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Impact of the introduction of mandatory generic substitution in South Africa: private sector sales of generic and originator medicines for chronic diseases

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Abstract

OBJECTIVE To assess the impact of mandatory offer of generic substitution, introduced in South Africa in May 2003, on private sector sales of generic and originator medicines for chronic diseases.
METHODS Private sector sales data (June 2001 to May 2005) were obtained from IMS Health for proton pump inhibitors (PPIs; ATC code A02BC), HMG-CoA reductase inhibitors (statins; C10AA), dihydropyridine calcium antagonists (C08CA), angiotensin-converting enzyme inhibitors (ACE-I; C09AA) and selective serotonin reuptake inhibitors (SSRIs; N06AB). Monthly sales were expressed as defined daily doses per 1000 insured population per month (DDD/TIM). Interrupted time-series models were used to estimate the changes in slope and level of medicines use after the policy change. ARIMA models were used to correct for autocorrelation and stationarity.
RESULTS Only the SSRIs saw a significant rise in level of generic utilisation (0.2 DDD/TIM; $P < 0.001$) and a fall in originator usage (−0.1 DDD/TIM; $P < 0.001$) after the policy change. Utilisation of generic PPIs fell (level 0.06 DDD/TIM, $P = 0.048$; slope 0.01 DDD/TIM, $P = 0.043$), but utilisation of originator products also grew (level 0.05 DDD/TIM, $P < 0.001$; slope 0.003, $P = 0.001$). Generic calcium antagonists and ACE-I showed an increase in slope (0.01 DDD/TIM, $P = 0.016$; 0.02 DDD/TIM, $P < 0.001$), while the originators showed a decrease in slope (-0.003 DDD/TIM, $P = 0.046$; −0.01 DDD/TIM, $P < 0.001$). There were insufficient data on generic statin use before the policy change to allow for analysis.
CONCLUSION The mandatory offer of generic substitution appeared to have had a quantifiable effect on utilisation patterns in the 2 years after May 2003. Managed care interventions that were already in place before the intervention may have blunted the extent of the changes seen in this period. Generic policies are an important enabling provision for cost-containment efforts. However, decisions taken outside of official policy may anticipate or differ from that policy, with important consequences.

keywords generic substitution, pharmaceutical policy, cost savings, South Africa

Introduction

As is the case in many middle- and low-income countries, South Africa is engaged in a concerted effort to ensure universal health coverage (UHC), in the form of a National Health Insurance scheme [1]. Containing expenditure of medicines has been a consistent feature of South Africa's post-apartheid health policy since the democratic transition in 1994. A National Drug Policy (NDP) was issued in 1996, and then appended to the White Paper on the Transformation of the Health System in South Africa in 1997 [2, 3].

The NDP largely followed the prescripts of WHO for such policies, last updated in 2003 [4], and committed to the use of interchangeable multisource pharmaceutical products (IMPP; generics), using the international non-proprietary name (INN), or generic name, in order to contain expenditure. The policy expressed the intent to ultimately achieve generic prescribing in both the public and private sectors, but saw generic substitution as the first step.

The mandatory offer of generic substitution came into effect in May 2003 with a range of safeguards. In the event that a generic equivalent existed, it was mandatory

that pharmacists offer generic substitution, which the patient could accept or refuse. In addition, the law allowed the prescriber to indicate 'no substitution' on the prescription. In such cases, the pharmacist was prohibited from substituting the brand prescribed with a lower-priced version. Lastly, the South African national medicines regulatory authority (the Medicines Control Council (MCC)) was required to provide a 'non-substitutable list'. A second Amendment Act in 2002 added an obligation on the pharmacist to take reasonable steps to inform the prescriber that a substitution had occurred. This last change is not expected to have had any material impact on the practice of substitution.

