully realized.

Deregulated health systems have the potential of restricting access and making medicines unaffordable. In the Malaysian example medicine prices were found to escalate faster than the prices in developed countries[23]. The study concluded that medicine prices in the private sector,

for both innovator brands and generics were high, innovator brands at high prices were available in the state sector with no generic equivalent, and that the availability of medicines even on the National Essential Drugs List (NEDL) in the state sector were low. This low availability of medicines in the public sector had direct impact on access as patients are forced into a out-of-pocket spend with affordability data suggesting that a large part of the population will not be able to pay.

In the assessment by Kristina SA et al.(2020)[24] in a cross-sectional study using the WHO/HAI methodology in Indonesia, they concluded that the availability of essential medicines in both the public (76.6%) and private (60.58%) was inadequate compared to the WHO standards. The procurement price of generic medicines in the public sector was within the reasonable range (0.98) while the private sector was 2.46 times the International Reference Price (IRP). The evidence from the study suggested that significant policy changes were required to optimise access to essential medicines for patients.

The history of the Philippines medicine programme follows closely with the South African policy changes. The National Medicines Policy (NMP) was created in 1987 and updated in 2008 with the addition of the Universally Assessible and Quality Medicines Act of 2008. Manufacturers were compelled to produce a unbranded equivalent with their branded medicine allowing for marketing of both medicines at the same time. The Act also allowed for the setting of maximum prices for medicines on their essential medicine list. The study by Batangan et al. (2009)[25] concluded that essential medicines were only partially available in the public sector (53.3%) but fully available in the private sector (100%). The length of duration of stockouts in both sectors indicated that medicines was not continuously available. In 2009 the Philippines's patients were purchasing medicines at a higher price than international reference prices (26.33 for branded and 7.97 for generics).

It is clear that a mix of policies are needed to make medicines more accessible and affordable. Further, policies must be evaluated for sustainability to ensure equity in access especially for the poor.

This study, related to the SEP regulations, attempted to look at the gap between branded molecules and generic medicines. The World Bank (2010)[26] recommended closure of the gap between brands and generics to assist the high cost of medicines in LMIC. Further, the move towards NHI will require health technology assessment processes and this pharmacoeconomic evaluation forms the basis for the country's early experience in this field. It is through this type

of research that we will be able to merge the strongest elements of all of our policies[27] in order to ensure sustainable access to quality, affordable, essential medicines.

Several global and regional initiatives including the guidelines by WHO (World Health Organization)[5] and Health Action International (HAI)[21] introduced in the past 15 years is used to improve medicine availability and affordability in some 50 countries internationally. This research uses some of these guidelines to measure and document the outcomes of policy changes in South Africa that may contribute to further development internally and also at the same time contribute to overcoming the scarcity of evidence of the impact of such policies in general and especially in LMIC[5].

1.3. Aims and Objectives

The study aimed to assess the impact of two regulatory changes implemented in 2004 by the South African Government. The first being the Single Exit Price (SEP) of medicines through changes in the Medicine and Related Substance Act[28] (2003) and the second was the Regulations Relating to the Ownership and Licensing of Pharmacy (GNR 553 of April 2003)[29]. The objectives of the study were as follows:

I. To determine the impact of the regulations on the price of medicines in the short term and ten years after implementation for both generic and originator medicines.
II. To determine the impact of the ownership regulation on access to community pharmacy in South Africa ten years after the regulation
III. To propose recommendations if required for these policies.

1.4. Research Method

A literature review and empirical investigation were conducted. On the medicine pricing investigation, a quantitative analysis approach using a longitudinal method for pharmaceutical policy evaluation with a specific application of the interrupted-time series was implemented.

The licensing policy was evaluated as a quantitative study as well, using GPS coordinates (QGis-V3.6) to determine opening and closures over a specified period before and after the implementation of the regulation.

1.4.1. Literature review

The literature review used the PRIMSA[30] (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) from a variety of sources including journals, books, and university on-line libraries but also included multiple databases search between the dates 1994–2018. It incorporated some technical reports from Governments and other agencies. The electronic database included the World Bank, the World Health Organization and the Health Action International. Major Medical Subject Headings (MeSH) search terms included policy, originator and generic/s medicines, LMIC, medicine regulations, pricing regulations, single exit price, pharmaceuticals, and pharmacy ownership. The review included international and South African literature which provided background, historical context, and international experiences.

1.4.2. Empirical research

A quantitative analytical approach was used. Pricing data for a basket of fifty (50) molecules and their generics were sourced from pharmacy computer vendors responsible for maintaining price files and verified via pharmacy dispensing systems spanning the period 1999 to 2014. Longitudinal trends using the specific application of the interrupted-time-series (ITS) were compared before and after the policy changes. Stata (13 MSI), a statistical package was used to analyse the data, generate the necessary variables, compute the statistical analysis and produce the necessary graphs[31].

For the research on ownership, the South African Pharmacy Council database of all registration up to and including 2014 was assessed and mapped using QGIS (V3.6) and in accordance with population census figures for provinces and districts.

1.4.3. Ethical Considerations

The study was granted ethical clearance by the University of KwaZulu-Natal Human and Social Sciences Research Ethics Committee (HSS/0154/013) (see Appendix A). Medicine pricing data was obtained from those responsible for update of price files and directly at a pharmacy level. Price files are not linked to patient data, are available publicly from multiple sources such as the National Department of Health and directly from the manufacturer of the products and therefore did not require signed consent. Pharmacy registration data was obtained

from the South African Pharmacy Council and is available to the public from the Council website, again needing no consent from the pharmacy themselves.

1.5. Division of Chapters

The thesis is contained in six chapters.

Chapter 1 Introduction

This chapter provides a general overview of the subject matter and includes the rationale and significance of the study. It also provides the aims and objectives and research methodology. The chapter ends with the general division of the chapters in the presentation.

Chapter 2A Literature Review (Pricing Policy)

This chapter looks at international and local studies on pricing interventions. It provides the documented context for interventions around pricing policies of medicines in private pharmacy in South Africa.

Chapter 2B Literature Review (Ownership)

This chapter looks at the literature around ownership and liberalisation of pharmacy both nationally and internationally.

Chapter 3 Paper 1

Evaluating the impact of the single exit price policy on a basket of originator medicines in South Africa from 1999 to 2014 using a time series analysis. The study evaluates the impact of the SEP on a basket of originator medicines, in terms of costs, immediate price reductions and projected price reductions.

Chapter 4 Paper 2

The impact of the single exit price policy on a basket of generic medicines in South Africa, using a time series analysis from 1999 to 2014. This study assessed the impact of the Single Exit Price (SEP) regulation introduced in South Africa in 2004 on a basket of generic

medicines. The study went further to compare the difference in impact to the basket of the originator and generic medicines.

Chapter 5 Paper 3

This chapter presents the paper submitted to a journal, that evaluates the impact of opening up ownership of pharmacies in South Africa.

Chapter 6 Conclusion

This chapter reviews the outcomes of the studies in terms of both the literature review and the empirical data. It provides the findings of the study and the recommendation, together with areas for further research.

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CHAPTER 2A LITERATURE REVIEW - MEDICINE PRICING

2A.1 Complex nature and need for policy changes

Nguyen TA et al. (2015)[1] suggested that the complex nature of any country's pharmaceutical supply chain makes it extremely sensitive to medicine pricing policy changes. It is even more difficult to make policy changes in LMIC where more than half and sometimes up to 90% of healthcare spending is out-of-pocket[2]. It is therefore vital that changes in policy, especially in LMIC be continuously monitored. The main reasons for pharmaceutical policy changes are due to the escalation of medicine cost worldwide, the lack of transparency in the market and classic market failure described by Carone G, et al. (2012)[3]. The per capita spending in pharmaceuticals investigated in Europe by Lu Y, et al. (2011)[4], as per the National Health Accounts (NHA) reports increased by approximately 50% (n = 135–148 countries) between 1995 and 2006. The World Health Organization (2015)[5] found that medicines in LMIC accounted for 20-60% of the country's healthcare budgets. Sudan introduced a National Health Insurance Fund (NHIF) in 1995 and achieved national cover by 2010[6]. Medicine expenditure between 2006 and 2010 in Sudan grew at an annual rate of 35.78%. This was assumed to be the direct result of increased utilization related to the higher coverage. Mousnad and colleagues (2013) further defined other multiple factors contributing to price increases, including the global economic crisis, increased government taxes, custom and clearance duties, and price increases in the exporting countries[6]. Countries need to have policies in place as sound pharmaceutical policies contribute to a country's socio-economic development and the countries need economic growth for healthcare systems to perform well[7].

2A.2 Types of international policy changes

Most European Union (EU) member states (n = 24), set their prices through External Reference Pricing (ERP), establishing a price based on the price of the same product in other countries). At the same time, some countries use an Internal Reference Price (IRP) where prices are based on market equivalent or similar products within the country[8]. Vogler et al. (2011) investigated prices of medicines that were likely to contribute to high expenditure for the public payers in high-income countries[9]. Information on the ex-factory price data of 30 medicines in 16

European countries was collected in April 2013. There were considerable differences in medicine prices, with 53% of the medicines surveyed having a unit ex-factory price (median) above 200 Euro. The price differences between the highest-priced country and lowest-priced country ranged between 25% and 100% for two-thirds of the medicines. The mainly low-priced medicines had a higher price differential up to 251%[8]. A Nigerian national survey of 129 medicine outlets where 34 prescription medicines were investigated showed consumers paid up to 64 times the international reference price[10].

Brazil in 1998 through its Federal Government implemented the Banco de Prescos em Saude (BPS) to facilitate a transparent measure that centralized the pricing information[11]. Schargrodsky et al. (2001) analysed the mandatory report of the purchase price in 33 hospitals in Buenos Aires[12]. The results confirmed that medicine prices significantly decreased after the mandatory policy, but this was not sustained, and prices eventually increased over time, an indication that mandatory reporting and publishing medicine prices as a policy is insufficient to impact on medicine price reduction. Ecuador in 2014[13] introduced price control for essential medicine which accounted for 54% of their pharmaceutical market and Colombia in 2011 introduced a compulsory cap on inpatient drug reimbursement by active ingredient, and in 2013 introduced an ERP using the markets in 17 countries and further regulated prices set at the 25 percentile. A study by Prada et al. (2018)[14] suggested that after implementation of direct price control there was a 43% decrease in price inflation, but expenditure doubled due to the disproportionate increase in units sold. The study concludes that pricing interventions should be implemented along with an active market monitoring to prevent market distortions such as inappropriate and unnecessary drug use[14]. Moreno-Torres (2011) analysed sixteen interventions introduced to control the pharmaceutical expenditure in Spain and found that twelve interventions were not effective[15]. Sood et al. (2009) in describing policy interventions in nineteen developed countries from 1992 to 2004, found that the cost reduction effects of price control increased the longer they remained in effect[16]. Introducing new policies in an unregulated market such as the US could significantly reduce pharmaceutical spending according to studies done by Abbot TA, (2007)[17].

Aitken M et al. (2016)[18], suggested other methods include creating a transparent pricing system for medicines (a key strategic imperative of the South African National Department of Health (NDoH)), regulating reimbursement or dispensers, controlling wholesale and intermediaries' margins, and fixing and publishing the manufacturer price of medicines. More complex methods include health-technology assessments to ensure cost-effectiveness of new

pharmaceuticals, and rational use of medicines to control public budgets[18]. Regulating pharmaceutical markets is one method used by policymakers to achieve savings. Carone, G et al. (2012) indicated that promoting the use of generic medicines was another cost-effective attempt at price control and containment[3]. In the WHO Guidelines on Country Pharmaceutical Pricing Policies [5], it is suggested that a gap exists in the quantitative assessment of the impact of policy change on generic medicines in LMICs. Countries enforcing a pro-generic policy should put in place a monitoring and evaluation programme to track data before and after a policy change using an experimental or quasi-experimental design so that if the policy has not provided the intended result, it should be reviewed. Hassali et al. (2013) recommended that the primary policy to promote generic medicines needs to be supported by complementary policies both to facilitate its implementation and also to overcome the barriers that hinder its effectiveness[19]. The policies promoting generic substitution are seen as means to contain pharmaceutical expenditures and are often at the forefront of yielding significant cost saving[3]. Very little is known about using pricing policies as a means to contain generic medicine prices. South Africa has done so, yet little published information exists regarding the impact of pricing policies that were implemented post-democracy. The potential for saving using generic medicines is huge. Cameron et al. (2012) in their study of middle to low-income countries concluded that or the medicines studied, an average of 9% to 89% could be saved by individual countries in the private sector with the change from originator to lowest-priced generics[20]. Also, the price of originator medicines internationally is two and a half (2.5) times more than their lowest-priced generics[21]. Bangalee et al. (2016) revealed in their study on cardiovascular drugs a 40% difference in prices of generics against the branded versions[22]. This supports the observation by Bangalee and Suleman (2016) that originator companies do not engage in price competition[22]. Veena, et al. (2017) in India suggested that branded medicines are 30%-200% costlier than generics[23].

Countries like Canada cap the price at which generics enter a market as a policy option. Canadian provinces followed the Alberta model for the pricing of generic drugs; a model suggested by academics Cambourieu et al. (2013)[24]; Hollis A (2008)[25] and Hollis A et al. (2015)[26]. In April 2014, Alberta introduced their generic policy where new generic entries start at 70% of the brand if there is only one generic entrant, and then subsequent generic medicines that entered the market were priced at 50%, 25% and 18% respectively of the originator. The first generic entrant keeps the advantage for one year after which the 50% price applies. The

savings through agreements with manufacturers using this model is expected to be $3.8 billion over three years to all payers[26].

Generic entry is also encouraged where there is a transparent pricing system[9]. It is suggested that countries need to examine their regulatory framework and look at trends that may limit the potential for savings by inadvertently encouraging higher-priced generics[27]. Seeley and Kanavos (2008) stated that the number of generic entrants is not a predictor of lower generic prices, but the market does need a significant number of entrants to impact the competition[27].

Each country should continue to examine the impact of its generic use policies. Vogler S (2012)[28], and Maisonneuve et al. (2013)[29], suggested that generic use can be attributed to countries policy implementation, e.g. a number of generics, prescribing practices and market structures. Strict regulation of medicine prices may contribute to lower penetration of generic medicines into markets[30]. This may be due to the reduced profitability and the inability of generics to cover their cost of market entry[31]. This is supported by Kaplan et al. (2016), who's study indicates that many European countries set the price of a generic at a specific percentage lower than the originator product, and indicate that countries with generic link policies have lower prices compared to countries that do not[32].

While this chapter focused on medicine pricing and generic use as possible solutions, there are many other factors that are available to improve access to medicines. These may include but not be restricted to improving the medicine regulatory infrastructure to ensure accelerated market entry of generic and biosimilars to foster competition that improves affordability and ensures availability. Multiple dossiers being registered by the same manufacturer results in a false back log in the regulator and the ability of the manufacturer to control pricing of the same molecule under different brand names. 'Evergreening" of medicines exclusively via patents or extensions on existing drugs results in a restricted market for other generic entries. While it is imperative that a countries regulatory authority is independent, the use of reciprocal drug approval arrangements with other regulatory agencies may result in quick entry of both life-saving originator medicines and cheaper generics to market.

An improved medicine evaluation methodology, with transparency from all parties involved, may result in a fair price to patient and an equitable model for sustainability of the supply chain. This must include greater transparency in the financial flow allowing disclosure of discounts to pharmacy benefit managers and insurance schemes. De-linking payments on list prices of medicines, as is the current reimbursement model in many countries, and a move to a fixed fee

that supports clinical care and rewards outcomes and cost savings, will improve access and affordability. Consolidating the countries purchasing power, rational medicine use off a scientific formulary, educating both healthcare professionals and the public and supporting a marketing code with implementable sanctions are import tools available to support affordability and availability of medicines[43].

2A.3 Pharmaceutical changes in South Africa

In South Africa, as in many parts of the world, affordability is a barrier to gaining[33] access to quality pharmaceutical therapies. Council for Medical Schemes (CMS) in South Africa indicated that medicine expenditure was the main cost driver in the 1980s and early 1990's peaking at 31.8% of the total medical scheme spend in 1999[34]. The South African Governments pre-1994, led several attempts to regulate the medicine-pricing environment, in terms of changes to the Medicines and Related Substances Act[35,36]. The introduction of the pricing regulations in South Africa created an ideal platform for pricing transparency, a concept that Vogler S, (2011) agreed can contribute to affordable patient access to medicines[9]. The SEP attempted to control medicine prices at the manufacturer level, a common strategy in price control policies seen in most European Union countries[37] where authorities set the price on a regulatory basis.

In 1996 the Government introduced the National Drug Policy[38] outlining among other policies, the intention to establish a pricing committee to regulate medicine prices, create transparency in the pricing structure from the manufacturer, wholesaler, distributor and providers of service, as well as to ensure a non-discriminatory pricing system. The Medicines and Related Substances Control Amendment Act 90 of 1997[35], implemented on 2 May 2003, banned the offer of discounts and rebates to patients and healthcare providers (bonusing section 18A and B), made provision for ethical marketing of pharmaceuticals (18C), introduced generic substitution (22F) and established a pricing committee (section 22G). The pricing committee made recommendations to the Minister of Health to implement the SEP[22] in 2004, effectively moving the private sector from a free market to a regulated environment.

The components of the single exit price include the ex-manufacturer price combined with the logistics fee (as determined by the manufacturer) and Value Added Tax (VAT)[39]. The SEP for each medicine in the market in 2004 was a mandatory declaration of the weighted average of

all 2003 sales after taking into account all discounts and off-invoice rebates[40]. In effect, the manufacturer listed their price and could only sell at that specified price to their customers[41], although they were allowed to apply to the NDOH to make price reductions for reasons such as competition, reduction in exchange rates or overstock stock issues. The NDOH through the pricing committee determines an annual increase based on a number of factors; the average Consumer Price Index (CPI), average Producer Price Index (PPI), Exchange rates, and Purchaser Power Parity (PPP), international pricing information relating to medicines and schedule-substances, comments received from interested persons (Reg 8(2)), and the need to ensure availability, affordability, and quality of medicines[42].

2A.4 Summary

While the pharmaceutical supply chain in any country is complex in nature, it requires constant monitoring and review by the regulators to ensure the best possible outcomes for the patient. The escalating medicine costs, lack of transparency, and the world-wide shift towards universal healthcare coverage has created an opportunity for each country to examine its pharmaceutical pricing policies and align it to international best practices.

It is clear from the literature review that there are many options available for setting of medicine prices and in most instances, a country may choose multiple policies interventions. Some may produce immediate gains and also show long term benefit for the duration of its implementation while other may have unintended and unforeseen detrimental consequences, especially so in LMIC where a vast majority of patients are faced with out-of-pocket payments.

South Africa chose to implement a transparent pricing system regulating medicines at a manufacturer level (SEP) and capping the fee related to any added professional service (Dispensing Fee). We also saw the added benefit of allowing for medicine interchangeability. After ten years of implementation it is important that these critical interventions are examined to determine its value to the country.

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CHAPTER 2B LITERATURE REVIEW- PHARMACY OWNERSHIP

2B.1 Background

In most European Union (EU) countries pharmacy is highly regulated[1]. Countries follow various routes of regulation in the establishment of community pharmacy depending on their expected needs. The common thread that runs through most highly regulated environments is the basic principle of autonomy of the pharmacist. This includes their clinical decisions making skills, the maintaining of ethical standards related to being healthcare professionals, and the issue of their social accountability not being overridden by economic interest associated with either ownership or market forces related to their employment[2]. There are also broader restrictions in terms of a positive and negative list of who can and cannot own a pharmacy, the most prevalent being medical doctors, pharmaceutical wholesalers and manufacturers of pharmaceuticals[2]. In LMIC pharmacy legislation and regulations are fragmented, and it is difficult for Governments to enforce these limited regulations due to resource constraints[3].

The International Pharmaceutical Federation (FIP) 2016, suggests that pharmacy finds itself at the crossroads between professionalism, accountability, professional autonomy and economic policy[2] and policy determination in most countries is dependent on where the country places its emphasis. This is supported by the view of Brazeau GA et al. (2009) that contemporary pharmacy education is strengthened by growth and enhancement in the clinical, social and administrative science of pharmacy giving practitioners the skills and knowledge to move from a product focus to patient-centred care[4]. This has resulted in graduates of pharmacy being refocused on patient-centred care, interprofessional teams, evidence-based practice, quality improvements and use of information[4]. Policy determination within a country must provide for these independent practitioners to pursue this unlimited professional practice role that can transform the health of a nation. Medicines involve compelling economic interest as 50% of household expenditure on health in developing countries is medicines and is also the second largest spend in government health budgets behind salaries. In industrial nations drug costs increase by 8-12% annually[5]. It is therefore imperative that pharmaceutical policies deal with the principles and meets its goal of contributing to overall health, welfare and well-being of society[6].

Almarsdottir AB et al. (2006) identified vital goals in policy making such as (a) maximizing access to medicines; (b) ensuring quality of medicinal products; (c) minimizing costs related to medicines and healthcare use, and (d) promoting rational use of medicines through prudent use of the healthcare workforce and warned that these goals may be conflictual[6]. In most countries where deregulation was attempted the rationale for change centred around[7] need for increased competition, containment of pharmaceutical expenditure, improved access to pharmaceutical care and improved opening of new outlets in areas of need.

2B.2 International Review

Community pharmacy is a critical part of pharmaceutical service delivery in many countries. Principle areas of practice in Europe are 78.5% in community, 8.9% in hospital and 12.6% in other areas[8]. The survey conducted by International Pharmaceutical Federation (FIP 2016) in 71 countries covering 80% of the world's population indicated that 66% of pharmacy ownership is non-exclusive to pharmacists alone and the balance of 34% (24 countries) was exclusive[2]. The Österreichisches Bundesinstitut für Gesundheitswesen (OBIG 2006)[7] report of the European Union countries indicated that 17 of the 25 member nations operated restricted ownership of pharmacies. The study showed a steady increase in the number of pharmacies in the deregulated states accompanied by urban clustering and fewer municipalities having access to service. Wisell K et al. (2015) found that Sweden operated state-owned community pharmacies since 1971 and only liberalised ownership in 2009 where the sector is currently dominated by chains and independents with one or a few pharmacies per owner[9]. The authors noted that the rationale for the deregulation was focused on price pressure, efficiency and better usage of medicine but was replaced with diversity in the market and entrepreneurship with the privatisation concepts not set out as the initial goals[9]. Liberalisation in the UK[10], on the other hand, is said to have made the system more efficient in operational terms. The authors' further stated that because the pharmacy, as in South Africa, is under the supervision of the pharmacist, quality issues should not be a concern. Lluch and Kanavos[1](2010) raised the concern of the risk associated with chains and vertical integration which may lead to forms of monopoly and suggests that policies addressing these risks should be considered. The authors concluded that restricting ownership does not have an impact on access (positive or negative). The opposite may lead to efficiencies in terms of economies of scale through vertical integration, but the liberal ownership and the consequent vertical and horizontal integration embeds risk of

oligopoly creating disincentives in the future[1].

Mossialos and Mrazek[11] (2003) looked at community pharmacy ownership in six OECD countries, Canada, France, Germany, Netherlands, Norway and the United States. Four countries with the exception of France and Germany allowed corporate ownership while these two countries restrict ownership to a registered pharmacist and impose a further restriction where a pharmacist is allowed to own only one pharmacy. A 1963 state law in the US restricting ownership to pharmacists or groups of pharmacists was tested via the North Dakota Pharmacy Ownership Initiative[12] in November 2014 where a chain pharmacy group attempted to have the law repealed and lost in a public referendum. It was shown that across every key measure of pharmacy care including prescription prices, levels of patient care and most importantly, rural access, North Dakota[13] outperformed other states. Two other countries, Hungary (2009) and Estonia (2015)[14], returned to regulated ownership based on the impact on professional independence of the pharmacists, lack of improvement in rural areas, and the poor financial viability of the remaining pharmacies. The North Dakota ruling was supported by the European Court of Justice (ECJ) ruling in May 2009 which ruled that, while restrictions on ownership and operation of pharmacies constitute a restriction on the freedom of establishment and the free movement of capital, these restrictions can be justified, and the EU Member States' national legislation may restrict pharmacy ownership and operation to persons having the status of a pharmacist[15,16].

