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Southern Med Review

An International Journal to Promote Pharmaceutical Policy Research

BigPharma and unethical marketing

*The Trans-Pacific Partnership Agreement
and access to medicines*

Access and local production of medical technologies

Essential medicines and reproductive health

Pharmacy practice in Qatar and Macedonia

*Pharmaceutical policies in
European countries*

*Medicines information
in Slovenia*

ADR reporting in Malaysia



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Context: In developing countries where health systems and health policy are constantly evolving, there is a great need to publish informative research. However, there are few avenues to do so. Also, some of the other challenges are inexperienced or untrained researchers, topics out of the scope of current mainstream journals and limited funding.

Aims and Objectives: *Southern Med Review* provides a platform for researchers to disseminate commentary and empirical research findings, with a view to improve the rational use of and access to essential medicines.

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BigPharma and unethical marketing of medicinal products

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In today's environment, the main focus of the critical mass towards the multinational companies is on access to new patented and more expensive products. Many of them essential medicines, but many more non-essential 'me-too' medicines developed to get a piece of the blockbuster cake or to go from one patent to the next (evergreening). However, there are also other issues that BigPharma could be confronted with and help us solve. One of them is unethical marketing of products with no medical value or which are potentially dangerous.

We know that products being banned in some countries still exist and are actively promoted in other countries. The E-drug archives¹ and the WHO book of products² being banned have many examples of that. Often the companies' response when confronted will be that it is up to the country's regulatory authority to take action as they approved it. Of course we know that ideally that should be the case and I agree that some countries in Europe such as Germany definitely should have been able to clean the German market of such products, but in the developing world the capacity and skills are often not there. Should we accept that it is so? Or is it time to start getting tougher?

Recently, I was asked by a doctor to find Norwegian equivalents to some medicines a small child with a chronic disease had received in one of the worst conflict areas in Africa. Needless to say, whatever little money these people have should not be wasted. One of the medicines turned out to be a tonic, Mosegor, that Novartis sells in several countries in Africa and Asia (according to Google). I found it e.g. on a website (<http://thepharmaguide.com>) in Pakistan, one of many awful websites listing it.

The following indications are listed on the website mentioned above: anorexia in underweight patients, mood elevation in the elderly, prophylactic (interval) treatment of migraine. The syrup and tablets contain four B-vitamins and pizotifen, a sedating antihistamine, which was registered for migraine prophylaxis (Sandomigran) and still can be found in a few countries under the name Sandomigran or as Mosegor³. Pizotifen also has anticholinergic effects, hence it is not safe. Several websites promote it as an appetite stimulant. Even with no indication listed for use in children, Novartis gives dosage recommendations down to children aged 2 years old!

Novartis is a research-based pharmaceutical company that promotes an image of a responsible company with a public

health focus. So why then promote useless tonics for under-/malnourished children in poor countries?

This case reminds me of other useless products I have come across such as Encephabol (pyritinol) from the German company, Merck³. When I worked in Botswana in the late 1980's I received requests from doctors for this – for use in malnourished children as it 'supposedly improves glucose uptake in the brain'. Surprisingly, that product still exists even in Germany with the indication 'organic brain disorder', in other countries also with other indications such as mental function disorder, but officially, not malnutrition.

There are of course numerous examples of potentially toxic or irrational products out there and many companies besides the multinationals that market such products. As I write this editorial, I have been told that Roche is continuing to manufacture Halfan for both children and adults. Halfan contains halofantrine, an antimalarial that has serious side effects but worryingly still seems to be on the French, Portuguese and South African markets³ as well as in many low- and middle-income countries.

By pointing finger at the multinationals, I want to highlight the paradoxes in the research-based companies that on the one side claim to do so much good for public health but continue to produce products detrimental to people's health. Of particular concern is of course medicines for children. How can large research-based companies defend marketing useless products for malnourished children who need proper nutrition?

It is time we start confronting BigPharma also with this side of their business. Other examples will be most welcome on E-drug!

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The Trans-Pacific Partnership Agreement: a threat to affordable medicines and public health

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The 1995 Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) made it mandatory for World Trade Organization (WTO) member states to allow 20 year patents on all products including medicines. This triggered a global counter-movement challenging monopoly pricing of essential medicines. Public health advocates urge governments to use public health 'flexibilities' available under TRIPS such as compulsory licensing and nationally defined criteria for patentability. There is now a vibrant global debate on alternatives to patents as mechanisms for funding of medical research¹. The 2001 WTO Doha 'Declaration on the TRIPS Agreement and Public Health' was a response to the global mobilisation for public health and justice. The Declaration affirmed that TRIPS 'can and should be interpreted and implemented in a manner supportive of WTO members' right to protect public health and, in particular, to promote access to medicines for all'².

The United States since 2001 has sought to undermine the letter and spirit of the Declaration on TRIPS and Public Health through 'TRIPS-plus' provisions in bilateral and regional 'free trade' agreements^{3,4}. One such regional initiative is the Trans-Pacific Partnership Agreement (TPPA) being negotiated between Singapore, New Zealand, Chile, Brunei, the United States, Australia, Peru, Vietnam and Malaysia. Other countries such as Japan, South Korea, and India are likely to join the process. The TPPA is not limited to 'trade' but potentially impacts on the capacity of national governments to implement domestic policy in a range of areas including environmental protection, the regulation of tobacco and alcohol, and health more broadly.

A leaked draft of the negotiating position of the United States Trade Representative (USTR) reveal demands for IPR protection that go well beyond the requirements of TRIPS⁵. The USTR is linked closely to business groups such as the Pharmaceutical Research and Manufacturers of America (PhRMA) which represents 'big pharma'. The determined objective of PhRMA and the USTR is to obstruct and delay as far as possible price competition resulting from the entry of cheaper generic brands. It is a depressing irony that monopoly privileges, granted by governments – patents and other forms of 'intellectual property' – which impede competition, are pursued in the name of 'free trade'.

PhRMA has long criticized medicines insurance schemes premised on cost-effectiveness and reference pricing such as the Pharmaceutical Benefits Scheme (PBS) in Australia and PHARMAC in New Zealand. The PhRMA submission to the USTR on the TPPA specifically targets alleged 'market access barriers... inadequate consultative mechanisms and transparency concerns in countries like New Zealand'⁶. But the governments of Australia and New Zealand are unlikely to accept the whole-sale winding-back of the PBS and PHARMAC. The Australian government affirms that it 'has not and will not accept provisions that limit its capacity to put health warnings or plain packaging requirements on tobacco products or its ability to continue the Pharmaceutical Benefits Scheme'⁷. But US pressures may well result in incremental policy adjustments which weaken cost-effectiveness assessments and reference pricing. The largest generics supplier to the PBS, Alphapharm (a subsidiary of the global generics firm Mylan), is 'deeply concerned about the impact that the [TPPA] could have on the generic pharmaceutical industry in Australia, on consumers and on the Government's budget'⁸.

Of particular concern is the potential impact of the TPPA on access to affordable medicines in developing countries. Prices on first generation HIV drugs have come down radically in the past decade through generics competition, notably through the entry of Indian suppliers such as CIPLA. International programs to treat HIV/AIDS depend on access to affordable quality generic drugs. Leaked documents reveal clearly that the USTR is pursuing aggressive TRIPS-Plus measures, categorises by the Médecins Sans Frontières as follows⁹:

- a. *The USTR is seeking to broaden the scope of patentability to facilitate patenting of new forms of old medicines that offer no added therapeutic efficacy. Governments should no longer be able to define key terms such as 'novelty', 'inventive step' and 'industrial applicability' in a way that reflects national priorities. In India this conflict is focused on paragraph 3(d) in the Indian Patent Act which prevents 'evergreening' by accepting patents on known substances only for therapeutically effective modifications.*
- b. *The USTR wants to disallow pre-grant patent opposition and enhance the legal rights of pharmaceutical companies.*

Pre-grant opposition allows third parties, including NGOs, public health groups, and competing firms, to challenge a patent application as unmerited, thus expediting generic competition.

- c. *The USTR is seeking to bring in new forms of IP enforcement, allowing 'custom officials to seize shipments of drugs on mere suspicion of IP infringement and to increase damages for IP infringement'*¹⁰.
- d. *The USTR is seeking to expand data exclusivity. Data exclusivity prevents, for a certain number of years, access for generics companies to existing clinical trial data. This results in extension of monopoly pricing beyond the patent period since it is uneconomical (and unethical) for clinical trials already undertaken to be replicated. Data exclusivity is not required under TRIPS.*
- e. *The USTR is seeking patent term extensions beyond twenty years to compensate for administrative delays in the regulatory process. This has the effect of delaying generic competition.*
- f. *The USTR is seeking to make drug regulatory authorities, charged with evaluating the safety, quality, and efficacy of medicines, responsible also for monitoring of IPRs. 'Linking drug registration and patent status can delay generic entry into the market and is an aggressive TRIPS plus measur'*¹¹.

The TPPA is the first trade agreement negotiated under the Obama administration. Remarkably, the US position under Obama represents a step back from the 2001 Doha Declaration on TRIPS and Public Health, the 2008 WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property and even the policy adopted by the Bush Administration in 2007¹².

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Local production of medical technologies and its effect on access in low and middle income countries: a systematic review of the literature

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Abstract

Objectives: The objective of this study was to assess the existing theoretical and empirical literature examining the link between “local production” of pharmaceuticals and medical devices and increased local access to these products. Our preliminary hypothesis is that studies showing a robust relationship between local production and access to medical products are sparse, at best.

Methods: An extensive literature search was conducted using a wide variety of databases and search terms intending to capture as many different aspects of this issue as possible. The results of the search were reviewed and categorized according to their relevance to the research question. The literature was also reviewed to determine the rigor used to examine the effects of local production and what implications these experiences hold for other developing countries.

Results: Literature addressing the benefits of local production and the link between it and access to medical products is sparse, mainly descriptive and lacking empirical evidence. Of the literature we reviewed that addressed comparative economics and strategic planning of multinational and domestic firms, there are few dealing with emerging markets and lower-middle income countries and even fewer that compare local biomedical producers with multinational corporations in terms of a reasonable metric. What comparisons exist mainly relate to prices of local versus foreign/multinational produced medicines.

Conclusions: An assessment of the existing theoretical and empirical literature examining the link between “local production” of pharmaceuticals and medical devices and increased local access to these products reveals a paucity of literature explicitly dealing with this issue. Of the literature that does exist, methods used to date are insufficient to prove a robust relationship between local production of medical products and access to these products. There are mixed messages from various studies, and although the studies may correctly depict specific situations in specific countries with reference to specific products, such evidence cannot be generalized. Our review strongly supports the need for further research in understanding the dynamic link between local production and access to medical products

Keywords: Pharmaceutical Policy, Industrial Policy, Access to Medicines, Pharmaceuticals.

Introduction

Local production (LP) of essential medical technologies is at the interface of industrial/economic development policy and public health policy. From an industrial policy perspective, generating assured quality products by having a competitive pharmaceutical/medical device industry with sufficient economies of scale would

be desirable for low and middle income countries (LMICs)¹. Clearly, countries such as India, Brazil, and others have proven that this is possible for medicines²⁻⁶. It is not clear whether it is possible for other LMICs to successfully repeat these efforts due to the need for major investments in human resources, financing and infrastructure to support innovation.

Local production of medical technologies

This question has been receiving much high-level attention in recent years with work funded by various governmental and non-governmental agencies including the United Kingdom (UK) Department for International Development- DFID⁷, the American Enterprise Institute⁸, the German Development Institute⁹, the World Bank^{1,10}, Deutsche Gesellschaft für Internationale Zusammenarbeit GmbH, GIZ¹¹⁻¹⁴, the African Union¹⁵ and the Southern Africa Development Council¹⁶.

We further note the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA-PHI) of the World Health Organization (WHO) that includes a mandate to support development cooperation, partnerships, and networks to build and improve transfer of technology related to health innovation¹⁷. The WHO, in partnership with the United Nations Conference on Trade and Development (UNCTAD) and the International Centre for Trade and Sustainable Development (ICTSD), and with funding by the European Union (EU), is undertaking a project on improving access to medical products in developing countries through local production and related technology transfer¹⁸.

From a public health perspective, understanding how changes in LP capacity will impact access to medical products is of great significance. We pose this as a question: "Does local production of medical products have beneficial impact on the resulting access to these products?" Such beneficial impact might, in principle, manifest itself as greater availability and/or lower prices for locally produced products, as opposed to imported products.

In this paper, we present results of a systematic literature review, summarizing existing theoretical and empirical work on LP of pharmaceutical products in LMICs, and its potential impact on access to medicines in LMICs. We assess to what extent the linkages between LP and access to medical products are explored in such studies; critically analyze whether the methods employed in the literature are sufficient to suggest a robust relationship between local production and access; and evaluate whether results obtained could be directly applied to local production conditions in developing and least developed country contexts.

Methodology

What do we mean by "local production"?

It is important to define what we understand by the term local production. Some "local" manufacturers are subsidiaries of multinational corporations (MNCs) and some are locally owned small-scale manufacturers serving a portion of the domestic market¹⁹. We use a jurisdictional, not an ownership definition. If production takes place in-country to produce biomedical products, this is "local production". For pharmaceuticals, "production" can be primary (manufacture of active pharmaceutical ingredients (APIs) and intermediates from basic substances), secondary (production of finished dosage forms from raw materials and excipients or tertiary (packaging and

labelling finished products or repackaging finished products). For vaccines, technology is specific for each inactivated or live attenuated vaccine product and may include isolating viral particles, producing "seed" viruses, bulk manufacture, and assembling polyvalent vaccines. For medical devices, the "device" component can be simple to complex, e.g. a bed to a Magnetic Resonance Imagery (MRI) machine²⁰.

What are "low- and middle- income" countries?

United Nations categorizations provide no established convention for the designation of "developed" and "developing" countries. The World Bank classifies countries according to income and this does not necessarily reflect development status. Significantly, all the World Bank low- and middle-income countries are considered to be "developing" under the United Nations classification.

For this review, we classify LMICs according to the widely used World Bank system²¹ which divides countries according to 2009 Gross National Income (GNI) per capita (calculated using the World Bank Atlas method): low income, \$995 or less ; lower-middle income, \$996 – \$3,945; upper-middle income, \$3,946 – \$12,195. All other countries according to the World Bank scheme, are considered "developed"/high income countries (GNI per capita \$12,196 or more. Middle-income countries such as Brazil, India, Mexico, South Africa and Taiwan have been called "emerging markets" using other classification systems.

What is "access to medicines"?

In the context of local production, "access" includes: (a) lower prices (thus greater affordability); (b) greater availability through the presence of locally made products and local distribution networks. In principle, these penetrate rural markets better than MNC produced products; (c) local adaptation of existing products by local firms through incremental innovation efforts; (d) new forms of innovative medicines and products developed locally and tailored to the local population(s).

Search strategies

The primary objective of this review was to identify operational or implementation/analytical studies identifying empirically robust links between LP and access to biomedical products in LMICs. The kind of robust evidence that would satisfy our primary objectives can be summarized in Table 1.

We based our literature search strategy on a single working hypothesis: studies showing a robust relationship between LP and access to medical products are sparse or even non-existent.

Issues related to local production of medical products are often unlikely to be labelled as such, since "local production" is not a common term in academic research. Because of its cross-cutting nature, the "local production" literature is likely scattered in writings on innovation capacity, science and technology, industrial and pharmaceutical policy, intellectual property analysis and sometimes, health economics.

Table 1. Criteria for robust evidence regarding LP and access

Criteria	Explanation
Study objective	Define the relationship between LP and 'access' to biomedical products (medicines and/or diagnostics)
Study design	Interrupted time series analysis, and/or Repeated measures studies, and/or Controlled or uncontrolled before (-LP) and after (+LP) studies and/or One-time descriptive comparisons of local and foreign-made products.
Study sites	Low and middle income countries Public and/or private health care institutions and/or pharmaceutical retail sector and/or public or private biomedical manufacturing site(s)
Preferred Study outcomes	Demonstrating a causal or strongly inferential link between LP of a medical product and improved/modified/enhanced access to that product

We carried out a literature search using key words and their synonyms, “local, national, regional, domestic” and “production, manufacturing” and “pharmaceutical, medicine, diagnostic” in various combinations and searched in the title and/or abstract. Each database, however, has a unique set of keywords and search terms. This is why the search terms vary among the various databases, although the overall strategy remains the same (See Appendix 1). Specifically, MeSH terms were used for PUBMED and major subject headings used for EMBASE, CSA/PAIS, and POPLINE. The search strategies were meant to capture both “high income” countries (e.g., U.S., Europe, Canada, Japan, New Zealand, Australia and the like) and “low- and middle- income” countries. In addition, there is a large amount of literature comparing MNCs and local producers in various countries with regard to finances, Foreign Direct Investment (FDI), and labour productivity that spans across sectors. “Local production” is not an economic term, so a further search was done for literature on comparative economics between domestic and foreign manufacturers in terms of business performance. The databases were searched using combinations of terms such as “comparison, foreign, multinational, domestic, local, performance, price, pharmaceutical, emerging market”. PUBMED search terms are in Appendix 1.

The specific databases used were: AfricaWide Information, PUBMED (including the “Health Services” Subcategory, CINAHL, EMBASE, Thomson Reuters (formerly ISI) Web of Science, EconLit, CSA International Bibliography of Social Science, International Network of Rational Use of Medicines (INRUD), PAIS International, POPLINE (One Source), and Google Scholar®. References from PUBMED (including the “Health Services” Subcategory, CINAHL, EMBASE, Thomson Reuters (formerly ISI) Web of Science, EconLit, CSA International Bibliography of Social Science, PAIS International, and POPLINE were placed in EndNote® bibliographic software files. We reviewed these

EndNote® files and searched within all articles with abstracts for terms “local, national, regional, domestic” and “production, manufacturing” and “pharmaceutical, medicine, diagnostic” in various combinations. We read each of the resulting abstracts or full-length articles (if available) and then applied the “screening” criteria of Table 1.

To search for so-called gray literature, we reviewed the following websites and any associated databases for literature dealing with both local production and access: OECD, the World Bank, the World Health Organization (WHO), Pan American Health Organization (PAHO), the Medicines Transparency Alliance (MeTA), UNIDO/GTZ, UNDP, LEXISNEXIS, e-medicine archives, Google®, Google Scholar®. We then applied the “screening” criteria of Table 1 to the result.