South Africa has a fragmented health system, with the majority of patients catered for by the public sector. However, a well-resourced private sector provides healthcare services predominantly to those who have health insurance. There are currently approximately 8.8 million beneficiaries of the 87 medical schemes registered in South Africa [5]. The balance of the population (about 44.2 million) is catered for predominantly by the public sector, although some out-of-pocket purchasing by uninsured patients does occur in the private sector, including from medical practitioners who are licensed to dispense. The mandatory substitution law only targeted the private sector in South Africa. In the public sector, medicines on the National Essential Medicines List were already largely generic. As only those medicines procured on tender are available in public sector facilities, substitution is not possible. The South African pharmaceuticals market was worth ZAR30 billion in 2011 (approximately US$1.9 billion at current exchange rates), of which the private market accounted for 25% by volume, but 65% by value [6]. In 2014, generic medicines were estimated to account for about 65% of all items dispensed in the private sector, and 40% of expenditure [7]. Data on generic utilisation are only reported publicly by one of the medical scheme administrators, which provide services to a number of medical schemes with a total of about 1 million beneficiaries. In 2014, generic medicines accounted for 55.6% of items claimed on behalf of these beneficiaries [8].

Only one assessment of the impact of the introduction of the new generic policy on utilisation patterns in the South African private sector has been reported. Based on the utilisation of only one beta-blocker (atenolol) by beneficiaries of the largest medical scheme (Discovery Health), Deroukakis showed a significant change in claims patterns per 1000 beneficiaries between May 2002 and April 2004 [9]. However, visually, there appeared to be a premature change in claims in late 2002, 'in anticipation of the implementation of the law'. This study therefore aimed to assess the impact of the introduction of mandatory offer of generic substitution on private sector sales of generic and originator medicines, with a particular focus on medicines used for chronic non-communicable diseases. This study has wider implications although, in terms of the continued global efforts to sustain access to needed medicines, and in particular to contain the effects on medicines expenditure of highly-priced medicines, many of which are biological.

Methods

Data source and setting

South African private sector monthly sales data from June 2001 to May 2005 were obtained from IMS Health for the following selected therapeutic groups: proton pump inhibitors (PPIs; ATC code A02BC), HMG-CoA reductase inhibitors (statins; C10AA), dihydropyridine calcium antagonists (C08CA), angiotensin-converting enzyme inhibitors (ACE-I; C09AA) and selective serotonin reuptake inhibitors (SSRIs; N06AB). The choice of pharmacological groups was guided by the availability of generic equivalents, with none of the products tracked being included on the MCC's 'non-substitutable' list [10]. Similar categories have been tracked in other markets [11].

Products were classified as originator or generic on the basis of registration with the South African medicines regulatory authority (MCC). For each active pharmaceutical ingredient, dosage form and strength, the first product obtaining market authorisation was defined as the originator product. Generic equivalents were thus subsequently authorised equivalents, registered on the basis of an abbreviated dossier and intended to be interchangeable. Monthly sales were converted to defined daily doses per 1000 insured population per month (DDD/TIM), using the information from the Anatomical Therapeutic Chemical (ATC)/defined daily dose (DDD) database maintained by the WHO Collaborating Centre for Drug Statistics Methodology [12]. The denominator was taken as the total number of medical scheme beneficiaries reported by the Council for Medical Schemes for each year [13].

Data analysis

Interrupted time-series analyses were conducted at the therapeutic group level to estimate changes in the slope (depicting longer-term changes)and level of use (depicting immediate changes) of originator and generic medicines after the introduction of mandatory offer of generic substitution [14]. Interrupted time-series analysis provides

the strongest quasi-experimental research design [15]. This method is appropriate for conducting impact evaluations when it is not possible to control the implementation of the intervention and repeated observations over time are available, in the form of time-series data.

As the policy change was implemented on 2 May 2003, the 6-month gap between February 2003 and July 2003 was used as the interruption in the series. To ensure unbiased estimation, it is important to take stationarity and autocorrelation 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.

As a sensitivity analysis, the duration of the interruption in the series was varied between 1 and 4 months and assessed using Quandt likelihood ratio (QLR) statistics [16]. All analyses were conducted with STATA version 12 (StataCorp LP, College Station, TX, USA).