Burton S et al. (2019)[17] found that in Africa, some countries such as Chad, Nigeria, Senegal, Côte d' Ivoire, and Cameroon restrict ownership to pharmacists only while Kenya followed the South African model of ownership. Countries with pro-competitive policies often driven by competition authorities sometimes drive deregulation. Deregulation in most countries results in corporatisation of community pharmacy[17,18,19]. There is also the mixed-ownership type where ownership must include the pharmacists but may include other non-pharmacists or corporates as shareholders. Pharmacist majority shareholding in these entities is seen in Austria, Cyprus and Latvia (51% minimum) with Lithuania and Spain having a 75% shareholding[17].

2B.3 South Africa

The study focused on medicine distribution legislation that went into effect in 2004 related to the liberalisation of pharmacy ownership. The main goal was to look at the issue of access to medicines, but it is essential to interrogate the main arguments presented to parliament before the legislation. The National Drug Policy (1996)[20] outlined the plan to liberalise ownership of pharmacy – where it is deemed to be in the interest of the public and provided that comprehensive pharmaceutical care is ensured, ownership of pharmacies by lay-persons and other healthcare professionals will be considered. Further to the issue related to access, it was stated that medical practitioners and nurses would not be permitted to dispense drugs, except where separate pharmaceutical services are not available. Extensive debate took place in parliament with motivation for the ruling party the African National Congress (ANC) in 1997[21]. It was noted that black pharmacists[21] who qualified in the '80s and early '90s were not allowed to own pharmacies in urban areas. Opening up of ownership would reduce the price of medicines, promote healthy competition and create more jobs. Various cautions were raised in the process of the debate[21].

- Regulations made in terms of Section 14 be very carefully drafted.
- Secondly, the ruling party specified that the authority given to the Director-General of Health is a policy decision to ensure that pharmacy outlets open in communities where they are most needed.
- Concern was raised about the suffocation of small business and the development of monopolies.

On 22 October 1997 the African National Congress[22] publication outlined its motivation in support of the Bill:

- To increase the number of outlets able to dispense medicines to improve public access.
- To increase competition which should reduce prices to consumers.
- To increase job opportunities amongst pharmacists and pharmacy assistants.
- Increase opportunities for emerging entrepreneurs to establish pharmacies in historically disadvantaged areas.

The document further stated that the Health Minister is extending access to pharmacy services by 'breaking up the pharmacist's monopoly over ownership" and that South Africa will get the

same access to pharmacy services as is enjoyed by people in Britain, America and many other countries. The Regulations Relating to the Ownership and Licensing of Pharmacies (sec 22 & 22A of the Pharmacy Act, 1974 (Act No. 53 of 1974) was published in GNR. 553 of 25 April 2003[23].

Early findings by Ward K et a. (2014) in South Africa supported the international findings that deregulation did not improve access in rural and areas of need but saw substantial corporate growth concentrated in urban and economic hubs with a decline of the provision in terms of pharmacy to population ratio in rural communities[24].

2B.4 Rural Access

Mossialos and Mrazek[11] (2003) in their report prepared for the Office of Fair Trading found that most countries, like South Africa, move to open ownership with the view to improving rural access, however very few countries achieve this goal[11,15]. Rural Canada, Netherlands and South Africa allow physicians to dispense to ensure access to medicines in these areas. Norway maintains an operational subsidy for pharmacies to expand in rural areas. Germany provides no direct subsidy but makes an exception to the single pharmacy ownership rule, allowing owners to open a second pharmacy provided it is in remote areas. The Netherlands does not impose restriction on location but may control the location in terms of the offer of contract with the principle insurer (the State). This is further supported by the fact that banks will provide loans to the opening of new pharmacies based on the holding of these contracts[11].

2B.5 Summary

It is clear that the pharmacy profession is at a crossroad between professional accountability, professional autonomy and economic policy. The emphasis placed on each of these elements may be different in various countries depending on the needs of the policy makers. Pharmacists see themselves as an extension of the healthcare system providing an essential public service irrespective of where they perform their professional skills.

The literature indicates that countries may choose various models of pharmacy ownership from those restricted to ownership by the pharmacist, pharmacies owned by the state, to complete ownership by non-pharmacists at the other end of the spectrum. Further restriction may be

imposed on different models of ownership from attempting to encourage rural access with incentives, preventing clustering by imposing population or distance perimeters, to limiting number of pharmacies that an entity can own to prevent monopolies. Most attempts at deregulation focused on price pressure, efficiency and better usage of medicine but ultimately gets replaced with diversity in the market and entrepreneurship with the privatisation concepts not set out as the initial goals. Concerns raised in many markets after liberalisation related to monopoly or oligopoly on the entry of corporations to own. Some prevented this eventuality by placing limitation on the horizontal and vertical integration of these entities.

Countries that did not meet their policy goals upon re-examination, moved back from liberalization to restricted ownership, putting ownership of pharmacies back into the hands of the pharmacists.

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CHAPTER 3 PAPER 1

3.1 Evaluating the impact of the single exit price policy on a basket of originator medicines in South Africa from 1999 to 2014 using a time series analysis

This chapter addresses the objective outlined in Chapter 1 related to a comparative of medicine prices before and after regulations, evaluate the impact on the prices of medicines immediately after regulations and then ten years after regulations, for originator medicines. The empirical findings are based on the analysis of the Single Exit Price (SEP) observed over a period of 16 years (1999-2014).

The Paper, entitled "**Evaluating the impact of the single exit price policy on a basket of originator medicines in South Africa from 1999 to 2014 using a time series analysis**" has been published in the "*BMC Health Service Research"*.

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The databases for the research were obtained from Pharmacies and Computer Vendors. The Ethics certificate can be found in Annexure A. This chapter presents the published paper as per the journal stipulated format and limitations in terms of graphs, tables and word count.

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RESEARCH ARTICLE Open Access

Evaluating the impact of the single exit price policy on a basket of originator medicines in South Africa from 1999 to 2014 using a time series analysis

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Abstract

Background: Affordability and availability of quality medicines to all its citizens has been a key priority area for South Africa since democracy in 1994. In order to introduce transparency in the private market the government introduced the Single Exit Price (SEP) for medicines in 2004, for all prescription medicines, comprising of a fixed ex-factory price with a logistics fee component (and value added tax) for medicines sold to all purchasers other than the State. This is complemented with a provision for an annual regulated maximum percentage increase. The study evaluates the impact of the SEP on a basket of originator medicines, in terms of costs, immediate price reductions and projected price reductions.

Method: This is an analytical, quantitative study. A basket of medicines was selected, based on the WHO/HAI list, and adapted to include registered medicines in South Africa. Prices of 50 originator medicines were assessed from 1999 to 2014 in terms of the single exit price and the changes in prices in accordance with legislation using a time series analysis methodology.

Results: Of the 50 originator medicines investigated 35 showed a statistically significant change in level. For the Global Core list, the percentage change ranged from 2.45–39.12% (mean = 19.87%, SD = 10.62%, IQR = 10.2%). The range for the Regional Core list was 1.77–42.17% (mean = 23.38%, SD = 12.43%, IQR = 15.65%). The Supplementary list was 11.68–55.86% (mean = 22.97%, SD = 16.26%, IQR = 17.34). This study indicates that the SEP regulation had an impact on medicine pricing in South Africa in both the short and long term. Most medicines investigated showed a smaller yearly increase in price compared to before regulations due to the controlled pricing environment introduced by Government.

Conclusion: This study provides evidence of the impact of medicine pricing intervention from a middle–income country, and other developing countries looking at introducing medicine price controls can draw useful lessons.

Keywords: Single exit Price, South Africa, Time series, Medicine pricing policy

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Background

The complex nature of any country's pharmaceutical supply chain makes it extremely sensitive to medicine pricing policy changes [1] especially in low to middle-income countries (LMICs). It is therefore important that when change does occur the impact of the change is measured.

Growing expenditure on pharmaceuticals in both the public and private sector in many parts of the world has been a source of concern for healthcare professionals, patients, funders and Governments alike. The per capita spending in pharmaceuticals [2], as per the National Health Accounts (NHA) reports increased by approximately 50% ($n = 135–148$ countries) between 1995 and 2006. Medicine spend [3] in low and middle-income countries accounts for 20–60% of the health care budgets. Further to this, the World Health Organisation (WHO) [3] estimated that 90% of peoplein developing countries buy medicines through out of pocket payments, resulting in this being the second largest family spend next to food.

Many governments have thus introduced pricing interventions to reduce medicine prices for payers and patients alike, but very little evidence exists as to their impact. Moreno-Torres [4] analysed sixteen interventions introduced to control the pharmaceutical expenditure in Spain and found that twelve interventions were not effective in decreasing medicine prices even in the short term, and the other four interventions did not have sustained impact in the long term resulting in a moderate annual saving.

Sood et.al [5] in describing policy interventions in nineteen developed countries from 1992 to 2004, found that cost reduction effects of price control increased the longer they remained in effect. The authors further concluded that introducing new policies in an unregulated market [6], such as the United States (US) could greatly reduce pharmaceutical spending. If the US did introduce pricing policies it is projected that prices of medicines could fall by 20.3% [5].

Carone et al. [7] suggests that regulating pharmaceutical markets "comes as an answer to classic market failures of healthcare markets". Most European Union member states ($n = 24$), set their prices through external reference pricing (ERP -establishing a price on the basis of price of the same product in other countries) while some countries use an internal reference price (IRP) where prices are based on market equivalent or similar products within the country [8].

Other low and middle-income countries have introduced pricing policies to manage medicine prices. Brazil in 1998 through its Federal Government implemented the Banco de Prescos em Saude (BPS) to facilitate a transparent measure that centralized the pricing information [9]. Argentina has a mandatory report of purchase price policy. Schargrodsky et al. [10] analysed the mandatory report of purchase price in 33 hospitals in Buenos Aires. The results confirmed that medicine prices significantly decreased after the mandatory policy, but this was not sustained, and prices eventually increased over time [10]; an indication that mandatory reporting and publishing medicine prices as a policy is insufficient to impact on medicine price reduction.

Ecuador in 2014 [11] introduced price control for essential medicine which accounted for 54% of their pharmaceutical market. Colombia in 2011 introduced a compulsory cap on inpatient drug reimbursement by active ingredient, and in 2013 introduced an ERP using the markets in 17 countries and further regulated prices set at the 25 percentile. A study by Prada et al. [12] suggested that after implementation of direct price control there was a 43% decrease in price inflation, but expenditure doubled due to the disproportunate increase in units sold.

Many of these examples in the South American region illustrate the government efforts to improve transparency in pricing and procurement [9]. Kohler et.al [9] concluded that pricing transparency should allow for decrease in medicine prices, but other measures are required to ensure sustainability of price optimization.

In terms of pricing regulations within the African context, Sudan introduced a National Health Insurance Fund (NHIF) in 1995 and achieved national cover by 2010 [13]. Medicine expenditure between 2006 and 2010 in Sudan grew at an annual rate of 35.78%. This was assumed to be the direct result of increased utilization related to the greater coverage. Mousnad and colleagues [13] further defined other multiple factors contributing to price increases, including the global economic crisis, increased government taxes, custom and clearance duties, and price increases in the exporting countries.

Nguyen et al. [1] suggest that there is sufficient evidence to show that high-income countries are using a variety of pricing and purchasing methods to contain pharmaceutical expenditure. In low income countries with more than half and sometimes up to 90% of out-of-pocket expenditure on medicines ([14], it has not been easy to implement pricing policies.

South Africa's policy changes

South Africa experienced similar issues in terms of increasing medicine costs and expenditure. Data from Council for Medical Schemes (CMS) in South Africa indicated that medicine expenditure was the main cost driver in the 1980's and early 1990's peaking at 31.8% of the total medical scheme spend in 1993 [15].

The South African Governments pre-1994, led several attempts to regulate the medicine-pricing environment,

in terms of changes to the Medicines and Related Substances Act [16], primarily in Section 18A and Section 22G [17]. These changes attempted to introduce a transparent pricing system by firstly ensuring that there was a Single Exit Price (SEP) for all medicines sold by the manufacturers to all distributors/dispensers in the country. The SEP is set by the manufacturer, and covers all medicines registered in South Africa. Exemptions have been provided to over-the-counter medicines (schedule zero medicines in South Africa) and veterinary medicines. The policy thus applies to all prescription medicines in the private sector. The SEP is composed of the ex-manufacturer price (as determined by the manufacturer), the logistic fee (as determined by the manufacturer) and the value added tax component (14%) for these medicines sold to all purchasers other than the State. This is complemented with a provision for a regulated maximum percentage increase in the single exit price, determined annually by the Minister of Health, on the recommendation of the Pricing Committee. This was combined with the removal of all bonuses, discounts and sampling of medicines (Section 18A).

The only published study on medicine pricing in South Africa, was done in December 2004 [18], that highlighted the issue of medicine prices in the Gauteng Province. The study utilized a similar methodology as outlined by WHO and Health Action International (HAI) [19] but utilized data primarily from the period before the full implementation of the SEP. The authors recommended in their conclusion that further studies be conducted to include all provinces in the country after full implementation of the SEP.

With regulatory changes showing different outcomes in various parts of the world [4] it is critical that the impact of these interventions in South Africa be measured. Evidence is needed to determine firstly, if the legislative changes did achieve the intended outcomes and secondly to give guidance to policy makers regarding any national and institutional problems that may have arisen as an unintended consequence. For South Africa in particular, this study may form an important tool in determining pricing strategies in the new National Health Insurance (NHI) and Universal Health Coverage (UHC).

There has been some research conducted on medicine expenditure post SEP implementation. A substantial decrease occurred between 2004 and 2005 [20]. The authors estimated that the SEP changes contributed to a 22% decrease in the average prices of medicines.

The Mediscor Medicines Review 2004 [16] suggested that various parties believed that the SEP regulations reduced medicine prices by between 18 and 19% translating to a R2.5 billion reduction in the industry turnover. From January 2004 to August of the same year Mediscor experienced a 19% decrease in medicine SEP, viz. a 14% reduction in branded products and 35% in generic equivalents [16] . The top 5 classes of medicines decreased in SEP as follows, cardio vascular agents 12%, central nervous system agents 16.3%, antimicrobials 25.9%, endocrine agents 15.5% and respiratory system agents by 27.3%.

The National Department of Health reported a 19% average reduction of SEP in 2004 with a 25–30% reduction in generic medicines and a 12% reduction in originators prices [17]. Medscheme in their submission to the Market Health Inquiry [21] indicated that annual SEP increases since the introduction of the regulation in 2004 fell mostly below Consumer Price Index increases and on a typical basket of medicines the average price increase fell below the published SEP increases [21].

However, no focused research has been conducted on the impact of the SEP policy on medicine prices, to ascertain whether actual sustained price reductions were achieved. This paper thus tries to address this gap by evaluating the impact of SEP on a basket of originator medicines, in terms of costs, and impact on prices.

Methods

A quantitative analytical approach was used in this study. The setting was the South African private sector, as the SEP regulation did not apply to the state sector where medicines are largely acquired via a tender system. The study was granted ethical clearance by the University of KwaZulu-Natal Human and Social Sciences Research Ethics Committee (HSS/0154/013). In looking at the impact of legislative changes on prices, a longitudinal method [22] for pharmaceutical policy evaluation was used with the specific application of the interrupted-time series (ITS). Longitudinal trends were compared before and after the introduction of policy changes. The research tracked annual price changes on a basket of products five years before regulatory changes and then measured annual SEP changes over the next ten years, following the intervention, viz. from 1999 to 2014.

The changes in medicine prices over a specified period prior to 2004 formed the time series i.e. a sequence of medicine prices over a range of medicines taken at a regular spaced interval – prices registered in December of each year (when there were no more price changes in the system). The time of the regulatory introduction formed the change point. This is the specific points in time where the values of the time series should exhibit a change from previous established pattern, in this case a regulatory or policy change.

Commonly used data source for time series is cost data obtained from pharmacy dispensing files, claims data, and other routinely collected data. SEPs of medicines listed were obtained from the computer vendors responsible for maintaining price files for pharmacy and verified through the pharmacy dispensing systems spanning the period 1999 to 2014. The Government medicine price database [23], was created after the introduction of the SEP, and only exists post the

intervention and therefore could not be utilized. It was also important to utilize a single complete data source to ensure accuracy of results.

Pricing data for the medicines being studied could not be obtained before 1999 in the country and was identified as a limiting factor. Stata (13 MSI), a statistical package was used to analyse the data, generate the necessary variables, compute the statistical analysis and produce the necessary graphs [24].

Selection of the basket of products

A basket of fifty (50) medicines were chosen implementing the World Health Organisation/Health Action International (WHO/HAI) [25] recommendation. This was to ensure that our research measuring medicine prices was in keeping with the international methodology currently being applied in more than 50 countries [25]. Utilizing these standard guidelines also allows us to contribute to the research evidence classified by WHO/HAI as 'scarce' in low-and middle-income countries [25].

The Global Core of fourteen items (14) allows for international comparison, a Regional Core of fifteen (15) items allows for regional differences in medicine usage whilst still enabling comparison across countries and the twenty-one (21) medicines from a supplementary list selected for their local importance [25] completed the basket. While the May 2016 update on the WHO/HAI [14] recommendation indicate a removal of the Regional Core in favour of 36 medicines chosen by the national investigator, this study used the original recommendation since the investigation spanned the 1999 to 2014 period. Further, since the regulations affected mainly the private sector in South Africa, an assessment of the top 50 medicines dispensed (by volume) in the private sector (IMS Health) in 2014 was taken into consideration. This data was sourced from IMS Health and used in the supplementary list. Consideration was also given to the list used in the 2004 study [18] for further comparison. Once the 50 medicines were selected, the originator product was listed together with the strength, form, pack-size and National Pharmaceutical Product Index (NAPPI). The NAPPI code is a unique coding system used in South Africa. This allowed ease of reference when pricing was compared from different data files. Any price change listed on the data file in December of each year was captured.

Table 1 Interrupted time-series analysis for originator molecules in the global core list, using pricing data from 1999 to 2014 with 2004 as the interruption in the series ($P < 0,05$)

INN		Trend	(*P* value)	Change in level	(*P* value)	Change in slope	(*P* value)	Constant	(*P* value)	Int 1	*% Change in level 2004*
Salbutamol 2 mg/5mls Syr	1, Ventolin	0,018	0,000	−0,065	0,000	−0,014	0,000	0,19	0,000	0,28	−23,47
Glibenclamide 5 mg tab	2, Daonil	0,228	0,000	−0,771	0,001	−0,047	0,382	2,45	0,000	3,59	−21,51
Atenolol 50 mg caps	3, Tenormin	0,427	0,000	−1242	0,000	−0,209	0,007	2,56	0,000	4,70	−26,45
Captopril 25 mg tabs	4, Capoten[a]	0,044	0,014	−0,117	0,071	0,016	0,365	2,09	0,000	2,31	−5,07
Simvastatin 20 mg tabs	5, Zocor	−0,997	0,001	− 1078	0,225	0,832	0,004	9,56	0,000	4,58	−23,54
Amitriptyline 25 mg tabs	6, Tryptanol	0,176	0,000	−0,397	0,000	−0,169	0,000	1,70	0,000	2,58	−15,42
Ciprofloxacin 500 mg tabs	7, Ciprobay	−1028	0,002	−5113	0,000	1560	0,000	18,21	0,000	13,07	−39,12
Co-Trimoxazole 8 + 40 mg/ml syr	8, Bactrim	0,364	0,000	−2267	0,000	−0,247	0,000	2,46	0,000	4,28	−52,94
Amoxicillin 500 mg caps	9, Amoxil[b]	0,334	0,000	−0,127	0,429	−0,274	0,001	3,52	0,000	5,19	−2,45
Ceftriaxone 1 g/vial inj	10, Rocephin	4302	0,081	−82,503	0,000	−3371	0,237	121,81	0,000	143,32	−57,57
Diazepam 5 mg	11, Valium	0,318	0,000	−0,772	0,000	−0,213	0,000	1,00	0,000	2,59	−29,83
Diclofenac 50 mg tabs	12, Voltaren	0,063	0,013	−0,209	0,025	0,021	0,373	1,16	0,000	1,48	−14,17
Paracetamol 25 mg/ml syr	13, Panado	0,001	0,702	−0,030	0,017	0,014	0,000	0,18	0,000	0,18	−16,57
Omeprazole 20 mg tabs	14, Losec	−0,610	0,036	1183	0,245	1298	0,000	11,58	0,000	8,53	13,87

Withdrawn- [a]2009 [b] 2008
Each item carries the® for trademark reference

Results

Tables 1, 2 and 3 below represents the results of the interrupted time-series analysis (ITSA) for three groups of fifty (50) originator medicines listed as Global Core, Regional Core and Supplementary respectively. The global core in Table 1 contains the data for 14 originator molecules. Of the fourteen (14) original molecules ten (10) showed a statistically significant ($P < 0.05$) change in level. The level change indicated an immediate decrease in the medicine price on the introduction of the regulation in 2004. 71.43% of the molecules showed a statistically significant ($P < 0.05$) change in slope indicating that the policy will continue to benefit medicine prices over time.

Table 2 contains the data for the regional core basket of 15 original medicines. Of the 15 originator molecules 11 showed a statistically significant change in level ($P < 0.05$) with 7 showing statistically significant change in slope.

In the 21 molecules (Table 3) analysed in the supplementary basket 14 showed statistically significant change in level (66.67%) and 16 (76.19%) showed statistically significant change in slope ($P < 0.05$).

The following formula was used to calculate the limits used to define outliers in the data set for each of the three categories:

$$\text{Upper limit}: \quad Q3 + (IQR \times 1.5)$$

$$\text{Lower limit}: \quad Q1\text{-}(IQR \times 1.5)$$

Anything outside of the calculated limits was identified as an outlier and excluded from the data set. Once the outliers were excluded, descriptive statistics were performed on the three data sets including calculations of the mean, standard deviation, and inter-quartile range (IQR). The descriptive statistics are presented in boxplot below.

The boxplots of percentage change in level for each category of medicines are reflected below. For the Global Core (Fig. 1) the percentage change ranged from 2.45–39.12% (mean = 19.87%, SD = 10.62%, IQR = 10.2%). The range for the Regional Core (Fig. 2) was 1.77–42.17% (mean = 23.38%, SD = 12.43%, IQR = 15.65%). The Supplementary list (Fig. 3) was 11.68–55.86% (mean = 22.97%, SD = 16.26%, IQR = 17.34). The negative values in the minimum reflects an increase in price (positive change in level), and all calculations excludes outliers.