For the Google® searches, we also looked for specific countries: Argentina, Ghana, Nigeria, Brazil, Egypt, Jordan, South Africa, Thailand, Bangladesh, Philippines, Tanzania, Mexico, and India. We reviewed all articles up to the first 20 “hits”. The most relevant of the first 20 articles (based on whether it was concerned with both local production and access) were then searched for all hyperlinked “related articles”. We repeated this search twice, once for “medicines” and again for “diagnostics” (See Appendix 2). For all Google® based searches that were not country specific, the total number of initial “hits” was enormous so we limited ourselves to reviewing the first 100 references and applied the screening criteria of Table 1.

Results

We found a total of 154 relevant references and based on the Table 1 screening tool, we narrowed this down to a total of 20 (See Tables 2-4). See Appendix 1 and Appendix 2 for more information on search terms for these references.

We have identified two themes of the literature that are relevant:

1. The business and economics literature on the comparative economics and strategic planning of multinational and domestic firms. Of this literature, there are few references on emerging markets or LMICs and even fewer with regard to comparing local and MNC pharmaceutical producers.
2. The sparse and descriptive literature on the benefits of local production.

Theme 1: Comparing the “behavior” of domestic and foreign producers (MNCs) in-country

There is an extensive literature showing that MNCs and local firms are different, based on the fact that MNCs are relatively more intensive in research and development (R&D) and advertising assets than non-MNCs²²⁻²⁵. The theoretical literature attempts to explain the existence of MNCs in foreign markets when they are at a disadvantage relative to local firms with respect to knowledge of domestic markets. Theories focus on explaining

Table 2. Summary of literature on comparative behavior of MNCs and local pharmaceutical/chemical producers

Country	Analytical Method	Conclusion(s)	Reference
Turkey	Surveys	Comparison of the product structure of MNCs and that of local firms. No significant difference between them in terms of the products that they produce and market. The author could NOT conclude that the presence of local firms in the Turkish pharmaceutical industry had been beneficial because; "...all the negative aspects of pharmaceutical production and exchange which the critics have attributed solely to MNCs have been similarly reproduced by local firms in the pharmaceutical industry in Turkey." Local firms and MNCs were equally involved in overpricing activities. The available evidence indicated that MNCs overpriced to an even higher extent than local firms.	(26)
India	Firm-level data from National Statistics Office: Econometric study	Domestic firms, most of which are controlled by family based structures, enjoy higher efficiencies (operating profit margins, net profit margins, fixed asset turnover, working capital, inventory holding period, and many others) than affiliates of MNCs	(27)
Bangladesh	Stock exchange data/Econometric study	Domestic production's cost advantage over large MNCs gives local products a price advantage. MNCs have more advantageous infrastructures, technology, finances and administration	(28)

how MNCs overcome these disadvantages by possessing proprietary, knowledge-based and generally intangible assets related to production techniques and processes, marketing networks and/or management ability.

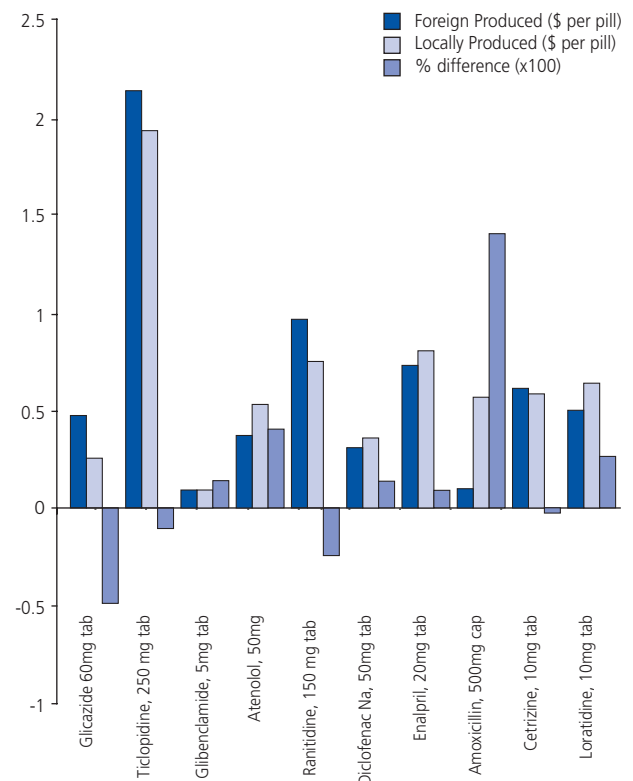
We have identified literature on the comparative behavior of MNCs and local pharmaceutical and chemical producers (Table 2). The study on India is not directed at "access" specifically but at structural and functional properties of domestic firms versus MNCs²⁷. The comparative study on Bangladesh asserts that local producers have a distinct cost advantage over MNCs but there is no data in the paper to support this²⁸.

Theme 2: Benefits of local production of medical products:

Competitive costing. In principle, a dedicated local production facility could be competitive against the lowest cost international producers on the basis of improved process technology, continuous (as opposed to batch) processing, and better economies of scale. The extent of the cost saving depends on which products are being manufactured and what processing steps are required. Table 3 summarizes the evidence gathered from our review on this topic.

Figure 1 (opposite) is adapted from Table 1 of reference 33. The solid dark blue bars show the average price of the listed foreign-produced generic medicines (\$ per pill: Y axis) of Germany, Cyprus, India, Canada, Italy, and the bars to their right are the average price (\$ per pill: Y axis) of the Malaysian generic counterpart. The light blue bars are the percentage (x100) difference in price between the foreign and locally-produced generics. The foreign generic version was more expensive than the locally-produced generic version in just 4 of the 10 medicines (glicazide 60 mg, ticlopidine 250 mg, ranitidine 150

Figure 1.



Notes: % difference in price between foreign (F) and local producer (LP) = (difference in price between the average of the F prices and the average of the LP prices)/ average value of the all F and LP prices) X 100.

mg and cetirizine 10mg). The locally-produced generic versions of atenolol, loratidine and amoxicillin were significantly more expensive than the foreign-produced versions.

Reliability of supply. Local production in-country would improve security of supply and extend procurement options,

Table 3. Summary of literature on cost of locally produced and imported medicines

Country	Analytical Method	Conclusion(s)	Reference
Tanzania	Survey	Nearly half (46%) of various tracer medicines were locally made; only injectable, some chronic illness medicines, and one antibiotic were solely available as imports. No significant differences existed between prices of medicines from the three main countries of origin (India, Kenya, Tanzania), suggesting competitive pricing with no apparent advantage given to the Tanzanian products	(29) (39)
Tanzania	Survey	Local production supplies approximately 30% of private and public markets. Various "tracer medicines" were widely available in shops and non-government facilities. Of these medicines, 66% were locally made (compare the 46% figure cited above by ref. 30) and "...few significant price differentials by country of origin for the most widely distributed medicines among ... tracer drugs".	(30)
Brazil	Time series	As of 2006, prices for Brazil's locally produced generics were generally much higher than corresponding global prices. These prices have risen in Brazil while declining globally. The estimated "excess" costs of Brazil's locally produced generics totaled US\$110 million from 2001 to 2005.	(31)
Various sub-Saharan African countries	Economic modeling	Domestic production of a variety of medicines may have a "modest" impact on medicine affordability. "Modest", defined as between a 1-26% reduction in <i>ex works</i> price. This price reduction was found to be very sensitive to increase in API prices or a loss of (or failure to reach) market share and this could "easily" negate price reductions.	(7)
India	Economic modeling ⁱ	"Significant" additional expenditure that the representative Indian consumer would need to incur in the face of the domestic product withdrawal(s) and assumed to be an impact on "access" due to "...differences in the marketing and distribution networks, domestic products being more readily available to Indian consumers than products produced by foreign subsidiaries." In absolute terms, without any price regulation, the prices of foreign patented products would rise between 100% and 400% when local production ceased.	(32)
Malaysia	Survey	Some local generics were more expensive than imported generic medicines. Retail markups for both were assumed identical and local producers may not be "efficiently producing affordable medicines" and are passing the high costs on to the consumer (See Figure 1, below).	(33)
Bangladesh	Survey	Pricing differentiation of 35 essential medicines between local producers and multinational pharmaceutical companies showed that only two products (Aspirin 300 mg, Chlorpromazine 25 mg) out of 35 essential medicine products had locally-produced unit prices higher than the corresponding MNC products. The prices of various locally produced dosages of ibuprofen and paracetamol were only slightly less than the MNC versions. The majority of locally produced anti-infectives were less expensive than their MNC counterparts. Five essential medicine products for chronic conditions (Atenolol 50 mg, Glibenclamide, Amitriptyline, Griseofulvin and Salbutamol) had exactly the same prices for locally produced and MNC-produced.	(34)
Vietnam	Survey	Locally produced HIV/AIDS medicines I (anti-retrovirals: ARVs) are priced considerably lower than imported ARVs currently on the Vietnamese market, but they are five to seven times higher than the current best offer on the international market.	(35)
Vietnam	Survey	Locally produced drugs are "less expensive than those imported from the West, Malaysia and Thailand" but this statement is not supported by any data.	(36)
Palestine	Survey	Although only at a single Palestinian pharmacy, locally produced pharmaceuticals were significantly cheaper than their foreign counterparts.	(37)
Palestine	Survey	Analysis of 34 single and 6 combination antibiotic preparations of local and foreign firms (including those marketed by Israel) showed that in all cases the "... price difference was in favor of the locally manufactured products, as all the prices of local antibiotics are less than imported ones." (no data presented)	(38)

ⁱThe basic counterfactual scenarios all involve the withdrawal of one or more of the locally produced product groups from the market in the face of patent protection. The idea is that if patents for, e.g., ciprofloxacin, had been recognized in India, not all domestic products containing ciprofloxacin would be present in the market. That would leave only the foreign ciprofloxacin product group in the market.

although proving this empirically would be difficult. In Tanzania, the government procurement agency obtains supplies through one large annual tender³⁹. (See Table 4)

Improved quality standards. In principle, local production with regular surveillance on quality control issues in conjunction

with health authorities could lead to improved quality standards without compromising on cost (See Table 4).

Foreign import savings. Local production may, to an extent, offset the very large import deficit and foreign exchange exposure that is almost inevitable for some medicines that are

Table 4. Summary of literature on presumed benefits of local production of medical products

Potential Benefit of LP	Country	Analytical Method	Conclusion(s)	Reference
Reliable supply	Tanzania	Survey	In Tanzania, there are several competing supply chains: 1. Delivery chain of mostly ARV and Tuberculosis (TB) medicines from only international firms to facilities treating free at point of use. 2. Supply chain from local firms and Indian importers to public/NGO facilities for out-of-pocket payment. 3. Private market without a controlled supply chain, selling both subsidized imports and local and imported commercial supplies. The ARV/TB supply chain excludes local suppliers. The supply chain for public/NGO facilities tends to encourage local suppliers, and could lead to "...upgrading of local industrial capabilities and employment", although the validity of this assertion was not analyzed.	(40)
Improved quality standards	Seven African countries	Survey/chemical analyses of a pilot study to assess the quality of chloroquine syrup (CQS) or tablets (CQT)	There were quality failures of 56% (27/48) among locally made products, compared to 47.2% (17/36) for foreign products for CQT active ingredient content, and 28% (7/25) versus 13% (3/23) for CQS active ingredient content.	(41)
	Kenya	Cross-sectional laboratory analysis and survey of pharmaceutical companies in Nairobi	Private pharmacies stocked few of the locally manufactured products due to "low doctor and/or patient acceptance." Varying factors contributed to poor availability and acceptability of some locally manufactured products in Kenya.	(42)
Developing innovation capacity	Uganda	Survey; case studies	Ugandan pharmaceutical companies upgraded their technology by a combination of upstream vertical linkages to suppliers, their existing linkages downstream in the chain as importers and retailers of pharmaceuticals for the domestic market, and by the government policies. The Ugandan companies have upgraded by importing finished technologies and knowledge, not by learning production methods. Production is at a low level technologically and has not increased the companies' technological capabilities.	(43)
Developing human capital	Tanzania	Survey of a single company whose staff comprised mainly of Indian and British expatriates	Tanzanian staff was in the minority and that this was "... a major problem." The company would prefer to employ Tanzanian staff, but the competency needed for pharmaceutical production is simply not available in the country. In total the company employs 800 people in Tanzania. The Tanzanian employees are unskilled and work in the packaging area, whereas the Indian and British staff is skilled.	(12)

produced primarily by MNCs (e.g., ARVs). We could find no literature fitting our criteria to support this for LMICs.

Development of further innovation capacity. Many policy makers in LMICs have competed rigorously in attracting foreign direct investment (FDI). A common justification for this incentive-based competition is the argument that FDI provides not only capital and additional employment but also new knowledge to recipient economies. In LMICs, dependence on foreign production explains the large number of studies emphasizing the importance of accessing and absorbing international knowledge for acquiring competitiveness and fostering economic growth in these countries, and in particular the important role that international knowledge spillovers could play in that process. The literature is vast⁴⁴. See Table 4 for the evidence supporting the role of local production as a means of furthering innovation in medical products.

Creation of enhanced export capacity. In principle, a local producer could also become a significant exporter. Although the

initial intention of a 'local producer' is most likely to develop as a local supplier of a highly strategic or niche product, ultimately this could assist in building a regional production capacity which would benefit, for instance, the entire African continent. From a macroeconomic view, this may help improve any trade imbalance. But this will also depend on the products themselves, their patent cover and the scope of any voluntary license agreements which may cover patented products. We found no direct evidence fitting our criteria to support the link between LP and increased exports e.g. Sub-Saharan Africa (see Table 1).

Development of human capital. Most of the essential skills for a successful biomedicine manufacturing sector may already be well developed in certain countries (e.g., India, Thailand, South Africa) within academic institutions (organic chemistry, chemical engineering, mechanical engineering, pharmacology, etc). At the same time, it may be that experienced local professionals with knowledge of pharmaceutical manufacturing within an industrial environment are very limited (See Table 4).

Discussion

Absence of evidence is not evidence of absence. There are surely observable links between local production and access to medical products in LMICs. We infer from the literature that the link between local production and price, if such a link exists, should be observable and measurable. Further, the link between local production and accessibility should be similarly observable. Nonetheless, we have not seen rigorous evidence for either of these links in the literature we have reviewed. In short, the direct evidence in LMICs is too weak to answer the question of whether or not local production of medical products has a salutary effect on the resulting access to these products. There is a preponderance of case studies and descriptive surveys. Two key points emerge from this work.

- The vast majority of pricing surveys observed do not distinguish the price of “local” versus “foreign” producers on a product-by-product basis. An important first step in development of this literature would be if even a few of the comprehensive analyses of price, accessibility and affordability performed by the WHO and Health Action International (HAI) were repeated using distinctions between local- and foreign-made identical products⁴⁵⁻⁴⁹.
- There is an almost complete absence of rigorous information on the link between LP and access to medical devices. Modern technology is producing an abundance of medical devices at a rate that soon makes the latest device obsolete. Furthermore, there is an extreme diversity in the medical device arena in terms of types of devices, degrees of complexity, applications, usage, users and categories. Just as with pharmaceuticals, research in medical devices can be mismatched with actual public health needs. Furthermore, almost all medical devices present in developing countries have been designed for use in industrialized countries. Whether or not local production of medical devices can contribute to improved access to devices is an open question.

In retrospect, there are several reasonable explanations for the apparent lack of published evidence in general. First and foremost, many of the complexities of investigating the link between LP and access to medical products are simply not susceptible to formal academic analysis. For the most part in many LMICs, relevant data sets are limited and are of doubtful quality¹⁰. While there is excellent long term data primarily compiled by international pharmaceutical market research audit companies, beyond the OECD such data is sparse¹⁰.

Second, the relationship between LP and access to medical products is extremely dynamic. The literature provides a retrospective view but the business of developing policy, of technology transfer and of manufacturing a product for market

will not wait for academicsⁱ. The most useful information may indeed be available directly in-country and in real time.

Third, notwithstanding some national policies in LMICs that support local production, “access to medicines” is not the primary reason for building a local factory. At present, the business and industry pressures to build a local producer in an LMIC will still render health policy concerns of secondary importance. It could be that links between LP and access have not been explored because it is harder to make access a particular concern for an individual firm, and at the collective level, accountability is hard to enforce (since it cannot be broken up for each and every firm)ⁱⁱ.

We cannot state unequivocally that the references found here are the only potentially useful and reliable sources of information on this subject. Although we attempted to create a systematic search strategy, one could certainly find additional documents using a less efficient free form search. It is almost certainly true that this search strategy has not covered the entire literature, given its cross-cutting nature. However, what is presented here covers sufficient ground to serve as a starting point. In our view, we can say with confidence that while some details have been missed in our search strategy, overall, this is the general sense of the literature at the present time.

Going further, if we are going create a more robust evidentiary framework for the linkage between LP and “access”, we need better monitoring and evaluation. In principle, it is possible to create longitudinal data or cross-sectional time series data, where the same subjects (e.g., several local and MNC producers) are observed at multiple time periods. One can imagine a nationally representative sample of local producers and /or MNC subsidiaries and/or a sample of pharmacies, clinics and the like, each member of the panel being surveyed repeatedly over multiple years for various phenomena. Realistically, there is likely to be very poor access to firm- and/or plant-level data. The lack of good data may make it impossible to sort out the various influences that are involved over time. For example, one might observe in a region dominated by local producers a time series that shows higher prices than an adjacent “control” region dominated by MNC producers, this may result from the fact that foreign MNCs are more capital and technology intensive and that this price difference would disappear if differences in capital intensity could be controlled for.

An interrupted time series may be useful in studying the linkage between LP and access⁵⁰⁻⁵¹. In this analysis, the effect of an intervention on an outcome variable can assume a variety of forms over time. In this case, the intervention is made by someone other than the researcher and it is not normally made for experimental purposes and would be considered a natural experiment. If available, one creates a time series beginning

ⁱ The dynamic nature of this can be illustrated by the United States. Medicine shortages in the United States have been growing in number, driven by many factors such as shortage of raw materials, manufacturing delays, business decisions to manufacture another product, a tendency by hospitals and wholesalers to order medicines on demand rather than stockpile supplies^{52, 53}.