Results

The results of the interrupted time-series analysis for four therapeutic groups (selective serotonin reuptake inhibitors, proton pump inhibitors, dihydropyridine calcium antagonists and angiotensin-converting enzyme inhibitors) are shown in Table 1. As there were insufficient data on statin usage before the policy intervention, this group was excluded from the analysis.

Only for the SSRI group was the change in level statistically significant and the changes in both level and slope in the expected direction, in that there was an increase in generic utilisation (0.179 DDD/TIM; $P < 0.001$) and a decrease in originator usage (-0.090 DDD/TIM; $P < 0.001$). The trends over time are depicted in Figure 1.

Changes in the utilisation of PPIs were more complex, as shown in Figure 2. Utilisation of generic PPIs decreased by 0.063 DDD/TIM ($P = 0.048$), with a slope increase of 0.005 DDD/TIM per month ($P = 0.043$). However, the use of PPIs originator products also increased, as shown by a level change of 0.053 ($P < 0.001$) and a slope change of 0.003 ($P = 0.001$). A delayed increase in generic utilisation was apparent from visual inspection.

Utilisation of generic calcium antagonists did not show statistically significant changes in level, but a statistically significant sevenfold slope increase from 0.001 to 0.007 DDD/TIM ($P = 0.016$). There was also a statistically significant slope decrease in utilisation of the originator products (-0.003 DDD/TIM; $P = 0.046$), as shown in Figure 3. Generic ACE-I utilisation showed a

Table 1 Interrupted time-series analysis for four selected therapeutic groups, using February to July 2003 as the interruption in the series

	Selective serotonin reuptake inhibitors		Proton pump Inhibitors		Dihydropyridine calcium antagonists		Angiotensin- converting enzyme inhibitors	
	Generic	Originator	Generic	Originator	Generic	Originator	Generic	Originator
Trend (*P* value)	0.005 (0.036)	0.001 (0.249)	0.001 (0.602)	−0.001 (0.228)	0.001 (0.605)	0.001 (0.198)	0.002 (0.515)	−0.0002 (0.901)
Change in level (*P* value)	**0.179 (<0.001)**	**−0.090 (<0.001)**	**−0.063 (0.048)**	**0.053 (<0.001)**	−0.025 (0.548)	0.026 (0.228)	0.081 (0.157)	0.031 (0.231)
Change in slope (*P* value)	−0.004 (0.120)	−0.0004 (0.814)	**0.005 (0.043)**	**0.003 (0.001)**	**0.006 (0.016)**	**−0.003 (0.046)**	**0.018 (<0.001)**	**−0.009 (<0.001)**
Constant (*P* value)	0.291 (<0.001)	0.337 (<0.001)	0.030 (0.196)	0.239 (<0.001)	0.048 (0.154)	0.322 (<0.001)	0.329 (<0.001)	0.487 (<0.001)

Statistically significant values ($P < 0.05$) are shown in bold.