Table 2 Interrupted time-series analysis for originator molecules in the regional core list, using pricing data from 1999 to 2014 with 2004 as the interruption in the series. Statistically significant values ($P < 0,05$)

INN		Trend	(*P* value)	Change in level	(*P* value)	Change in slope	(*P* value)	Constant	(*P* value)	Int 1	*% Change in level 2004*
Albendazole 200 mg tabs	15, Zentel[a]	0,571	0,002	−2812	0,000	0,740	0,001	12,272	0,000	15,127	−18,59
Amlodipine 5 mg Tabs (99,100,101)[g]	16, Norvasc	0,305	0,082	−2447	0,002	−0,201	0,254	4278	0,000	5803	−42,17
Atovastatin 20 mg Tabs (102,103,104)[g]	17, Lipitor	0,349	0,001	−2645	0,000	−0,114	0,170	7665	0,000	9,41	−28,11
Beclomethasone100mcg/dose inh	18, Becotide[b]	−17,698	0,035	− 6847	0,809	18,412	0,269	164,637	0,000	76,147	−8,99
Cephalexin 250 mg caps	19, Keflex[c]	0,78	0,004	−7919	0,000	−0,752	0,093	5665	0,000	9565	−82,79
Enalapril 10 mg tabs	20, Renitec	−0,56	0,000	0,159	0,589	0,573	0,000	3859	0,000	1059	15,01
Fluoxetine 20 mg tabs	21, Prozac	0,579	0,000	−2787	0,000	−0,324	0,001	6021	0,000	8916	−31,26
Gliclazide 80 mg tabs	22, Diamicron[d]	0,093	0,004	−0,311	0,010	−0,055	0,084	0,873	0,000	1338	−23,24
Hydrochlorothiazide 25 mg tabs	23, Dichloride[e]	0,031	0,178					0,742	0,009	0,897	0,00
Ibuprofen 200 mg tabs	24, Brufen[f]	0,034	0,000	−0,103	0,000	−0,019	0,006	0,419	0,000	0,589	−17,49
Metformin 500 mg tabs	25, Glucophage	−0,021	0,027	−0,2	0,000	0,038	0,001	0,606	0,000	0,501	−39,92
Metronidazole 200 mg tabs	26, Flagyl	0,195	0,000	−0,609	0,000	−0,125	0,000	0,721	0,000	1696	−35,91
Nifedipine Retard 10 mg tab	27, Adalat Ret	0,324	0,000	−0,632	0,003	−0,147	0,016	1788	0,000	3408	−18,54
Ranitidine 150 mg tabs	28, Zantac	0,333	0,005	−0,101	0,777	0,024	0,824	4038	0,000	5703	−1,77
Sodium Valproate 200mg Tab	29, Epilim	0,151	0,000	−0,307	0,016	−0,035	0,292	1344	0,000	2099	−14,63

Withdrawn [a] 2010 [b] 2006 [c]2006 [d] 2009 [e]2001 [f] 2009
Each item carries the® for trademark reference
[g]number for molecules with no data in the list

Table 3 Interrupted time-series analysis for originator molecules in the supplementary .list, using pricing data from 1999 to 2014 with 2004 as the interruption in the series. Statistically significant values ($P < 0,05$)

INN		Trend	(*P* value)	Change in level	(*P* value)	Change in slope	(*P* value)	Constant	(*P* value)	Int 1	*% Change in level 2004*
Acyclovir 200 mg tabs	30, Zovirax	0,677	0,000	−0,429	0,422	−0,2	0,187	8551	0,000	11,936	−3,59
Carbamazepine 200 mg tabs	31, Tegretol	0,175	0,000	−0,477	0,001	−0,078	0,023	1464	0,000	2339	−20,39
Amox/Clav inj 600 mg (146,147)[a]	32, Augmentin	3,13	0,000	−9,99	0,001	−2211	0,006	7841	0,000	23,491	−42,53
Digoxin 0,25 mg tab	33, Lanoxin	0,021	0,000	−0,09	0,000	−0,014	0,001	0,206	0,000	0,311	−28,94
Fluconazole 200 mg cap (149, 150, 151)[a]	34, Diflucan	−0,238	0,729	−6626	0,013	2738	0,004	50,703	0,000	49,513	−13,38
Ketoconazole 200 mg Tab (153)[a]	35, Nizoral	2079	0,000	−3,45	0,017	−1107	0,031	13,609	0,000	24,004	−14,37
Losartan 50 mg Tab (154, 155)[a]	36, Cozaar	−0,017	0,948	− 0,096	0,911	− 0,276	0,381	5213	0,000	5128	−1,87
Phenytoin 100 mg caps (156)[a]	37, Epanutin	0,13	0,000	−0,43	0,000	−0,055	0,028	0,979	0,000	1629	−26,40
Rifampicin 150 mg caps (157)[a]	38, Rimactane	0,185	0,000	−0,555	0,000	−0,132	0,000	0,542	0,000	1467	−37,83
Rosuvastatin 10 mg Tabs (158, 159, 160)[a]	39, Crestor (no data)	0,239	0,000					4551	0,000	5746	0,00
Ofloxacin 200 mg Tabs (162)[a]	40, Tarivid	2128	0,000	−5167	0,000	−1113	0,004	10,353	0,000	20,993	−24,61
Aminophylline 250 mg inj	41, Aminophylline	2178	0,000	−7891	0,000	−0,944	0,040	16,003	0,000	26,893	−29,34
Miconazole Nitrate 2% crm (166)[a]	42, Daktarin	0,526	0,000	−0,971	0,001	−0,269	0,003	2,4	0,000	5,03	−19,30
Erythromycin 250 mg tabs	43, Erythrocin	0,329	0,323	0,7	0,611	−1915	0,004	4346	0,000	5991	11,68
Azithromycin 500 mg Tabs (169, 170, 171)[a]	44, Zithromax	2872	0,000	−10,698	0,000	−1595	0,017	27,625	0,000	41,985	−25,48
Cimetidine 200 mg tabs	45, Lenamet	−0,22	0,000	−0,31	0,001	−0,238	0,000	1655	0,000	0,555	−55,86
Lisinopril 10 mg Tabs (175, 177)[a]	46, Zestril	0,187	0,231	−1,66	0,231	−0,217	0,186	2917	0,000	3852	−43,09
Loratadine 10 mg Tabs (178, 179, 180)[a]	47, Clarityne	0,249	0,267	− 1013	0,230	−0,667	0,012	5342	0,000	6587	−15,38
Ceftazidime I1g/vial inj (181, 182, 183)[a]	48, Fortum	10,593	0,000	−35,972	0,000	−7382	0,004	98,727	0,000	151,692	−23,71
Isosorbide Mononitrate 20mgT	49, Ismo	0,377	0,000	−1195	0,000	−0,255	0,000	1153	0,000	3038	−39,34
Thyroxine 50mcg Tab (185, 186)[a]	50, Eltroxin	0,034	0,001	−0,028	0,303	−0,004	0,614	0,333	0,000	0,503	−5,57

Each item carries the® for trademark reference
Crestor- no pre- date available
[a]number for molecules with no data in the list

Three trends emerged from all the medicines examined (see Table 4). These trends are further explained in the text that follows.

Trend 1

Between 1999 and 2004, prior to the intervention, these medicines showed a significant year-on-year increase in price. Upon introduction of the intervention the medicines showed an immediate drop in price with a subsequent rate of increase being much less than before. Salbutamol (Fig. 4 and Table 5) will be used to illustrate the changes.

A visual inspection of the interrupted time series graph for Ventolin® above indicates that the medicine prices prior to 2004 showed a year-on-year steady rate of increase (slope 0.018 ($P = 0.000$) [CI 95% (0.012 - – 0.023)]. The introduction of the single exit price (SEP) regulations in 2004 saw a price reduction as indicated by

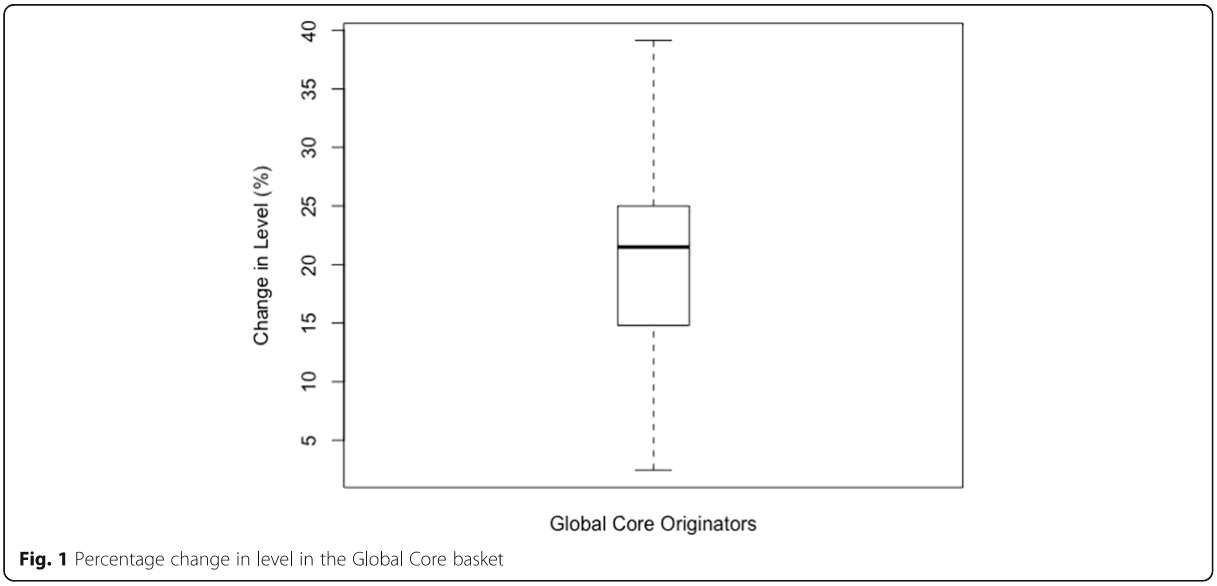

Fig. 1 Percentage change in level in the Global Core basket

the change in level – 0.065 (P = 0.000) [CI 95% (– 0.085 - – 0.046)]. In addition, the average rate of increase before the regulation was higher than the average rate of increase after the regulation as indicated in the change in slope of – 0.014 (P = 0.000) [CI 95% (– 0.02–0.009)].

The Adjusted R-Squared for Ventolin® is relatively high at 93.54% indicating that the fitted value closely correlates to the observed prices. The *P*-Value is 0.000 indicating that there is a probability of a significant difference in price of the medicine after the policy intervention.

Trend 2

In trend 2 medicine prices were already decreasing prior to the intervention in 2004 as is evident in the visual inspection with Ciprobay® 500 mg (see Table 5). The average rate of decrease before intervention of Ciprobay® was ZAR 1.028 per year ($P = 0.002$) [CI 95% (– 1.579 - -0.478)] reflected in the slope. After intervention the medicine saw a price reduction as indicated by the change in level of – 5.113 ($P = 0.000$) [CI 95% (– 7.188 - -3.038)]. The average price increase after the introduction of the intervention in 2004 as opposed to a decrease

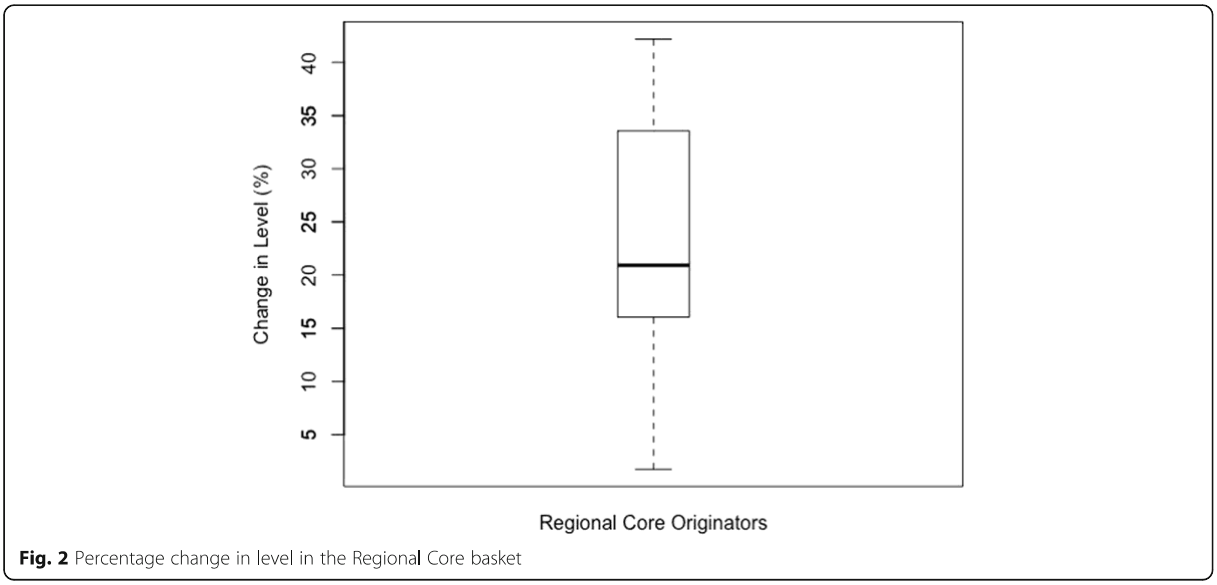

Fig. 2 Percentage change in level in the Regional Core basket

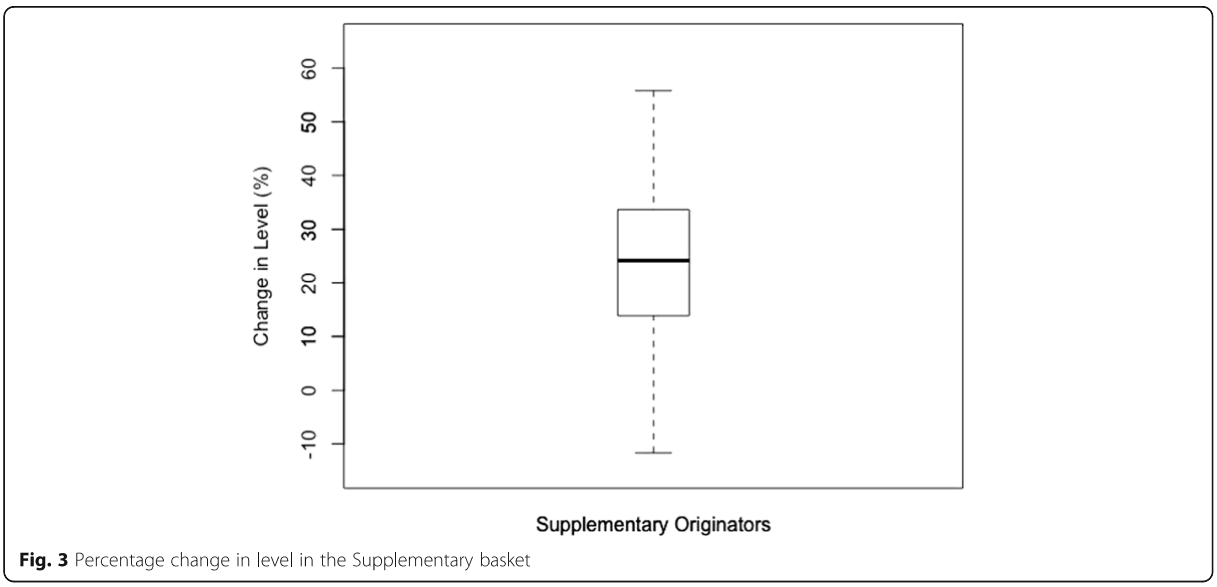

Fig. 3 Percentage change in level in the Supplementary basket

is reflected in the change in slope of ZAR 1.560(P = 0.000) [CI 95% (0.996–2.124)]. The slope change in Trend 2 indicates that the medicines will lose most of their gains over time (see Fig. 5).

Trend 3

Trend 3 is reflective of medicines that were withdrawn between 4 and 9 years after the introduction of the SEP regulations. There was a small number of medicines (11) in this basket, and the trend needs to be interpreted with care. Most (8 of 11) medicines showed overall price decrease of between 0.89–82.16% from 2004 until their withdrawal.

Trend 3 is illustrated using Tryptanol® 5 mg tablet (see Fig. 6 and Table 5). The Adjusted R-Squared for Tryptanol® 5 mg tablet is 98.79%. The *P*-Value is 0.000 indicating that there is a probability of a significant difference in price of the medicine after the policy intervention. The price reduction of the medicine due to the introduction of the intervention in 2004 is reflected in the change in level – 0.397 (*P* = 0.000) [CI 95% (– 0.541 - -0.252)] and the change in slope ZAR 0.169 (P = 0.000) [CI 95% (– 0.208–0130)].

Medicines not subjected to SEP

One of the medicines of interest in the study was Paracetamol (Panado®) syrup. Paracetamol appeared on the list suggested by HAI and WHO in the Global Core and was therefore included but not subjected to the SEP (as it is schedule zero in South Africa and these medicines are exempt from pricing regulations). While the medicine showed an immediate 15% decrease in price in 2004 the price increased by 536% by 2014 as compared to the estimated value (see Table 6). If the medicine were subjected to the normal increase of SEP as determined and published by the National Department of Health Paracetamol (Panado®) Syrup would have been priced 18% less to the consumer today.

Discussion

This study of 50 originator medicines evaluated the legislated price control on the exit price of medicines in South Africa, a low-to middle-income country. Majority of the medicines investigated showed an immediate reduction in price in 2004. Moreno–Torres [4], looked at measures of price regulation in Spain over time. These interventions include reference pricing, mark-up reduction of wholesale distributors' and retailers' fees and compulsory reductions of ex-factory manufacturer prices. The results of the study [4] indicated that there was a negative impact on expenditure per capita, that was significant, by four of the interventions, while seven interventions with a negative impact on price and one with a positive impact on price. Three interventions had a positive impact on the number of prescriptions per capita (only one resulted in a reduction). This study indicates that the SEP regulation had a major impact on medicine pricing in South Africa in both the short and long term. Most medicines investigated showed a smaller yearly increase in price compared to before regulations due to the controlled pricing environment introduced by Government. Each year a stringent process exists where manufacturers apply for price increases through the established Pricing Committee and can only increase their medicines after the Minister of Health publishes an endorsed increase in medicine pricing (Regulation 8) [26]. The regulation also allows, under

Table 4 Emerging trends of originator medicines

	Trend 1	Trend 2	Trend 3
Global Core	1. Ventolin®	5. Zocor	4. Capoten
	2. Daonil®	7. Ciprobay	6. Tryptanol
	3. Tenormin	14. Losec	9. Amoxil
	8. Bactrim		
	10. Rocephin		
	11. Valium		
	12. Voltaren		
	13. Panado		
Regional Core	16. Norvasc	25 Glucophage	15 Albendazole[a]
	17. Lipitor	20 Renitec	18 Becotide [a]
	21. Prozac		19 Keflex
	26. Flagyl		22 Diamicron
	27. Adalat Retard		23 Dichloride
	28. Zantac		24 Brufen
	29. Epilim		
Supplementary	30. Zovirax	34. Diflucan	39. Crestor[b]
	31. Tegretol	45. Lenamet	43. Erythrocin
	32. Augmentin		
	33. Lanoxin		
	35. Nizoral		
	36. Cozaar		
	37. Epanutin		
	38. Rimactane		
	40. Tarivid		
	41. Aminophylline		
	42. Daktarin		
	44. Zithromax		
	46. Zestril		
	47. Clarityne		
	48. Fortum		
	49. Ismo		
	50. Eltroxin		
	30. Zovirax		
	31. Tegretol		
	32. Augmentin		
	33. Lanoxin		
	35. Nizoral		
	36. Cozaar		
	37. Epanutin		
	38. Rimactane		
	40. Tarivid		

[a]Change in dosage form
[b]Manufactured in 2006

exceptional circumstances, for the Minister to approve increases as contemplated in Regulation 9 of the Medicines and Related Substances Act [26] taking into consideration the unintended consequences of business viability as an example. The results show that where there was a lower increase (slope) compared to prior to regulations the patients will continue to benefit from the regulations, a concept discussed in Sood et.al [5] where they concluded that the impact of price control measures on cost reduction increased the longer they remained in effect.

Further studies need to be done to determine availability and access [27] and possible negative impact of this type of pricing model. In addition, manufacturers currently determine their own costs, which may provide a potential risk to transparency. The previous stated intention to introduce international bench marking by government may overcome this potential threat. The South African policy may provide sufficient security to this risk in section 9 of the Medicines Act [26].

Those medicines in the study that reduced their prices prior to the introduction of the regulations (Trend 2) also showed a further saving in the 2004 period but lost this advantage as the manufacturers tended to take the annual price increases offered by Government. Further investigation is needed to understand why certain medicines decreased their prices even before the Government intervention. It may have been due to these medicines coming of patent, the introduction of generics or companies preparing for the expected price reduction as a business strategy so that a large sudden drop in the price did not adversely impact their market.

Of concern are the 16% (8 of 50) medicines that were withdrawn from the South African Market. One of the overarching policy considerations of the WHO/HAI Policy [25] document suggested that the policy choice should not undermine/impact a reliable supply of quality products. In the case of South Africa each of these medicines that were withdrawn had adequate supplies of quality generics available.

Their withdrawal therefore may have been as a result of competitive pricing of the generics; introduction of new generics or a business decision related to the subsequent non-profitability of the said medicine items to the manufacturer. Marie–Paule Kieny, WHO Assistant Director General for Health Systems and Innovation suggested that "When low prices preclude profits, companies leave the market – and leave a hole in the availability of quality products" [28]. It would be valuable to investigate all withdrawn molecules since 2004 and conduct an in-depth study to determine reasons for same.

The introduction of the pricing regulations (SEP) in South Africa created an ideal platform for pricing transparency, a concept that Vogler [29] agreed can

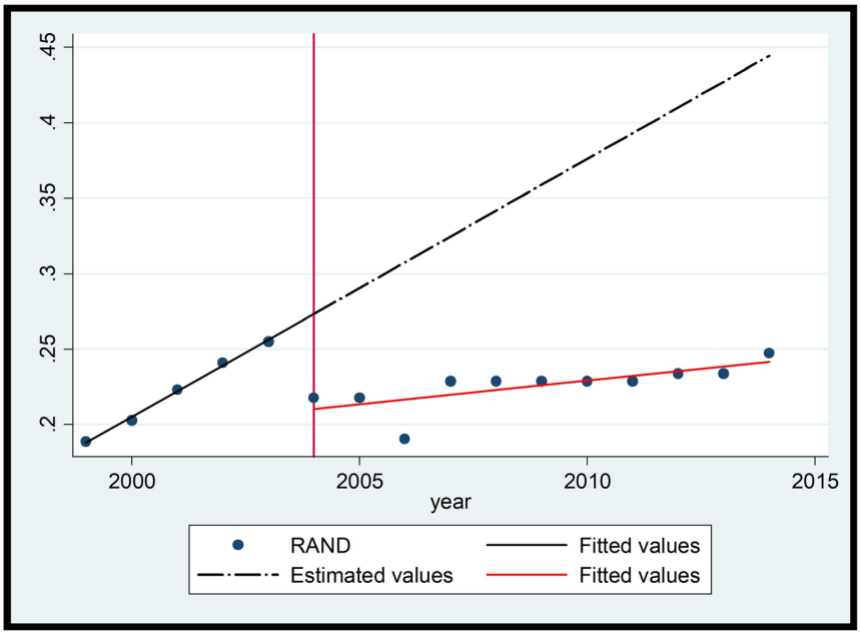

Fig. 4 Ventolin® (Salbutamol 2 mg/5 ml) Syrup

contribute to affordable patient access to medicines. Clearly, the intervention showed a substantial decrease in medicine prices with most medicines showing a continued gain because of the controlled nature of the subsequent annual increases. The findings in this study concur with the conclusion previously articulated by Sood et.al [5], that the longer price control remained in effect, the greater the impact on cost reduction.

Controlling medicine prices at the manufacturer level is a common strategy in price control policies seen in most European Union countries [30] where authorities set the price on a regulatory basis. South Africa's policy to do the same is thus in line with international practices. Internal reference pricing, international benchmarking, maximum prices, index pricing, price negotiations and volume based pricing are common pricing intervention methods used by various countries. A Cochrane review of the effects of pharmaceutical pricing and purchasing policies on health outcomes, healthcare utilization, drug expenditure and medicine use [30], included 18 studies in their main results, 17 of reference pricing (one included maximum pricing) and one of index pricing. The authors concluded that reference pricing may reduce relative expenditure on reference drugs but could not conclude on the shift to cost sharing with patients. The effects of other pricing policies studied in the review were uncertain due to sparse evidence and the authors concluded that studies needed to be spread to include low to middle-income countries. This study thus tries to add to the body of literature on pricing policies other than reference pricing, and from low and middle-income countries.

