What do we really know about reference pricing for pharmaceuticals?
Evidence from a systematic review of the literature

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Summary: Health policy-makers worldwide have adopted different Reference Pricing (RP) systems for pharmaceuticals. Systems may differ concerning their effects on pharmaceutical prices, firms’ strategies, market structure, public and private expenditure, health outcomes and Research and Development (R&D) investments. We present evidence from a recent systematic review of the effects of RP across different systems. Evidence suggests RP successfully decreases drug prices and expenditures in the short-run. Prices drop more where generics have more market power. There is no evidence of negative health effects associated with patients switching between drugs. More research is needed on the long-term effects of RP and its impact on R&D.

Key Words: Reference Pricing, Pharmaceutical Markets, Evidence-based Policy, Generics Competition.

Introduction
Expenditure on pharmaceuticals has been increasing at a faster rate than total health spending: per capita spending on pharmaceuticals rose by >50% between 1995 and 2005.1 This trend poses serious concerns about the financial sustainability of public health systems and has motivated a series of cost-control policies.

In this context, many countries have adopted Reference Pricing (RP) as a reimbursement system for pharmaceuticals. RP policy consists of clustering drugs according to some equivalence criteria and defining a reference price for each cluster. Drugs can be clustered according to chemical (identical products with same active principal), pharmacological (chemically different but pharmacologically related drugs) or therapeutic equivalence (all drugs used to treat a particular condition). The combination of these options gives rise to several variants of RP schemes. For example, a so-called generic RP (GRP) applies only to products with expired patents and generic competition, and clusters drugs according to chemical equivalence (same form and active compound), while therapeutic RP (TRP) applies to clusters of drugs that are therapeutically equivalent.

Under all RP systems, the third-party payer will reimburse no more than the reference price for each drug in that cluster. If a consumer buys a drug at a price that is lower or equal to the RP of that cluster, then the drug is reimbursed up to the RP value. In contrast, if the purchased drug is priced higher than the RP, the consumer will pay the difference between the RP value and the actual drug price. RP is generally seen as an effective mechanism for the reduction of drug prices, as it is believed to encourage self-restraint and to promote appropriate drug use and therefore control the demand for expensive drugs. However, the effectiveness of RP ultimately depends on its ability to promote the financial responsibility of consumers and to enhance competition in pharmaceutical markets.

In the last decade a number of countries have introduced RP schemes (Belgium, Hungary, Italy, Norway, South Africa and...
Spain) following the experiences of Canada, Germany and New Zealand, where RP has been operating for nearly twenty years. The time is thus ripe for an assessment of the overall effects of RP:

- What are the effects of RP on the pharmaceutical market?
- How do firms react to this policy mechanism?
- Which RP scheme seems to work best?

In order to answer these and other questions we systematically reviewed the existing literature on RP.

In what follows, we start by describing the selection criteria of the studies included in the review, and then present the main findings of the literature. The final discussion is intended to summarise the existing evidence on the effects of RP and to suggest some ideas for future research on the topic.

**Objectives of the systematic review and selection criteria**

A number of articles exist which, directly or indirectly, refer to the RP and to its effect on pharmaceutical markets. Most of them, however, either consist of comments on existing evidence, or mainly provide qualitative and descriptive policy analyses. In our review, we aimed to only include studies which provide either original theoretical insights or new and robust quantitative evidence to evaluate the impact of RP on health and economic outcomes.

To be eligible for our review, the studies had to be published in a peer reviewed journal, written in English and accepted before September 2009. Studies could be either theoretical or empirical. A theoretical contribution was considered original when it presented new analytical insights and original suggestions guiding and motivating empirical investigation. An empirical study was considered original when it presented new data.

Given the inherent differences, the selection of theoretical and empirical papers was based on different criteria. In order to be included, theoretical papers had to present: (i) original insights motivating and qualifying results from empirical investigation and (ii) strong analytical rigour. On the other hand, in order to be included, empirical studies had to adopt a robust identification strategy, and in particular to employ either a Before-and-After (relevant variables are compared before and after the introduction of the RP) or a Difference-in-Difference (variables are compared in time, but with a control group of drugs to which the RP does not apply) approach.

The initial search (on PubMed and EconLit) provided 468 articles. After applying the above mentioned selection criteria, five theoretical and 30 empirical studies remained. A total of ten countries are represented in the empirical literature: Belgium, Canada, Germany, Hungary, Italy, New Zealand, Norway, South Africa, Spain and Sweden. Most of these countries applied a GRP, with the notable exception of Canada, Germany, Hungary and New Zealand, where products were clustered according to therapeutic similarities. The function linking prices to the reimbursement level is different from country to country, as is the market power of the generic producers. All these details make the country-specific analysis difficult to generalise. However, it is worthwhile to emphasise some common results emerging from the analysis of the 35 included papers.

**Results: theoretical studies**

The theoretical studies focus on different aspects of RP regulation, and it is thus difficult to sum up their results in few lines. In particular, the evaluation of the RP crucially depends on the policy used as a comparison, on the assumed characteristics of the market, and on the details of the policy design used in the theoretical model. However, some results seem robust to all specifications:

1. RP works well in reducing prices above the reimbursement level.
2. There are no strong incentives for generic firms to reduce prices once the Reference Price has been set. Hence, RP might not be effective in the long run.
3. RP can trigger price increases on therapeutic substitutes not covered by the policy. Again, this phenomenon might jeopardise the long-run effectiveness of the RP, especially if RP is applied to narrow clusters of products no longer covered by patents.
4. Firms can react to RP by setting prices strategically. In this sense, despite using market forces to regulate reimbursement prices, RP might not completely achieve the envisaged goal of perfectly competitive prices. This partial failure is due to the strategic interactions that RP itself is likely to trigger.
5. RP can discourage Research and Development (R&D) efforts by lowering the profitability of the drugs included in the clusters. At the same time, it can encourage a reallocation of R&D towards more innovative and breakthrough drugs to increase expected profits. Hence, the overall effect on R&D is ambiguous.