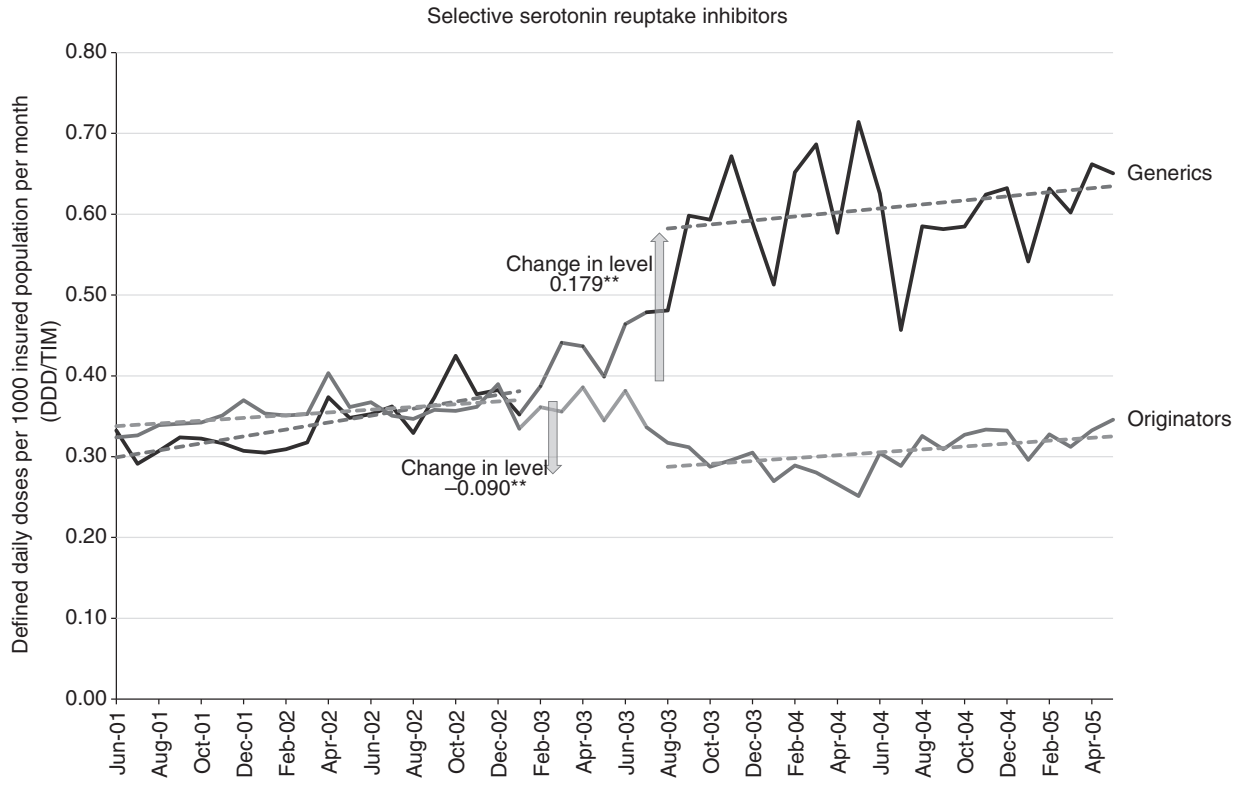

Figure 1 Change in level and slope: selective serotonin reuptake inhibitors.

tenfold slope increase from 0.002 to 0.02 DDD/TIM ($P < 0.001$), without a change in utilisation level (Figure 4). The expected decrease in the utilisation slope of originator ACE-I products was also significant (−0.01 DDD/TIM ($P < 0.001$), with no significant changes in utilisation level. (Figure 3).

The sensitivity analyses, in which the interruption in the series was varied from 1 to 4 months, did not affect the overall results found (Appendix S1). Only for the PPIs and the SSRIs was an interruption at the end of April 2003 evident. However, an interruption in the series during April 2004 was shown for all therapeutic groups.

Discussion

The results of this study provide evidence of a quantifiable effect of the introduction of mandatory offer of substitution, at least in respect of the four commonly used therapeutic groups for the treatment of chronic conditions in the South African private sector. To our knowledge, this is the first study to have rigorously analysed the impact of this policy change on several therapeutic groups in South Africa using interrupted time-series analysis. Whereas generic SSRIs replaced originator products after the implementation of the law in 2003, the effect on ACE-I and calcium channel blockers was less pronounced, but still statistically significant. For PPIs, the intended effect of the policy was not detected.

In order to interpret the results, it is important to take into consideration the context for this policy implementation process. The initial policy intent had been signalled in the 1996 National Drug Policy, and included in an amendment to medicines legislation in 1997. However, litigation (primarily aimed at the apparent change in intellectual property provisions in the law) had delayed the implementation of the law until 2003. Thus, although the pro-generic stance in the National Drug Policy was not the primary target, its implementation was nonetheless delayed. In the private sector medical schemes, a range of managed care interventions aimed at increasing the utilisation of lower-priced generic medicines had already been implemented prior to May 2003. For instance, a process of internal reference pricing, where a maximum medical aid price (MMAP) was set for particular molecules when generic equivalents were available, was first introduced in 1985 [17]. Theoretically, this