ⁱⁱ We note, however, the Access to Medicines Index (<http://www.accessmedicinindex.org/>) which ranks 27 MNCs, comprising 20 originators and seven generics manufacturers. The ranking is based on 106 indicators that measure activities across four strategic and seven technical areas, including pricing, patenting and philanthropy.

from well before the intervention and continuing through and after it. For instance, prior to, during, and after a major financial investment and/or a policy change and/or a new factory going “on line”, one could look at: 1. product-by-product price comparisons of various local vs. MNC products; or 2. market share surveys of availability of local vs. MNC-produced generics/brand names on a product-by-product basis from the same sites; or 3. repeated surveys of patterns of medicine distribution of a suite of local producers vs. importers/in-country MNCs. The limiting factors are again the existence of data on medicine production, or price or access/affordability, volume market share and the like.

Conclusions

This appears to be the first such review of the literature that attempts to answer the question regarding the kinds of evidence linking LP and access to medical products. Our conclusions appear to support our preliminary working hypothesis that studies showing a robust relationship between LP and access to medical products are sparse at best.

Although “local production” is being actively pursued in many LMICs, the link between local production and access to medical products remains implicit in most cases. The extent to which local production for medical products and new investments in this area in developing countries are aligned with those countries’ public health needs is an important question and requires close examination and policy attention. Even if such policies are aligned, how can the link between local production and access to medicines be supported by good evidence? In this regard, we hope that this document contributes towards beginning an evidence-base linking industrial and health policy.

Authors’ contribution

WAK carried out the study, developed the search strategy, searched relevant databases, reviewed the literature and wrote the article. LSR and MV developed the search strategy, searched relevant databases, reviewed the literature and wrote an early draft of the abstract.

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Conflict of interest

The authors have declared that no conflict of interest exists.

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Appendix 1: Search terms used for databases and number of references identified

The search terms for PUBMED were as follows:

1. (domestic[All Fields] AND ("economics"[MeSH Terms] OR "economics"[All Fields] OR "production"[All Fields])) AND ("pharmacy"[MeSH Terms] OR "pharmacy"[All Fields] OR "pharmaceutical"[All Fields] OR "dosage forms"[MeSH Terms] OR ("dosage"[All Fields] AND "forms"[All Fields]) OR "dosage forms"[All Fields])
2. "medicine industry"[Mesh] AND "medicine"[Mesh]
3. (Medicine[ti] OR Pharmaceutical[ti] OR Diagnostic[ti] OR

"Medicines, Essential/supply and distribution"[MAJR]) OR "Medicines, Essential/economics"[MeSH Terms]) AND (Production[tiab] OR Manufacture[tiab]) AND (Local[tiab] OR regional[tiab] OR national[tiab] OR domestic[tiab]) NOT (("cells"[MeSH Terms] OR "cells"[All Fields] OR "cell"[All Fields]) NOT clinical[All Fields])

4. Limits – Humans

5. Search Terms to find "Developing Countries"

"Developing Countries"[Mesh] OR Africa[Mesh] or "Africa South of the Sahara"[Mesh] or Asia[Mesh] or "South America"[Mesh] or "Central America"[Mesh] OR Africa[tiab] or Asia[tiab] or "South America"[tiab] or "Latin America"[tiab] or "Central America"[tiab]

Database(s)	Search term key words for database(s)	Number of initial "hits"	Number relevant	Number after "screening"
LEXIS NEXIS	Local, production, pharmaceutical, medicine diagnostic	997	0	0
GOOGLE®/GOOGLE SCHOLAR®	Local, innovation, pharmaceutical, medicine, diagnostic, access	1000	51	0
AfricaWide Information	Local production pharmaceutical, medicine diagnostic	0		
CINAHL		0		
OECD	Local production	68	0	0
PUBMED	Drug Industry {MeSH} AND Medicine {MeSH}	2057	26	0
HEALTH SERVICES SUBSET OF PUBMED	Local production	4	0	0
POPLINE	medicine / pharmac* / diagnostic & production / manufacture	21	3	0
ECONLIT	medicine / pharmac* / diagnostic & production / manufacture	32	9	3
ECONLIT	Comparative AND (foreign OR multinational) AND (domestic OR local) AND performance OR price AND "pharmaceutical"	1127	27	6
CSA	Local production pharmaceutical medicine diagnostic	13	3	0
ISI Web of Knowledge	Local production pharmaceutical medicine diagnostic	429	8	2
CSA	Comparative AND (foreign OR multinational) AND (domestic OR local) AND performance OR price	818		
	Same as immediately above AND "pharmaceutical"	38	13	3

Local production of medical technologies

Database(s)	Search term key words for database(s)	Number of initial "hits"	Number relevant	Number after "screening"
BioOne Abstracts and Indexes	(local or domestic or national) and AB=production and AB=(pharmaceutic* or medicine or diagnostic)	12	3	0
PAIS International	local or domestic or national) and AB=production and AB=(pharmaceutic* or medicine or diagnostic)	12	6	0
Worldwide Political Science Abstracts	local or domestic or national) and AB=production and AB=(pharmaceutic* or medicine or diagnostic)	8	5	1
International Bibliography of the Social Sciences	AB=(local or national or domestic) and AB=production and KW=(medicine or pharmaceu*)	22	0	0

AB= abstract; KW= keywords

Appendix 2: Search term used for Google Scholar® country specific searches

Database	Search term key words for database(s)
GOOGLE SCHOLAR® COUNTRY SPECIFIC	<p>I. Specific country AND pharmaceutical</p> <p>AND</p> <p>with the exact phrase: "production"</p> <p>AND</p> <p>with at least one of these words: "local domestic national regional diagnostic"</p> <p>II. Specific country AND diagnostic</p> <p>AND</p> <p>with the exact phrase: "production"</p> <p>AND</p> <p>with at least one of the words: "local domestic national regional pharmaceutical"</p>

Essential medicines for reproductive health: developing evidence based interagency list

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Abstract

Objectives: Although poor reproductive health constitutes a significant proportion of the disease burden in developing countries, essential medicines for reproductive health are often not available to the population. The objective was to analyze the guiding principles for developing national Essential Medicines Lists (EML). The second objective was to compare the reproductive health medicines included on these EMLs to the 2002 WHO/UNFPA list of essential drugs and commodities for reproductive health. Another objective was to compare the medicines included in existing international lists of medicines for reproductive health.

Methods: The authors calculated the average number of medicines per clinical groups included in 112 national EMLs and compared these average numbers with the number of medicines per clinical group included on the WHO/UNFPA List. Additionally, they compared the content of the lists of medicines for reproductive health developed by various international agencies.

Results: In 2003, the review of the 112 EMLs highlighted that medicines for reproductive health were not consistently included. The review of the international lists identified inconsistencies in their recommendations. The reviews' outcomes became the catalyst for collaboration among international agencies in the development of the first harmonized Interagency List of Essential Medicines for Reproductive Health. Additionally, WHO, UNFPA and PATH published guidelines to support the inclusion of essential medicines for reproductive health in national medicine policies and EMLs. The Interagency List became a key advocacy tool for countries to review their EMLs.

In 2009, a UNFPA/WHO assessment on access to reproductive health medicines in six countries demonstrated that the major challenge was that the Interagency List had not been updated recently and was inconsistently used.

Conclusion: The addition of cost-effective medicines for reproductive health to EMLs can result in enhanced equity in access to and cost containment of these medicines, and improve quality of care. Action is required to ensure their inclusion in national budget lines, supply chains, policies and programmatic guidance.

Keywords: Reproductive health, Essential medicines, World Health Organization, Interagency list

Introduction

In 1977, the World Health Organization (WHO) launched its first Model List of Essential Medicines ("the Model List"). The Model List was designed to prioritize the most important medicines from a public health perspective and was the centerpiece of a

strategy to enhance their availability, especially in developing countries. Essential medicines are selected on the basis of a set of guiding principles, which includes; a review of the latest evidence of safety and efficacy of a particular treatment for the most common diseases in a given country, and summarizing the recommended use in a standard treatment guideline¹. They are

a critical tool for improving and maintaining health, as essential medicines lists (EMLs) give priority status to medicines that address a country's most pressing public health problems whilst taking into account the cost component of the treatment. After immunization for common childhood illnesses, appropriate use of essential medicines is one of the most cost-effective components of modern health care². For almost three decades, WHO has devoted substantial effort to support essential medicines programmes that seek to improve access to the most needed medicines.

Reproductive and sexual health problems, such as early and unwanted childbearing, HIV infection, sexual transmitted infections (STIs), and pregnancy-related illness and death account for a significant part of the disease burden among adolescents and adults in developing countries³. Reproductive and sexual ill-health (maternal and perinatal mortality and morbidity, cancers, STIs and AIDS) account for nearly 20 per cent of the global burden of ill-health for women of reproductive age and some 14% for men^{4,5}. These statistics do not capture the full burden of ill-health, however. Gender-based violence, gynaecological conditions such as severe menstrual problems, urinary and faecal incontinence due to obstetric fistulae, uterine prolapse, pregnancy loss, and sexual dysfunction – all are currently underestimated in present global burden of disease estimates. In poor resource settings, WHO estimates unsafe sex to be the second most important global risk factor to health^{6,7}.

Essential medicines for reproductive health include medicines to ensure healthy pregnancy and delivery, contraceptives and medicines for prevention and treatment of STIs and HIV/AIDS. Although poor reproductive health constitutes a significant proportion of the disease burden in developing countries, essential medicines for reproductive health often are not available to the majority of the population. A survey estimated that some 210 million couples at risk of unintended pregnancy who would like to space or limit their births are not using modern contraception to do so^{4,8}. In 2005, WHO estimated that globally there were 448 million new cases of the four sexually transmitted infections: *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, syphilis and *Trichomonas vaginalis*, in adults between the ages of 15 and 49⁹. Lack of access to medicines including contraceptives threatens the well-being of individuals, families, and communities. In 2000, in response to a growing need for access to reproductive health medicines, United Nations Population Fund (UNFPA) and its partners presented a strategic approach called A Global Strategy for Reproductive Health Commodity Security (RHCS). The strategy draws largely on the experience of implementation of the essential medicines concept and national medicine policy approach introduced by WHO in the 1970s¹⁰.

One of the goals agreed at the International Conference on Population and Development was to achieve universal access to reproductive health by 2015^{8,11}. In 2003, WHO Department of Medicines Policy and Standards (WHO/PSM) in collaboration with WHO Department of Reproductive Health and Research (WHO/RHR) reviewed 55 national medicine policies and 112

national Essential Medicines Lists (EMLs) of WHO member countries to determine the degree to which they facilitate access to reproductive health medicines¹².

The WHO framework for access to essential medicines addresses factors that ensure evidence based selection of medicines, sustainable financing and affordability and reliable supply chains that deliver quality products. Hence, the first step in improving access to essential medicines for reproductive health would be to ensure that these items are included in national medicine policies and essential medicine lists, and in equitable financing mechanisms and budget lines².

Hence, the study objectives were to analyze the guiding principles and procedures for developing each national EML as defined in the national medicine policy. Another objective was to compare the selection of reproductive health medicines included on these national EMLs to the 2002 draft WHO/UNFPA list of essential drugs and other commodities for reproductive health services (called "the UNFPA List")¹³. The third objective was to compare the medicines included in existing international lists of medicines for reproductive health.

Methodology

The authors collected 112 national Essential Medicines Lists and calculated the average number of medicines for each of the following clinical groups: reproductive and maternal health, family planning, sexually transmitted infections (STI)/reproductive tract infections (RTI) and HIV/AIDS and compared these average numbers of medicines with the number of medicines per clinical group included on the UNFPA List. Additionally, the authors compared the content of the lists of medicines for reproductive health developed by various United Nations (UN) agencies involved in reproductive health programmes. This review conducted in 2003 compared the content of the following lists: (1) the 13th WHO Model List of Essential Medicines, 2003 ("the 13th Model List")¹⁴, (2) the draft WHO/UNFPA List of Essential Drugs and Commodities for Reproductive Health Services, 2002 ("the UNFPA List")¹³ and (3) the Draft Interagency UNFPA/UNAIDS/WHO Reproductive Health Medicines and Commodities List, 2002 ("the Interagency List").

Results

The findings of the study highlighted that although the national medicine policies in those countries allowed for evidence based selection of medicines for the development of a national EML, essential medicines for reproductive health were not consistently included in national EMLs, even when strong evidence for their effectiveness existed. For example, magnesium sulfate is a cost-effective medicine for preventing pre-eclampsia and treating eclampsia, one of the leading causes of maternal morbidity and mortality¹⁵. Approximately 3.2% of all pregnancies are affected, resulting in more than 63,000 maternal deaths worldwide each year.¹⁶ Yet magnesium sulfate was included in only 45 (40%) national EMLs reviewed. Table 1 compares the

Table 1. Comparison between the average number of reproductive health medicines included in 112 national Essential Medicines Lists (EMLs) and the 2002 draft WHO/UNFPA list of essential drugs and other commodities for reproductive health services, 2003

	Number of medicines in the 2002 draft WHO/UNFPA list	Average number of medicines listed in 112 national EMLs
Reproductive and maternal health (eg., antihypertensives, oxytocics, antimalarial)	111	75
Family planning (hormonal contraceptives and condoms)	9	3
STI/ RTI medicines (antibiotics and antifungals)	22	12
HIV/AIDS medicines (ARVs and OI medicines)	27	5

number of medicines per clinical groups included on the UNFPA list with the average number of medicines found on national EMLs. On average, only three out of nine family planning methods surveyedⁱ could be found in the EMLs reviewed. Zidovudine, an essential antiretroviral, part of the nucleoside reverse transcriptase inhibitors, was included in only 19 (17%) of national EMLs. Condoms, an important barrier method in preventing unwanted pregnancy and the primary method for preventing transmission of STIs, including HIV, were listed in only 31(35%) of national EMLs. Out of 22 STI/RTI medicines and 27 HIV/AIDS medicines surveyed, only 12 (55%) and five (18%) respectively, were found on the EMLs reviewed¹².

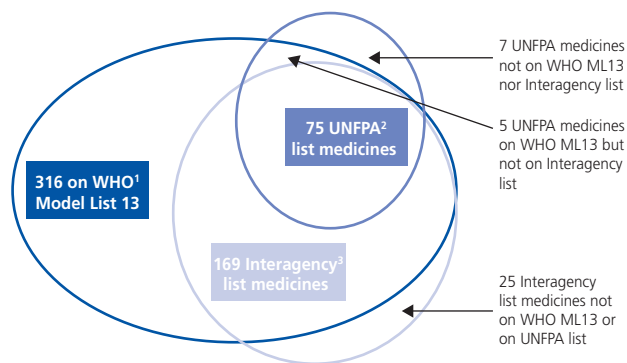
The review of the international lists identified various inconsistencies, as reported in Figure 1. Thirty seven medicines were included in either one or two lists but not in all three. The Interagency List included 25 medicines that were not on the 13th Model List or on the UNFPA List. The UNFPA List included seven medicines that were not on the 13th Model List or on the Interagency List.

Discussion

The inconsistent inclusion of effective essential medicines for reproductive health in the national EMLs surveyed acted as a barrier to the access to life-saving medicines in those countries. Discrepancies among international lists not only posed a serious barrier to variation in supply, but had the potential to lead to inconsistent technical assistance in recipient countries. The outcome of the two reviews became the catalyst for collaboration among key international agencies in the development of a harmonized evidence based interagency

ⁱ Low-dose combined pills, progestin-only pills, spermicides, contraceptive foams/gels, medroxyprogesterone acetate (depot injection), copper intrauterine device, condoms, and diaphragms.

Figure 1. Distribution of 37 discrepancy medicines identified in international lists of medicines for reproductive health, 2003



¹The 13th WHO Model List of Essential Medicines
²Draft WHO/UNFPA List of essential drugs and other commodities for reproductive health services
³Draft interagency UNFPA/UNAIDS/WHO Reproductive Health Medicines List

list of essential medicines for reproductive health that is fully aligned with the WHO Model List.

Development of a harmonized Interagency List of Essential Medicines for Reproductive Health

Between 2003 and 2004, three interagency consultationsⁱⁱ on the selection and delivery of essential medicines and commodities for reproductive health were convened to discuss the findings of the comparative review of the lists, including identified discrepancies in medicine selection. All parties agreed that, as a prerequisite, the harmonized Interagency List of Essential Medicines for Reproductive Health would be a subset of the latest WHO Model List. Following evidence-based reports on the discrepancy medicines, the interagency working group decided to (1) delete nine medicines from all reproductive health medicine lists and guidelines and (2) prepare evidence-based applications for 14 medicines for inclusion in the 14th WHO Model List of Essential Medicines. Consequently, the interagency working group commissioned systematic reviews of the evidence to prepare applications for inclusion on the WHO Model List. Applications were submitted to the WHO Expert Committee on the Selection and Use of Essential Medicines ("the Expert Committee") for review at its 14th meeting in March 2005 as detailed in Table 2.

In March 2005, the Expert Committee approved the five following reproductive health medicines submitted by the interagency working group: misoprostol, misoprostol and mifepristone, cefixime, clotrimazole and nifedipine as a tocolytic. Ten applications were rejected including four applications for new contraceptives due to lack of superior efficacy/safety in comparison to other contraceptives already on the WHO Model List.

ⁱⁱ Participating agencies included: John Snow International (JSI), Médecins Sans Frontières (MSF), PATH, United Nations Children's Fund (UNICEF), UNFPA, WHO.

Table 2. Medicines suggested for systematic review and applications for inclusion or retention in the 14th edition of the WHO Model List of Essential Medicines to the 14th WHO Expert Committee on the Selection and Use of Essential Medicines, March 2005

	UNFPA List 2002	Interagency list 2002	13th WHO Model List 2003	14th WHO Model List 2005
cefixime (only for gonorrhoea), capsule	-	x	-	x
clotrimazole, vaginal tablet or cream	x	x	-	x
ergometrine, injection	x	x	x	x
estradiol cypionate + medroxyprogesterone acetate, inj	x	-	-	-
estradiol valerate + norethisterone enantate, inj	x	-	-	-
labetolol, tablet	-	x	-	-
levonorgestrel-releasing IUDs	x	-	-	-
medroxyprogesterone acetate, tablet	-	x	x	x
mifepristone + misoprostol, tablet	-	x	-	x
misoprostol, vaginal tablet	-	x	-	x
nifedipine (as tocolytic), capsule	-	-	x	x
oxytocin UNIJECT delivery system	-	-	-	-
salbutamol, tablet (as tocolytic)	-	x	x	-
subdermal contraceptive implants	-	x	-	-

The Expert Committee declined to list several contraceptive medicines and recommended that contraceptives as a class should be reviewed and further (re)submissions should be made at the next revision of the list in 2007¹⁷.