In the WHO Guidelines on Country Pharmaceutical Pricing Policies [3], a panel of experts recognized that the quality of research and evidence in relation to pharmaceutical policy implementation in developing countries was poor. South Africa adopted some of the key recommendations found in this policy document around medicine pricing for the private sector. Added to this the South African Government introduced control on the supply chain towards the retail price with the

Table 5 Changes in levels and slopes of the three medicines illustrating the three trends observed

	Change in Level (*P*-Value)	95% Conf. Interval	Change in Slope (*P*-value)	95% Conf. Interval
Trend 1				
Salbutamol 2 mg/5mls Syr 1. Ventolin	−0.065 (0.000)	−0.085 - -0.046	−0.014 (0.000)	−0.02 - -0.009
Trend 2				
Ciprofloxacin 500 mg Tabs 7. Ciprobay	−5.113 (0.000)	−7.188 - -3.038	1.560 (0.000)	0.996–2.124
Trend 3				
Amitriptyline 25 mg Tabs 6. Tryptanol	−0.397 (0.000)	− 0.541 - -0.252	−0.169 (0.000)	− 0.208- -0.130

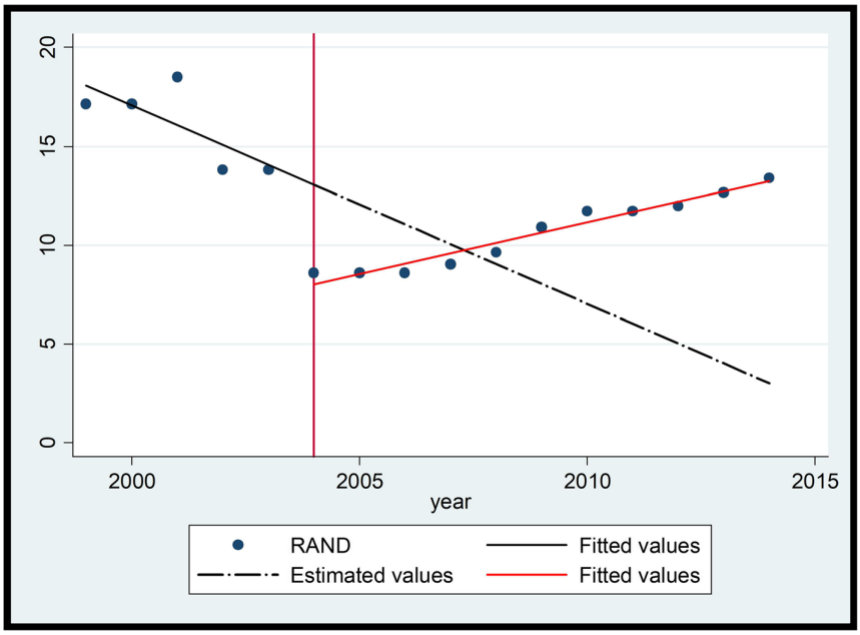

Fig. 5 Ciprobay® (Ciprofloxacin 500 mg) Tablets

introduction of the regulated dispensing fee and a proposal to regulate distribution fee in the wholesale environment.

Certain limitations of this study must be taken into account. The first is the limited data available prior to implementation of the regulations. Bernal et.al [31] suggest that there are "no fixed limits regarding the number of data points". The power depends on "various other factors, including distribution of data points before and after the intervention, variability within the data, strength of effect, and the presence of confounding effects such as seasonality" [30].

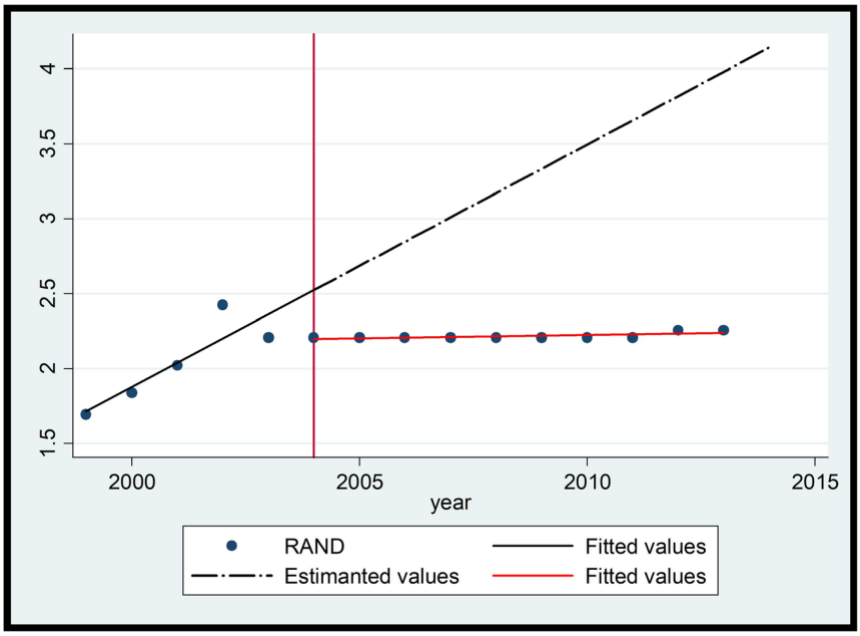

Fig. 6 Tryptanol® (Amitriptyline 25 mg) Tablets

Table 6 Price trend for Paracetamol (Panado®) Syrup from 2004 to 2014

SEP Increases (%)	Year	Actual	Price with SEP	Diff bet Actual and SEP	% Increase
0	2004	0.16	0.16	0	0
0	2005	0.17	0.16	0.01	4.69
5.20	2006	0.18	0.17	0.01	5.84
0.00	2007	0.19	0.17	0.02	10.76
6.5	2008	0.21	0.18	0.03	12.46
3.2	2009	0.22	0.21	0.02	8.24
7.4	2010	0.24	0.23	0.00	1.06
0	2011	0.26	0.23	0.03	9.72
2.14	2012	0.27	0.24	0.04	12.98
5.8	2013	0.28	0.25	0.04	12.29
5.82	2014	0.31	0.27	0.05	15.26

In inspecting the visual results, which is a recommendation by Bernal et.al [31], it can be seen that the trend before intervention does not show drastic changes. There is also a clear differentiation between the pre- and the post-intervention period with a well-defined period of implementation- in this case an immediate change [30].

The authors note the nonexistence of a control as a further limitation. Using the same selected medicines in the public sector was not possible as the state is subject to a tender process and the price data is limited. The state is also undergoing its own reform in the form of STGs, EML and class tenders. In this case while it may be possible to use non-equivalent control as suggested by Penfold [32] this did not exist.

A further limitation is acknowledged in the price files collected from the vendor supplying pharmacies. However, these price files are derived from the SEP database and organized in terms of electronic format for pharmacy use. Thus all pharmacies are reliant on these price and data files. The company has a track record of more than 20 year and supplies these price files to more than 65% of the industry. The SEP is further checked at pharmacy level when claims are submitted to payers for verification.

The study evaluates the impact of the SEP on a basket of original medicines, in terms of costs, immediate price reductions and projected price reductions. The authors acknowledge the limitation that a change in medicine price determines change in expenses but it doesn't imply savings. This could be the subject of further research.

The last limitation is the linear trend assumed by the segmented regression model that was used [22]. Despite these, this study provides evidence of the impact of medicine pricing intervention from a middle–income country, and useful lessons can be drawn by other developing countries looking at introducing medicine price controls.

Conclusion

South Africa embarked on attempting to reduce medicine prices through SEP. This study attempted to quantify the impact of the Single Exit Price (SEP) regulation.

The research conducted here confirms that substantial price reductions have been achieved through the introduction of the SEP regulation, despite the fact that other research in this field suggests that single interventions may not be sufficient in delivering affordable, accessible medicine.

Abbreviations

CMS: Council for Medical Schemes; COMED: Central Procurement Agency for medicines in South Africa; EML: Essential Medicine List; ERP: External Reference Price; HAI: Health Action International; IRP: Internal Reference Price; ITS: Interrupted Time Series; LMICs: low to middle-income countries; MCC: Medicine Control Council; NAPPI: National Pharmaceutical Product Index; NDP: National Drug Policy; NHA: National Health Accounts; NHI: National Health Insurance; No-POS: Complimentary Health Plan of Colombia; OECD: Organisation for Economic Co-operation and Development; POS: Compulsory Health Plan of Colombia; SEP: Single Exit Price; STGs: Standard Treatment Guidelines; UHC: Universal Health Coverage; WHO: World Health Organisation; ZAR: South African Rand

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Not applicable.

Authors' contributions

FS and RM conceptualized and designed the study. RM undertook data collection and data analysis. FS undertook data validation and review of the paper. Both authors read and approved the final manuscript.

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Availability of data and materials

The data file can be made available on request to the authors.

Ethics approval and consent to participate

The study has been granted ethical approval from the University of KwaZulu-Natal Humanities and Social Sciences Research Ethics Committee, Ethics. number: HSS/0154/013.

Consent for publication

Not applicable as data was sourced from price data files.

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

CHAPTER 4 PAPER 2

4.1 The impact of the single exit price policy on a basket of generic medicines in South Africa, using a time series analysis from 1999 to 2014

This chapter addresses one objective outlined in Chapter 1 related to a comparison of medicine prices before and after regulations, evaluate the impact on the prices of medicines immediately after regulations and then ten years after regulations, for generic medicines. The empirical findings are based on the analysis of the Single Exit Price (SEP) observed over a period of 16 years (1999-2014).

The Paper, entitled "**The impact of the single exit price policy on a basket of generic medicines in South Africa, using a time series analysis from 1999 to 2014**" has been published in the "PLoS ONE 14(7): e0219690*"*.

Reference: Moodley & Suleman (2019) **The impact of the single exit price policy on a basket of generic medicines in South Africa, using a time series analysis from 1999 to 2014**
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The databases for the research were obtained from Pharmacies and Computer Vendors. The Ethics certificate can be found in Annexure A. This chapter presents the published paper as per the journal stipulated format and limitations in terms of graphs, tables and word count.

PLOS ONE

RESEARCH ARTICLE

The impact of the single exit price policy on a basket of generic medicines in South Africa, using a time series analysis from 1999 to 2014

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Abstract

Background

Regulating pharmaceutical markets have become a key strategy by most governments in ensuring the availability and accessibility of quality medicines to its citizens. The South African government, when faced with high medicine prices, implemented the Single Exit Price (SEP) in 2004. This study assessed the impact of the of the Single Exit Price (SEP) regulation introduced in South Africa in 2004 on a basket of generic.

Method

Private sector price data of a basket of medicines (December 1999 to December 2014) was obtained from various price files (Pharmacy Software Vendors and Community Pharmacy). The price of the medicine was expressed in a single unit dose. The medicines investigated used the WHO/HAI methodology. The Interrupted Time-Series (ITS) model was used to estimate the change in slope and level of medicines investigated (50 originator and its available generics) before and after the policy change.

Results

Majority of the medicines analysed reflect a substantial decrease in medicine prices immediately after implementation of the pricing regulations as reflected in both the change in level and the change in slope using the interrupted time series analysis.

Discussion

This study indicates that the SEP regulation had an impact on medicine pricing in South Africa in both the short (immediately on the introduction) and long term (over the study period). Most medicines investigated showed a smaller yearly increase in price compared to before regulations.

Conclusion

This study provides evidence of the impact of medicine pricing intervention from a middle–income country, and useful lessons can be drawn by other developing countries looking at introducing medicine price controls.

Introduction

In South Africa, as in many parts of the world affordability is a barrier to gaining access to quality pharmaceutical therapies.[1] Regulating pharmaceutical markets is one method used by policy makers to achieve savings.[2] Carone, et al. indicated that promoting the use of generic medicines was one cost-effective attempt at price control and containment.[2] Other methods include creating a transparent pricing system for medicines (a key strategic imperative of the South African National Department of Health (NDoH)), regulating reimbursement for dispensers, controlling wholesale and intermediaries margins, and fixing and publishing the manufacturer price of medicines. More complex methods include health-technology assessments to ensure cost-effectiveness of new pharmaceuticals, and rational use of medicines to control public budgets.[3]

With the introduction of democracy in 1994 the new South African government was faced with high medicine prices in the private sector, which included a 29.9% (1994) spend of all claims reimbursed on medicines.[4] In 1996 the Government introduced the National Drug Policy outlining among other policies, the intention to establish a pricing committee to regulate medicine prices, create transparency in the pricing structure from manufacturer, wholesaler, distributor and providers of service, as well as to ensure a non-discriminatory pricing system. [5] The Medicines and Related Substance Control Amendment Act 90 of 1997, implemented on 2 May 2003, banned the offer of discounts and rebates to patients and healthcare providers (bonusing section 18G) and establishing a pricing committee (section 22G). [6] The pricing committee made recommendations to the Minister of Health to implement the Single Exit Price (SEP) in 2004, effectively moving the private sector from a free market to a regulated environment.[7] The components of the single exit price include the ex-manufacturer price combined with the logistics fee (as determined by the manufacturer) and Value Added Tax (VAT). [8] The SEP for each medicine in the market in 2004 was a mandatory declaration of the weighted average of all 2003 sales after taking into account all discounts and off-invoice rebates. [9] Further, the 1997 amendments to the Medicines and Related Substances Act in terms of section 18A, prevented pharmaceutical manufacturers from offering discounts and or rebates. [7]

The SEP is the only price available in the private sector across the country before the addition of the regulated dispensing fee to the end user or patient. There is an annual regulated adjustment and the regulation applies to all registered medicines and Schedule substances as per the Medicines Act except those classified in the Schedule zero category which has been specifically exempted by the Minister from the pricing regulations. The SEP regulation excludes the Government or public sector where a tender process applies.

Sound pharmaceutical policies contribute to a country's socio-economic development and the country needs economic growth for healthcare systems to perform well. [10] This further requires strategic long-term planning, effective regulations to ensure minimizing inefficiencies and unnecessary mark-ups in the supply chain and best possible pricing models to ensure access. Policy makers are aware that savings can be achieved with generic medicines, without compromising quality, if pharmaceutical markets are properly regulated.[2]

It is suggested that countries need to examine their regulatory framework and look at trends that may limit the potential for savings by inadvertently encouraging higher priced generics. [11] Seeley and Kanavos stated that the number of generic entrants is not a predictor of lower generic prices, but the market does need a significant number of entrants to impact the competition.[11] Countries like Canada, also cap the price at which generics enter a market as a policy option. Canadian provinces followed the Alberta model for pricing of generic drugs, a model suggested by academics Cambourieu, et al. [12]; Hollis,[13]; Hollis and Grootendost, [14]. In April 2014, Alberta introduced their generic policy where new generic entries start at 70% of the brand if there is only one generic entrant, and then subsequent generic medicines that entered the market were priced at 50%, 25% and 18% respectively of the originator. [14] The first generic entrant keeps the advantage for one year after which the 50% price applies. The savings through agreements with manufacturers using this model is expected to be $3.8 billion over three years to all payers.

Hassali, et al. recommended that the main policy to promote generic medicines needs to be supported by complementary policies both to facilitate its implementation and also to overcome the barriers that hinder its effectiveness. [15] The policies promoting generic substitution is seen as means to contain pharmaceutical expenditures and are often at the forefront of yielding significant cost saving. [2] Very little is known about using pricing policies as a means to contain generic medicine prices. South Africa has done so, yet no published information exists regarding the impact of pricing policies that were implemented post democracy.

Aim of the study

The aim of the study was to examine the impact of the regulatory change, the SEP, on a basket of generic medicines from 1999–2014. The study went further to compare the difference in impact to the basket of the originator and generic medicines.

Methodology

The interrupted time series (ITS) was used in this longitudinal pharmaceutical policy evaluation method in studying the impact of legislative changes on pricing of generic medicines in the South African private market. A quantitative analytical approach was used in this study. [16] Longitudinal trends were compared before and after the introduction of policy changes. The research tracked annual price changes on a basket of products five years before regulatory changes (1999–2003) and then measured annual price changes over the next ten years (2004–2014), following the intervention, namely, the Single Exit Price (SEP) of medicines.

The segmented linear regression was used for the interrupted time series analysis (ITSA). This divides the time series into pre- and post- intervention segments. As the regulations were introduced in 2004 (a year after the Act) and became immediately implementable, 2004 was chosen as the intervention between segments. The linear regression model has two parameters, the change in level and the change in slope. The difference between the two segments was quantified by testing the change in these two parameters. It must be noted that the pricing intervention was scheduled to come into effect one year after promulgation of the Act, hence the use of 2004 as the intervention point with data being collected on the 31 December of each year.[17]

Commonly used data source for time series is cost data obtained from pharmacy dispensing files, claims data, and other routinely collected data. SEP prices of medicines listed were obtained from the computer vendors responsible in maintaining price files for pharmacy and verified through the pharmacy dispensing systems spanning the period 1999 to 2014. The Government medicine price database[18], was created after the introduction of the SEP, and only

exists post the intervention and therefore could not be utilized. It was also important to utilize a single complete data source to ensure accuracy of results.

Pricing data for the medicines being studied could not be obtained before 1999 in the country and was identified as a limiting factor. Stata (13 MSI) (StataCorp LP, College Station, TX, USA), a statistical package was used to analyse the data, generate the necessary variables, compute the statistical analysis and produce the necessary graphs. [19] To ensure unbiased estimation, stationarity and autocorrelation were taken into account as observations over time are correlated. Autocorrelation and stationarity were therefore tested and corrected for, if present, using autoregressive moving average (ARIMA) models. The following formula was used to calculate the limits used to define outliers in the data set for each of the three categories:

$$\text{Upper limit}: \ Q3 + (\text{IQR x } 1.5)$$

$$\text{Lower limit}: \ Q1 - (\text{IQR x } 1.5)$$

Anything outside of the calculated limits was identified as an outlier and excluded from the data set. Once the outliers were excluded, descriptive statistics were performed on the three data sets including calculations of the mean, standard deviation, and inter-quartile range (IQR). The descriptive statistics are presented in boxplots.

Selection of the basket of products

A basket of fifty (50) originator medicines were chosen implementing the WHO/HAI methodology. [20] The maximum number of generic molecules were chosen with a history of pricing from 2004 resulting in at least three to four generics per originator medicine with a total of 136 generic medicines being examined.

The Global Core of fourteen items (14) originator and forty six (46) generics allows for international comparison, a Regional Core of fifteen (15) originator and forty two (42) generics items allows for regional differences in medicine usage whilst still enabling comparison across countries and the twenty-one (21) originator and forty eight (48) generic medicines from a supplementary list selected for their local importance [20] completed the basket. The May 2016 update on the WHO/HAI [21] methodology removed the Regional Core and replaced it with thirty-six (36) medicines. This study used the original method as the investigation period covered 1999–2014. Further, since the regulations affected mainly the private sector in South Africa, an assessment of the top 50 medicines dispensed by volume in the private sector (IMS Health) in 2014 was taken into consideration. This data was sourced from IMS Health and used in the supplementary list. Consideration was also given to the list used in the 2004 study by Xiphu and Mpanza [22] for further comparison. Once the 50 medicines were selected, the originator and generic product was listed together with the strength, form, pack-size and National Pharmaceutical Product Index (NAPPI). The NAPPI code is a unique coding system used in South Africa. This allowed ease of reference when pricing was compared from different data files. Any price change listed on the data file in December of each year was captured.

Results

The results of the interrupted time-series analysis (ITSA) for three groups of medicines listed as Global Core, Regional Core and Supplementary are presented in Tables 1, 2 and 3 respectively. The total number of molecules included in the three baskets were 186. Of this, 65 molecules had insufficient data either being withdrawn before the end of the study or introduced later in the study period.

Table 1. Global core interrupted time-series analysis for originator and generic molecules using pricing data from 1999 to 2014 with 2004 as the interruption in the series (P < 0,05).

INN	Trade names (Originator in bold)	Trend	(P value)	Change in level	(P value)	Change in slope	(P value)	Constant	(P value)	Int 1	*% Change in level 2004*
Salbutamol 2mg/5mls Syr	**1, Ventolin**	0,018	**(0,000)**	**-0,065**	**(0,000)**	**-0,014**	**(0,000)**	0,19	**(0,000)**	0,28	-23,47
(53)*	51, Asthavent	-0,001	0,677	-0,004	0,358	**0,005**	**0,002**	0,08	**(0,000)**	0,08	-4,64
	52, Venteze	0,007	**(0,000)**	**-0,031**	**(0,000)**	**-0,004**	**0,005**	0,07	**(0,000)**	0,11	-28,97
Glibenclamide 5mg tab	**2, Daonil**	0,228	**(0,000)**	**-0,771**	**0,001**	-0,047	0,382	2,45	**(0,000)**	3,59	-21,51
	54, Glycomin	0,116	0,011	**-0,764**	**(0,000)**	**-0,171**	**0,001**	0,86	**(0,000)**	1,44	-53,24
	55, Bio-Glibenclamide	-0,001	0,939	**-0,192**	**0,001**	0,007	0,557	0,33	**(0,000)**	0,32	-59,26
	56, Sandoz-Glibenclamide	0,150	**(0,000)**	**-1,436**	**(0,000)**	**-0,141**	**(0,000)**	0,82	**(0,000)**	1,57	-91,52
Atenolol 50mg caps	**3, Tenormin**	0,427	**(0,000)**	**-1,242**	**(0,000)**	**-0,209**	**0,007**	2,56	**(0,000)**	4,70	-26,45
	57, Hexa Bloka	0,053	**(0,000)**	**-0,910**	**(0,000)**	**-0,025**	**0,01**	1,07	**(0,000)**	1,34	-68,01
	58, Sandoz-Atenolol	0,013	0,442	**-0,849**	**(0,000)**	0,008	0,644	1,14	**(0,000)**	1,20	-70,75
	59, Ten Bloka_2	0,042	0,005	**-0,681**	**(0,000)**	0,001	0,912	1,13	**(0,000)**	1,34	-50,90
Captopril 25mg tabs	**4, Capoten**	0,044	0,014	-0,117	0,071	0,016	0,365	2,09	**(0,000)**	2,31	-5,07
	60, Zapto	0,006	0,308	**-0,628**	**(0,000)**	0,005	0,394	0,84	**(0,000)**	0,87	-72,52
	61, Capto-Hexal	-0,164	**(0,000)**	**-0,309**	**0,002**	**0,183**	**(0,000)**	1,41	**(0,000)**	0,59	-52,02
	62, Mylan-Captopril	-0,052	**(0,000)**	**-0,612**	**(0,000)**	**0,061**	**(0,000)**	1,00	**(0,000)**	0,74	-82,37
Simvastatin 20mg tabs (63,64,65)*	**5, Zocor**	-0,997	0,001	-1,078	0,225	**0,832**	**0,004**	9,56	**(0,000)**	4,58	-23,54
Amitriptyline 25mg tabs	**6, Tryptanol**	0,176	**(0,000)**	**-0,397**	**(0,000)**	**-0,169**	**(0,000)**	1,70	**(0,000)**	2,58	-15,42
(68)*	66, Trepiline	0,115	**(0,000)**	**-0,715**	**(0,000)**	**-0,094**	**(0,000)**	0,66	**(0,000)**	1,23	-57,94
	67, Sandoz Amitripyline	0,081	**(0,000)**	**-0,696**	**(0,000)**	**-0,072**	**(0,000)**	0,71	**(0,000)**	1,11	-62,59
Ciprofloxacin 500mg tabs	**7, Ciprobay**	-1,028	0,002	**-5,113**	**(0,000)**	**1,560**	**(0,000)**	18,21	**(0,000)**	13,07	-39,12
(69,71)*	70, Cifloc	-5,526	**(0,000)**	***1,672***	**(0,000)**	**5,603**	**(0,000)**	16,24	**(0,000)**	***-0,34***	***-499,10***
	72, Cifran	-5,122	**(0,000)**	***2,556***	**0,003**	**4,927**	**(0,000)**	15,60	**(0,000)**	***0,24***	***1078,48***
Co-Trimoxazole 8 +40mg/ml syr	**8, Bactrim**	0,364	**(0,000)**	**-2,267**	**(0,000)**	**-0,247**	**(0,000)**	2,46	**(0,000)**	4,28	-52,94
(75)*	73, Purbac	0,051	**(0,000)**	**-0,490**	**(0,000)**	**-0,040**	**(0,000)**	0,36	**(0,000)**	0,61	-80,20
	74, Cozole	0,051	**(0,000)**	**-0,490**	**(0,000)**	**-0,040**	**(0,000)**	0,36	**(0,000)**	0,61	-80,20
	76, Adco-Co-Trimoxazole	0,057	**(0,000)**	**-0,426**	**(0,000)**	**-0,053**	**(0,000)**	0,32	**(0,000)**	0,61	-70,30
Amoxicillin 500mg caps	**9, Amoxil**	0,334	**(0,000)**	-0,127	0,429	**-0,274**	**0,001**	3,52	**(0,000)**	5,19	-2,45
	77, Moxymax	0,062	**(0,000)**	**-1,331**	**(0,000)**	**-0,051**	**0,001**	1,36	**(0,000)**	1,67	-79,56
	78, Betmox	0,011	0,5	**-1,277**	**(0,000)**	0,007	0,666	1,58	**(0,000)**	1,64	-77,91
	79, Zoxil	0,017	0,827	**-0,894**	**0,008**	-0,022	0,781	1,73	**(0,000)**	1,81	-49,31
Ceftriaxone 1g/vial inj	10, Rocephin	4,302	0,081	**-82,503**	**(0,000)**	-3,371	0,237	121,81	**(0,000)**	143,32	-57,57
(80,81,82)*	83, Aspen Ceftriaxone	1,444	0,456	**-82,325**	**(0,000)**	-1,974	0,328	117,15	**(0,000)**	121,48	-67,77
Diazepam 5mg	11, Valium	0,318	**(0,000)**	**-0,772**	**(0,000)**	-0,213	**(0,000)**	1,00	**(0,000)**	2,59	-29,83
(86)	84, Pax	0,003	0,376	**-0,063**	**(0,000)**	0,003	0,457	0,13	**(0,000)**	0,15	-42,86
	85, Betapam	0,003	0,064	**-0,057**	**(0,000)**	0,001	0,685	0,09	**(0,000)**	0,11	-54,29
Diclofenac 50mg tabs	12, Voltaren	0,063	0,013	**-0,209**	**0,025**	0,021	0,373	1,16	**(0,000)**	1,48	-14,17
(88)*	87, Diclohexal	0,071	**(0,000)**	**-1,002**	**(0,000)**	-0,053	**(0,000)**	1,05	**(0,000)**	1,41	-71,32
	89, Panamor	0,043	**(0,000)**	**-1,119**	**(0,000)**	-0,032	**(0,000)**	1,16	**(0,000)**	1,38	-81,15
Paracetamol 25mg/ml syr	13, Panado	0,001	0,702	**-0,030**	**0,017**	0,014	**(0,000)**	0,18	**(0,000)**	0,18	-16,57