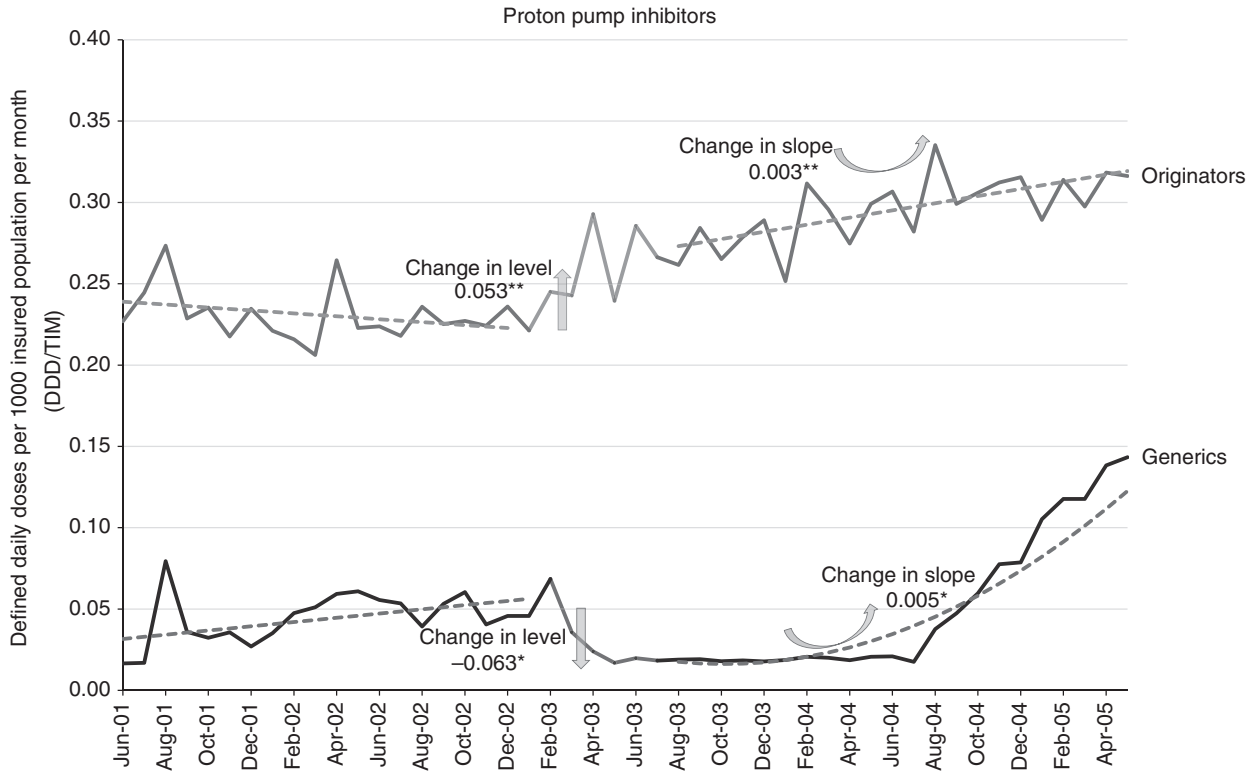

Figure 2 Change in level and slope: proton pump inhibitors.

policy required the pharmacist making a substitution to obtain prior permission from the prescriber, at least in the form of a telephonic prescription. To what extent this legal requirement was complied with, in the face of pressure from medical schemes in the form of the MMAP policy is unknown. It may well be that the 'premature' changes described by Deroukakis [9] in relation to atenolol were also occurring with at least some of the therapeutic groups assessed in this study. Thus, although the change in law which came into effect on 2 May 2003 made substitution easier, the mandatory element in the system had already been introduced by managed care interventions such as MMAP. This may explain the lack of clear evidence for a dramatic substitution effect for ACE-I and dihydropyridine calcium antagonists.