The Expert Committee noted that the approach to provision of contraceptives for family planning was a philosophy of choice which requires a wide list of options. This philosophy is contrary to the Model List of Essential Medicines principles which identify the most appropriate generic medicine that addresses a specific priority health problem. As the provision of additional methods of contraception has an opportunity cost for health services generally, the Expert Committee recommended that in order to facilitate further consideration of contraceptive applications in the future, it would be important to undertake and present to the Expert Committee a systematic review of the evidence supporting the philosophy of informed choice.

Table 3. Contraceptives included in the 5th invitation to manufacturers of reproductive health products to submit an Expression of Interest (Eoi) for a product evaluation by the WHO Prequalification Programme, for the WHO Model List of Essential Medicines and in the WHO reproductive health guidelines, May 2010

Oral hormonal contraceptives
<ul style="list-style-type: none"> • ethinylestradiol + desogestrel, tablet 30 micrograms +150 micrograms • ethinylestradiol + levonorgestrel, tablet 30 micrograms + 150 micrograms • levonorgestrel, tablet 30 micrograms • levonorgestrel, tablet 750 micrograms (pack of two); 1.5 mg (pack of one) • norethisterone, tablet 350 micrograms • norgestrel, tablet 75 micrograms
Injectable hormonal contraceptives
<ul style="list-style-type: none"> • medroxyprogesterone acetate, depot injection 150 mg/ml, in 1-ml vial • medroxyprogesterone acetate + estradiol cyprionate, injection 25 mg + 5 mg • norethisterone enanthate, injection 200 mg • norethisterone enanthate + estradiol valerate, injection 50 mg + 5 mg
Implantable contraceptives
<ul style="list-style-type: none"> • two-rod levonorgestrel-releasing implant, each rod containing 75 mg of levonorgestrel (150 mg in total) • etonogestrel, implant, 68 mg of etonogestrel

Systematic review of contraceptive medicines “Does choice make a difference?”

As recommended by the 14th Expert Committee in 2005, a Cochrane systematic review^{18,19} of the literature was undertaken to examine whether a policy of providing a wide range of contraceptive methods, as opposed to the provision of a limited range, improves health outcomes such as contraceptive uptake, acceptability, adherence, continuation and satisfaction; reduction of unintended pregnancy; and improved maternal health and wellbeing. The results are presented as a hierarchy of evidence, with the cross-cutting concerns of meeting the needs of women through the stages of life, of particular groups (such as adolescents, those infected or at-risk of HIV or with medical conditions), and of those seeking to space birth or limit their families. In 2007, the 15th Expert Committee considered the conclusions of this review and confirmed that it will take an evidence-based approach to listing contraceptives. The Committee agreed to assess new products on a case-by-case basis using the accepted criteria of comparative efficacy, comparative safety and comparative cost, as well as suitability and acceptability¹⁸. Table 3 summarizes the contraceptives included in the 5th invitation to manufacturers of reproductive health products to submit an Expression of Interest (Eoi) for products evaluation to the WHO Prequalification Programme published in May 2010 on the basis of contraceptives included in the 16th WHO Model List published in March 2010^{20,21}.

Table 4. List of activities carried out to improve access to quality essential medicines for reproductive health following the development of the Interagency List of Essential Medicines in 2006

- Systematic review and preparation of submissions of the reproductive health essential medicines initially rejected by the WHO Expert Committee for inclusion on the 15th WHO Model List
- Systematic review of contraceptive medicines “Does choice make a difference?”
- Systematic review of the management of hypertension during pregnancy
- Review of WHO Standard Treatment Guidelines (STGs) for reproductive health. As an example, ketoconazole and itraconazole are two antifungals listed in WHO standard treatment guidelines. It has been suggested that both medicines be replaced with fluconazole, listed on the WHO Model List, on the basis of available evidence.
- Preparation of the review process of the interagency list. The review will occur every two years, subsequently to the review of the WHO Model List.
- Launch of a prequalification scheme by the WHO Prequalification Programme to support the procurement of a core list of reproductive health essential medicines.
- Harmonization of WHO and UNFPA prequalification scheme for male latex condoms and Copper T 308A inter-uterine devices of the WHO essential medicines.
- Preparation of an interagency list of essential medical devices for reproductive health as a tool to support planning for the selection, quality assurance and procurement of medical devices to implement the Maternal and Newborn Health (MNH) interventions.*
- Development of a procurement tool kit for reproductive health medicines by PATH and WHO and dissemination in countries

*Interagency list of essential medical devices for reproductive health, 2008. Document no. WHO/PSM/PAR/2008.1. Available at: <http://www.who.int/medicines/publications/MRfinalmedcaldevskhoct08.pdf>

Publication of the Interagency List of Essential Medicines for Reproductive Health

In 2006, WHO and UNFPA published the Interagency List of Essential Medicines for Reproductive Health (“the Interagency List”) as a subset of the 14th Model List^{22,23}. The Interagency List only included medicines from the 14th Model List relevant to reproductive health and contains 148 medicines. The Interagency List was officially endorsed by key partners involved in Reproductive Health programmes, including International Planned Parenthood Federation (IPPF), John Snow, Inc (JSI), Program for Appropriate Technology in Health (PATH), Population Services International (PSI), United Nations Population Fund (UNFPA), the World Bank and other members of the Reproductive Health Supplies Coalition (RHSC)²⁴. Once published, it became a key advocacy tool to (1) guide country decisions regarding what reproductive health essential medicines to include in their national EML, policies, guidelines and procurement budget lines and improve access to quality reproductive health essential medicines including a choice of contraceptives, (2) to guide international bulk procurement and support a core list of priority reproductive health essential medicines for inclusion in the WHO/UNFPA prequalification scheme for bulk procured essential medicines.

In addition, WHO/UNFPA/PATH published a guideline in 2006

to support the inclusion of essential medicines for reproductive health in national EMLs. The guideline includes 16 policy briefs providing a summary of the evidence for priority reproductive health essential medicines²⁵.

The guide presents background on the EML process and the importance of including reproductive health medicines on EMLs. It provides an overview of the process for including reproductive health medicines in national essential medicines lists based on the essential medicines concept. It is intended to be used by reproductive health programme managers, national-level essential medicines committees, and those responsible for selecting, procuring, and ensuring quality of reproductive health medicines.

As the United Nations Millennium Project notes, “expanding access to sexual and reproductive health services, including family planning and contraceptive information and services, and closing funding gaps for supplies and logistics are achievable priorities”²⁶. The development of an evidence-based list of essential medicines for reproductive health has led to a significant number of activities focused on supporting improved access to and use of quality reproductive health medicines in countries, as listed in Table 4.

In March 2009, the Expert Committee on the Selection and Use of Essential Medicines at its 17th meeting added misoprostol 200 micrograms tablet for management of incomplete abortion to the 16th WHO Model List. The evidence showed that misoprostol is as effective as surgery and in some settings, may be safer as well as cheaper²⁷. Recently, at its 18th meeting in March 2011, the Expert Committee made recommendations regarding additional reproductive health-related applications. First, after consideration to the evidence for safety and efficacy, the Committee decided to add misoprostol tablet, 200 micrograms to the list as prevention of postpartum hemorrhage in settings where oxytocin is not available or cannot be safely used. Second, the Committee recommended that the term ampoule be deleted from the right end column of the listing for oxytocin to allow consideration of other alternative oxytocin presentations²⁸. These evidence-based reviews of essential medicines for reproductive health by the Expert Committee should be translated more systematically into updated Interagency List to provide up to date information to national programmes. The cost of updating and regularly publishing the interagency list is justified, because it is reliable and could be used for to build reliable and evidence based information. This has also been described in the *WHO Progress Report 2010*²⁹.

In addition, UNFPA in collaboration with WHO undertook in 2008 and 2009, a rapid assessment of the current status of access to reproductive health essential medicines, particularly for maternal and newborn health care and reproductive health, in six countries. These countries were DPR Korea, Ethiopia, Laos, Nepal, Philippines and Mongolia³⁰. This assessment was designed to provide a snapshot of the current situation in the selected countries regarding the availability and use of the selected life-saving essential medicines. The six critical medicines chosen for these studies were selected because they are the WHO

recommended medicines for the prevention and management of three major causes of maternal mortality, as detailed in Table 5. As family planning has a considerable impact on reducing maternal mortality, the assessment included one temporary method of family planning, depo medroxyprogesterone acetate (DMPA) injections (three and one-month formulations).

The assessment was designed to not only develop a rapid assessment methodology, but also guide institutional support and capacity building in the area of reproductive health commodity security including improving access and quality assurance processes. The major challenge, as one of the key findings of the assessment, was that the Interagency List of Essential Medicines for Reproductive Health had not necessarily been updated for a long time and was inconsistently used. However the medicines were available but prone to incidences of stock outs and/or over supply. Standard treatment guidelines were not necessarily available and there existed knowledge to practice gaps. The rapid assessment also found challenges with regulation, quality assurance and storage condition. This shows the importance of linking the production of evidence-based guidance with strong, coordinated efforts to translate that guidance into practice. Without the concomitant level of political will, financial and technical support and effective coordination, the production of evidence-based guidance will not have the desired impact on improving the quality of health care, particularly reproductive health.

Conclusion

The reviews of national EMLs and international lists of medicines for reproductive health showed the lack of consistent inclusion of effective medicines for reproductive health in national lists and of harmonized technical guidance. The addition of reproductive health medicines to national EMLs can result in enhanced equity in access and can improve quality of care. Reproductive health experts must understand the national EML process and invest time and effort to bring about changes in national EMLs on the basis of the regularly updated Model List. Action is required to ensure that essential medicines for reproductive health, including contraceptives are incorporated into national budget lines, national procurement and logistics management systems, national policies, programmatic guidance and pre-service education.

Authors' contributions

SL who was the principle writer of the article has shared with SJ and MUP, the conception of the research. SJ, HM and MUP participated in the reviews, policy analysis and in the writing of the article. HM and KA managed all aspects of the review of status of access to a core set of reproductive health medicines in selected countries and provided comments on the writing of the article. MUP supervised all aspects of the reviews and of the writing.

Conflict of Interest:

The authors declare no conflict of interest.

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Pharmaceutical policies in European countries in response to the global financial crisis

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Abstract

Objective: The objective of this paper is to analyze which pharmaceutical policies European countries applied during the global financial crisis.

Methods: We undertook a survey with officials from public authorities for pharmaceutical pricing and reimbursement of 33 European countries represented in the PPRI (Pharmaceutical Pricing and Reimbursement Information) network based on a questionnaire. The survey was launched in September 2010 and repeated in February 2011 to obtain updated information.

Results: During the survey period from January 2010 to February 2011, 89 measures were identified in 23 of the 33 countries surveyed which were implemented to contain public medicines expenditure. Price reductions, changes in the co-payments, in the VAT rates on medicines and in the distribution margins were among the most common measures. More than a dozen countries reported measures under discussion or planned, for the remaining year 2011 and beyond. The largest number of measures were implemented in Iceland, the Baltic states (Estonia, Latvia, Lithuania), Greece, Spain and Portugal, which were hit by the crisis at different times.

Conclusions: Cost-containment has been an issue for high-income countries in Europe – no matter if hit by the crisis or not. In recent months, changes in pharmaceutical policies were reported from 23 European countries. Measures which can be implemented rather swiftly (e.g. price cuts, changes in co-payments and VAT rates on medicines) were among the most frequent measures. While the “crisis countries” (e.g. Baltic states, Greece, Spain) reacted with a bundle of measures, reforms in other countries (e.g. Poland, Germany) were not directly linked to the crisis, but also aimed at containing public spending. Since further reforms are under way, we recommend that the monitoring exercise is continued.

Keywords: medicines, Europe, global financial crisis, cost-containment, policy measures, pricing, reimbursement

Introduction

Pharmaceutical pricing and reimbursement systems in European countries differ from the ones in many countries the world over. This is due to the overall organisation and funding of health care in which the pharmaceutical systems are embedded. All countries have as part of their obligation to the fulfillment of the right to health, the obligation to grant access to essential medicines, i.e., medicines that fulfill the priority needs of their population¹⁻³. This is ensured in many countries outside of Europe by the provision of a range of selected medicines (i.e. essential medicines) in public sector facilities that are procured by the state. While eligible patients can access essential

medicines in the public sector either free of charge or with a modest co-payment, they have to purchase medicines “out-of-pocket” in the private sector⁴⁻⁷. In European countries, the distinction between the public and private sectors is not always clear (medicines are often supplied through private channels, but largely publicly funded). Further, the health service coverage, i.e., reimbursement of health expenditure by a social health insurance or a national health service, is in general more comprehensive compared to the rest of the world.

Pharmaceutical coverage usually includes for the majority of the medicines dispensed in hospitals and medicines prescribed by physicians but the scope of coverage varies⁸. Around 75% of

health expenditure and two thirds of pharmaceutical expenditure is on average covered by the public payers⁹. While marketing authorization has been harmonized in the EU¹⁰, pharmaceutical pricing and reimbursement remains the competence of the Member States. A key provision which all EU Member States have to comply with is the Transparency Directive¹¹, which aims at guaranteeing pricing and reimbursement decisions to be taken in a transparent way within specific time-frames. It is however up to individual countries as to how they organize their pharmaceutical pricing and reimbursement system. While there are a few policies commonly used in several European countries (e.g. external price referencing), the specific design of the policy measures differs in the details^{8,12-14}. As a result, there are 27 different pharmaceutical pricing and reimbursement systems in the EU^{9,15}.

Even though the countries in Europe, in particular in the EU, are mostly high-income countries, cost-containment of pharmaceutical expenditure and equitable access to medicines have been long-standing issues because of public sector spending limits. Since the 1990s, countries have been undertaking reforms with the aim of containing cost, in particular those costs borne by public payers¹⁶⁻¹⁷. On average, public pharmaceutical expenditure in the out-patient sector has increased in EU countries by 76 percent between 2000 and 2009 (median: 53 percent; lowest value: 21 percent; highest value: 243 percent), with a growth of 79% in the EU-15 (i.e. EU Member States before 2004 – in general, high income countries in Western, Northern and Southern Europe) and 71% in the EU-12 (i.e. “new” EU Member States which acceded on or after May 2004 to the EU; mainly Central and Eastern European countries).

The financial global crisis hit European countries from 2008 on. The first country affected in Europe was Iceland with the collapse of all three major banks in September 2008. Shortly afterwards the crisis hit the three Baltic states Estonia, Latvia and Lithuania. From early 2010 onwards the Eurozone countries (i.e. countries with the Euro as currency) of Greece, Spain, and Ireland were hit by a debt crisis. In 2011, the Greek crisis escalated, concerning mostly the refinancing of Greek public debts; and Greece, together with Portugal and recently Italy, appeared on the political agenda of the EU meeting in spring/summer 2011. These countries were urged to implement measures for budget savings.

The aim of this study was to explore that how the global financial crisis impacted the regulatory framework in the pharmaceutical sector in European countries. Another objective was to determine the type of pharmaceutical policies implemented over this time and in particular, those relating to pricing and reimbursement. However, an assessment of the impact of this policy implementation is beyond the scope of this paper.

Methodology

We collected information about pharmaceutical policies implemented by European countries via a survey conducted with the public authorities for pricing and reimbursement represented in the PPRI (Pharmaceutical Pricing and Reimbursement Information) network.

PPRI is a networking and information-sharing initiative on pharmaceutical policies from a public health perspective which emerged from a European Commission co-funded project under the same name¹⁸. At the time of writing, PPRI consisted of more than 60 institutions; mainly Medicines Agencies, Ministries of Health, and Social Insurance institutions, from 38 countries, thereof all 27 EU Member States, eight further European countries and three non-European countries, plus European and international institutions (European Commission services and agencies, OECD, WHO and World Bank)ⁱⁱ.

The reasons why we decided to survey the information via PPRI were three-fold: Firstly, we consider the PPRI representatives as the ideal agency to have access to this kind of information, since they are dealing with pricing and/or reimbursement decisions on a daily basis in the representative countries. Secondly, a common understanding of concepts and a shared language built on a joint terminology has developed among members¹⁹, and this provides a level of quality assurance. Thirdly, this study was initiated by PPRI network members who, in the light of changes due to the financial crisis, proposed in spring 2010 to regularly monitor the reforms in the national pharmaceutical systems.

To collect the information, we developed a questionnaire asking for specific measures in the field of pricing (price cuts, price reviews, margin changes, discounts/rebates, changes in value-added tax) and reimbursement (changes with regard to reimbursement lists, reimbursement rates, co-payments, reference price systems, reimbursement reviews) and changes in generic policies. The questionnaire explicitly asked to list further measures. The first round of this policy monitoring exercise was launched on 1st September 2010, and the questionnaire surveyed the period from January 2010 to September 2010 including a discussion on planned measures. The investigation was repeated on 2nd February 2011 in order to obtain updated data for the second half of 2010 and the beginning of 2011, with an outlook on the first half of the year 2011.

In both rounds, the questionnaires were sent to all 33 PPRI member countries. Although the same cohort of countries were included in both rounds of surveys, some countries participated in only one round: 20 countries, thereof 15 EU Member States, out of the total of 33 European countries which were at that time represented in PPRI responded to at least one of the surveys. Sixteen countries, of 11 EU Member States, participated in the first survey and 13 countries, thereof

ⁱ Data from the PHIS (Pharmaceutical Health Information System) database, accessed on 11 August 2011; further information regarding the methodology (data sources, limitations, etc.) see the PHIS database, publicly accessible at <http://phis.goeg.at> and <http://whocc.goeg.at> from October 2011 on.

ⁱⁱ It is PPRI's policy not to list the names of staff and officials of institutions represented. The institutions which are members of PPRI are listed on the PPRI website (<http://ppri.goeg.at>).