(*Continued*)

Table 1. (Continued)

INN	Trade names (Originator in bold)	Trend	(P value)	Change in level	(P value)	Change in slope	(P value)	Constant	(P value)	Int 1	*% Change in level 2004*
(91)*	90, Napamol	0,006	0,272	**-0,092**	**(0,000)**	-0,004	0,471	0,09	**(0,000)**	0,12	-74,80
	92, Painamol	0,001	0,777	**-0,018**	**0,275**	0,006	0,273	0,07	**(0,000)**	0,07	-25,35
	93, Calpol	0,012	0,15	**-0,037**	**0,22**	0,002	0,782	0,14	**(0,000)**	0,20	-18,50
Omeprazole 20mg tabs(94,95,96)*	14, Losec	-0,610	0,036	**1,183**	**0,245**	1,298	**(0,000)**	11,58	**(0,000)**	8,53	13,87

Notes

Int 1(Estimate in 2004) = Cons + (Trend X Years)

Statistically Significant (P<0,05) in BOLD

Global Core List with Data (Originals: 14, Generics: 29) = 43

Change in level = 36 (83,72%)

Change in slope = 28 (65,12%)

Global Core List with no data * = 17

Global Core List Total = 60

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The global core in Table 1 contains the data for 43 molecules (14 originator, 29 generics). Of the fourteen (14) original molecules ten (10) showed a statistically significant (P<0.05) change in level with twenty-five (26) of the twenty-eight (28) generics showing a statistically significant change in level (P<0.05). The level change indicated an immediate decrease in the medicine price on the introduction of the regulation in 2004. 65.12% of the molecules showed a statistically significant (P<0.05) change in slope indicating that the policy will continue to benefit medicine prices over time.

Table 2 contains the data for the regional core basket of 40 molecules (14 original and 26 generics). Of the 14 originator molecules 11 showed a statistically significant change in level (P<0.05) with seven showing statistically significant change in slope. Twenty-three (23) of the 26 generics showed a statistically significant change in level (P<0.05) with 16 showing statistically significant change in slope.

In the 38 molecules analysed in the supplementary basket 31 showed statistically significant change in level (75.60%) and 26 (63.4%) showed statistically significant change in slope.

The boxplots of percentage change in level for each category of medicines are reflected below. For the Global Core (Fig 1) the percentage change ranged from 2.45%-39.12% (mean = 19.87%, SD = 10.62% IQR = 10.2%) for the originator medicines and 18.50%-91.5% (mean = 62.46%, SD = 18.64%, IQR = 24.81%) for their generics. The range for the Regional Core (Fig 2) was 1.77%-42.17% (mean = 23.38%, SD = 12.43%, IQR = 15.65%) for the originator medicines and -0.70%-78.03% (mean = 44.62%, sd = 23.04%, IQR = 37.41%) for their generics. The Supplementary list (Fig 3) was -11.68%-55.86% (mean = 22.97%, SD = 16.26%, IQR = 17.34) for the originator medicines and 9.78%-78.49% (mean = 48.37%, SD = 19.44%, IQR = 27.53%) for their generics. The negative values in the minimum reflects an increase in price (positive change in level), and all calculations excludes outliers.

Three trends emerged from all the medicines examined as can be seen from Table 4 and Figs 4, 5 and 6.

Trend 1

A visual inspection of the interrupted time series graph (see Fig 4) for Sandoz-Glibenclamide indicates that the medicine prices prior to 2004 showed a year-on-year steady rate of increase

Table 2. Regional core interrupted time-series analysis for originator and generic molecules using pricing data from 1999 to 2014 with 2004 as the interruption in the series. Statistically significant values (P < 0,05).

INN	Trade names (Originator in bold)	Trend	(P value)	Change in level	(P value)	Change in slope	(P value	Constant	(P value)	Int 1	*% Change in level 2004*
Albendazole 200mg tabs	**15, Zentel**	0,571	0,002	**-2,812**	**(0,000)**	**0,74**	**0,001**	12,272	**(0,000)**	15,127	-18,59
(98)*	97, Bendex	0,379	0,09	**-2,703**	**0,001**	0,139	0,527	9,638	**(0,000)**	11,154	-24,23
Amlodipine 5mg tabs (99,100,101)*	**16, Norvasc**	0,305	0,082	**-2,447**	**0,002**	-0,201	0,254	4,278	**(0,000)**	5,803	-42,17
Atovastatin 20mg tabs (102,103,104)*	**17, Lipitor**	0,349	0,001	**-2,645**	**(0,000)**	-0,114	0,17	7,665	**(0,000)**	9,41	-28,11
Beclomethasone100mcg/ dose inh	**18, Becotide**	-17,698	0,035	-6,847	0,809	18,412	0,269	164,637	**(0,000)**	76,147	-8,99
	105, Beclate	5,532	0,008	**-32,077**	**(0,000)**	-1,221	0,506	71,608	**(0,000)**	99,268	-32,31
	106, Beceze	0,502	0,683	0,791	0,859	-1,745	0,21	109,915	**(0,000)**	112,425	0,70
	107, Qvar	4,159	0,614	**-62,347**	**0,025**	3,355	0,685	157,942	**(0,000)**	174,578	-35,71
Cephalexin 250mg caps	**19, Keflex**	0,78	0,004	**-7,919**	**(0,000)**	-0,752	0,093	5,665	**(0,000)**	9,565	-82,79
(109)*	108, Ranceph	-0,417	(0,000)	**0,735**	**0,003**	**0,413**	**(0,000)**	1,839	**(0,000)**	***-0,246***	***-298,78***
	110, Cpl-Cephalexin	-0,263	(0,000)	**-1,158**	**(0,000)**	**0,273**	**(0,000)**	2,01	**(0,000)**	1,484	-78,03
Enalapril 10mg tabs	**20, Renitec**	-0,56	0	0,159	(0,589	**0,573**	**(0,000)**	3,859	**(0,000)**	1,059	15,01
	111, Pharmapress	-0,413	0	-0,133	0,238	**0,463**	**(0,000)**	2,55	**(0,000)**	0,485	-27,42
	112, Alapren	-0,433	0	**-0,19**	**0,025**	**0,438**	**(0,000)**	2,318	**(0,000)**	1,019	-18,65
	113, Enap	-0,387	0	-0,092	0,42	**0,426**	**(0,000)**	2,08	**(0,000)**	0,919	-10,01
Fluoxetine 20mg tabs	**21, Prozac**	0,579	0	**-2,787**	**(0,000)**	**-0,324**	**0,001**	6,021	**(0,000)**	8,916	-31,26
(116)*	114, Lorien	-1,602	0	**0,443**	**0,007**	**1,685**	**(0,000)**	4,085	**(0,000)**	0,881	***50,28***
	115, Nuzak	-0,117	0	**-1,458**	**(0,000)**	**0,162**	**(0,000)**	2,763	**(0,000)**	2,178	-66,94
Gliclazide 80mg tabs	**22, Diamicron**	0,093	0,004	**-0,311**	**0,01**	-0,055	0,084	0,873	**(0,000)**	1,338	-23,24
	117, Adco-Glucomed	0,012	0,53	**-0,264**	**0,002**	-0,004	0,822	0,817	**(0,000)**	0,877	-30,10
	118, Sandoz Gliclazide	-0,005	0,695	**-0,286**	**(0,000)**	0,002	0,91	0,85	**(0,000)**	0,825	-34,67
	119, Diaglucide	-0,157	0	**-0,1091**	**0,041**	**0,173**	**(0,000)**	1,26	**(0,000)**	0,632	-17,26
Hydrochlorothiazide 25mg tabs	**23, Dichloride (No data)**	0,031	0,178					0,742	0,009	0,897	0,00
	120, Ridaq	0,123	0	**-0,635**	**0(0,000)**	**-0,094**	**0,001**	0,693	**(0,000)**	1,062	-59,79
	121, Hexazide	-0,248	0	**0,32**	**0,001**	**0,26**	**(0,000)**	0,645	**(0,000)**	***-0,595***	***-53,78***
Ibuprofen 200mg tabs	**24, Brufen**	0,034	0	**-0,103**	**(0,000)**	**-0,019**	**0,006**	0,419	**(0,000)**	0,589	-17,49
(123)*	122, Inza	-0,016	0	**-0,149**	**(0,000)**	**0,021**	**(0,000)**	0,36	**(0,000)**	0,28	-53,21
	124, Ranfen	-0,015	0	**-0,168**	**(0,000)**	**0,016**	**(0,000)**	0,304	**(0,000)**	0,229	-73,36
Metformin 500mg tabs	25, Glucophage	-0,021	0,027	**-0,2**	**(0,000)**	**0,038**	**0,001**	0,606	**(0,000)**	0,501	-39,92
(125, 126, 127)*	128, Sandoz-Metformin	0,021	0,094	**-0,262**	**(0,000)**	**-0,022**	**0,099**	0,465	**(0,000)**	0,57	-45,96
Metronidazole 200mg tabs	26, Flagyl	0,195	0	**-0,609**	**(0,000)**	**-0,125**	**(0,000)**	0,721	**(0,000)**	1,696	-35,91
(131)*	129, Metazol	0,01	0	**-0,084**	**(0,000)**	**-0,006**	**(0,000)**	0,087	**(0,000)**	0,137	-61,31
	130, Trichazole	0,006	0,202	**-0,246**	**(0,000)**	**-0,004**	**0,381**	0,326	**(0,000)**	0,356	-69,10
Nifedipine Retard 10mg tab	27, Adalat Ret	0,324	0	**-0,632**	**0,003**	**-0,147**	**0,016**	1,788	**(0,000)**	3,408	-18,54
	132, Nifedelat	0,035	0,001	**-0,7**	**(0,000)**	**-0,007**	**0,365**	0,935	**(0,000)**	1,11	-63,06
	133, Cardifen	0,038	0,168	**-0,239**	**0,032**	**-0,049**	**0,095**	1,035	**(0,000)**	1,225	-19,51
Ranitidine 150mg tabs	28, Zantac	0,333	0,005	**-0,101**	**0,777**	**0,024**	**0,824**	4,038	**(0,000)**	5,703	-1,77
	134, Ultak	-0,272	0,016	**-0,721**	**0,027**	**0,31**	**0,008**	2,461	**(0,000)**	1,373	-52,51
	135, Histak	-0,304	0	**-1,488**	**(0,000)**	**0,344**	**(0,000)**	3,525	**(0,000)**	2,005	-74,21
	136, CPL Ranitidine	-0,972	0	**-1,009**	**(0,000)**	**0,999**	**(0,000)**	3,377	**(0,000)**	1,433	-70,41

(*Continued*)

Table 2. (Continued)

INN	Trade names (Originator in bold)	Trend	(P value)	Change in level	(P value)	Change in slope	(P value	Constant	(P value)	Int 1	*% Change in level 2004*
Sodium Valproate200mg Tab (137, 138)*	29, Epilim	0,151	0	**-0,307**	**0,016**	**-0,035**	**0,292**	1,344	**(0,000)**	2,099	-14,63

Notes

Int 1(Estimate in 2004) = Cons + (Trend X Years)

Statistically Significant (P<0,05) in BOLD

Regional List With Data = Originals:14, Generics: 26; Total = 40

Change in level = 34 (85%); n = 40

Change in level = 23 (57,5%); n = 40

Regional List with no data* = 17

Regional List total = 57

https://doi.org/10.1371/journal.pone.0219690.t002

(slope 0.150 (P = 0.000), [CI 95% (0.132- -0.167)]. The introduction of the single exit price (SEP) regulations in 2004 saw a price reduction as indicated by the change in level -1.436 (P = 0.000), [CI 95% (-1.500- -1.371)]. In addition, the average rate of increase before the regulation was higher than the average rate of increase after the regulation as indicated in the change in slope (-0.41 (P = 0.000) [CI 95% (-1.59- -0.28)].

The Adjusted R-Squared for Sandoz-Glibenclamide is relatively high at 99.77% indicating that the fitted value closely correlates to the observed prices. The P-Value is 0.000 indicating that there is a high probability of a significant difference in price of the medicine after the policy intervention.

Trend 2

In trend 2 medicine prices were already decreasing prior to the intervention in 2004 as is evident in the visual inspection with Mylan Captopril 25mg (see Fig 5). The average rate of decrease before intervention of Mylan Captopril was ZAR 0.052 per year(P = 0.000) [CI 95% (-0.067- -0.037)] reflected in the slope. After intervention the medicine saw a price reduction as indicated by the change in level of -0.612 (P = 0.000), [CI 95% (-0.669- -0.555)]. The average price increase after the introduction of the intervention in 2004 as opposed to a decrease is reflected in the change in slope of ZAR 0.061 [CI 95% (0.045–0.076)]. The slope change in Trend 2 indicates that the medicines will lose most of their gains over time.

Twenty-eight (28) of the generic medicines studied in the three baskets followed the pattern in Trend 2. Twenty-six (26) of these medicines showed a further drop in price after the intervention with only two showing an immediate price increase in 2004. Two medicines Cifloc 500mg tablet and Cifran 500mg tablet, the only two available generics to Ciprobay 500mg tablet at the time, showed an increase in 2004 following almost an identical pricing trend to each other during the study period.

Trend 3

Three (3) generics in the basket, Glycomin 5mg tablet, Aspen Ceftriaxone 1g injectable vial in the global core and Cardifen 10mg tablet in the regional core initially followed those in trend 1 where there was a steady increase in price between 1999 to 2004 with a steep drop in 2004. However, there was a subsequent decrease in price during the 2004–2014 period unlike in trend 1. This average rate of decrease after 2004 to 2014 was unusual as most medicines took the regulated increase offered by the National Department of health. Visual inspection of the

Table 3. Supplementary list interrupted time-series analysis for originator and generic molecules using pricing data from 1999 to 2014 with 2004 as the interruption in the series. statistically significant values (P < 0,05).

INN	Trade Names (Originator in Bold)	Trend	(P value)	Change in level	(P value)	Change in slope	(P value	Constant	(P value)	Int 1	*% Change in level 2004*
Acyclovir 200mg tabs	**30, Zovirax**	0,677	**(0,000)**	-0,429	0,422	-0,2	0,187	8,551	**(0,000)**	11,936	-3,59
(140)*	139, Cyclivex	0,047	0,344	**-1,827**	**(0,000)**	0,039	0,442	2,879	**(0,000)**	3,114	-58,67
	141, Lovire	0,041	**0,031**	**-1,585**	**(0,000)**	0,027	0,151	2,62	**(0,000)**	2,825	-56,11
	142, Adco-Acyclovir	0,072	0,504	-0,297	0,464	-0,165	0,165	2,678	**(0,000)**	3,038	-9,78
Carbamazepine 200mg tabs	**31, Tegretol**	0,175	**(0,000)**	**-0,477**	**0,001**	**-0,078**	**0,023**	1,464	**(0,000)**	2,339	-20,39
(144)*	143,Degranol	0,105	**(0,000)**	**-0,294**	**0,001**	-0,04	0,069	0,762	**(0,000)**	1,287	-22,84
	145, Sandoz Carbamazepine	0,132	**(0,000)**	**-0,781**	**(0,000)**	**-0,101**	**(0,000)**	0,781	**(0,000)**	1,309	-59,66
Amox/Clav inj 600mg (146,147)*	**32, Augmentin**	3,13	**(0,000)**	**-9,99**	**0,001**	**-2,211**	**0,006**	7,841	**(0,000)**	23,491	-42,53
Digoxin 0,25mg tab	**33, Lanoxin**	0,021	**(0,000)**	**-0,09**	**(0,000)**	**-0,014**	**0,001**	0,206	**(0,000)**	0,311	-28,94
	148, Purgoxin	0,019	**(0,000)**	**-0,055**	**0,001**	-0,004	0,223	0,187	**(0,000)**	0,282	-19,50
Fluconazole 200mg cap (149, 150, 151)*	**34, Diflucan**	-0,238	0,729	**-6,626**	**0,013**	**2,738**	**0,004**	50,703	**(0,000)**	49,513	-13,38
Ketoconazole 200mg tab (153)*	**35, Nizoral**	2,079	**(0,000)**	**-3,45**	**0,017**	**-1,107**	**0,031**	13,609	**(0,000)**	24,004	-14,37
	152, Ketazol	3,519	**0,001**	**-14,796**	**(0,000)**	**-3,239**	**0,002**	10,883	**(0,000)**	21,44	-69,01
Losartan 50mg tab (154, 155)*	**36, Cozaar**	-0,017	0,948	-0,096	0,911	-0,276	0,381	5,213	**(0,000)**	5,128	-1,87
Phenytoin 100mg caps (156)*	**37,Epanutin**	0,13	**(0,000)**	**-0,43**	**(0,000)**	**-0,055**	**0,028**	0,979	**(0,000)**	1,629	-26,40
Rifampicin 150mg caps (157)*	**38, Rimactane**	0,185	**(0,000)**	**-0,555**	**(0,000)**	**-0,132**	**(0,000)**	0,542	**(0,000)**	1,467	-37,83
Rosuvastatin 10mg tabs (158, 159, 160)*	**39, Crestor (no data)**	0,239	**(0,000)**					4,551	**(0,000)**	5,746	***0,00***
Ofloxacin 200mg tabs (162)*	**40, Tarivid**	2,128	**(0,000)**	**-5,167**	**(0,000)**	**-1,113**	**0,004**	10,353	**(0,000)**	20,993	-24,61
	161, Tafloc	-0,852	**0,025**	**-4,001**	**(0,000)**	**1,225**	**0,004**	11,688	**(0,000)**	9,984	-40,07
Aminophylline 250mg inj	**41, Aminophylline**	2,178	**(0,000)**	**-7,891**	**(0,000)**	**-0,944**	**0,04**	16,003	**(0,000)**	26,893	-29,34
	163, SFK Aminophylline	0,857	**(0,000)**	**-4,824**	**(0,000)**	**-0,488**	**(0,000)**	6,608	**(0,000)**	10,893	-44,29
	164, Merck A Aminophylline	1,729	**(0,000)**	**-9,478**	**(0,000)**	**-1,588**	**(0,000)**	3,43	**(0,000)**	12,075	-78,49
Miconazole Nitrate 2% crm (166)*	**42, Daktarin**	0,526	**(0,000)**	**-0,971**	**0,001**	**-0,269**	**0,003**	2,4	**(0,000)**	5,03	-19,30
	165, Covarex	0,098	0,011	**-1,453**	**(0,000)**	-0,068	0,057	1,969	**(0,000)**	2,263	-64,21
Erythromycin 250mg tabs	**43, Erythrocin**	0,329	0,323	0,7	0,611	**-1,915**	**0,004**	4,346	**(0,000)**	5,991	11,68
	167, Purmycin	0,048	**(0,000)**	**-0,794**	**(0,000)**	**-0,022**	**0,025**	1,097	**(0,000)**	1,289	-61,60
	168, Xeramel	0,189	0,104	**-1,003**	**(0,000)**	-0,163	0,161	1,065	**(0,000)**	1,443	-69,51
Azithromycin 500mg tabs (169, 170, 171)*	**44, Zithromax**	2,872	**(0,000)**	**-10,698**	**(0,000)**	**-1,595**	**-0,017**	27,625	**(0,000)**	41,985	-25,48
Cimetidine 200mg tabs	**45, Lenamet**	-0,22	**(0,000)**	**-0,31**	**0,001**	**-0,238**	**(0,000)**	1,655	**(0,000)**	0,555	-55,86
	172, Secadine	-0,311	**(0,000)**	**-0,283**	**0,002**	**0,326**	**(0,000)**	1,443	**(0,000)**	0,51	-55,49
	173, Cimlok	-0,19	**(0,000)**	**-0,397**	**0,006**	**0,198**	**(0,000)**	1,608	**(0,000)**	0,658	-60,33
Lisinopril 10mg tabs (175, 177)*	46, Zestril	0,187	0,231	**-1,66**	**0,231**	**-0,217**	**0,186**	2,917	**(0,000)**	3,852	-43,09
	176, Adco-Zetomax	-0,131	0,02	**-0,528**	**0,003**	**0,178**	**0,003**	2,148	**(0,000)**	1,624	-32,51
Loratadine 10mg tabs (178, 179, 180)*	47, Clarityne	0,249	0,267	**-1,013**	**0,23**	**-0,667**	**0,012**	5,342	**(0,000)**	6,587	-15,38

(*Continued*)

Table 3. (Continued)

INN	Trade Names (Originator in Bold)	Trend	(P value)	Change in level	(P value)	Change in slope	(P value	Constant	(P value)	Int 1	*% Change in level 2004*
Ceftazidime I1g/vial inj (181, 182, 183)*	48, Fortum	10,593	**(0,000)**	**-35,972**	**(0,000)**	**-7,382**	**0,004**	98,727	**(0,000)**	151,692	-23,71
Isosorbide Mononitrate 20mgT	49, Ismo	0,377	**(0,000)**	**-1,195**	**(0,000)**	**-0,255**	**(0,000)**	1,153	**(0,000)**	3,038	-39,34
	184, Elantan	0,168	**(0,000)**	**-0,531**	**(0,000)**	**-0,097**	**0,003**	0,868	**(0,000)**	1,708	-31,09
Thyroxine 50mcg tab (185, 186)*	50, Eltroxin	0,034	0,001	**-0,028**	**0,303**	**-0,004**	**0,614**	0,333	**(0,000)**	0,503	-5,57
	174, Adco-cimetidine	-0,064	0,236	**-0,305**	**0,026**	0,045	0,399	1,006	**(0,000)**	0,814	-37,47

Notes

Int 1(Estimate in 2004) = Cons + (Trend X Years)

Statistically Significant (P<0,05) in BOLD

Supplementary list With Data (Originals: 20, Generics: 18) = 38

Change in level = 31 (75,6%)

' Change in slope = 26 (63,4%)

Supplementary List with no Data– 31

Supplementary List Total = 69

https://doi.org/10.1371/journal.pone.0219690.t003

ITS graphs for all three molecules reflect that the manufacturing companies may have applied for a price reduction normally related to competition or stock issues.