In addition to the MMAP, other factors may have contributed to the increase in generic consumption. Although South African law did not allow for therapeutic substitution before 2003, it is possible that, under pressure from medical schemes' cost-containment measures, or on request for a lower-priced alternative from patients to reduce out-of-pocket expenditure (in the form of co-payments demanded as a brand premium), prescribers may have chosen to change patients from a medicine for which no generic equivalent existed to one for which such an equivalent did exist. Within each of the pharmacological categories selected in this study, options for such substitutions existed. Conversely, options also existed where a product for which no generic equivalent was yet marketed was available. The launch of esomeprazole (first registered in South Africa in 2002) would have provided such an option, obviating the possibility of substitution if branded omeprazole was prescribed instead.

The results of our study are similar to the findings from an analysis of the effects of the introduction of mandatory offer of generic substitution in Sweden in 2002, where a 'proportionally larger increase in sales of substitutable pharmaceuticals compared with sales of non-substitutable pharmaceuticals' was detected, at least for some therapeutic groups [11]. The same policy change had been shown to reduce patient co-payments and overall societal expenditure in Sweden, reversing a previous increase in the slope of both forms of pharmaceutical expenditure [18]. In contrast, a reference pricing

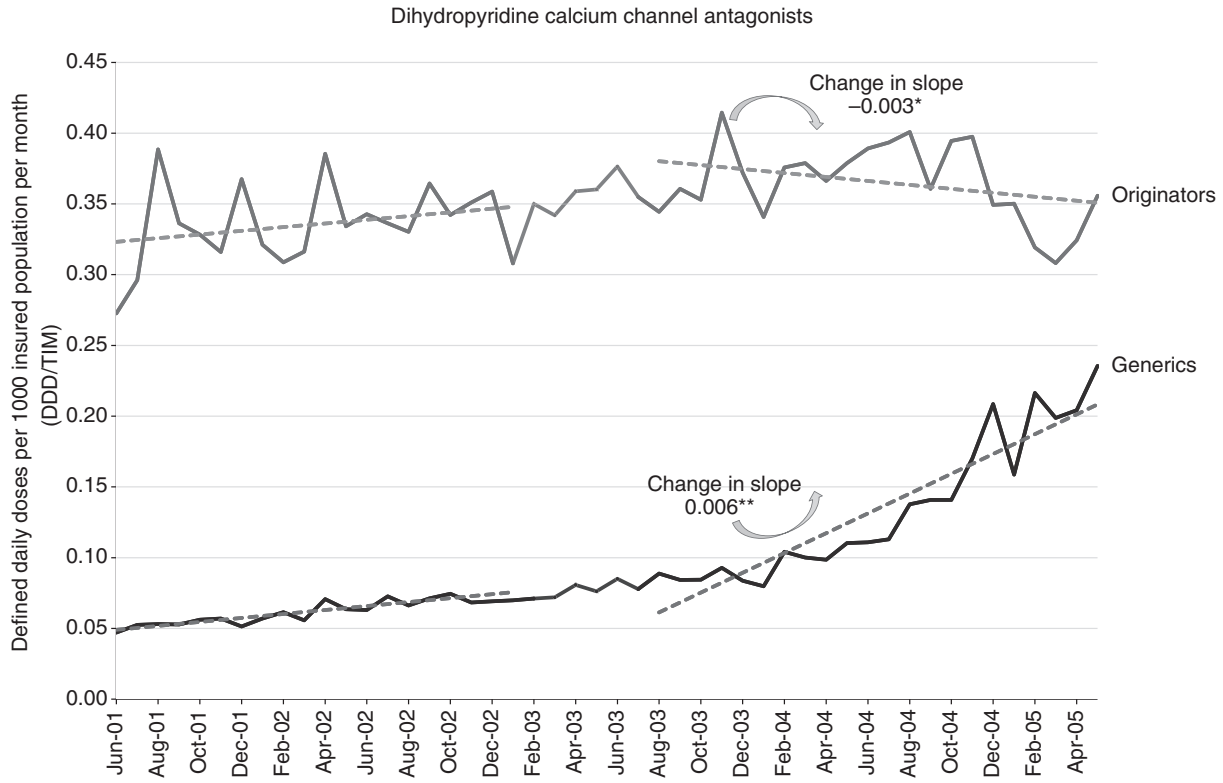

Figure 3 Change in level and slope: dihydropyridine calcium channel antagonists.

policy in Finland did not measurably add to the influence of previously implemented generic substitution in the medium to long term, based on a time-series analysis of costs associated with antipsychotics [19].