Table 1. Countries participating in the survey

European countries participating in PPRI *	Answered 1st round	Answered 2nd round	Provided further info. in review **	Supplementary research ***	Survey country of this study
European Union (EU) Member States					
Austria	Yes	Yes	No	No	Yes
Belgium	No	Yes	No	No	Yes
Bulgaria	No	No	No	No	Yes
Czech Republic	Yes	Yes	No	No	Yes
Cyprus	No	No	No	No	Yes
Denmark	Yes	Yes	Yes	No	Yes
Estonia	No	No	No	Yes	Yes
Finland	Yes	Yes	No	No	Yes
France	No	Yes	No	No	Yes
Germany	No	No	No	Yes	Yes
Greece	No	No	No	Yes	Yes
Hungary	No	No	No	No	Yes
Ireland	No	No	No	Yes	Yes
Italy	No	No	No	Yes	Yes
Latvia	No	Yes	No	Yes	Yes
Lithuania	Yes	No	No	Yes	Yes
Luxemburg	No	No	No	No	Yes
Malta	Yes	Yes	No	No	Yes
Netherlands	Yes	No	No	No	Yes
Poland	No	Yes	No	No	Yes
Portugal	Yes	Yes	Yes	No	Yes
Romania	Yes	No	No	No	Yes
Slovakia	No	No	No	Yes	Yes
Slovenia	No	No	No	No	Yes
Spain	Yes	No	Yes	Yes	Yes
Sweden	No	No	No	No	Yes
United Kingdom (UK)	Yes	Yes	Yes	No	Yes
Subtotal Yes / No	11 / 16	11 / 16	4 / 23	9 / 18	27 / 0

European countries participating in PPRI *	Answered 1st round	Answered 2nd round	Provided further info. in review **	Supplementary research ***	Survey country of this study
Further European, non- European Union (EU) member countries					
Albania	No	No	No	No	Yes
Croatia	Yes	No	No	No	Yes
Iceland	Yes	Yes	No	No	Yes
Norway	Yes	Yes	No	No	Yes
Switzerland	Yes	No	No	No	Yes
Turkey	Yes	No	No	No	Yes
Subtotal Yes / No	5 / 1	2 / 4	0 / 6	0 / 6	6 / 0
Total Yes / No	16 / 17	13 / 20	4 / 29	9 / 24	33 / 0

* As of September 2010 (i.e. start of the survey). Afterwards, two further countries (Republic of Serbia, and Macedonia) joined the PPRI network. The three non-European PPRI member countries (Canada, South Africa, South Korea) were disregarded for this study.

** Provided further information, clarifications and/or updates on their countries in the review of the draft article

*** Supplementary desk-top research (incl. grey literature and presentation provided by country representatives during meetings) and individual requests for information for those countries which were known to be strongly hit by the crisis but did not participate in (both rounds of) the survey

11 EU Member States, in the second round in February 2011. To ensure the highest possible level of information coverage, we undertook supplementary research, checking peer-reviewed and grey literature and considering information provided to us by country representatives in writing and through personal communications. In particular, we included information from presentations which country officials from Greece, Ireland, Spain and the three Baltic states (Estonia, Latvia, Lithuania) represented regarding their countries responses to the financial crisis. In a few cases, we contacted country representatives for updates and/or validation. Table 1 provides information about the involvement of the European PPRI countries in this study.

The survey was conducted from January 2010 to February 2011 with a discussion on planned measures. The rationale of having two rounds was to obtain updated information, as well as to receive information from those countries which had not participated in the first round. At the time of writing, a new round of the survey was being prepared which will be launched at the beginning of September 2011.

The terminology used in this paper is consistent with the PHIS (Pharmaceutical Health Information System) Glossary²⁰, which is the accepted terminology resource for pharmaceutical policy.

Data validation by the information providers was ensured in two ways: At the end of February 2011, a working paper summarizing all received information about policies was shared with the PPRI network members. Additionally, one of the authors (SV) presented the results during a network meeting in February 2011²¹. The authors informed the data providers about their intention to publish the information in this paper and shared a draft version with them.

Results

This paper provides an overview of the changes in response to the global financial crisis of pharmaceutical policies in the 27 EU Member States plus Croatia, Iceland, Norway, Switzerland and Turkey. From the beginning of 2010 to February 2011, 89 pharmaceutical policy measures were identified in 23 of the 33 countries surveyed. Fourteen countries reported measures under discussion or planned for the remainder of 2011 and beyond. Tables 2 and 3 provide an overview of the policy measures.

Policy interventions by type

Price reductions of pharmaceuticals were the most frequent cost-containment measure, which countries applied during the review period (a total of 15 price reductions in 11 countries).

The second most common measure was a change in co-payments, which constituted usually but not always an increase in cost for the patients (a total of 13 measures in nine countries, thereof increases in the prescription fee and higher co-payment due to the lower reimbursement rates). On eight occasions a policy change affected reimbursement lists and procedures (i.e. de-listings, introduction of a positive and/or negative list), and in 10 instances the reference price system (changes in the methodology allowing lower reference prices, broader clusters of similar medicines) and/or the pricing of generics in a cluster (“generic price link”) were observed. Generic promotion measures (e.g. making indicative INN prescribing mandatory, public awareness-raising campaigns) were among the most frequently mentioned measures in the category of “other measures”.

Table 2. Pharmaceutical pricing policy measures in 33 European countries in 2010 and 2011

Policy measure	Implemented			Planned / discussed
	1-6/2010	7-12/2010	1-2/2011	
Price reductions	<p>Czech Republic: price cut of 7% on reimbursable medicines</p> <p>UK: price cut of 1.9% on branded NHS medicines as part of 2009 PPRS</p> <p>Spain: price cut of 30% on generics</p> <p>Greece: quarterly price reviews followed by price cuts</p> <p>Ireland: price reductions on generics</p> <p>Lithuania: price cuts of 11% on non-reimbursable medicines</p> <p>Turkey: price cut under reference price on 20 years old medicines</p>	<p>Lithuania: price cut of 10% on reimbursable medicines</p> <p>Switzerland: implementation of price review into practice</p> <p>Portugal: price reduction for original medicines and for generics following annual price review</p> <p>Ireland: another price reduction on generics</p> <p>Germany: price freeze of reimbursable medicines</p>	<p>Czech Republic: price cut of 7% on non-revised medicines</p> <p>Ireland: price reductions on on-patent medicines</p> <p>Malta: price cuts in the private market</p>	<p>Iceland: price review of all medicines with predicted price cuts of 3%-5%</p> <p>Turkey: price cut on off-patent medicines under discussion</p>
Discounts, rebates, claw-backs/pack-back & other agreements	<p>Spain: 7.5% discounts on original medicines and 4% on orphans</p> <p>Romania: introduction of claw-back</p> <p>Lithuania: introduction of price notification for non-reimbursable medicines (before not regulated)</p>	<p>Estonia: introduction of price agreement also for 50% reimbursable medicines (before not regulated)</p> <p>Germany: increase in mandatory manufacturer's rebate to social health insurance (6% → 16%)</p> <p>Portugal: discount of 6% for reimbursable medicines</p> <p>Italy: choice between pay-back and price cuts</p> <p>Lithuania: extension of price-volume agreement to high-cost medicines</p>	<p>Portugal: 7.5% lower price than 2010 needs to be granted to NHS institutions for specific biologicals</p>	<p>Poland: new reimbursement law valid from 2012 on – several changes, e.g. obligatory pay-back in case of budget excess, voluntary in risk-sharing schemes; tax on manufacturers' income to publicly fund clinical trials</p>
External price referencing (EPR)	<p>Malta: introduction of EPR</p> <p>Switzerland: extension of basket (4 → 6 countries)</p> <p>Spain: specification in law to have EU Member States as reference countries</p>	<p>Lithuania: extension of basket (6 → 8)</p> <p>Iceland: change in calculation methodology for hospital medicines (lowest price)</p>	<p>Germany: EPR-like procedures provided for in law (implementation from 2012 on)</p>	<p>Slovakia: change in calculation methodology (6 lowest prices → 2 lowest prices of EU-26; in Parliament)</p>
Distribution remuneration (margin*)	<p>Iceland: pharmacy margin increase</p> <p>Switzerland: pharmacy margin cut</p> <p>Spain: increase of a part of pharmacy margin for expensive medicines</p> <p>Greece: wholesale margin cut for expensive medicines</p> <p>Lithuania: introduction of wholesale and pharmacy margin regulation for non-reimbursable medicines</p> <p>Portugal: pharmacy margin increase for non-reimbursable medicines</p> <p>Belgium: new pharmacy margin</p>	<p>Italy: wholesale margin cut & pharmacy margin increase</p>	<p>Latvia: wholesale margin cut</p>	<p>Portugal: discussion about pharmacy margin cut</p> <p>Germany: change in structure of wholesale margin from 2012 on</p> <p>Poland: new reimbursement law valid from 2012: pharmacy margin change</p>

Policy measure	Implemented			Planned / discussed
	1-6/2010	7-12/2010	1-2/2011	
Value added tax (VAT) on medicines	<p>Czech Republic: increase (9 → 10%)</p> <p>UK: increase on OTC/standard rate (had been temporarily reduced in 2008: 15 → 17.5%)</p> <p>Greece: increase (9 → 10%)</p>	<p>Finland: increase (8 → 9%)</p> <p>Portugal: increase (5 → 6%)</p> <p>Greece: increase (10 → 11%)</p>	<p>Greece: decrease (10 → 6.5%)</p> <p>Latvia: increase (10 → 12%)</p> <p>UK: increase on OTC (17.5 → 20%)</p> <p>Poland: increase (7 → 8%)</p>	

Abbreviations: EPR = external price referencing (= international price comparison), EU = European Union, NHS = national health service, OTC = over-the-counter medicines, PPRS = Pharmaceutical Price Regulation Scheme (UK)

* Please note that the term "margin" is used in this table as a broad term covering different kinds of distribution remuneration (e.g. margins, mark-ups, fees).

Table 3. Pharmaceutical reimbursement and other policy measures in 33 European countries in 2010 and 2011

Policy measure	Implemented			Planned / discussed
	1-6/2010	7-12/2010	1-2/2011	
Reimbursement lists / (de)listing/ reimbursement procedure	<p>Malta: listing of new medicines (on-going 2010/2011)</p> <p>Iceland: changes in reimbursement status (from general to individual) for some medicines (e.g. respiratory)</p> <p>Portugal: procedural changes (shorter reimbursement decision time for generics)</p>	<p>Greece: re-introduction of positive list and negative list</p> <p>Iceland: changes in reimbursement status (from general to individual) for some medicines (e.g. antidepressants)</p>	<p>Czech Republic: ongoing review of all medicines (started already in 2008)</p> <p>Germany: new reimbursement law – value assessments</p> <p>Portugal: Delisting of OTC medicines</p>	<p>Poland: new reimbursement law valid from 2012 – several changes, e.g. quicker reimbursement decision, but granted for limited time (2-5 years)</p> <p>Czech Republic: discussion about introduction of negative list</p> <p>France: change of reimbursement system under discussion</p> <p>Netherlands: change in funding of TNF-inhibitors (2012)</p>
Co-payments	<p>Austria: annual increase of prescription fee</p> <p>Belgium: annual indexation of co-pay.</p> <p>Iceland: increase in co-pay.</p> <p>Portugal: temporary exemption (6/2009 – 5/2010) from co-pay. for low-income pensioners for generics was changed (from generics to 5 lowest priced medicines in a cluster)</p>	<p>Belgium: increase of percentage co-pay. for some medicines (at different times during 2010)</p> <p>Lithuania: change in minimum co-pay.</p> <p>Latvia: increase of reimbursement rate for cardiovascular medicines (50% → 75%)</p> <p>Portugal: introduction of co-pay. on medicines which low-income pensioners had been exempted from before</p>	<p>Denmark: increase in co-pay. for fertility products</p> <p>France: decrease of reimbursement rate (35 → 30%)</p> <p>Austria: annual increase of prescription fee</p> <p>Belgium: annual indexation of co-pay.</p> <p>Iceland: increase in co-pay.</p> <p>Latvia: change in new co-pay.</p>	<p>Poland: changes in co-pay. following new reimbursement law</p> <p>Under discussion in Czech Republic, France, Iceland, Latvia, Portugal</p>
Reference price system (RPS)	<p>Portugal: higher RP for more patients</p> <p>Spain: change in methodology allowing lower RP (average of 3 lowest prices → lowest priced product in a cluster)</p> <p>Lithuania: new rules of price of generics compared to equivalents</p>	<p>Estonia: inclusion of 50% reimbursable medicines in RPS (before not) (7/2010)</p> <p>Romania: change to therapeutic reference pricing (broader clusters)</p> <p>Estonia: new rules for price of generics and biologicals in the RPS (10/2010)</p>	<p>Latvia: new rules for price of generics in a cluster (lower prices)</p> <p>Portugal: change in methodology of RP (lower RP)</p> <p>Belgium: new rules for price of generics in a cluster (lower RP)</p> <p>Lithuania: change in methodology of price of most expensive medicines in a cluster (lower prices)</p>	<p>Czech Republic: discussion about tendering for generics</p> <p>Lithuania: discussion about change to therapeutic reference pricing (broader clusters)</p> <p>Ireland: introduction of RPS planned</p> <p>Poland: changes in generic price links due to new reimbursement law (2012)</p> <p>Romania: discussion about extending RPS</p>

Policy measure	Implemented			Planned / discussed
	1-6/2010	7-12/2010	1-2/2011	
Other measures (not directly linked to pricing & reimbursement)	<p>Lithuania: obligation for pharmacies to offer least expensive medicine to patients and to have it on stock (1/2010)</p> <p>Estonia: introduction of e-prescribing (1/2010)</p> <p>Estonia: obligation for pharmacies to offer least expensive medicines to patients and to have it on stock (4/2010)</p> <p>Lithuania: obligation for pharmacies to install price monitoring systems (5/2010)</p> <p>Lithuania: INN prescribing becomes mandatory (6/2010)</p>	<p>Estonia: generics promotion campaign addressed to the public</p> <p>Spain: generics promotion campaign addressed to the public</p>	<p>France: definition for "quasi-generic"</p> <p>UK: Quality, Productivity and Prevention programme on-going (introduced 2009)</p>	<p>Czech Republic: enforcement of INN prescribing</p> <p>Portugal: e-prescribing as prerequisite for reimbursement (originally planned from 3/2011 on, postponed for 8/2011)</p> <p>Portugal: continued generics promotion</p> <p>Slovakia: draft law about INN prescribing becoming mandatory</p> <p>Poland: new reimbursement law valid from 2012 on: information duties of pharmacies about least expensive equivalent medicines and having them on stock</p> <p>UK: discussion about introduction of value-based pricing in 2013 (after PPRS ending)</p>

Abbreviations: co-pay. = co-payment, INN = international non-proprietary name, OTC = over-the-counter medicines, PPRS = Pharmaceutical Price Regulation Scheme (UK), RP = reference price, RPS = reference price system (= reimbursement system in which identical or similar medicines in a cluster are granted a specific reimbursement limit), TNF = tumor necrosis factors

Further, frequently reported measures included increases in the value-added tax (VAT) rates on medicines (in seven countries, with Greece raising its VAT twice during 2010 and then reducing again in 2011) and changes in the payment schemes for the distributors (nine countries). It is worth noting that some countries (e.g. Spain) increased the standard VAT rate, but normally this had no impact on medicines (except UK: standard rate is applied for OTC medicines), since usually lower VAT rates apply specifically to medicines. There were decreases in pharmacy margins in Switzerland and in the wholesale margins in Greece and Italy. However, Spain, Portugal, and Italy increased the pharmacy margin, or parts of it for the expensive price segment.

With regard to external price referencing (i.e. comparing to medicines prices in other countries as basis for a pricing and/or reimbursement decision), two countries (Malta, Germany – under specific circumstances, only applicable from 2012 on) introduced this pricing procedure, while four European countries changed their already existing external price referencing system, mainly extending their basket of reference countries, but also changing the methodology for calculation aimed at obtaining a lower price.

Policy interventions by countries

The highest number of measures were implemented in the Baltic states, Greece, Spain, Portugal and Iceland.

Greece started to react to the crisis in spring 2010, with a bundle of emergency measures – some of which implemented temporarily. From May 2010 onwards, several price reductions were implemented, together with a reduction in the wholesale

margin and twice an increase in the VAT on medicines followed by a decrease at the beginning of 2011. The frequency of price reviews for medicines having entered the market during the last four years increased from one, to three times a year. Generic prices were set at 90% of the original medicines' prices (before: equal level). A positive list and a negative list were planned to be re-introduced. The competence for pricing, previously split among three ministries, was shifted to the Ministry of Health in spring 2011²².

Spain introduced two emergency laws in March and May 2010. The price of expensive generics were cut by 30%, while original medicines and orphan medicines were discounted by 7.5% and 4% respectively on the pharmacy retail price, which were borne by industry, wholesale and pharmacies together, were implemented instead of price cuts. Spain also instituted procedural changes, e.g. in the reference price system and external price referencing, allowing lower prices and aligning the laws with existing practice²³.

The reaction of Ireland, the third country hit by the crisis during 2010, was slightly different. Ireland did not take so many measures as Spain and Greece, and also considered the pharmaceutical industry as a considerable investor and employer within the Irish economy. Some policies had already been implemented earlier, such as the wholesale and pharmacy margin in 2009, and a refinement in external price referencing (e.g. HTA assessment for new medicines from 2009 on). In 2010, Ireland imposed different waves of price reductions, negotiated with and offered by the pharmaceutical industry, on generics. This occurred in February and October 2010 and on on-patent medicines at the end of 2010. A political decision to implement a reference price system was taken in 2010. However, legislation

is still awaited as it was postponed until after the elections to be held in spring 2011²⁴.

During the survey period, major reforms of the pharmaceutical system were also planned or underway in Germany and Poland.

In Germany, the reform was prepared after a change in government in 2009 and came into effect on 1 January 2011. Pharmaceutical companies in Germany are now obliged to produce a scientific dossier with a value assessment demonstrating the added therapeutic benefit of a new medicine compared to treatment alternatives – which can be used later for negotiations about the price and rebates with the sickness funds. Furthermore, the reform law expects that medicine prices in other countries should be taken into consideration in the decision about the reimbursement prices in Germany. Cost-containment measures applied in August 2010 until the end of 2013, comprised of a freeze on pharmaceutical prices and an increase from 6% to 16% in the mandatory rebate the Social Health Insurance imposes on pharmaceutical manufacturers²⁵.