Trend 3 is illustrated using Glycomin 5mg tablet (Fig 6). The Adjusted R-Squared for Glycomin 5mg tablet is 89.22%. The P-Value is 0.000 indicating that there is a high probability of a significant difference in price of the medicine after the policy intervention. The price reduction of the medicine due to the introduction of the intervention in 2004 is reflected in the change in level -0.764 [CI 95 percentage (-1.075- -0.453)] and the change in slope ZAR 0.171 [CI 95% (-0.260–0.081)].

Fig 1. Percentage change in level in the Global Core Basket.

https://doi.org/10.1371/journal.pone.0219690.g001

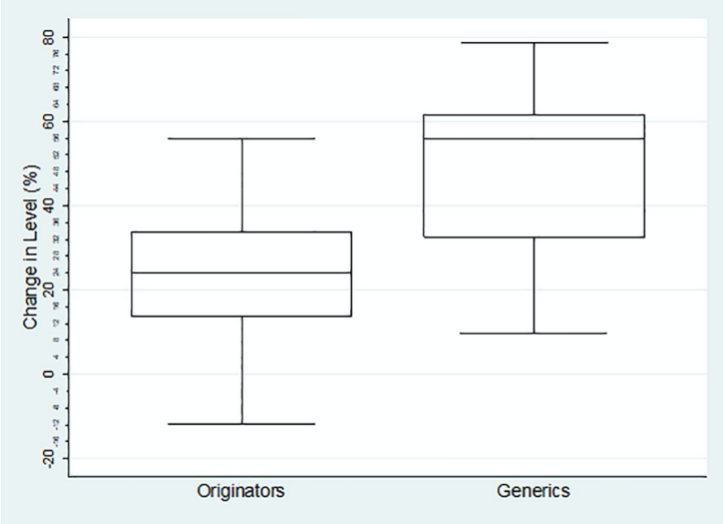

Fig 2. Percentage change in level in the Regional Core Basket.

https://doi.org/10.1371/journal.pone.0219690.g002

Discussion

In the WHO Guidelines on Country Pharmaceutical Pricing Policies [21], it is suggested that a gap exists in the quantitative assessment of the impact of policy change on generic medicines in LMICs. Countries enforcing a pro-generic policy should put in place a monitoring and evaluation programme to track data before and after a policy change using an experimental or quasi-experimental design so that if the policy has not provided the intended result it should be reviewed. [21]

A number of policies exist to promote the use of generics and/or lower medicine prices. Many countries facilitate easy market entry, promote substitution by dispensers, introduce

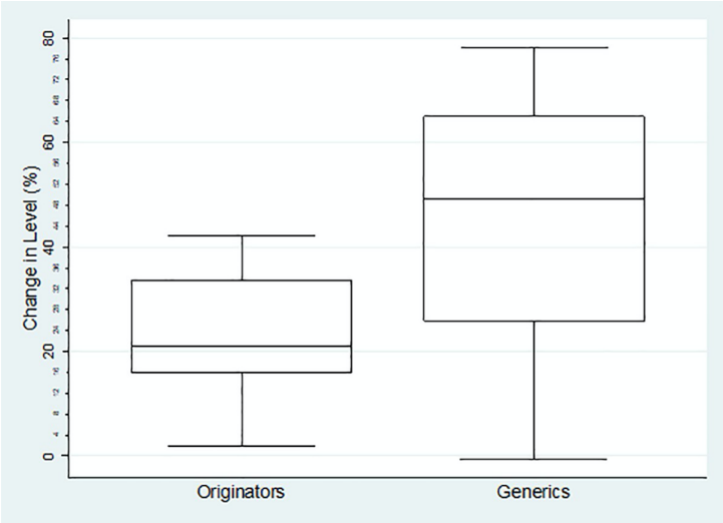

Fig 3. Percentage change in level in the Supplementary Basket.

https://doi.org/10.1371/journal.pone.0219690.g003

Table 4. Three emerging trends with changes in slope and level.

	Change in Level (P-Value)	95% Conf. Interval	Change in Slope (P-value)	95% Conf. Interval
Trend 1 **Glibenclamide 5mg tab** 56 Sandoz-Glibenclamid2	-1.436 (0.000)	-1.500 - -1.371	-0.141 (0.000)	-1.59 - -0.28
Trend 2 **Captopril 25mg tabs** 62. Mylan Captopril	-0.612 (0.000)	-0.668 - -0.555	0.061 (0.000)	0.045–0.076
Trend 3 **Glibenclamide 5mg tab** 54. Glycomin	-0.764 (0.000)	-1.075 - -0.453	-0.171 (0.001)	-0.260- -0.081

https://doi.org/10.1371/journal.pone.0219690.t004

international reference prices, promote competition in the market, and encourage use of generics amongst providers and consumers. [21] One of the key contributors to generic use is the assurance of quality and South Africa performs this adequately through its medicine

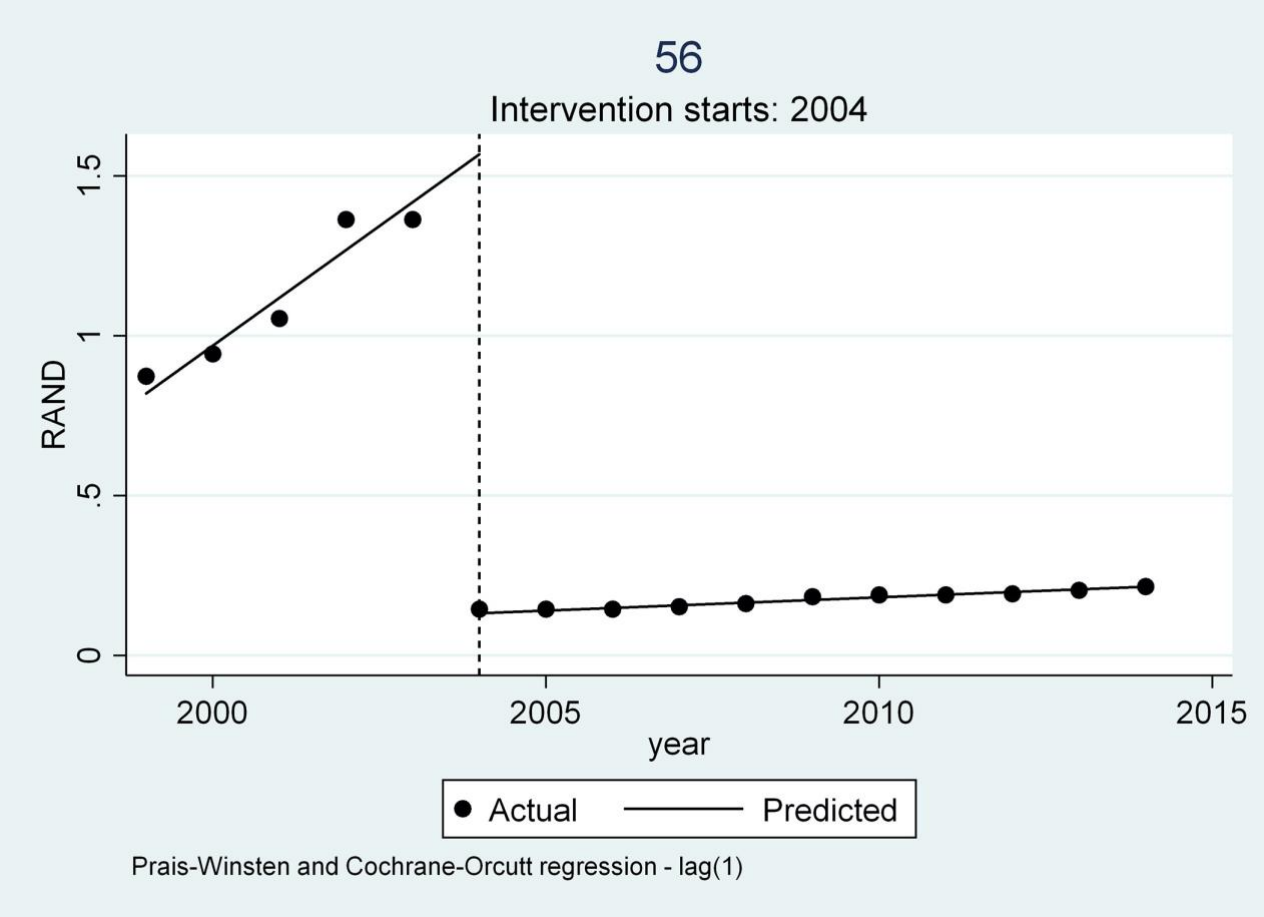

Fig 4. Trend 1 as depicted by Sandoz Glibenclamide.

https://doi.org/10.1371/journal.pone.0219690.g004

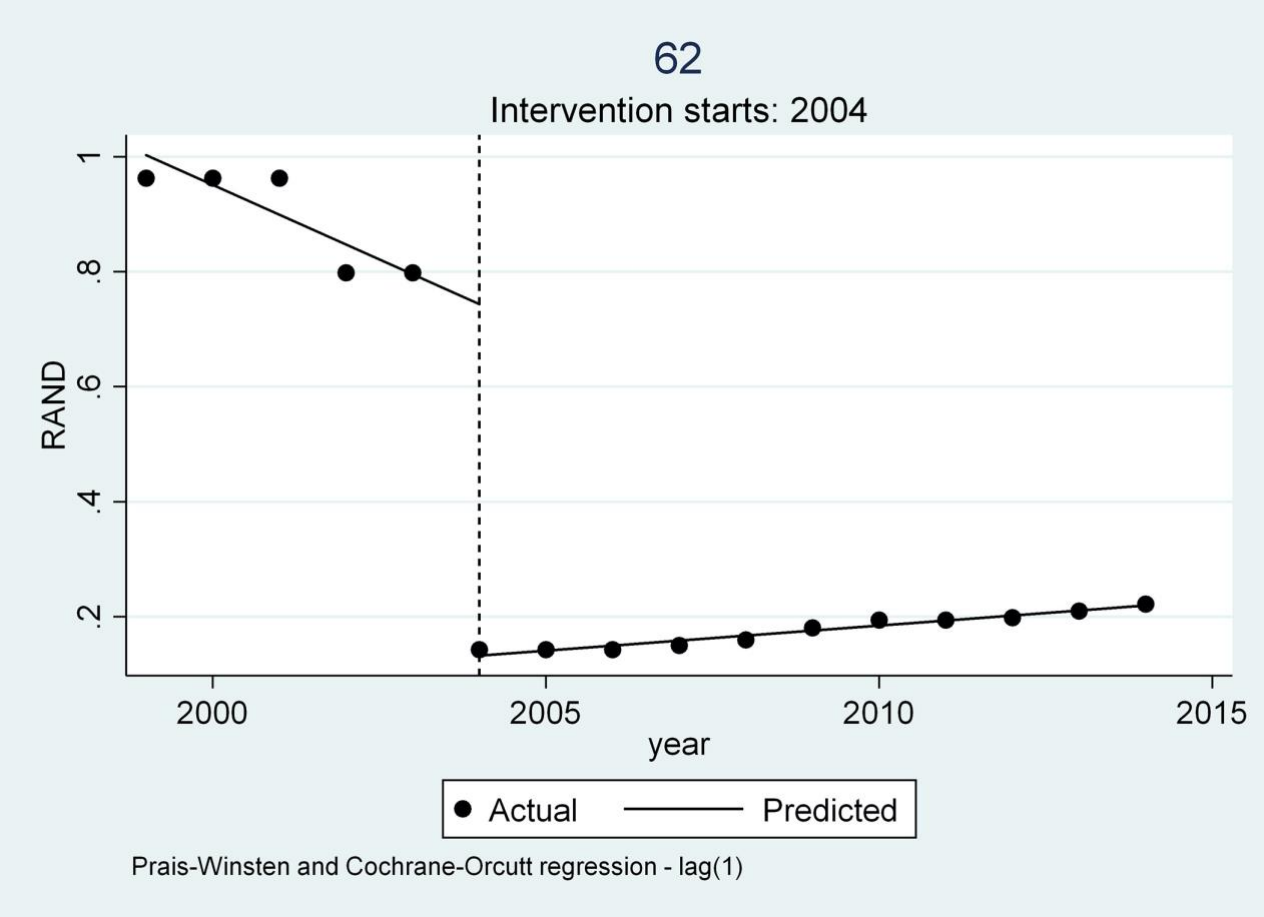

Fig 5. Trend 2 as depicted by Mylan Captopril.

https://doi.org/10.1371/journal.pone.0219690.g005

regulatory authority (previous Medicine Control Council (MCC)- now South African Health Product Regulatory Authorities (SAHPRA)). Generic entry is also encouraged where there is a transparent pricing system.[23]

The price of originator medicines internationally are two and a half (2.5) times more than their lowest priced generics. [24] In LMIC this difference could be more than 10 fold. [25] If we examine the Global Core the difference in price is 4.29 times lower than the originator prior to 2004. Directly after the introduction in 2004 of the SEP the difference between the price of the originator molecule and their cheapest generic showed a 11.1 fold increase in South Africa, in line with Cameron and Laing (2010) [25] suggestion for LMICs. Bangalee, et al. revealed in their study on cardiovascular drugs a 40% difference in prices of generics against the branded versions, [7] and this is confirmed in the pre 2004 comparative in this study (42.9%). This study further suggests that the introduction of the SEP increased this differential, at least in the global core basket, to 111%. This supports the observation by Bangalee and Suleman (2015) that originator companies do not engage in price competition. [7] This may also provide a reason for eight (8) of the fifty (50) originator molecules being withdrawn after 2004.

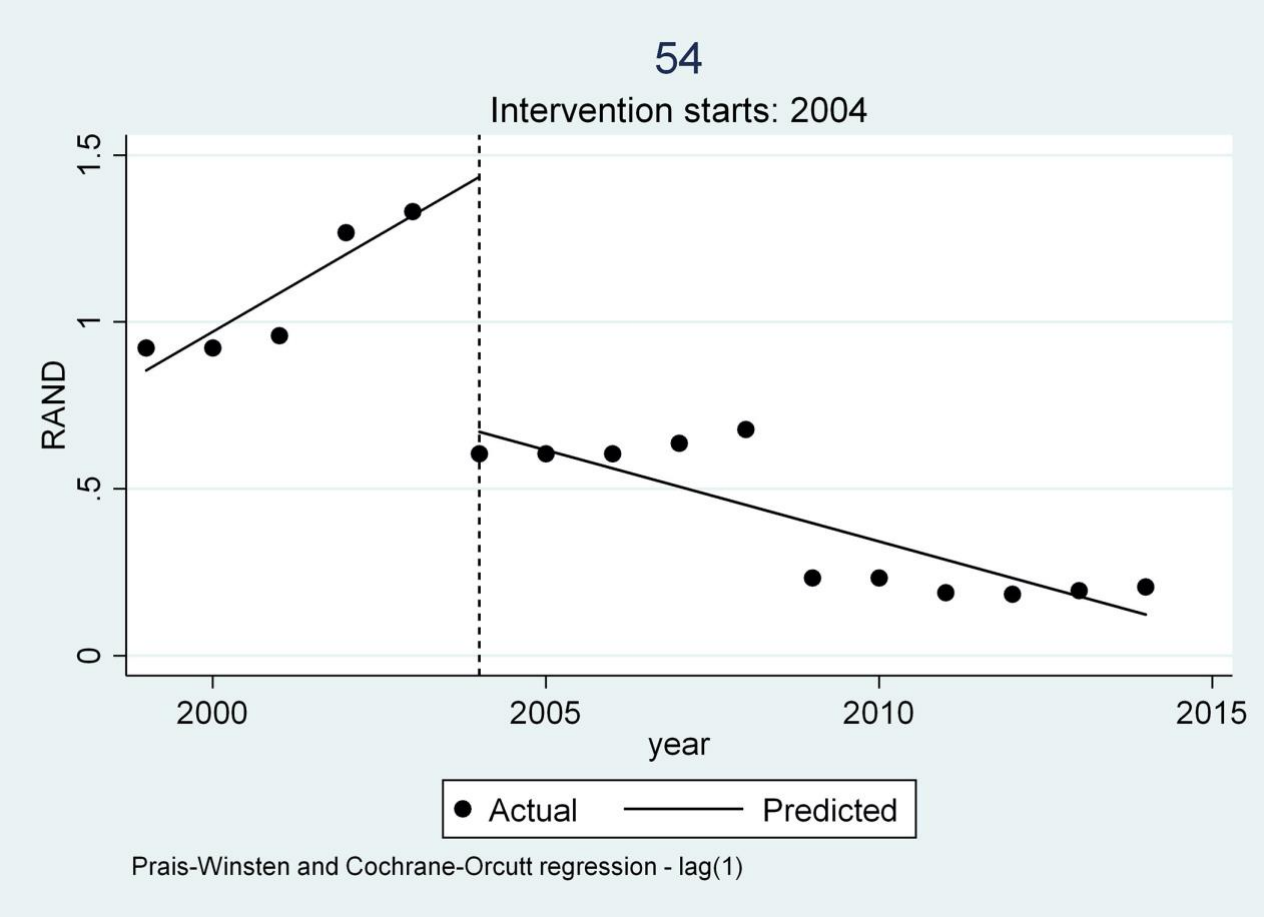

Fig 6. Trend 3 depicted by Glycomin.

https://doi.org/10.1371/journal.pone.0219690.g006

Veena, et al. in India suggested that branded medicines are 30%-200% more costlier than generics. [26] Cameron, et al in their study of middle to low income countries concluded that for the medicines studied, an average of 9% to 89% could be saved by individual countries in the private sector with the change from originator to lowest-priced generics. [27] A Nigerian national survey of 129 medicine outlets where 34 prescription medicines were investigated consumers paid up to 64 times the international reference price. [28]

Medicines as indicated in trend 2 were already on a downward slope prior to the regulations. This may well be related to pressure on manufacturers to have their medicines listed on preferred formularies with medical scheme payers in the private market or to meet the Maximum Medical Aid Price (MMAP), a common tool used in South Africa to reimburse medicines. Other factors to consider may be the entry of other generics that create competition, or in preparation for the anticipated regulatory changes, which was in discussion in South Africa a few years prior to the 2004 implementation when draft regulations were published some seven years earlier. [29]

While most medicines post the intervention took the Government regulated prices increases on a yearly basis, some as in Trend 3 tended to have an average decrease in price over the study period. This was also true for medicines in the data set that could not be fully

assessed because of insufficient pre-2004 data (reflected in the supplementary files on the ITSA analysis). Manufacturers of these medicines opted to take one or more voluntary price decreases during the study period. This may have been necessary to fall in line with other similar priced molecules especially if their initial declaration/disclosure prior to 2004 was an overestimation compared to their competitor, introduction of competing medicines in the same generics, stock issues such as over production and short expiry, or pressure in the reimbursement models from medical scheme.

Both generic and originator medicines in the study showed an immediate price decrease in most medicines, a lower yearly increase as compared to yearly increases prior to the regulations and a possible saving due to price reduction over the study period. This is in direct contrast to the Moreno–Torres [30] which concluded that twelve of sixteen pricing interventions introduced in Spain were not effective even in the short term and four were not impactful. This study indicates that the SEP regulation had an impact on both originator and generic medicine pricing in South Africa immediately after introduction and continued over the study period.

There is no doubt that generic penetration creates a saving in any healthcare system but this is dependent on the price levels that the generic is set at and the differential between the originator and generic medicine. [11] Seeley and Kanavos in their examination of seven OECD countries (United States of America(US), France, Germany, Italy, United Kingdom (UK) and Canada) suggested that generic penetration varies significantly and could be improved especially in Italy and France where it appears to be the lowest. [11] Spain and Canada exhibited average levels while the US, UK and Germany showed the highest levels of generic penetration. [11]

According to Kaplan et al (2016) [31], many European countries set the price of a generic at a specific percentage lower than the originator product, and indicate that countries with generic link policies have lower prices compared to countries that do not. Vogler et al. [32] investigated prices of medicines that were likely to contribute to high expenditure for the public payers in high-income countries. Information on the ex-factory price data of 30 medicines in 16 European countries was collected in April 2013. There were considerable differences in medicine prices, with 53% of the medicines surveyed having a unit ex-factory price (median) above 200 Euro. The price differences between the highest-priced country and lowest-priced country ranged between 25% and 100% for two-thirds of the medicines. The mainly low-priced medicines had higher price differential up to 251%.

Generic product sales accounted for 30% of the total pharmaceutical sales in South Africa in 2012. [33] Generic utilization rates (generic items claimed as a percentage of total items claimed from one pharmacy benefit manager in South Africa) in 2013 reached 54.5% in the private sector. [34] Vogler, [35] and Maisonneuve, [36] suggested that generic use can be attributed to countries policy implementation e.g. number of generics, prescribing practices and market structures. Strict regulation of medicine prices may contribute to lower penetration of generic medicines into markets. [37] This may be due to the reduced profitability and the inability of generics to cover their cost of market entry. [38]

The impact of the combination of the SEP policy, with the mandatory offer of generic policy is largely unknown, in terms of both price transparency and generic penetration. There is clear indication in this study that the SEP regulations had a greater impact on generic medicines than it did on originators. Using the global core as an example, the basket of generic molecules showed a markedly better average percentage decrease in level than the originator basket; showing a 42.66% difference. Seventy-five percent of the generic molecules decreased in price by more than 52.32%, while twenty-five percent of the generic molecules showed an even greater decrease of 77,13%. Half of the generic molecules showed a decrease in price between

52.33–77.13%, while the bulk of the originator molecules only showed a decrease of between 14.79–25%, indicating that the generic basket performed much better with the implementation of the 2004 price change regulations. This is also true for both the Regional Core and the Supplementary baskets as reflected in Figs 2 and 3 which reinforces the observation that originator companies do not engage in price competition. [7]

Certain limitations of this study must be considered. The first is the limited data available prior to implementation of the regulations. Bernal, et al. [39] suggest that there are "no fixed limits regarding the number of data points". The power depends on "various other factors, including distribution of data points before and after the intervention, variability within the data, strength of effect, and the presence of confounding effects such as seasonality". [27] If the data was done every quarter it would have produced 20 data points over 5 years. Medicine prices in South Africa tend to be stable year-on-year. In viewing the data in the database, we found that the price was stable over four quarters in majority of the medicines. Hence the need to select a single reference point and access the price at that point.