There are a number of possible explanations for the increase in consumption of originator PPIs and the apparent lack of effect of mandatory offer of substitution in this therapeutic group. Increasingly, manufacturers of branded original medicines are competing in the market with their own variably-priced equivalents (sometimes referred to as 'clones'). The launch of chiral alternatives can also counter the loss of sales that follow patent expiry and generic entry. This has particularly been the case with the launch of esomeprazole, as an alternative to the heavily genericised omeprazole. This PPI was one of the products highlighted in an analysis of the impact of product 'evergreening' in Swiss hospitals [20]. An overall increase in total PPI utilisation, as was reported in Australia [21], may also have distorted the picture in South Africa. Overall, generic market share has increased in South Africa's private sector between 2001 and 2011 [22]. However, as these authors point out, the situation is often 'complex and nuanced at the level of individual medicines'.

The changes in generic policy also did not occur in isolation. In terms of the Medicines Amendment Act, a range of pricing interventions came into effect on 2 May 2004, a year after the generic substitution change [23]. The first stage involved the introduction of a non-discriminatory single exit price (factory gate price) in 2004, which took into account the weighted average of all discounts and rebates offered to private sector purchasers in the preceding year. A ban on bonusing, sampling and any form of incentive scheme was also introduced. However, due to legal challenges, the maximum dispensing fees for pharmacists and other licensed dispensing practitioners, and the maximum annual increase in the single exit price (SEP), was only implemented in 2007, after the period under review in this study. While the possibility cannot be ruled out, the impact of the cost-neutral introduction of the SEP in 2004 on generic utilisation is expected to have been minimal. In other settings, the introduction of new pricing and co-payment schemes has had potentially deleterious effects on access to medicines. In South