Poland drafted a law to significantly reform the pharmaceutical reimbursement system in order to contain costs and, to comply with the EU law after an infringement procedure. This related to time-lines for decision on pricing and reimbursement regulated in the EU Transparency Directive. The new reimbursement law, which was passed in Parliament in spring 2011 after much discussion and with alterations and will come in effect in 2012, contains a number of policy changes in several fields (see Tables 2 and 3).

The Baltic countries (Estonia, Latvia, Lithuania) started to implement several new cost-containment measures in reaction to the crisis from 2008/2009 onwards. Lithuania reported approximately 28 measures undertaken in recent years²⁶. In 2010, the policy interventions within the Baltic states were focused on improving rational use of medicines, including generics promotion and, in some cases, cancelling strict cost-containment measures from the year before²⁷⁻²⁹.

Discussion

In 2010 through to the beginning of 2011 a large number of cost-containment measures (around 90) were undertaken in 23 of the 33 European countries surveyed. On average 2.7 policy interventions per country were set in the 14 month investigation period. The reforms were concentrated in Iceland, the Baltic states, Greece, Spain and Portugal, which were, starting at different times, hit by a budget crisis. Price reductions, changes in the co-payments, in the VAT rates on medicines and in the distribution margins were among the most common measures.

The contribution of this research is that it focuses on changes in pharmaceutical policies. While the pharmaceutical systems of European countries, or some elements of them are well described (in particular of the larger countries such UK, France, Germany, but increasingly also other countries³⁰⁻³³), cross-country surveys of policy changes are few in number^{12,16}.

The average number of 2.7 policy interventions per country demonstrates that European countries were active in developing and implementing pharmaceutical policies over the time period of the survey. Our study supports a previous observation from the 1990s that EU Member States perform, on average, at least one policy measure per year³⁴. However, it is important to realize that the average number of measures implemented per country might be misleading. This is because, at least for the years 2010/2011, policy changes were concentrated in a few countries – labeled “crisis countries”, as well as a few other countries which had reforms that were not directly attributable to the financial crisis (e.g. Germany, Poland, a current discussion about organizational changes in France following the Mediator scandal³⁵). Whether affected by the crisis or not, containing pharmaceutical expenditure appears to be the key reason for countries aiming to reform their pharmaceutical sector. Our study adds to previous findings that cost-containment has been an issue for high-income countries, who aim to maintain equitable access to medicines within public sector spending constraints^{9,16-17}.

This paper does not assess the impact of the measures since, though considered important and adding on the impact analysis of the global economic recession on countries world-wide done by the World Health Organization³⁶, this would be premature and incomplete for the most recent crisis countries. Commonly set measures like increases in co-payments (including decrease in reimbursement rates) and in the VAT rates might be an indication for limited accessibility of medicines, even if exemptions from co-payments for vulnerable groups were observed (e.g. Portugal) and in some countries VAT for reimbursable medicines is not (fully) borne by the patients. Concerns arose about accessibility after the first wave of policy measures in response to the crisis in the Baltic countries in 2008/2009, and some of the measures instituted in 2010 aimed to reduce the burden for patients and improve equity of access to medicines by withdrawing, or easing some of the cost-containment measures²⁷⁻²⁹.

In the 1990s policy interventions in high-income European countries were successful in containing growth rates in pharmaceutical expenditure and, in particular, in public pharmaceutical expenditure, but this was done at the expense of the patients with increases in private pharmaceutical expenditure^{16,34}. In the new millennium some policy intervention proved successful in terms of cost-containment for public payers, and this was achieved without an increase of the out-of-pocket payments⁹. This was mainly due to more rational use of medicines, including greater application of instruments of health economics including HTA³⁷⁻³⁸ and a rational selection process for reimbursement in which reference price systems increasingly play a role³⁹. Demand-side measures collated under the “4 Es” methodology (i.e. education, engineering, economics, and enforcement)⁴⁰⁻⁴² are recommended. In the Baltic states strict cost-containment measures targeting all stakeholders, including patients, were observed as first reaction to the crisis; follow-up measures were implemented in the field of the “4 Es” and had a focus on the enforcement aspect (e.g. making INN prescribing

obligatory). We need to see if such developments will also take place in the more recent crisis countries. For this phase of the financial crisis we have data that the crisis response was successful in terms of savings in public expenditure which Spain, Greece and, to some extent, also Ireland could achieve²²⁻²⁴, but equity and accessibility aspects should also be explored. Another issue for future analyses could be an assessment if the outcomes achieved are worth the efforts made since these measures – no matter if in response to the crisis or generally aiming at cost-containment – are time-intensive for the officials, and if and how they might be implemented more efficiently. Nonetheless, the need to regularly refine and adjust pharmaceutical policies cannot be questioned: The impact of policies usually appears to be rather short-term, and its effect will probably fade out after two and three years unless no further and/or accompanying measures are set, since actors will adjust the situation according to their interests³⁴.

Measures affecting the pharmaceutical industry raised concerns about medicines availability, which has been an issue, especially for small national markets in European countries. At the beginning of the crisis in Greece, some pharmaceutical companies announced their withdrawal from the Greek market⁴³, as they claimed that they could not accept the price reductions, but to date this has not been the case (personal communication).

In the distribution chain, wholesale and pharmacies were equally affected by changes in their payment schemes, following on changes performed in the years before (e.g. in the Czech Republic, Ireland, Romania)⁴⁴. In spite of the crisis in a few countries (e.g. Spain, Portugal) pharmacy margins, or at least a part of it, were increased, partly following an agreement that pharmacies were compensated in return for other crisis-related reforms. In some cases, the margin changes were not linked to the crisis.

We acknowledge that countries might have undertaken further policy measures which were not included in our summary of results. Nonetheless, we attempted to gather information about the major reforms since we asked the technical people responsible for pharmaceutical pricing and reimbursement in the countries. We also repeated the survey after seven months (thus also guaranteeing full coverage for the survey period for those countries only answering the second round), and ensured data validation by the information providers and checked literature and materials, in particular for some missing countries. Due to their repeating character, annual measures (e.g. price and/or reimbursement reviews) are likely not to have been listed by all countries undertaking them. We could only assess policy measures to the extent as they were publicly known. As a result, confidential arrangements including discounts or other savings offered in return for avoiding other measures, which might have taken place, are not included in the results.

The counting of the measures posed some problems, as some (planned) reforms included a bundle of, sometimes, interlinked measures. Measures like price cuts and de-listings

which affected individual products were only considered when undertaken systematically for a group of medicines and in such cases counted once.

One limitation of the study is the short survey period. The survey started at the beginning of 2010, i.e. in the middle of the global financial crisis. In order to allow analyses over a longer time period and as the global financial crisis continues the authors plan to continue this policy monitoring exercise on a bi-annual basis. The survey methodology proved to be adequate for the purpose and will be, with some minor modification of the questionnaire, continued to be used. This regular exercise will also allow us to check which of the discussed and planned policy measures were actually implemented and in which form, and what the results have been, and share the findings with interested parties, among those competent authorities, thus offering the possibility to learn from the experiences of other countries.

Conclusions

This study demonstrates that numerous cost-containment measures were undertaken in mainly high and middle income European countries during the 2010-2011 financial crisis. While a bundle of policy measures were implemented in countries which were hit significantly by the crisis, all countries appear to be constantly working on optimizing their pharmaceutical systems. In several countries reforms were undertaken, which also aimed at containing public pharmaceutical expenditure, but they were not directly linked to the crisis. Price cuts, changes in co-payments, distribution margins and VAT rates on medicines, which could be implemented rather swiftly, were used as first tools. Many initiatives included the promotion of generic medicine use and the enforcement of policies for more rational use of medicines. Since further reforms are under way, changes in pharmaceutical policies will continue to be monitored. It is recommended to follow up with the applied methodology of this policy monitoring exercise which was piloted successfully in this study. Further research, in particular an impact assessment of the effects of the reforms on the availability and accessibility of medicines, is suggested and should also consider information collected in future policy monitoring exercises.

Authors contributions

All authors contributed to the paper's conception, design and production. SV drafted and revised the article with contributions from NZ, CL and KDJ and considering feed-back by PPRI network members. NZ developed the policy monitoring exercise tool in close cooperation with the other authors, performed the survey and compiled the preliminary results. All authors participated in a critical revision and have approved the final version for submission.

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Conflict of interest

None

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Analyzing readability of medicines information material in Slovenia

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Abstract

Objective: Readability has been claimed to be an important factor for understanding texts describing health symptoms and medications. Such texts may be a factor which indirectly affects the health of the population. Despite the expertise of physicians, the readability of information sources may be important for acquiring essential treatment information. The aim of this study was to measure the readability level of medicines promotion material in Slovenia.

Methods: The Flesch readability formula was modified to comply with Slovene texts. On the basis of determining the Slovene readability algorithm, the readability ease related to the readability grade level of different Slovene texts was established. In order to estimate an adjustment of the texts to the recommended readability grade level of the targeted population, readability values of English texts were set. One sample t-test and standard deviations from the arithmetic mean values were used as statistical tests.

Results: The results of the research showed low readability scores of the Slovene texts. Difficult readability values were seen in different types of examined texts: in patient information leaflets, in the summaries of product characteristics, in promotional materials, while describing over-the-counter medications and in the materials for creating disease awareness. Especially low readability values were found within the texts belonging to promotional materials intended for the physicians. None of researched items, not even for the general public, were close to primary school grade readability levels and therefore could not be described as easily readable.

Conclusion: This study provides an understanding of the level of readability of selected Slovene medicines information material. It was concluded that health-related texts were not compliant with general public or with healthcare professional needs.

Keywords: Ease of readability, Flesch readability formula, readability algorithm, promotional drug texts, Slovenia

Introduction

Establishing readability or the readability grade level has been widely used in many countries. An appropriate level of readability is important in health and drugs texts, since understanding them may influence treatment decisions and potentially, patient outcomes. An inappropriate ease of readability has been globally recognized and in some developed countries the solutions have been suggested. The present study has aimed at contributing to the present knowledge and at exposing an established problem. Namely, English text studies related to the medications have often been published¹⁻⁸, however Slovene texts have just started to be analyzed.

Alongside many pharmaceutical companies, one generic drug producer has been present on the Slovenian market for some time; another pharmaceutical producer of generic drugs was also active, but was taken over by a larger international producer. The cost of the majority of prescription drugs is covered by health insurance schemes, when treatments comply with

necessary prescription procedures and the patients have been paying their premiums regularly. The Slovenian pharmaceutical market has become increasingly competitive. Drug registration procedures have been largely facilitated by common European Union procedures, and some new drugs registered according to national and other procedures. Areas of responsibility of the Agency for Medicinal Products and Medical Devices of the Republic of Slovenia encompass protection of public health through regulation and supervision of medicinal products and medical devices, blood, tissues and cell cultures and related activities in the private and public sectors. Neither hospital drugs or over-the-counter (OTC) drugs usage have yet been systematically monitored. Rough estimates for total market value exceed 400 million Euros in Slovenia. Closer supervision of drug sales and related activities is supported by legislative provisions but promotional activities have not been sufficiently controlled. The advertising arbitration board has interceded in certain cases of allegedly inappropriate advertising for OTC drugs.

Advertising, as a specific part of the promotion through mass media, has been regulated in Slovenia. According to the Drug and Medical Devices Advertising Rules⁹, OTC medicines advertising is permitted in Slovenia, but prescription drug advertising to the general public has not been allowed.

As part of routine practice, in Slovenia, it is expected that the necessary instructions regarding prescription medications is provided by physicians and pharmacists. Patients should also be advised to carefully read Patient Information Leaflets (PILs). The authors have previously reported that analyzed PILs were too complex to be an appropriate source of information for consumers, hence emphasized that there was a need to improve communication¹. In Slovenia, prescription medications are dispensed following the advice of different healthcare professionals. On the other hand, when purchasing an OTC medicine, the pharmacy is the sole supplier of advice and proper written information on OTC medications such as PIL is warranted. The Summaries of Product Characteristics (SmPCs) have complied with professional public needs and official requirements.

Inadequate readability is related to a low level of literacy. Literacy has been increasingly recognized as a critical factor, affecting communication between the patient and the physician and therefore impacting on treatment outcomes¹⁰. Williams et al. have shown a frequently low health literacy level, especially in elderly persons. An appropriate literacy of the general public has been identified as: knowing an alphabet, an ability of fast and easy reading, a vocabulary and understanding, defined as deriving a meaning from a text, as described in the health literacy study¹¹. Rudd et al. found that increasing professional and a public health literacy awareness is important. In their study, education of medicine students and of the physicians and an improved communication ability between the patients and the physicians were emphasized¹¹. In PISA study, good reading skills have been related to an improved innovativeness¹².

According to Schutten and McFarland, readability has been referred to an ease with which a text can be read and understood². If an individual reading skill is significantly below that of the readability level of the document, then it is reasonable to assume that the individual is not able to fully understand the text². Readability formulas are tools that have often been used for determining the readability of text; as the ease of understand text by the average reader can be estimated. Usability of a readability formula has been described to enable easy understanding of the documentation¹³. The patient health education can also be improved on the basis of readability formulas. The readability ease formula by Flesch and the Flesch-Kincaid readability grade level formula have often been used very often¹⁴.

Pelcher et al. noted that many patients seem to retrieve information from searches on the Wikipedia³. The average readability grade level of websites which included 50 most common prescribed medications in the USA amounted 15.4, therefore well above the high school grade level. Within the English algorithm the material posted on these websites can be

described as difficult to read. Pelcher et al. concluded that these articles were not aiming at educating patients. An adjusted readability ease of health and medication promotional texts was recognized as an important factor for the comprehension of a dose regime⁴. Improving the readability and understanding the texts can facilitate the communication between the physicians and the patients and also patient understanding¹⁵. Creating easily understandable health information is particularly important for the persons with reading or comprehension difficulties¹⁶. The readability within the 4th and the 6th grade level range can lead to the required level of comprehension. This range coincided with a readability ease description of 'very easy'.

Appropriate readability does not always translate into ease of comprehension. Even the texts with a low readability grade can be difficult to understand, when organization, layout and design have not been considered¹⁷. Pelcher et al. found that simplification has not always equated to better readability³. Therefore simplification of the wording alone has not been sufficient for increasing the comprehension; keeping the cohesion of a text has also been essential.

This study was designed by assuming that there is a problem with regards to inappropriate readability in Slovenia. The readability formulas were used to measure the readability ease. The present research has been set out to explore the following hypotheses.

H₁: Health-related texts are not adjusted to the targeted public.

According to the present knowledge, readability levels in English texts are not compliant with those advised, and a similar situation is assumed for Slovene texts.

H₂: Medication risks are less readable than the benefits of the promoted medicines.

Benefits are assumed to be better and the risks less accentuated, due to the tendency of pharmaceutical companies to promote demand and play down the importance of perceived risks.

H₃: Readability values of patient information leaflets, creating disease awareness materials and OTC promoting materials, all belonging to the group for the general public, are predicted to be higher than readability values of the materials, intended for the scientific public, encompassing summaries of product characteristics and the materials for promoting to physicians.

The texts for health professionals should be easily readable to facilitate transferring the message to the patients and in-order to be less time-consuming for the health professional. The ease of readability was assumed to differ according to the type of analyzed material. Final readability standards can be determined after testing established readability values. We find establishing readability levels important, since poor readability of medication texts is predicted to be related to potentially improper behaviour, coincided with unexpected treatment results and adverse events. However, this can only be confirmed by further research results. Hence, the aim of this study was to measure the readability level of medicines information material in Slovenia.

Table 1. Slovene and English readability algorithm (values were rounded to the integers), with average and intermediate values. The Slovene algorithm was validated by two newspapers.

Slovene algorithm		Slovene newspapers		English algorithm	
Readability ease		Readability ease		Readability ease	
Readability	Description	Average value	Intermediate values	Readability	Description
50 - 60	Easy			90 – 100	Very easy
				80 - 89	Easy
				70 - 79	Fairly easy
40 - 49	Standard			60 - 69	Standard
< 39	Difficult	20* 3**	6, 20, 13, 18, 22, 16, 1, 29, 15, 35, 28, 26, 34 17, -1, 2, 22, 18, 32, -29, 26, -39, -5, 12, -7, 2, -5, 3, 5	50 - 59	Fairly difficult
				30 - 49	Difficult
				< 29	Very confusing

*Slovenske novice (03/09/2010), ** Finance (06/09/2010)

Methodology

Slovene readability values were determined in accordance with the Flesch method. An algorithm was validated by applying it to two daily newspapers. The sample and statistical methods are described in this section.

Readability formulas and algorithms

Readability formulas have been used to determine a readability ease and a readability grade level for the average reader in order that level of understanding of the text could be estimated.

The Flesch formula involves the following calculation¹⁸:

$$206.835 - (1.015 \times \text{Number of words/Number of sentences}) - (84.6 \times \text{Number of syllables/Number of words})$$

$$\text{Number of words/Number of sentences} = \text{Average length of a sentence}$$

Flesch and Kincaid established a year of education, complying with understanding a text¹⁸:

$$\text{Readability grade level} = (0.39 \times \text{Average sentence length}) + (11.8 \times \text{Average number of syllables per a word}) - 15.59$$

Readability scale in English¹⁸ has been included in the Table 1. Readability ease values are from a scale between 0 and 100. The values can reach below 0. Higher values relate to more easily readable texts. The readability ease and the readability grade level can also be determined by computer algorithms. A manual calculation confirmed the accuracy of readability calculations of English texts¹⁹.

A Slovene readability algorithm was identified and served as a standard. It was introduced due to a difference in both language

syntaxes and in scholarly systems. Text samples were collected from the textbooks for the first, the third, the fifth, the seventh and ninth graders. Further samples were extracted from the textbooks for the first, the third graders of the high school and the university, respectively. The sample from the literature for the university graduates was also taken²⁰. The values were obtained by the established Flesch formula. A regression analysis was then performed to acquire new values within the Slovene algorithm (Table 1) and a new formula was derived:

$$\text{Readability ease} = 206.835 - (0.306 \times \text{Number of words/Number of sentences}) - (83.585 \times \text{Number of syllables/Number of words})$$

The readability ease of two newspapers was determined to validate the Slovene readability algorithm. Finance has been termed as a financial daily newspaper with economic analyses. Everyday news have been encompassed in daily newspaper *Slovenske novice*. An average readability value of Finance reached the level of higher university grade levels and was at the initial university level in *Slovenske novice*.