**Results: empirical studies**

Concerning the evidence on prices, virtually any country that implemented generic RP experienced a significant price reduction for drugs under RP. Price reductions are larger for prices originally higher than the Reference Price (as predicted by theory) and for markets where generic competition is stronger. Prices of substitute products not under RP can also be affected. However, the empirical results here are ambiguous and no robust conclusion can be drawn. Finally, the empirical literature does not provide sound evidence on the pricing behaviour of the firms producing generic drugs. It is not clear, for example, how prices of generics react once the Reference Price is introduced and how the RP changes as a consequence of generics competition. Further empirical research on this topic is needed.

The main reason why RP is introduced is to control expenditure. Regarding this issue, the empirical literature points to significant short-run savings due to the introduction of RP. Most of the studies conducted in Canada, Germany, Belgium, South Africa, Italy, Spain and Sweden confirm this prediction. For example, RP induced a one year saving of $Can6.7 million (€4.8 million) for ACE inhibitors in Canada, corresponding to 6% of annual expenditure. Although these savings are statistically and economically significant, often they are not large enough to translate into significant reductions in overall pharmaceutical expenditure. Moreover, once again the long-run effects of RP have not been properly investigated.

Other important variables can be affected by the RP. First, the quantities sold of active compounds; in principle, demand for a compound might be reallocated to other close substitutes in order to avoid low prices due to RP. The empirical evidence suggests that under TRP, demand switches to cheaper active compounds. In GRP, the literature shows a slow but systematic reallocation of the demand towards products still under patent protection. However, empirical results here are not
robust and further research is needed.

Second, by switching to the least expensive drug, patients might visit their physicians more often and/or consume more health care services. Moreover, switching between drugs might be associated with changes in health status. Regarding health care consumption, studies in Canada show that initially patients do actually consume more non-drug health services. However, a few months after the implementation of RP, generally there was a return to the previous pattern of health care consumption. Even more importantly, the existing evidence does not confirm the existence of negative significant health effects associated with patients switching between drugs.

Finally, concerning industry profitability, the main issue is whether prematurely forcing chemicals still under patent protection into the competitive arena, by clustering them together under RP, might lower pharmaceutical innovation by decreasing profitability. In theory, this is possible. Empirically, this still seems to represent only a remote possibility as we found only one study analysing the link between R&D and RP. Data for this study refer to Canada (TRP), and the results suggest that the R&D expenditure in the pharmaceutical industry did not change significantly when RP policies were adopted.

Discussion

The variety of analyses of RP reflects the heterogeneity of countries and regulatory contexts to which this regulatory tool is applied. A systematic review of the existing literature helps to identify the effects which seem robust across all experiences. Looking at the evidence from articles published in scientific, peer-reviewed journals, what can we claim to know about the effects of RP after more than twenty years of application around the world? According to our results, some evidence is very robust, while some is less robust and needs to be further researched.

There are three robust conclusions. First, we can now accurately predict the theoretical effects of RP on prices, quantities and R&D. Even though the intensity of the effects depends on the precise analytical framework, prices of brand-name products should decrease, while there is no reason why prices of generic drugs should be affected; demand should be reallocated towards cheaper products or drugs not under RP; and firms can react to the RP by setting prices strategically. Second, empirical short-run effects on prices and expenditure are clear cut. Prices drop more where generics have more market power and under GRP, while expenditure after one year reduces consistently in all countries. Third, the impact of the GRP on the market for generics is such that demand within the chemical compound under RP reallocates toward cheaper versions, mostly generic drugs.

Besides these robust findings, some other effects have been shown to hold in certain contexts but are not generalisable to all contexts. The most important is related to the (lack of) health effects related to the TRP due to patients’ switching to cheaper active compounds. On this issue, the strongest evidence comes from Canada, where no significant impact on patient health after the introduction of RP was found. Two studies found negative health effects from switching. However, their sample size was relatively small and patients were selected non-randomly. Furthermore, the results have been open to criticism. In any case, more evidence is certainly required on this topic.

Finally, we found that two key issues are widely under-investigated in the existing literature. First, the long-run effects of RP have not been sufficiently considered, neither under a theoretical nor an empirical approach. Theoretical analysis has mainly focused on static models. The dynamic deriving from the link between firms’ strategies and reimbursement levels has not been fully explored. Empirically, no analysis has described the dynamic of the RP and the link between prices and reimbursement levels. The second key topic which should receive more attention is the empirical relationship between RP and pharmaceutical R&D. Although theoretical results are clear in this sense, the question of whether more competitive after-patent markets discourage investments in R&D or reallocate R&D towards more innovative projects is of crucial importance.

References


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Health technology assessment and health policy-making in Europe. Current status, challenges and potential

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New technologies with the potential to improve the health of populations are continuously being introduced. But not every technological development results in clear health gains. Health technology assessment (HTA) provides evidence-based information on the coverage and usage of health technologies, enabling them to be evaluated properly and applied to health care efficaciously, promoting the most effective ones while also taking into account organisational, societal and ethical issues.

Now available in Russian, this book reviews the relationship between HTA and policy-making, and examines how to increase the contribution such research makes to policy- and decision-making processes. By communicating the value and potential of HTA to a wider audience, both within and beyond decision-making and health care management, it aims ultimately to contribute to improving the health status of the population through the delivery of optimum health services.