In inspecting the visual results, a recommendation by Bernal, et al., it can be seen that the trend before intervention does not show drastic changes. There is also a clear differentiation between the pre- and the post-intervention period with a well-defined period of implementation- in this case an immediate change. [27] The last limitation is the linear trend assumed by the segmented regression model that was used. [16]

Conclusion

Further studies need to be done to determine availability and access [40] and possible negative impact of this type of pricing model. Price comparative to international markets may be required to benchmark the introduction price and this could, especially in the originator market, influence the price setting of the SEP. After 14 years of pricing regulations more studies need to be performed on reasons for the introduction of the many generics after 2004, setting of the SEP prices and its international comparisons, influence of reference pricing in the private market, the price of medicines in a single market system as compared to the private/public system in South Africa.

Using the Interrupted Time Series in this study we can conclude that the data reflects a decrease in medicine prices with possible savings having been achieved through the introduction of the SEP regulation in both the originator and generic markets in the private sector in majority of medicines. Despite the limitations highlighted under discussion this study provides evidence of the impact of medicine pricing intervention from a middle–income country, and useful lessons can be drawn by other developing countries looking at introducing medicine price controls.

Supporting information

S1 Table. Global core list data.
(XLSX)

S2 Table. Regional core list data.
(XLSX)

S3 Table. Supplementary list data.
(XLSX)

Author Contributions

Conceptualization: Fatima Suleman.

Methodology: Rajatheran Moodley, Fatima Suleman.

Supervision: Fatima Suleman.

Validation: Rajatheran Moodley.

Writing – original draft: Rajatheran Moodley.

Writing – review & editing: Fatima Suleman.

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CHAPTER 5 PAPER 3

5.1 To evaluate the impact of opening up ownership of pharmacies in South Africa

To evaluate the impact of opening up ownership of pharmacies in South Africa.

This chapter explored the impact of liberalization of the pharmacy regulations on rural access, ownership, and on existing community pharmacies in South Africa before and after the introduction of the regulation.

The Paper, entitled "To evaluate the impact of opening up ownership of pharmacies in South Africa" has been sent for publication to the "*BMC Health Services Research".*

The databases for the research was obtained from the South African Pharmacy Council.

The Ethics certificate can be found in Annexure A.

This chapter presents the published paper as per the journal stipulated format and limitations in terms of graphs, tables and word count.

BMC Health Services Research

To evaluate the impact of opening up ownership of pharmacies in South Africa

--Manuscript Draft--

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Full Title:	To evaluate the impact of opening up ownership of pharmacies in South Africa
Article Type:	Research article
Section/Category:	Health systems and services in low and middle income settings
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Abstract:	Background Following the democratic elections in 1994 the South African private pharmaceutical services were mostly urban and metropolitan centred with a scattering of pharmacies in small towns and rural communities. The Government introduced regulations relating to the ownership and licensing of pharmacies on the 25th of April 2003 to improve access to pharmaceutical services by removing ownership restriction to only pharmacists. Objective To assess the outcomes of the policy implementation in improving access to pharmacies Method: The register of pharmacies at the South African Pharmacy Council was analysed from 1994 to 2014. Each registration was assigned GPS coordinates using Q-GIS(V3.6) and mapped per province at a district level, following clean-up and verification of the register. New registrations were also categorised as either corporate or independent pharmacy. Population census was obtained from Statistics South Africa and used to determine the number of pharmacies per 100 000 population. Main Outcome Measure(s): Number of active pharmacies; Number of independent pharmacies; number of pharmacies in each district Results: The number of active pharmacies increased from 1624 at the end of 2003 to 3021 by 2014. The closure rate decreased from 137 to 86 pharmacies per year post regulations, a 37.23 % reduction with a net gain of approximately 127 pharmacies per year. About 38.30% of all pre-2003 pharmacies (622 of 1624) closed by 2014. The population increase in the study period was approximately 20.66% but the overall growth of pharmacies was only 1.88 pharmacies per 100 000 population (3.55 to 5.43). Following the regulations in 2004, 23.9% of pharmacies active within the system closed between 2004-2014, of which, 91.7% of them were independent pharmacies. Conclusion: Opening up of pharmacy ownership in South Africa increased the number of pharmacies in the country but did not result in increased access in previously disadvantaged and rural areas. There was still urban clustering of pharmacies, with a steady growth in corporate pharmacy (35%) ownership.
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Title: To evaluate the impact of opening up ownership of pharmacies in South Africa

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Abstract

Background

Following the democratic elections in 1994 the South African private pharmaceutical services were mostly urban and metropolitan centred with a scattering of pharmacies in small towns and rural communities. The Government introduced regulations relating to the ownership and licensing of pharmacies on the 25th of April 2003 to improve access to pharmaceutical services by removing ownership restriction to only pharmacists.

Objective

To assess the outcomes of the policy implementation in improving access to pharmacies

Method:

The register of pharmacies at the South African Pharmacy Council was analysed from 1994 to 2014. Each registration was assigned GPS coordinates using Q-GIS(V3.6) and mapped per province at a district level, following clean-up and verification of the register. New registrations were also categorised as either corporate or independent pharmacy. Population census was obtained from Statistics South Africa and used to determine the number of pharmacies per 100 000 population.

Main Outcome Measure(s):

Number of active pharmacies; Number of independent pharmacies; number of pharmacies in each district

Results:

The number of active pharmacies increased from 1624 at the end of 2003 to 3021 by 2014. The closure rate decreased from 137 to 86 pharmacies per year post regulations, a 37.23 % reduction with a net gain of approximately 127 pharmacies per year. About 38.30% of all pre-2003 pharmacies (622 of 1624) closed by 2014. The population increase in the study period was approximately 20.66% but the overall growth of pharmacies was only 1.88 pharmacies per 100 000 population (3.55 to 5.43). Following the regulations in 2004, 23.9% of pharmacies active within the system closed between 2004-2014, of which, 91.7% of them were independent pharmacies.

Conclusion:

Opening up of pharmacy ownership in South Africa increased the number of pharmacies in the country but did not result in increased access in previously disadvantaged and rural areas. There was still urban clustering of pharmacies, with a steady growth in corporate pharmacy (35%) ownership.

Key Words:

Ownership, South Africa, Liberalisation, Medicine Access, Pharmacy, Ownership

Impact of findings on practice statements

1. Opening up ownership of pharmacies to non-pharmacists may not result in a large increase in pharmacy access in previously disadvantaged and rural areas
2. Policymakers need to consider other incentives to improve access in underserved areas.
3. Policymakers should monitor implementation of the policy to avoid monopolies being developed

Introduction

Following the 1994 democratic elections the new Government in South Africa had the opportunity to introduce policies that ensured the availability and accessibility of cost-effective medicines to all South Africans. A National Pharmaceutical Policy Committee was established by the Government post elections in April 1994 [1], which led to the publication of the National Drug Policy [2]. The key concept related to pharmacy ownership was contained in the following statement; "Where it is deemed to be in the interests of the public, and provided that comprehensive pharmaceutical care is ensured, ownership of pharmacies by laypersons and other health care professionals will be considered [2]."

It is important to reflect on the intention of the Minister in introducing the Bill to parliament in 1997 for debate. Black pharmacists [3] who qualified in the 80's and early 90's were not allowed to own pharmacies in urban areas where trade was lucrative and profitable. Private pharmaceutical services were only accessible to affluent communities situated in metropolitan areas [4]. The Bill sought to improve access to pharmaceutical services by removing restriction of ownership to only pharmacists. Further debate centred around the Minister's powers in determining who should own pharmacies, and ownership being determined on a need basis. Part of the motivation heard in parliament [3] was that opening up of ownership would reduce the price of medicines, promote healthy competition and create more jobs.

The Regulations Relating to the Ownership and Licensing of Pharmacies was published in GNR. 553 of 25 April 2003 [5] where the responsibility to issue a license was moved from the South African Pharmacy Council to the National Department of Health. Unlike many low income countries where pharmacy oversight, regular inspection and law enforcement is weak [6], the South African Pharmacy Council has a well-defined and stringent process.

In most countries where deregulation was attempted, the rationale for change centred around the need for increased competition, containment of pharmaceutical expenditure, improved access to pharmaceutical care and opening of new outlets in areas of need [7]. The Österreichisches Bundesinstitut für Gesundheitswesen Austrian Health Institute (OBIG) 2006 report [7] of the European Union (EU) countries indicated that 17 of the 25 member nations operated restricted ownership of pharmacies. The study went further to do a comparative analysis of three EU countries that were regulated i.e. Austria,

Finland and Spain compared to the deregulated states of Ireland, Netherlands and Norway. The study showed a strong increase in the number of pharmacies in the deregulated member states accompanied by urban clustering and fewer municipalities having access to service.

A 2015 survey conducted by the International Pharmaceutical Federation (FIP) [8] in 71 countries covering 80% of the world's population indicated that 66% of pharmacy ownership is non-exclusive to pharmacists and the balance of 34% (24 countries) were exclusive. Non pharmacist ownership ranged from state ownership to complete liberalisation. Other factors that determined ownership related to workforce capacity where the number of pharmacists may not be sufficient to cover the areas of need. Some countries have liberalisation but provide additional restrictions [8], the most frequent being restricting other authorized non-pharmacist prescribers from ownership, banning vertical integration in a supply chain, or restricting horizontal integration to prevent dominance. Strong regulated environments are built on restricted ownership to pharmacists, combined with geographic conditions [9] based on number of inhabitants per pharmacy and minimum distance from each other. This is meant to create a spread of pharmacies across geographic areas allowing for sustainability.

Challenges of restrictive ownership in Germany and Italy were brought to the European Court of Justice [8]. The court ruled that restriction with the justification of safety and quality is allowed. Two other countries, Hungary (2009) and Estonia (2015) [10], returned to regulated ownership based on professional independence of the pharmacists, lack of rural improvement, and financial unviability of the remaining pharmacies. In Africa, some countries such as Chad, Senegal, and Cameroon restrict ownership to pharmacists while Kenya and Nigeria, follow the South African model of liberal ownership. Countries with pro-competitive policies driven by competition authorities often drive deregulation [11].

In countries where ownership is exclusive to pharmacists [8] there is an understanding that community pharmacists form an extension of the healthcare system and provide an essential public service. These models exist extensively in Africa, Eastern Mediterranean, Australia and Europe. Multiple models of open ownership and restricted ownership in the United States (US) exist as in the case of South and North Dakota respectively. A 1963 state law restricting ownership to pharmacists was tested via the North Dakota Pharmacy Ownership Initiative [12] in November 2014 where a chain pharmacy group attempted

to have the law repealed and lost in a public referendum. It was shown that across every key measure of pharmaceutical care including prescription prices, levels of patient care and most importantly rural access, North Dakota outperformed other states [13].

Other models of ownership which include non-governmental organisations, charities, religious groups and humanitarian organisations [8] are found in 28% of countries surveyed in a study by the Federation of International Pharmacy (FIP). Brazil has a unique model of municipal owned community pharmacies (Farmacias Populares do Brasil) [8] dispensing medicines off their essential medicine lists and employing pharmacists. Since 2009 when Sweden liberalised pharmacy ownership the sector is dominated by chains and independents [10]. The rationale for the deregulation which included pricing, efficiency and usage of medicine were replaced by diversity, entrepreneurship and privatisation goals [10].

Aim of Study

The aim of this research was to explore the impact of opening up of ownership on rural access and ownership type before and after the introduction of the regulation in South Africa.

Methods

Although licenses are granted by the National Department of Health since 2004, service can only be activated with a SAPC certificate of registration. Thus an analysis of the South African Pharmacy Council registers for the period 1994 to 2014 was conducted. The register data was cleaned and allocation was done in terms of provinces. A verification process involving reconciling register records with Medpages[14] followed by random telephone sampling was conducted. GPS coordinates were assigned using Q-GIS (V3.6) before mapping at a district level. Population census to determine pharmacies per 100 000 population was obtained from Statistics South Africa (StatsSA)[15]. Opening and closures of pharmacies through the study period was recorded. Both district and municipal information was sourced from the Municipal Demarcation Board[16]. Community pharmacies were classified and mapped as independent and corporate, and compared to the pre-2004 data.

Results:

Insert Table 1 here

The number of active pharmacies (Table 1) increased from 1624 in 2003 to 3021 in 2014. The closure rate reduced from 137 per year pre 2004 to 86 per year post regulations, a 37.23 % reduction, gaining 127 pharmacies per year. The net gain was largest in Gauteng (39.51%) with Eastern Cape (1.93%), Northern Cape (1.36%), Free State (5.08%) , North West (8.02%) and Mpumalanga (7.30%) showing increases in the number of new pharmacies. Of the pharmacies that were open in 2004 (Pre-2003 pharmacies) 38,30% (622 of 1624) were closed by 2014.

The census indicated a population growth of 20.66% but pharmacies grew by only 1.88 pharmacies per 100 000 population (3.55 to 5.43). Pharmacies have continued to close during the identified study period (2004-2014) as follows: 622 of the pre 2003 registrations, 43 corporate and 284 independents registered post 2003; 23.9% of active pharmacies closed between 2004-2014 of which 91.7% were independent pharmacies.

Most provinces show a similar percentage closure of new pharmacies (2004-2014) – Western Cape (14%), Gauteng (16.6%), Kwa Zulu Natal (14.1%), Free State (13.9%), and Mpumalanga (14.4%). The more rural provinces such as the Eastern Cape (3.4%), North West (9.0%) and Limpopo (7.7%) showed a lower closure rate with the Northern Cape being most affected as 31% of new pharmacies closed within the study period.

Insert Table 2 here

From Table 2, it can be seen that Manguang district in the Free State showed a substantial increase in the number of pharmacies from 19 (2004) to 47 (2014). The majority are located in densely populated areas. Increases in all other districts remained low with the Xhariep district having only 5 pharmacies by 2014. Little or no improvement was seen in the sparsely populated rural settlements.

In Kwa-Zulu Natal most districts in Quintile 1 had marginal increases in numbers of pharmacies. The Umgungundlovu district increased by 42 pharmacies post regulation with a total of 65 located mostly within the city centre. This may be due to it being the second most populated district in the province, having both a Deprivation Index(D/I) of 2.28 and placed in Quintile 3. Despite an increase of 16 to 32

pharmacies in the Ugu district, access did not improve as new pharmacies were located where access already existed. The Ethekwini Municipality showed an improvement with most pharmacies located within or close to existing pharmacies (3.95 to 7.37 per 100 000). Kwa Zulu Natal improved marginally from 3.45 to 5.43 per 100 000 population indicating the lack of growth in the rural area. The number of active pharmacies in the province increased from 315 in 2003 to 340 by 2014. In the same period 156 pharmacies closed (108 pre 2003 and 48 post 2003 registrations)

The Mpumalanga province showed the most improvement: Ehlanzeni (16 to 67), Nkangala (31 to 63) and Gert Sibanda (32 to 51). All three districts have large populations and are classified in Quintiles 3 and 4. There has been growth both in the city and regional service centres as well as in the populated rural areas especially in Ehlanzeni. The province started from a low base of 2.53 per 100 000 population and improved to 4.71 per 100 000.

Limpopo province grew by 13% and showed the best new pharmacy growth (10.67%) gaining approximately 13 pharmacies per year. All districts showed improvement in the number of pharmacies in both city and densely populated rural areas. Most districts have a large population base of over a million persons. The Capricorn district improved from 1.56 to 3.98 pharmacies per 100 000. Overall, the province saw an improvement from 1.14 to 3.55 pharmacies per 100 000 population. While new pharmacies showed a comparatively low closure rate (7.7%), the combined closure of pre and post 2003 pharmacies was 13.45% between 2004-2014.

The North West district of Bojanale with a population of 1.66 million people showed a marked increase in the number of pharmacies post 2003 growing from 21 to 80 active pharmacies in 2014 with a growth from 1.76 to 4.83 per 100 000 population. The Dr Kenneth Kaunda district also showed improvement from 21 to 55 pharmacies primarily in the urban centres. The North West province gained a net of 10 pharmacies per year since the regulations growing from 1.99 to 4.62 per 100 000 population.

Three districts in the Gauteng province (Tshwane 221, Ekurhuleni 159, and City of Johannesburg 321) showed a large increase in number of new pharmacies. The data indicates an increase in the number of pharmacies per 100 000 population (Tshwane 4.08 to 9.22, Ekurhuleni 3.16 to 7.28, City of Johannesburg

3.34 to 8.67). The smaller districts such as Sedibeng (3.1 to 6.06) and Westrand (2.1 to 5.24) also showed increases. The province moved from 5.52 to 7.99 per 100 000 population. The rate of closure of pharmacies was 25.1% between 2004 to 2014 with new pharmacies experiencing a lower closure rate of 16.6% compared to a 39.8% closure rate from the pre 2003 pharmacies showing a reduction from a 527 in 2004 to 317 in 2014.

The Northern Cape showed a marginal increase from 3.25 to 4.27 per 100 000 with none of the districts showing significant increases. Frances Baard showed a slight improvement from 2.76 to 5.42 per 100 000 population although 33.3% of new pharmacies that opened after regulations closed by 2014. There was low growth of 1.73 pharmacies per year contributing marginally (1.36%) to the overall growth of pharmacies in South Africa with 31% of all new pharmacies closing during the period 2004 to 2014.

Pharmacies that were registered pre -2003 in the Eastern Cape districts of Alfred Nzo and OR Tambo all closed by 2014 with only 9 and 19 respectively still active post 2003 registrations . The economic hubs of Nelson Mandela Bay and Buffalo City showed improvement in the cities and large regional centres increasing from 3.9 to 7.52 and 1.85 to 5.27 respectively per 100 000 population. The closure of new pharmacies in the Eastern Cape was low at 3.4% (5 of 147). By 2014 56.0% of active pharmacies in 2004 had closed leaving the province with 229 pharmacies in 2014 (87 +142).

Western Cape increased from 5.77 to 9.55 per 100 000 population with the City of Cape Town showing a marked improvement of 3.8 to 7.59 per 100 000 population mostly in the city and large regional centres. Also evident was the dominance of corporate pharmacy (150 new openings) compared to 144 independents. The Central Karoo and Overberg area showed little improvement with other districts improving only marginally. The province showed an average attrition rate of new pharmacies of 14%. Approximately 66.37% of new pharmacies opened in the City of Cape Town with the bulk of the balance being shared between Eden (12.7%) and the Cape Winelands (11.7%).

A summary of all the active pharmacies per province in 2014 (3021) is presented in Table 3 below. Of these, 2019 pharmacies (66.8%) opened after the regulation with Gauteng, Western Cape and Kwa Zulu Natal showing the most new openings.

Insert Table 3 here

Discussion

The increase in the number of pharmacies post regulations from 1624 in 2004 to 3021 in 2014 (Table 3) is in keeping with the OBIG 2006 European [7] study which showed that there was an increase in the number of pharmacies in countries that had introduced liberalisation. Norway has 8500 [18] inhabitants per pharmacy with the regulated Spain (2050) and Austria (3700). Ireland, a deregulated zone has 3000 inhabitants per pharmacy . South Africa moved from 28 000 to 18 000 inhabitants per pharmacy, short of the acceptable international standards.

Most growth of new pharmacies occurred in Gauteng, Kwa Zulu Natal and Western Cape. These provinces contain the major metropolitan areas; Tshwane, Ekurhuleni, , City of Johannesburg; Ethekwini; and City of Cape Town. These five large districts obtained 52% of all new pharmacies. This urban clustering and lack of improvement in rural areas is in keeping with local [4,11] and international [7,8] study findings. Areas with the highest deprivation had fewer pharmacies per 100 000 population. Within the framework of current legislation South Africa must find a way to incentivise the opening of pharmacies in areas of need.

After Norway's [7] deregulation in 2001 every second municipality had no pharmacy. Urban clustering, vertical integration and chain ownership by wholesalers resulted in 4 of 5 pharmacies being owned by 1 of 3 chains. Pharmacists own only 19% of Norwegian pharmacies. The Norwegian experience led researchers to believe that deregulation leads to market dominance and minimises competition. Principle areas of practice in Europe are 78.5% in community, 8.9% in hospital and 12.6% in other areas [19]. In South Africa 68.3% of registered pharmacists practiced in the community sector in 2014 [20]. Any regulation must be carefully monitored to ensure stability and job security in this market. Deregulation in most countries [11] results in corporatisation of community pharmacy. In South Africa following deregulation 35% of new pharmacies were corporate listed. Similarly, Norway (96%), Sweden (86%), US (64%), and UK (61%) showed dominance of corporatisation post deregulation [11,21].

In Sweden the Agency for Growth Policy Analysis (Ministry of Enterprise, Energy and Communication) found that after deregulation, new pharmacies opened in urban and not rural areas, and the price of over-the-counter medicines did not decrease [22]. Lluch and Kanavos [23] highlighted the risk associated with chains and vertical integration leading to monopoly. Policies addressing these risks should be considered.

The study does have limitations. The pharmaceutical service per population ratio is only reflective for community pharmacy and excludes the public sector. The type of ownership was restricted to independent and corporate pharmacy only. The primary source document which was the Council register had inaccuracies as well as insufficient ownership data. The study did not look into quality of service provided, or operational efficiencies.

Future research should include investigating:

- means of improving "rural policy, rural health services and rural practice [24]"
- The cost implication of the disruption of existing pharmacies in terms of capital and infrastructure loss
- the implications of concentration of pharmacy staff within the same location for service delivery in areas of need
- the long term impact on pharmacy skills development as new pharmacists are forced into prematurely taking on responsible pharmacist roles [10,25]
- the overall cost of pharmaceutical care in respect of duplication as opposed to rationalization of resources
- benchmark indicators of accessibility, quality and expenditure, which ranks better in strict regulated environments than in the non-regulated countries [13]

Conclusions

While liberalisation laws in South Africa may have increased the number of pharmacies, it did not result in a large increase in pharmacy access in previously disadvantaged and rural areas. There is a gradual shift from independent pharmacist to corporate ownership. Other incentives and policies are required to improve access to disadvantaged areas.

Declarations

Ethics approval and consent to participate: Ethics approval for the study was obtained from the Ethics Committee of the University of KwaZulu-Natal (HSS/0154/013).