Sample: text for analysis

A sample of examined materials was based on the larger sample with 1,474 materials and 10,396 products for the treatment or for the care, as it is described below. This original sample included materials describing OTC medicines, publications, materials with nutritional supplements, materials with cosmetic products, materials packaged with medical devices, materials for creating disease awareness, educational materials, materials with social marketing messages, materials not complying with advertising for the general public and other materials.

In Table 2 please see corresponding shares of material groups, used for a part of the present study, within an original sample.

Table 2. An original sample, as a source for the materials for analysis

Original sample – materials	% of the materials in the sample
Materials describing OTC medication	22.0 %
Publications (also containing OTC medication descriptions)	4.3 %
Materials for creating disease awareness	2.6 %
Other groups of medication and health-related materials	71.1 %

Materials comprised of texts on medication products were identified. The texts were collected from a representative sample of Slovene pharmacies, as part of a previous study^{21,22}. Material relating to OTC medicines and some disease awareness samples were obtained through systematically visiting the pharmacies, and every different material reviewed in all selected pharmacies. Twenty six Slovene pharmacies were visited, 19 public and 7 private ones. Three therapeutic OTC drug groups; for treating viral infection, allergies and osteoporosis were identified. The discussed osteoporosis treatment medication has contained a combination of two active substances from the bisphosphonates in combination group. There has been a rationale for selecting the materials from these therapeutic groups. The medications from the three groups mentioned were widely dispensed at Slovene pharmacies.

Thirty OTC drug promotional materials were collected, spread equally across the therapeutic groups. Six leaflets (materials) from the creating disease awareness group, related to three therapeutic groups in both languages, were evaluated. Other materials were collected in one sample each, in both languages in comparable texts. At sampling, the third paragraphs of every second page were analysed. As per Flesch's criteria, each part of the text that was analysed had to include at least 100 words, or an addition of words to finish a particular sentence¹⁴. A part of the sample was derived from specific websites, mainly official websites of the manufacturers of targeted medicines. English versions were analyzed when the texts were comparable.

Statistical analysis

The intention was to compare the readability values and to estimate statistical significance, related to the test value. Statistical significance, determined by the one sample t-test was used, with a 99% confidence interval. A two-tailed statistical significance was attributed when the p-value was lower or equal to 0.01. T-test was performed when enough values were available to enable the calculations to be undertaken. The null hypothesis claimed that the population mean was equal to the specified value. For testing the null hypothesis, arithmetic means were compared to test values. When the p-value associated

with t-test was small ($p \leq 0.01$), this is evidence that the mean is different from the hypothesis value. When the p-value is not small ($p > 0.01$), the null hypothesis is not rejected. As test values, the readability ease of 45 was used at Slovene texts and 90 at English texts, as readability values relate to the recommended 4th to 6th grade level, corresponding to a very easy to an easy level. These values were used for the materials directed at the general public¹⁶, as well as for the materials directed at health professionals¹³, since low grade levels were advised also for the medical documentation. The deviations from arithmetic means were determined by the quotient between mean differences and test values. The calculations were made for Slovene and English texts.

Results

The results are presented according to the material type. The values have been presented textually and in the tables within four sub-sections. Statistical estimations have been included.

Readability of Patient Information Leaflets and Summaries of Product Characteristics

The results show (Table 3) that the Patient Information Leaflet (PIL) has greater readability than the Summary of Product Characteristics (SmPC), regardless of the language used. The readability of the Slovene PIL (10) as well as of the SmPC (-11) is described as difficult. Slovene texts were compared to the English ones. The English PIL, with a readability ease score of 34, was identified as difficult to read. The text of the English SmPC was marked as very confusing (-5). The content of SmPCs in both languages were highly comparable. A statistical t-test ($p = 0.01$) showed a non-significant difference between the Slovene PIL and the test value (45) and a non-significant difference between the English PIL according to the test value (90). The Slovene and English SmPC demonstrates a significant difference related to the corresponding test values. Larger deviations of readability values from the arithmetic means were established for Slovene texts in comparison with English texts. This was the case for PILs (0.79 vs. 0.63 in absolute values), as well in the case of SmPCs (1.25 vs. 1.06). In Table 3, average and intermediate values are stated. t-test; confidence interval = 99%, $p = 0.01$

Readability of promotional materials for osteoporosis treating drugs, intended for the professional public

Slovene and English texts were selected relating to osteoporosis treatments containing a combination of two active substances from a group of bisphosphonates in a combination. After analyzing these texts, grade levels which exceeded the graduates grade level, were established. The values appeared to be very low (Table 3). Even lower readability values were found in Slovene (-47), described as difficult, compared with English texts (-33) described as very confusing. A non-significant difference (t-test, $p = 0.01$) was attributed to English promotional materials for physicians, with the deviation 1.37 from the arithmetic mean.

Table 3. Readability values of comparable Slovene/English PIL, SmPC and creating disease awareness texts, respectively.

Material	Slovene texts				English texts			
	Readability ease				Readability ease			
	Description	(Mean) value; standard deviation	Intermediate values	t-test	Description	(Mean) value; standard deviation	Intermediate values	t-test
Patient Information Leaflet	Difficult	10; d = 0.79	25, 23, -19	t= 2.463 p=0.133 NS	Difficult	34; d = 0.63	27, 9, 50, 49	t= 5.734 p=0.011 NS
Summary of Product Characteristics	Difficult	-11; d = 1.25	-23, -39, -23, 16, 13	t= 5.155 p= 0.007 S	Very confusing	-5; d = 1.06	17, -25, -8, -12, -4, 0, -4	t= 19.809 p= 0.000 S
Materials for physicians	Difficult	-47	/		Very confusing	-33; d = 1.37	-7, -59	t= 4.731 p=0.133 NS
Viral diseases awareness material	Difficult	19	/		Difficult	34	/	
Allergy awareness material	Difficult	23	/		Very confusing	24	/	
Osteoporosis awareness material	Difficult	5	/		Very confusing	11	/	

Readability of texts for creating a disease awareness

Slovene disease awareness texts as related to all three therapeutic groups, were compliant with a description 'difficult' within the Slovene algorithm. Slovene texts were also compared with English disease creating awareness texts, due to a content similarity. English texts for creating awareness of viral diseases reached the readability ease value 34 and, were described as difficult. With a readability score of 24 and of 11, a description 'very confusing' was assigned to a creating allergies awareness and osteoporosis awareness texts respectively (Table 3).

Readability of texts for promoting OTC medications

The statements regarding the benefits and possible risks of treatment with specific OTC medications were extracted from text segments. Readability values for all texts were rated as difficult (Table 4). The texts, related to possible risks of taking these medications, were less readable than the text with a description of the benefits, regardless of the chosen therapeutic group. Readability ease values of the benefits related to treatment of viral diseases and allergy treatment were 4 and 0 respectively. The readability ease of the text describing medicines risks for the treatment of viral diseases reached -19 and, a similar value (-17) was reported for allergy related medicines. Especially low readability values were attributed to OTC medicines for osteoporosis with the benefit readability score of -3 and risks

of -40. In Table 4, average and intermediate values are stated. t- test; confidence interval = 99%, p = 0.01.

A statistically significant difference in readability, relating to test values, was observed at the benefits and risks (p ≤ 0.01) of texts relating to OTC medicines for treating viral diseases. A non-significant difference was seen for the benefits related to OTC medicines for osteoporosis treatment (p = 0.033). Comparison of the deviations of readability values demonstrated a larger deviation for medicines for treating viral infections (1.43). Comparatively lower deviations were noted for the benefits of treating osteoporosis (1.07) and viral infection (0.92).

Discussion

The Slovene algorithm reveals decreasing values of the readability ease as grade levels are higher. This study has shown inappropriate readability grade levels of texts, confirming results from previous studies^{3,5,6,7,8}. This study shows that the readability of the Slovene PIL was difficult. Within the corresponding algorithm, the English PIL was also described as difficult to read. A statistical difference concerning corresponding test values, defined above as the values we are aiming at, was not found, regardless of the language. It can be concluded from this study that an advancement should be made in both language materials.

Table 4. Readability values of risks and benefits of OTC medication texts

Material	Texts about benefits				Texts about risks			
	Readability ease				Readability ease			
	Description	(Mean) value; standard deviation	Intermediate values	t-test	Description	(Mean) value; standard deviation	Intermediate values	t-test
OTC drugs for treating viral diseases	Difficult	4 ; d = 0.92	5, 17, 37, -2, -18, 3, 13, 9, 1, -8, 12, -26	t= 8.686 p= 0.000 S	Difficult	-19 ; d = 1.43	-15, -1, -48, -13	t= 6.381 p= 0.008 S
OTC drugs for treating the allergies	Difficult	0			Difficult	-17		
OTC drugs for the osteoporosis treatment	Difficult	-3 ; d = 1.07	-8, 14, -16	t= 5.389 p= 0.033 NS	Difficult	-40		

In comparable studies, a high readability grade level and letter size slightly below the recommended within a PIL for inhaled corticosteroids products have been reported⁵. Exceeding a recommended readability grade level, calculated by a Flesch-Kincaid formula, was also evident in PILs for selected eye medications¹. Inappropriate readability grade levels have also been associated with texts about warfarin⁴. When researching hospital PILs, an average readability ease 60 was determined by the Flesch method, with a Flesch-Kincaid grade of 7.8.

This study found that the Slovene SmPC was rated as difficult to read and the English SmPC as very confusing to read. The difference between the stated readability values and the test values was substantial and statistically significant. Although a high educational level of experts should enable comprehension, easier readability should facilitate the experts' work.

The results of this study, related to PILs and SmPCs, has also shown larger standard deviations in readability values when Slovene texts were compared with English. These findings, along with discrepancies between this study and previous published results^{1, 4, 6} suggest that lack of use of readability formulas with Slovene medicines information material may have lead to lesser concern and lower uniformity of text readability.

Promotional materials for physicians written in Slovene and English largely exceeds university graduates grade level. However, in English the promotional material for professionals, statistical significance was not achieved. Since similar results derived from the SmPC analysis, it can be concluded that more attention should be dedicated to adjusting the texts based on the needs of health professionals.

High readability grade levels of the materials which relate to creating disease awareness were observed in our study. Slovene materials regarding disease awareness were described as difficult to read, in accordance with the Slovene algorithm. Viral diseases

awareness materials in English were described as difficult to read and the materials related to the other two therapeutic groups were described as very confusing to read. This study supports the notion that all targeted texts should be adjusted to appropriate readability levels. Materials for educating on HIV infections intended for the patients have also been reported to have excessive readability grade levels^{7, 8}.

Awareness materials related to viral infections and for allergies (derived from Internet sources) had slightly higher readability ease values (19 and 23) than osteoporosis awareness materials (5), which were obtained from a pharmacy. The results of the materials for creating disease awareness in Slovene and in English are comparable, however this suggests there is a need to ensure optimal readability of all forms of text analysed in this study.

Irrespective of the therapeutic groups, readability ease values of benefits and risks, related to OTC drug texts were described as difficult. The readability of risks is rated as more difficult than the readability of benefits within the analyzed promotional texts. A statistically significant difference in viral infection therapeutic group and a non-significant difference concerning the benefits of the osteoporosis therapeutic drug group was demonstrated. These results have confirmed our previously defined set of hypotheses.

This imbalance in readability between the benefits and risks in medicines promotional materials show that it did not meet the standards. According to the recommendations of the Food and Drug Administration (FDA), the usage of appropriate language and content should help to present risk information more clearly²³. The results of this study suggest that the text relating to benefits of OTC medications is presented more clearly than the risks, with standard deviations taken into account. Besides the possibility that neither Slovene text was appropriately

prepared to ensure ease of readability, the benefits may have been deliberately presented more clearly than the risks. This may have been undertaken to enhance the apparent advantages of the promoted medicine. Hence, a policy is needed to authorize competent institutions to test readability levels as a part of standard practice.

Research limitations and future research

To make the findings of this study more generalizable, a wider range of therapeutic groups could be analyzed. There is also a requirement to focus on exploring readability of materials for professionals, where less work has been undertaken. Likewise, also the benefits and the risks in OTC texts, including those from other therapeutic groups, are advised to be further studied. It is imperative that after testing factual grade levels and a decision-makers consensus, standards should be set for Slovene text. Besides printed materials, television OTC adverts could be subject of further research.

Conclusion

This study provides an understanding of the level of readability of selected Slovene medicines information texts. It was concluded that health-related texts were not compliant with general public or with healthcare professional needs. Since none of the studied Slovene texts for the general public complied with the primary school grade level of readability, the texts should be adjusted to appropriate levels. Due to their public health purpose, public-health organizations are expected to initiate the efforts to increase the readability of the texts with the medicines information.

Authors contribution

Both authors contributed to the paper's design and to the research implementation, analysis and interpretation of the results.

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Conflict of interest

We declare that we have no conflict of interest.

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Pharmacy practice in the Republic of Macedonia

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Abstract

As part of wider reforms within the pharmaceutical sector, the pharmaceutical care concept has been introduced in the Republic of Macedonia. This article provides discussion on current opportunities and challenges which pharmacy practice face in Macedonia. The emphasis is on three prerequisites for the implementation of pharmaceutical care including: organization of pharmaceutical services, legislation, and professional training. The author argues that Macedonia possesses a favorable pharmacy workforce, solid legal basis and supportive structures of healthcare services in order to implement pharmaceutical care. Implementing pharmaceutical care has not been without its challenges, such as: lack of clinical skills, inadequate continuing education and the current remuneration structure for pharmacy services. While Good Pharmacy Practice (GPP) Guidelines have been developed, wider professional debate and practical steps have not been undertaken to promote the concept of pharmaceutical care nationally. Therefore, an integrated national approach to develop strategy, standards and tools for patient-oriented pharmaceutical practice has to be formulated. In addition, there is a need to undertake more comprehensive analysis of current pharmacy practice, to explore the awareness and willingness of the pharmacists to embrace pharmaceutical care practices, and to identify the opportunities and barriers for implementation of pharmacy practice.

Keywords: Pharmaceutical care, pharmacy practice, Republic of Macedonia, organization of pharmaceutical services, legislation, professional training.

Introduction

The pharmacists' role has gradually shifted from compounding to dispensing medicines, and recently towards patient-centered services based on models of clinical pharmacy and pharmaceutical care¹⁻³. The potential barriers for implementing pharmaceutical care in practice have been classified into four categories: education, skills, resources and environment. Other barriers include: deficient clinical knowledge and communication skills, insufficient time and inappropriate space, absence of a recognized reimbursement system, lack of adequate drug information resources, poor relationships with doctors and lack of access to patient health records⁴.

The pharmaceutical care concept has been recently introduced in the Republic of Macedonia, as part of wider reforms within the pharmaceutical sector⁵. This article seeks to discuss current opportunities and challenges which the pharmacy profession faces when implementing pharmaceutical practice in Macedonia.

Country healthcare profile

The Republic of Macedonia is a small Balkan country in South Eastern Europe with around two million inhabitants⁶. The

country gained independence from the Federation of Yugoslavia in 1991 in a peaceful secession and established its own political system as a parliamentary democracy. The country has been going through slow transition from a centrally planned to a free market economy and the ongoing reforms include the health sector, supported by the World Health Organization (WHO) and the World Bank^{7,8}. The disease prevalence pattern is similar to other European countries, with cardiovascular diseases, cancer, mental health problems, injuries and violence, and respiratory diseases as the most prominent causes of morbidity and mortality, while other diseases like HIV and TB are less prevalent⁷.

The World Bank classifies Macedonia as an upper middle income country with a GDP per capita of US\$ 4,520 in 2010⁹. According to the WHO 2009 estimates, the total health expenditure as a percentage of GDP was 6.9%¹⁰. The total pharmaceutical expenditure as a percentage of total health expenditure was estimated to be 13.5%¹⁰. Health insurance coverage in Macedonia is universal and the basic benefit package is broad, covering all health services within the public healthcare system¹¹. The general government expenditure on health as a percentage of total expenditure on health was 66.5%^{7,10}.

Organization of pharmaceutical services and resources

Following independence, reforms in the pharmaceutical sector included the adoption of a National Drug Policy, development of the foundation of the Medicines Information Centre and the Adverse Drug Reaction Centre, while the Centre for Pharmacovigilance is yet to be established⁷. The pharmaceutical sector operates on the basis of a positive list of medicines that defines which medicines are covered by the health insurance system¹¹. Some of the biggest challenges in the pharmaceutical sector during the transition period comprise: sporadic shortages of medicines from the positive list, lack of any systematic development of treatment protocols and guidelines and irrational prescribing practices⁷.

Over the past 20 years, the nation-wide chain of state-owned pharmacies has been privatized and the number of new community pharmacies has grown significantly. At present, all community pharmacies are privately owned and only pharmacies that provide medicines supply to medical centres and hospitals remain under public ownership⁷. Community pharmacies have to enter into annual contractual agreements with the national Health Insurance Fund (HIF) in order to dispense medicines eligible for reimbursement to insured patients^{12, 13}. Community pharmacies are licensed and regulated by the Ministry of Health through the National Medicines Agency¹⁴. The pharmacy minimum area must be 16m². Ownership of pharmacies is not restricted to pharmacists, so there are many chain pharmacies owned by pharmaceutical wholesalers, or local pharmaceutical manufacturers. As in other countries undergoing transition, this wide spread liberalization led pharmacy to be increasingly seen as part of the commercial sector and, less part of the professional system within healthcare¹⁵⁻¹⁷.

Prescribing of prescription-only medicines is restricted to medical doctors, while dispensing is limited to pharmacists working in pharmacies⁷. The pharmacy remuneration fees are related to pharmacy dispensing services. Official data indicates the existence of 874 pharmacies in the country; 841 are community pharmacies (746 have contracts with the HIF) and 33 are internal pharmacies attached to medical centres and hospitals. The community pharmacy to population ratio is 1:2,500¹⁸. No geographic or population standards have been set for the establishment of new pharmacies. As a result, pharmacies are mostly concentrated in towns leaving a number of rural settlements with limited or no access to pharmacy services¹⁹.