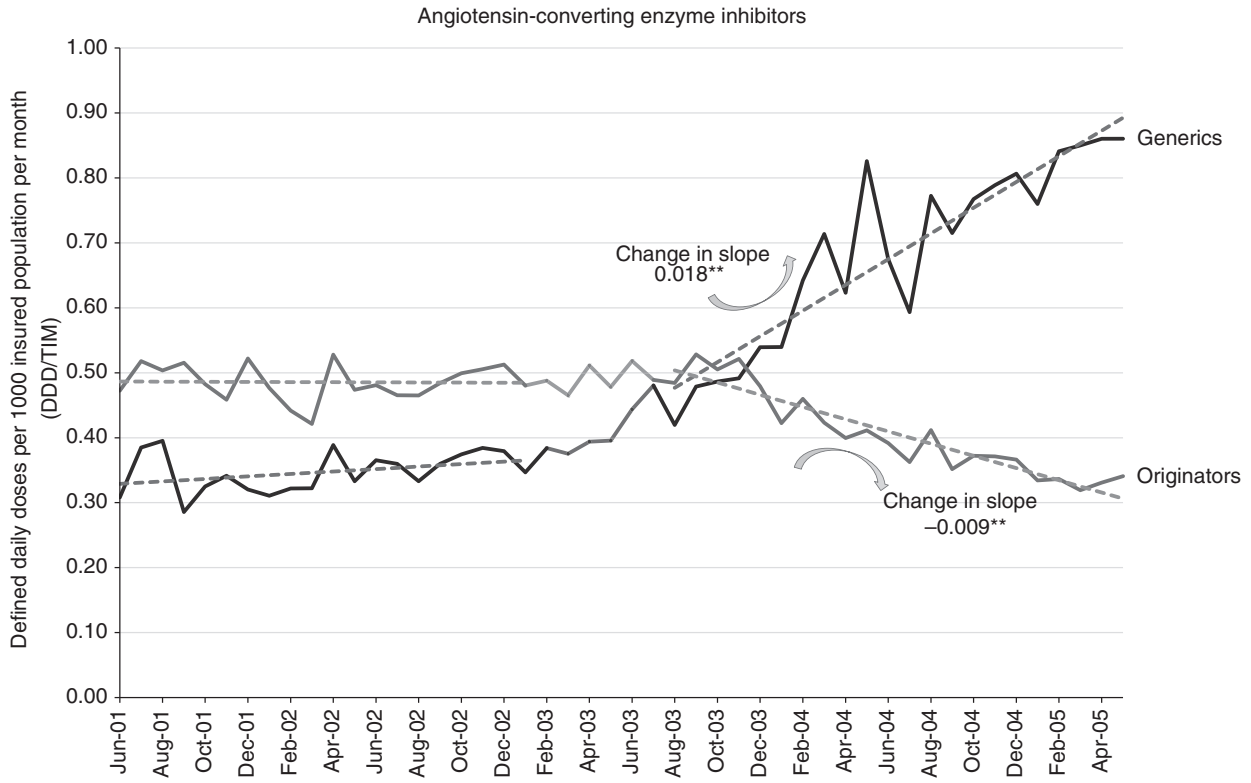

Figure 4 Change in level and slope: angiotensin-converting enzyme inhibitors.

Korea, for example such policies were estimated, on the basis of interrupted time-series analysis, to have resulted in decreased numbers of prescriptions being filled for both branded and generic antihypertensive medicines [24]. Nonetheless, where a dominant single payer system is in place, costs savings can be achieved without negative health impacts. For example, a shift from branded originator to generic olanzapine was achieved in New Zealand, with 99.7% of patients switching and no measurable impacts on health service utilisation or mortality [25].

This study has some limitations. The analysis is entirely dependent on the accuracy of the sales data collected and reported by IMS Health. However, this is an industry-standard process on which all manufacturers rely for data to guide marketing efforts. The denominator used was the total of all medical scheme beneficiaries reported by the Council for Medical Schemes. This figure ignores the possibility of purchases of prescription medicines in the private sector by non-beneficiaries, who pay out-of-pocket. However, this proportion was not expected to be large, nor was it expected to change markedly during the period under review. Although the choice of pharmacological groups assessed was guided by previous work [11], and captured an important set of medicines used for chronic, non-communicable diseases, it remained a small subset of the entire market. It may be that other pharmacological groups showed different trends, or even a lack of effect of the change in generic policy. As with all such analyses, the lack of a control group cannot be avoided. Although the analysis has been conducted some years after the initial policy change, the policy question remains a valid one.

Beyond the national context, this study has important implications for global cost-containment measures, in particular in relation to high-priced biological medicines. Increasingly, global markets will have access to biosimilars' versions of such biological medicines, authorised on the basis of comparability data, but not considered to be interchangeable. Much effort has been expended in deciding how best to name such products, with unique names rather than international non-proprietary names such as have been used for small molecule medicines [26]. Nonetheless, the possibility of data supporting interchangeability, and therefore, substitution has been

identified as an important cost-saving measure [27]. It may well be that, as perhaps happened in South Africa with generic substitution, pressure from reimbursement bodies or insurers will drive changes in practice in advance of official policy or legal enablement. In the absence of sufficient data, such practices may put patients at risk, but also undermine confidence in biosimilars.

Conclusions

This study demonstrated a quantifiable change in generic utilisation of medicines used for chronic non-communicable diseases following the introduction of a law requiring the mandatory offer of generic substitution by pharmacists and other dispensers in South Africa's private sector in 2003. Generic substitution policies are an important enabling provision for a range of cost-containment measures, including internal and external reference pricing, the use of limited lists (essential medicines lists) and standard treatment guidelines. Such policies are important enablers of the sustainability of UHC systems in all countries. The lessons learned from the introduction of generic substitution policies are also relevant to the debates about interchangeability of biological medicines, including biosimilars.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Results from the Quandt likelihood ratio statistic.

Table S2a. Sensitivity analysis: selective serotonin reuptake inhibitors.

Table S2b. Sensitivity analysis: proton pump inhibitors.

Table S2c. Sensitivity analysis: dihydropyridine calcium antagonists.

Table S2d. Sensitivity analysis: angiotensin-converting enzyme inhibitors.

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