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Table 1: Summary of Community Pharmacy Availability and Ownership Type from Pre 2003 to 2014

		Free State	Gauteng	Kwa Zulu Natal	Limpopo	Northern Cape	Western Cape	Eastern Cape	Mpumalanga	North West	Total
Pre2004 Registered Pharmacies	**Pre 2004 Registered**	217	1449	671	122	68	578	213	185	208	**3711**
	Closed before 1994	59	393	132	20	18	111	3	57	64	**857**
	Closed 1995-2003	85	529	224	45	18	189	8	49	83	**1230**
	Active in 2004	73	527	315	57	32	278	202	79	61	**1624**
	Rate of Closure per year (1995-2003)	9.44	58.78	24.89	5.00	2.00	21.00	0.89	5.44	9.22	**136.67**
	Closed Post 2003	22	210	108	18	10	113	115	17	9	**622**
	Active in 2014	51	317	207	39	22	165	87	62	52	**1002**
	Pharmacy to 100000 Population ratio	2.78	5.55	3.30	1.14	3.25	6.01	2.88	2.35	1.99	**3.55**
Post2004 Registered Pharmacies	**Post 2003 Registered**	108	914	340	181	42	342	147	139	133	**2346**
	Independent Pharmacy Closure	14	131	43	14	13	37	4	19	9	**284**
	Corporate Pharmacy Closure	1	21	5	0	0	11	1	1	3	**43**
	Rate of Closure per year (2004-2014)	3.36	32.91	14.18	2.91	2.09	14.64	10.91	3.36	1.91	**86.27**
	Independent Active 2014	62	472	192	148	16	144	94	91	84	**1303**
	Corporate Active 2014	31	290	100	19	13	150	48	28	37	**716**
	Total Active in 2014	144	1079	499	206	51	459	229	181	173	**3021**
	Net gain/year	6.45	50.18	16.73	13.55	1.73	16.45	2.45	9.27	10.18	**127.00**
	Percentage Net Gain	5.08	39.51	13.17	10.67	1.36	12.96	1.93	7.30	8.02	**100.00**
	Pharmacy/100000 Population ratio	5.08	8.05	4.51	3.55	4.27	7.31	3.27	4.17	4.62	**5.43**
Population Census	**2001**	2623956	9501134	9535936	4995535	983653	4624336	7022968	3365886	3072342	**45725746**
	2016	2834715	13399725	11065245	5799091	1193783	6279731	6996974	4335964	3748437	**55653665**

Table 2: Opening and Closing of Pharmacies at District Level

District	Deprivation		Population		Pharmacies Registered Pre 2003					Pharmacies Registered Post 2003	
					Inactive in 2014			Active in 2014	Total Active in 2003	Active in 2014	Inactive in 2014
	Quintile	Dep. Index	2001	2016	Total	Active in 2003	Inactive in 2003				
Free State											
Thabo Mofutsanyane	3	46082	725939	779330	26	3	23	13	16	**15**	**2**
Fezile Dabi	4	29952	460315	494777	24	4	20	11	15	**20**	**2**
Lejweleputswe	4	42767	657012	646920	57	5	52	14	19	**19**	**2**
Xhariep	3	19756	135250	125884	6	1	5	3	4	**2**	**0**
Mangaung	5	43466	645440	787804	53	9	44	10	19	**37**	**9**
Total			**2623956**	**2834715**	**166**	**22**	**144**	**51**	**73**	**93**	**15**
Kwa Zulu Natal											
Umkhanyakudi	1	26390	573341	689091	7	0	7	3	3	7	1
Zululand	1	46844	854779	892310	18	2	16	5	7	9	2
Uthungulu/King Cetshwayo	2	13210	885964	971135	16	3	13	16	19	18	7
Umzinyathi	1	18719	480413	554883	12	0	12	1	1	9	2
Amajuba	3	31444	468036	531328	25	5	20	6	11	12	1
Uthukela	2	20149	656984	706589	11	3	8	6	9	10	1
Umgungundlovu	3	46784	927845	1095865	63	24	39	23	47	42	4
Illembe	2	11018	560389	657613	14	4	10	6	10	11	3
Ethekwini	5	35431	3090121	3702231	271	61	210	122	183	151	26
Harry Gwala	1	24167	334033	510864	5	1	4	3	4	7	0
Ugu	2	17593	704031	753336	22	5	17	16	21	16	1
Total			**9535936**	**11065245**	**464**	**108**	**356**	**207**	**315**	**292**	**48**
Mpumalanga											
Ehlanzeni	3	26696	1447052	1754931	29	4	25	12	16	55	10
Gert Sibanda	3	26696	900007	1135409	46	2	44	30	32	21	4
Nkangala	4	27061	1018827	1445624	48	11	37	20	31	43	6
Total			**3365886**	**4335964**	**123**	**17**	**106**	**62**	**79**	**119**	**20**
Limpopo											
Mopani	2	22341	1061448	1159186	16	3	13	5	8	42	3
Vhembe	2	13210	1198055	1393949	7	4	3	6	10	33	2
Capricorn	2	16497	1154691	1330436	33	10	23	8	18	45	5
Waterberg	3	14277	614156	745758	20	0	20	13	13	26	2
Sekhukhune	1	31837	967185	1169762	7	1	6	7	8	21	2
Total			**4995535**	**5799091**	**83**	**18**	**65**	**39**	**57**	**167**	**14**

District	Deprivation		Population		Pharmacies Registered Pre 2003					Pharmacies Registered Post 2003	
					Inactive in 2014			Active in 2014	Total Active in 2003	Active in 2014	Inactive in 2014
	Quintile	Dep. Index	2001	2016	Total	Active in 2003	Inactive in 2003				
North West											
Dr Kenneth Kaunda	4	45323	628436	742822	76	1	75	20	21	35	7
Bojanale	2	43891	1188457	1657149	50	2	48	19	21	61	5
Ngaka Modiri Molema	3	15738	806587	889108	22	5	17	8	13	20	0
Dr Ruth Segomotsi Mompati	1	14305	448862	459358	8	1	7	5	6	5	0
Total			**3072342**	**3748437**	**156**	**9**	**147**	**52**	**61**	**121**	**12**
Gauteng											
Tshwane	5	26299	1982234	3275152	297	61	236	81	142	221	56
Ekurhuleni	5	27395	2752678	3379104	251	51	200	87	138	159	28
Sedibeng	5	36161	796756	957529	60	15	45	25	40	33	6
City of Johannesburg	5	25934	3225309	4949346	478	74	404	108	182	321	54
Westrand	4	27030	744157	838594	46	9	37	16	25	28	8
Total			**9501134**	**13399725**	**1132**	**210**	**922**	**317**	**527**	**762**	**152**
Northern Cape											
John T Gaetsewe	2	44015	175125	242265	6	1	5	2	3	4	3
Frances Baard	4	12451	325501	387742	23	4	19	9	13	12	6
Pixley ka Seme	2	29618	164607	195596	8	2	6	5	7	2	0
Namakwa	4	16438	108110	115489	7	3	4	2	5	3	1
Z F Mgcawu	3	28126	210310	252691	2	0	2	4	4	8	3
Total			**983653**	**1193783**	**46**	**10**	**36**	**22**	**32**	**29**	**13**
Eastern Cape											
Alfred Nzo	1	29312	392180	867864	3	2	1	0	2	9	1
O R Tambo	1	22007	1676590	1457384	1	1	0	0	1	19	0
Joe Gqabi	1	21976	350211	372911	5	2	3	3	5	5	0
Chris Hani	1	32933	809582	840054	8	5	3	6	11	7	1
Amathole	1	15036	1675901	880791	5	5	0	2	7	6	0
Cacadu/Sarah Baartman	3	43497	388207	479922	10	9	1	22	31	11	1
Nelson Mandela Bay	5	35796	1028016	1263051	69	66	3	41	107	54	2
Buffalo City	4	23377	702281	834997	25	25	0	13	38	31	0
Total			**7022968**	**6996974**	**126**	**115**	**11**	**87**	**202**	**142**	**5**
Western Cape											
Central Karoo	4	18264	60483	74247	3	0	3	1	1	2	0
Eden	4	25204	454924	611279	34	15	19	20	35	37	7
Overberg	5	44562	203519	286786	8	1	7	10	11	10	2

District	Deprivation		Population		Pharmacies Registered Pre 2003					Pharmacies Registered Post 2003	
					Inactive in 2014			Active in 2014	Total Active in 2003	Active in 2014	Inactive in 2014
	Quintile	Dep. Index	2001	2016	Total	Active in 2003	Inactive in 2003				
Cape Winelands	5	44197	730494	866001	33	10	23	14	24	35	5
City of Cape Town	5	14611	2892243	4005015	324	83	241	110	193	194	33
West Coast	5	1.00	282673	436403	11	4	7	10	14	16	1
Total			**4624336**	**6279731**	**413**	**113**	**300**	**165**	**278**	**294**	**48**

Note

*This South African Index of Multiple Deprivation (SAIMD) includes indicators from four domains: income and material deprivation, employment deprivation, education deprivation, and living environment deprivation, measured at either the individual or household level according to the indicator.

*The overall SAIMD combines these individual domains of deprivation using equal weights.

* The results were produced at ward level, with the most deprived ward given a rank of 1 and the least deprived a rank of 4 277.[17]

*Each district was ranked according to level of deprivation and categorised into a socio-economic quintile (SEQ).

*Districts that fall into Quintile 1 (lowest quintile) are the most deprived districts. Those that fall into Quintile 5 are the least deprived (best-off)[17]

Table 3: Active Registered Pharmacies in 2014

Active Pharmacies in 2014						
	Independents	**Corporate**	**Total**	**Pre 2003 registrations**	**Total Active**	**% Growth (New)**
Eastern Cape	94	48	142	87	229	7.03
Free State	62	31	93	51	144	4.61
Kwa Zulu Natal	192	100	292	207	499	14.46
Mpumalanga	91	28	119	62	181	5.89
Limpopo	148	19	167	39	206	8.27
North West	84	37	121	52	173	5.99
Gauteng	472	290	762	317	1079	37.74
Northern Cape	16	13	29	22	51	1.44
Western Cape	144	150	294	165	459	14.56
TOTAL	**1303**	**716**	**2019**	**1002**	**3021**	**100.00**

CHAPTER 6 SUMMARY AND RECOMMENDATIONS

The focus of this research centred around two key regulatory reforms implemented in 2003/4 with the intention of regulating the private sector in terms of medicine affordability and availability. The Medicines and Related Substances Control Amendment Act 90 of 1997, implemented on 2 May 2003, banned the offer of discounts and rebates to patients and healthcare providers (bonusing section 18G) and establishing a pricing committee (section 22G)[1]. The pricing committee made recommendations to the Minister of Health to implement the Single Exit Price (SEP) in 2004. The Regulations Relating to the Ownership and Licensing of Pharmacies was published in GNR. 553 of 25 April 2003[2], where any person may, subject to the provisions of Regulation 7, own or have a beneficial interest in a community pharmacy in the Republic of South Africa.

Both regulations had positive and negative findings, as indicated in both the empirical data and the literature review and their conclusions will be discussed together with recommendations. This chapter will also attempt to outline the limitations encountered in the study process, offer further policy change recommendations and possible areas for further study.

6.1 Study Summary and Conclusions

The summary focuses on the key areas of:

a. The Complex Nature of Medicine Pricing
b. Achieving transparency
c. Affordability
d. Availability

Pricing policies as per the literature internationally is **(a) *complex*** *in nature*[3,4], and this is undoubtedly true in the case of South Africa's attempt to regulate the private sector. The competing nature of various policies in the democratic government may sometimes not be in line with what needs to be achieved by a particular government department. While the National Department of Health attempted to regulate medicine prices, those in the free market economy[5] saw this as a threat to business viability having a negative

impact on economic growth, and an impact on job creation, all of which were also policy imperatives for various other departments within the South African Government. South Africa suffered a further delay in its implementation of the regulation when the Pharmaceutical Manufacturers Association and 39 of its member companies prevented its implementation through court action[6]. It is therefore important that regular monitoring and evaluation of all aspects of health policy changes be in place to counter any unintended consequences. The study did indicate the 16% of originator molecules were withdrawn (8 of 50) but had little impact on access as there were sufficient quality generic medicines available. What would be of interest would be to determine the exact reason for withdrawal and its consequences on the manufacturing companies, the economy and on the issue of industry jobs. Kieny (2016) suggested that low profitability results in companies leaving the market and creating gaps[7].

(b) Pricing transparency was a key imperative in the introduction of the regulations by the government, and it did contribute to making medicines more affordable[8] to the patient as suggested from the empirical results provided. The literature suggests that more could be achieved if the NDOH took a more uniform approach to the regulations. By only focusing on the SEP and the dispensing fee there was a missed opportunity to introduce better transparency[9] through a regulated logistic fee, and international benchmarking. More than ten years after the regulation, the logistic fee lacks transparency, is not consistent between the manufacturer and logistic companies, and is not in the public domain as envisaged by the transparent pricing system. Medicine prices remain artificially inflated (25% higher)[4] compared to the same product internationally[9]. Manufacturers, still at their own discretion, get to set their introductory price, and there is still a gap in the market in terms of the presence of incentive schemes[10]. Further, there is a tendency to prolong patents by marginally adapting their product without clinical or price advantage to the patient (ever-greening). A poor regulatory performance in the registration process and allowing multiple dossiers of the same product creating backlog often prevents the more cost-effective medicines getting to patients sooner[4].

(c) Affordability As medicine prices reduce, it becomes more accessible at a patient level and is seen as an important measure of overall affordability in a country. The study on both the originator and generic molecules indicated that the introduction of

the SEP regulations had a major impact on medicine pricing in South Africa both immediately and over the ten-year study period.

The percentage change in level for each category of medicines is reflected below.

Global Core (originator) 2.45% -39.12% (*mean = 19.87%,* SD = 10.62% IQR = 10.2%)

Global Core (Generic) 18.50%-91.5% (*mean = 62.46%,* SD = 18.64%, IQR = 24.81%)

Regional Core (Originator) 1.77%-42.17% (*mean = 23.38%,* SD = 12.43%, IQR = 15.65%)

Regional Core (Generics) -0.70%-78.03% (*mean = 44.62%, SD* = 23.04%, IQR = 37.41%)

Supplementary (Originator) -11.68%-55.86% (*mean = 22.97%,* SD = 16.26%, IQR = 17.34) Supplementary (Generic) 9.78%-78.49% (mean = *48.37%, SD* = 19.44%, IQR = 27.53%)

The second finding related to medicine affordability was the positioning of originator medicines against their generic equivalent. While the results above reflect a reduction in prices of originator molecules between 19.87%-23.38% depending on the basket, the gap between the price of the originator and its generics grew larger. Kanavos and Vandoros (2011)[11] suggested that originator companies do not engage in price competition. The price of originator medicines internationally are two and a half (2.5) times more than their lowest-priced generics[12]. In LMIC this difference could be more than 10–fold[13]. If we examine the Global Core, the difference in price is 4.29 times lower than the originator prior to 2004. Directly after the introduction in 2004 of the SEP, the difference between the price of the originator molecule and their cheapest generic showed an 11.1 fold increase in South Africa, in line with Cameron and Laing (2010)[13] suggestion for LMICs. Bangalee et al. (2016) revealed in their study on cardiovascular drugs a 40% difference in prices of generics against the branded versions[14], and this is confirmed in the pre-2004 comparative in this study (42.9%). This study further suggests that the introduction of the SEP increased this differential, at least in the global core basket, to 111%. This may also provide a reason for eight (8) of the fifty (50) originator molecules being withdrawn after 2004.

A further observation of the results, supported by Bangalee et al. (2016)[14], indicate that increased generic competition is not a predictor of lower prices. Generic entries tend to clump together at a similar price to the existing generics. One solution to overcome this phenomenon is to use the Canadian Alberta model. In April 2014, Alberta introduced their generic policy where new generic entries start at 70% of the brand if there is only one generic entrant, and then subsequent generic medicines that entered the market were priced at 50%, 25% and 18% respectively of the originator[15].

(d) Availability Pharmaceutical care is an important spectrum of healthcare in any country. "Ensuring access to quality medicines in under-served areas has been one of the most difficult bottlenecks to overcome in global health", says Ariel Pablos-Mendez, assistant administrator for Global Health at USAID(2016)[16]. Regulating access to medicines and pharmaceutical services in rural communities is just as complex as regulating the price of medicines themselves. Ownership changes in themselves in the private sector do not seem to improve access in areas of need[17,18,19,20,21]. While pharmacists and pharmacies play a critical role at multiple levels including making medicines accessible, they face the challenges of low volumes, limited and expensive workforce, low-profit margins, slow economic growth in rural economies, inability to participate in economies of scale, unsupportive regulations and weak profit margins[22]. The issue of being able to generate sufficient income[23] to support a rural operation was further highlighted in the Rural Policy Brief by Salako et al. (2017). In South Africa, Ward et al. (2014) agreed in their findings from key opinion leaders that the problem of service provision by the private pharmacy in rural and township areas was a conflict of profitability and provision of pharmaceutical care[21]. Other perceptions in the Ward et al. (2014) study confirmed that the regulations did not reverse the inequity in distribution, that the process of acquiring licences from the NDOH could not be trusted and that the criteria for issuing of these licenses need to be re-evaluated.

Post-1994 saw a steady year-on-year influx of rural population into the urban economic hubs to the extent that the United Nations projects that by 2030, 71.3% of the South African population will be urbanised[24]. The migration pattern mention by Cross (2009)[25] where the population outflow from Limpopo, Free-State, Mpumalanga and northern KwaZulu Natal into Gauteng and Western Cape (WC) reflects in our study the poor growth in pharmacy numbers in these four areas and the growth in both the WC and Gauteng. Migration also affects other healthcare professionals in the area and

contributes to the lack of support for business viability. For the majority of the country except in the urban metropolitan, the pharmacy growth did not keep pace with both government expectation and the population growth.

6.2 Policy Recommendations

Because of the complex nature of the medicine policy environment, it is imperative that Governments create a permanent monitoring and evaluation committee. South Africa has a Pricing Committee (PC) and a register of medicines reflecting the SEP. It may be necessary for key questions around pricing models to be identified by the PC and offered as areas of research at the universities as masters and PhD programmes. There is a need to identify possible problem areas before and after policy implementation through the ongoing assessments via a pharmaceutical analytics unit whose ongoing task will be to provide technical support, develop reimbursement protocols, monitor utilization and have stakeholder engagements to pool efforts in pricing policy.

In most high-income countries, either the state or insurance covers the costs of pharmaceuticals, giving them the edge to negotiate better prices with manufacturers through bulk purchasing. In low-income countries more than half and up to 90% are out of pocket payments. As South Africa moves towards Universal Health Coverage, we have an opportunity to investigate a single purchaser model at least for the medicines considered on the Essential Medicines List (EML). The current tender model used by the South African Government has achieved a significant price decrease on most medicines showing a substantial price discrepancy between private and public[27]. This public benefit policy could have a positive impact on the prices of medicines to the private payer through pooled funding. There is a need for a better understanding of how manufacturers price differently in the public and private space to allow policymakers to improve procurement through a single purchaser system without causing unintended consequences to the pharmaceutical market.

The National Drug Policy in 1996 specified a national essential list but allowed the medical schemes to use this as a guide. This resulted in schemes being responsible for their own selection, creating a multitude of lists adding unnecessary holding costs to the supply chain. It may be wise to follow the tenant of the NDP in rationalising the

drug pricing system in the private sector by mandating the use of the *lowest-priced generics*, allowing in the interim, as we move towards UHC, a reference price system or the use of a maximum medical aid price (MMAP). Enforcing other aspects of the medicine pricing model initially proposed having a fixed and regulated logistic fee together with a fixed professional fee will add transparency to the private market.

More can be achieved through international benchmarking. While South Africa has achieved substantial price reduction in the private sector as determined in this study, the country still pays high prices for their medicines. The Government notice on the 17 December 2010 outlining the Methodology for International Benchmarking of Prices of Medicines and Scheduled Substance in South Africa with the aim to remove the *price distortion* for medicines was never implemented. It would be a key policy regulation implementation in the immediate future to maintain the downward trend in medicine prices in South Africa.

Price clustering, as reflected in our study around generic medicines, maybe a result of some payers in the private sector setting reference prices. Manufacturers of expensive drugs may lower their prices to meet referencing, equally, there is the danger of lower-priced medicines increasing their price to meet reference prices and thus increase their profit. There is a need for a better generic pricing policy from setting a cap on the introduction of the first generic relative to the originator to introducing the second, third and subsequent generics at a much lower reducing price than the first as reflected in countries like Canada. This may add to the generic substitution policy already in place in South Africa and lead to lower medicine prices.

The final policy recommendation relates to the licensing of pharmacies. A transparent pricing system must ensure that each step of the process has appropriate regulations, including the Single Exit Price (SEP), a fixed and regulated logistic fee and an appropriate, affordable fixed dispensing fee. Medicine will be available in any part of the country at the same regulated fee, a key motivation by the National Department of Health in its formulation of the policy. If the competition aspect of this essential service is removed, then access to where medicines become available will be based on areas of need. It will remove the need for duplication of services in the same location as seen in the current model in South Africa and in other parts of the world where urban and metropolitan clustering, as seen in this study, is the order of the day. Restricting the

number of pharmacies by a single owner, a tool successfully employed in other countries, unless it meets the demand in a rural area will help solve the problem of making services available in outlying areas. Encouraging service delivery may not be a licensing issue alone. It may require further stimuli such as higher dispensing fees or rural allowance as in the case of Government pharmacists in South Africa, assisted rental structures in government buildings and preferential contracts to supply state patients. This will assist in overcoming the barrier seen currently in getting pharmaceutical services in areas of need.

6.3 Thesis Limitations

The lack of empirical data in LMICs[3] was a limitation in terms of the literature review and comparative analysis of the changes in South Africa. The author notes the limitation of data available prior to the implementation of the regulations reflected in the Interrupted Time Series graphs produced. Bernal et al. (2016)[38] suggests that there are "no fixed limits regarding the number of data points". The power depends on "various other factors, including distribution of data points before and after the intervention, variability within the data, strength of effect, and the presence of confounding effects such as seasonality"[39]. Inspection of the visual results shows that the trend before intervention does not show drastic changes.

Penfold's et al. (2013)[40] suggestion of using a non-equivalent control was not possible as it does not exist in South Africa. The only comparative is the public sector that uses a tender system where data is not publicly available. The price files accessed were from computer vendors and community pharmacies where prices are further verified via payment systems on SEP from payers. Segmented regression assumes a linear trend[41], but as medicine prices do not tend to change within the year and remain stable over the four quarters, hence a single data point was used to reflect the price for the year.

As the ownership regulations did not impact the location of public and private institutional pharmacies in the country, their location was removed from the data set. As a result, the pharmaceutical service per population ratio may not be reflective except for the community pharmacy. The type of ownership was restricted to the independent and corporate pharmacy only where lay ownership was not investigated as this does not appear on the SAPC database. Only a single database was examined and mapped as it

is assumed that a pharmacy can only open once it is recorded on the SAPC register. Even if a license is issued, it may not be an active pharmacy unless determined active by Council after an inspection.

6.4 Recommendations for Future Research

The authors acknowledge the limitation that a change in medicine price determines change in expenses, but it may not imply savings to the end user. This could be the subject of further research.

South Africa had in 2004 also introduced the Single Exit Price for pharmaceuticals and the regulation relating to the dispensing fee, both with the intention to control costs of pharmaceuticals. The consequences of this regulated market, which reduced profitability and the open ownership, which reduced volumes of prescription to small pharmacies may have had an additive impact on that lack of growth in rural and underserved areas. While it is beyond the scope of this study, it may be of value in future investigation.

Liberalisation, like in many other countries, has resulted in multiple pharmacies in the same location. This may have an impact on the South African 2030 human resource plan for the country and may need to be assessed. Added to this, it has created a demand for young pharmacists who tend to move directly for community service to be the Responsible Pharmacist (RP) without gaining the requisite skills in this senior management role. It is important to access the impact on the quality of service provision in these environments.

6.5 Contribution of the Thesis/Conclusion

A large body of research and literature can be found in developed markets[28] with well-funded health insurance scheme and universal coverage, but little exists in LMIC[42], especially those with similar health systems as South Africa. This thesis will contribute to the research pool in LMIC. This study provides evidence of the impact of medicine pricing intervention from a middle–income country, and useful lessons can be drawn by other developing countries looking at introducing medicine price controls.

Measuring outcomes of policy changes as was done in this study, allows comparison to Governments target levels and expectation, make a comparison to international

available study outcomes and identify areas of strength and weaknesses for further improvements. Systematic assessments and monitoring based on standard indicators recommended, in this case by WHO/HAI[31], should be a routine part of planning and programme management and the objective indicators researched will contribute to South Africa's ongoing need to provide equitable, affordable and accessible medicines.

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Appendix A: Letter confirming ethical approval from the University Of KwaZulu-Natal Humanities and Social Science Research Ethics Committee

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

12 April 2013

Professor Fatima Suleman 621698
School of Health Sciences
Westville Campus

Protocol reference number: HSS/0154/013
Project title: Assessment and evaluation of South Africa's private sector pricing and public sector pharmaceutical policies, strategies and other interventions on access to and appropriate use of quality medicines – lessons for LMICs

Dear Professor Suleman

I wish to inform you that your application has been granted full approval. **Expedited Approval**

Any alteration/s to the approved research protocol i.e. Questionnaire/Interview Schedule, Informed Consent Form, Title of the Project, Location of the Study, Research Approach and Methods must be reviewed and approved through the amendment/modification prior to its implementation. In case you have further queries, please quote the above reference number. Please note: Research data should be securely stored in the school/department for a period of 5 years.

I take this opportunity of wishing you everything of the best with your study.

Yours faithfully

.....
Professor Steven Collings (Chair)

/px

Humanities & Social Sc Research Ethics Committee
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