There are currently about 1960 registered pharmacists in Macedonia, equating to a pharmacist to population ratio of approximately 1:1,000, even though not all pharmacists work in pharmacies¹⁹. The role of community pharmacists involves dispensing of medicines and providing information to patients on proper medicines use. In the public hospital sector, pharmacists are often substituted by pharmacy technicians or nurses. Located within the central pharmacy, hospital pharmacists only provide, and internally distribute, medicines prescribed by medical doctors and administered by nurses, and do not interact with patient-care teams in the hospital wards.

Legal provision

The Macedonian pharmaceutical sector's regulation was harmonized with the EU legislation in 2007. The Law on Medicinal Products and Medical Devices was revised and a number of by-laws were passed²⁰. In the current Macedonian legislation, pharmacy services and pharmacists' roles are still mostly defined from more of a product-oriented view and less frequently from a patient-care perspective.

For instance, the Law on Health Care from 1997 (article 118) describes pharmacies as product-oriented premises where pharmaceutical activities comprise of *acquisition, custody, storage, dispensing of medicines, analysis and quality control of medicines, preparation of magistral formula and galenic medicines, acquisition and dispensing of children items, dietary products, orthopedic aids and medical equipment, including only instructions on use of dispensed medicines* as a pharmaceutical care component²¹.

Unlike some developed countries, there is no special pharmacy law that regulates the practice of pharmacy and the scope of pharmacists' activities. Instead, it is the Law on Medicinal Products and Medicinal Devices from 2007 (articles 81, 82) that outlines details on the activities related to medicines retailing within pharmacies²². This Act considers pharmacies to be legal entities where purchase, storage, keeping and dispensing of medicines are undertaken. It is very encouraging that this law creates new opportunity for pharmacists by endorsing the need to introduce quality systems and to organize work process according to the principles of good pharmacy practice²².

In response, the Guidelines for the Principles for Good Pharmacy Practice were developed in 2009⁵. This document provides directions for the evolution of pharmaceutical activities into a pharmaceutical care concept. The guideline clearly places improved patient health as an ultimate objective of pharmaceutical care activity. The GPP guidelines define four core activities of pharmacists: 1) public health functions related to health promotion and disease prevention 2) supply of medicines and medical products of good quality as well as provision of relevant patient instructions and advice on medicines use 3) self-medication activities and related patient advice and 4) pharmacist contribution to rational prescribing and appropriate use of medicines⁵.

The GPP guidelines explicitly quoted the need for development of national GPP standards to guarantee professional roles of pharmacists and to ensure essential conditions are in place for GPP implementation⁵. Unfortunately, there has been no further follow up on the GPP guidelines in the country. To date, neither national GPP standards have been developed, nor has wider professional debate been initiated to promote the concept of pharmaceutical care on a national basis.

Training and professional development

Pharmacists in the Republic of Macedonia require work licenses in order to work in pharmacies. Pharmacists have to complete a five year Master of Pharmacy degree and one year residency

programme, as well as passing the state license exam^{21,23}. In contrast to the previous emphasis on chemistry, the pharmacy curriculum has been revised to integrate more practice-based subjects (social pharmacy, medicines information, pharmacotherapy, clinical pharmacy) which have mandatory course status^{24,25}. However, teaching of pharmaceutical care remains theoretical. During residency programmes, hospital rotations under the supervision of a licensed pharmacist still lack the appropriate clinical component. The university pharmacy practice departments have not been established yet, which perhaps could contribute toward research in this area^{24,25}.

In Macedonia, the initial work license must be renewed every seven years by attending continuing education courses, accredited by the Pharmacists' chamber^{7,21}. These are crucial activities for professional improvement because many licensed pharmacists have been trained under previous curricula and therefore, they lack the appropriate clinical skills. However, the accreditation criteria for continuing education courses are not clear. This reflects a lack of strategy by professional bodies of pharmacy in order to produce pharmacists competent to deliver pharmaceutical care services in Macedonia.

Pharmaceutical care only appeared once on the agenda of the continuing education courses. The Ministry of Health and the Pharmaceutical Chamber, supported by the World Bank, organized a training seminar titled "Developing pharmacy practice - pharmaceutical care" for community pharmacists in 2009²⁶. The event has had the relevant objectives of presenting the pharmaceutical care concepts and to describe the new roles, skills, added benefits, challenges and opportunities available to pharmacists, and it aroused considerable interest amongst the audience²⁶. Unfortunately, since then clinical courses have not been included in continuing education programmes and follow-up activities have not been undertaken to assess current pharmacy practices.

Key findings and discussion

Following independence in 1991, the Republic of Macedonia pharmaceutical sector has undergone numerous reforms. These reforms include the privatization of state-owned pharmacies, an increase in numbers of new community pharmacies and uneven territorial distribution of pharmacies. As in other countries undergoing similar reforms, this wide spread liberalization has led pharmacy to be increasingly seen as part of the commercial sector and less part of the professional system within healthcare.

The role of community pharmacists is reflected in the dispensing of medicines and the provision of information to patients on the proper use of medicines, while public health activity does not feature. Hospital pharmacists only provide and internally distribute medicines from central pharmacies and have no access to and little interactions with patient care teams in the hospital wards.

Official data demonstrate an optimal community pharmacy to population ratio of 1:2,500 and pharmacist to population ratio of 1:1,000. These are essential prerequisites for the provision of

pharmaceutical care services^{18,19}. Despite this, the implementation in practice might be difficult if there is only one pharmacist per relatively small pharmacy and if there are no regular pharmacy users due to sporadic shortages of medicines from the positive list. Furthermore, current remuneration of pharmacies is related to their dispensing services, and not to other aspects of patient care, which is important to consider given that all community pharmacies are private and commercially oriented.

The current legislation in Macedonia defines the pharmacy practice mostly from a product-oriented and less frequently from a patient-care perspective. However, it is encouraging that the Law on Medicinal Products and Medicinal Devices emphasizes the need to introduce quality systems and to organize work processes according to the principles of GPP²². This has led to development of the Guidelines for the Principles for Good Pharmacy Practice in 2009. These guidelines aim to facilitate the implementation of pharmaceutical care in practice by defining pharmacists' core activities. They also call for the development of national standards for GPP. Unfortunately, there has been no follow up on the GPP Guidelines. Neither national GPP standards have been developed, nor has there been wider professional debate promoting the concept of pharmaceutical care nationally.

Pharmacy education in the country offers a theoretical basis for pharmaceutical care subjects. However, the concept of pharmaceutical care is not integrated within the healthcare system, especially not in the hospitals. Therefore, the clinical component is usually missing from rotations and residency programmes. Continuing education for pharmacists is mandatory for all holders of work licenses. However, courses have unclear accreditation criteria, and the quality of education, relevance to practice and conflict of interest policy is not being assured.

Conclusions

The concept of Pharmaceutical Care has recently been introduced in the Republic of Macedonia. Pharmacists still face the challenge of embracing this concept in their daily practice, even though the country possesses a favorable pharmacy workforce, solid legal basis and supportive organization of health care services. This viewpoint highlights the need for clear and integrated national approach to develop a strategy for patient-oriented pharmaceutical care. Analysis of current pharmacy practices and identification of opportunities and barriers for pharmaceutical care implementation need further attention, if Macedonia is to advance its pharmacy practice activities and thereby improve patient care.

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Conflict of interest

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Pharmacy practice in Qatar: challenges and opportunities

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Abstract

The State of Qatar is a small oil and gas-rich Gulf country that is experiencing rapid development in health care services, including pharmaceutical services. To date, there is no autonomous professional pharmacy association or society that regulates or promotes the practice of pharmacy in Qatar, and the challenges that face the profession of pharmacy in Qatar mirror the challenges facing the profession in all other Middle Eastern countries. However, a set of initiatives and projects that include pioneering educational initiatives, close alignment of practice with the educational providers, stronger leadership from a National Health Strategy, and the development of pharmacy leadership groups at the practice level all contribute in the fast development of the practice of pharmacy in this country. In this commentary, we provide a snapshot of the pharmaceutical scene in Qatar, and in doing so, we shall discuss the challenges that face the practice, and the main landmarks and initiatives that are destined to move pharmacy forward in Qatar.

Keywords: Qatar, Pharmaceutical Situation, Pharmacy Practice.

Qatar's pharmaceutical scene: a practice on the move

The practice of pharmacy in the region known as the Middle East has been in a state of evolution throughout the last five to ten years due to multiple reasons that include international as well as regional influences¹. Internationally, cultural, economic, technological, and social globalization has unified the world's orders thus integrating regional economies, societies, and cultures through communication, transportation, and trade². Within the region, calls for democratization and regime change swept North Africa to the heart of the Arabian Peninsula, triggering unprecedented reactions, reviews, and social media activity³.

The Middle East is demographically young, with many countries having over 30% of the population aged under 15 years, the age group defined as "youth"⁴. It is no surprise that these calls for changes, sometimes leading to popular revolutions, were often led by young Arab men and women aspiring for change. That same youthful energy could shortly be helping to sustain a revolution in the pharmacy practice field in the region. The idea and ideals of pharmaceutical care, and its related practices and activities such as medication therapy management, are very familiar to Arab Pharmacists through seminars, talks, conferences and undergraduate courses taught in some schools of pharmacy¹. All this is inspiring young pharmacists and pharmacy students who are looking to take on new roles in

their practice of pharmacy and abandon old models of practice that dominated pharmacy in the region⁵.

The aim of this commentary is to provide a description of the practice of pharmacy in Qatar, with emphasis on the challenges facing it and the opportunities that will inevitably shape its future.

The State of Qatar (Qatar), an Arab Emirate that lies on the northeasterly coast of the Arabian Peninsula, has a population of approximately 1.7 million people, of which approximately 80% are expatriates⁶. Gas and oil produced and exported from this small country gives it one of the highest gross domestic product (GDP) per capita in the world. However, the dynamic leadership in Qatar is revolutionary in its vision and ambition to switch Qatar from a carbon-based economy to Knowledge based economy⁷.

One sector that is already witnessing tremendous change in Qatar is the health care sector, which has traditionally been dominated by expatriate professionals⁸. To support the development and growth in the health care sector, policy-makers in Qatar started programs that aim at training domestic graduates through hosting satellite campuses of the Weill Cornell Medical College (US based) and the Qatar branch of the University of Calgary nursing school⁸. Most recently, the College of Pharmacy was established at Qatar University, as shall be discussed below in more detail.

The pharmacy practice scene

To date, there is no autonomous professional pharmacy association or society that regulates, represents or promotes the practice of pharmacy in Qatar⁹. As a result, there is no code of ethics that binds pharmacy practitioners with a code of conduct, and (until recently) no set of competency standards to act as a bench mark to all pharmacists. The current pharmacy law places a great deal of emphasis on the pharmacy and pharmacist registration process, the structure of the pharmacy premises, and controlled drug regulations, but provides little guidance on practice issues¹.

Non-practice issues relating to pharmacy are reasonably well established in this country. Pharmacist registration comes under the jurisdiction of the Supreme Council of Health (SCH, Medical Licensing Department). The SCH also has a Department of Pharmacy and Drug Control, which controls pharmacy premises (registration and inspection) including community pharmacies, private hospitals, and drug stores (wholesale). This department also enforces the controlled drug regulations regarding import, export and distribution (Qatar is a signatory to International Conventions for Narcotics and Psychotropics) and for all medicines they control the registration, pricing, import and distribution for Qatar. Supported by a Drug Quality Control Laboratory, they also monitor herbal products and many food supplements.

Most pharmacists practicing in Qatar are expatriates and the majority of pharmacists received their degrees in Egypt, India, or Jordan¹⁰. As a result, practice models tend to reflect the practice one would find in those countries. In Qatar, there are 305 community pharmacies, over 20 primary care health centers, 8 government funded hospitals and 11 satellites providing urgent care and dialysis (managed by Hamad Medical Corporation, a Joint Commission International Accredited Health System)¹¹. Five more health facilities are planned, including a medical and research centre that is managed by Qatar Foundation for Education, Science and Community Development (QF). Several private hospitals also provide health care services in and around Doha city, the capital of the State of Qatar¹².

Drug procurement, storage, and supply in Qatar follows organized and well-established protocols. The rules and regulations governing these inventory-related activities in Qatar generally resemble those in other neighboring Middle Eastern countries; and several Gulf countries (members of the Gulf Cooperation Council, or GCC) purchase their annual quota of medicine through a joint procurement process¹³. This process enforces the political commitment of their member states and (through adopting a centralized tendering system) ensures a cost-effective procurement process. In a recent study conducted in Qatar, practicing pharmacists appeared to be satisfied with the processes associated with dispensing of medications in the retail setting, public clinics, and public hospital outpatient pharmacies, and felt that the regulatory processes for the procurement, storage, marketing, and pricing of medications are also acceptable⁸.

Challenges and opportunities for the pharmacy

The challenges that face the profession of pharmacy in Qatar are summarized below:

Pharmacy identity at the practice level

The very rapid expansion of health services along with a trend towards decentralizing their management has created several challenges for the hospital pharmacy services¹⁴. Workload (patients accessing the service) rises steadily and at a time when service models need to be defined there is a lot of energy going in to expanding and sustaining existing service models. In the private sector there are very few financial incentives to develop pharmacy services and with most Government hospitals dispensing to their own ambulatory care patients the revenues are limited to private sector prescribing, over the counter, and non-pharmacy product sales. Salaries are not very competitive and while there are some private pharmacy chains that are endeavoring to provide a modern professional service, they are not yet an integral part of secondary health care in Qatar⁸. The introduction of health insurance and opening up secondary care to the private sector would transform this sector.

Product focused practice model

In the community pharmacy sector, the practice is still dominated by dispensing and selling pharmacological and non-pharmacological products⁸. This is a phenomenon that characterizes the private pharmacy sector not only in Qatar but in most other countries in the region. In the hospital sector there are still many more pharmacists than technicians and limited use of automation to prepare medicines so it is not unusual to have a dispensary dominated by pharmacists. In their study that looked at medication use perceptions and professional satisfaction of pharmacists practicing in Qatar, El Hajj et al reported that over half of the pharmacists surveyed identified improvements to the professional role of the pharmacist and greater opportunities for professional development as major factors that would increase their professional satisfaction⁸. Others suggested enhancements in human resource-related conditions (e.g., adequate staffing, reduced workload, and better compensation) as important requirements⁸.

Opportunities for pharmacy practice

Recently, the pharmacy practice scene in Qatar started to go through rapid and important change and developments. The most important drivers of these changes can be summed up in the developing hospital pharmacy services, pharmacy education, Qatar's strategic health plans, and pharmacy leadership.

Developing hospital pharmacy

The hospital pharmacy sector provides and sustains a young, but a rapidly growing, clinical pharmacy service that was introduced in some of the public hospitals since 2006. One hospital

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(specialized in cancer therapy) provides clinical pharmacy services by two experienced clinical pharmacists (covering a total of 50 beds), and the department of pharmacy of this hospital has plans for adoption of pharmaceutical care and medication therapy management in its strategic future programs¹⁵. A recently opened government hospital has been designed to take full advantage of automated and computer controlled drug distribution, liberating more pharmacists to ensure that patients get safe and effective medication. Other larger hospitals are able to deliver clinical pharmacy services to high priority inpatient groups for example intensive care units, pediatrics and other vulnerable patient groups and acute admissions. The only published research that looked at physicians' acceptance of cognitive services provided by pharmacists in public hospitals showed that physicians were comfortable with the pharmacists' role in these patient care areas despite many unmet expectations¹⁶. Existing hospital pharmacies and pharmacy services in new hospitals being furnished will have the lion's share of new pharmacy graduates (the majority holding PharmD degrees) coming out from Qatar's national College of Pharmacy. These fresh graduates from a modern pharmacy program will ensure the growth and maturation of the hospital pharmacy sector into effective clinical services.

Pharmacy education

In 2007, Qatar University opened the first and only College of Pharmacy in the country. This is the newest public College of Pharmacy in the Gulf region at the time this article was written. Admission to the program requires completion of United States-based pharmacy college admission test (PCAT) as a component of the application process¹⁰. Admission also requires attending a structured interview, in addition to providing a personal statement and references. The College had secured provisional international accreditation from the Canadian Council on Accreditation of Pharmacy Programs (CCAPP) in 2008, making it the first and only accredited pharmacy program by the CCAPP outside Canada. The College had its plans for PharmD degree approved in early 2007, and its first candidate will start their degree in September 2011¹⁷. The PharmD degree program was designed to meet western accreditation standards and to provide advanced professional training opportunities for students wishing to pursue specialized clinical careers. The first baccalaureate and PharmD graduates from Qatar's College of Pharmacy will enter the workforce in 2011 and 2012, respectively. It is anticipated that these graduates will mark the beginning of qualitative improvement in how pharmacy is practiced in this country and may lead to fast-tracking of the introduction of patient-centered practices in several pharmacy outlets in Qatar.

The College of Pharmacy delivers a contemporary pharmacy curriculum. A course integration teaching strategy introduces a disease-based teaching and management strategy that uses pharmaceutical care approaches. Medication therapy

management is introduced as the clinical application of pharmaceutical care at different semesters, and integrated case-based learning demonstrates a problem-based learning strategy in teaching. Professional skills (like communication skills, writing skills, patient assessment skills, and care planning) feature prominently throughout the course of study¹⁷.

The College of Pharmacy adopts a strategy of involvement with health care policy and practice in the country through linking with multiple practice site and multiple local Stakeholders Group meetings involving hospital, community and other pharmacy practitioners, as well as supporting organizations¹⁸. In 2008, Qatar University's College of Pharmacy students joined the International Pharmacy Student Federation (IPSF) which has 350,000 students from over 70 countries and recently this young program successfully hosted the second annual Eastern Mediterranean Regional Symposium (EMPS) in Qatar (July 15-21, 2011), where over 150 pharmacy students from 14 countries in Europe, Africa and the Middle East attended the 7-day educational conference¹⁷.

A new pharmacy technician program has also recently opened in Qatar. This program is operated by the Qatar branch of the College of North Atlantic (Canada), and its graduates are trained to support local pharmacists in the delivery of competent health care¹⁰. This program has also been accredited by CCAPP making it the only Canadian accredited Pharmacy Technician program outside of Canada. Many of the students on this program are sponsored by local employers (including government health services) and many of its graduates have already entered the job market and are much sought after due to both their quality and scarcity in the labour market. As per the strategic planning of the pharmacy services at the main government provider (Hamad Medical Corporation), pharmacy technicians will start to provide most of the preparative and dispensing services and most pharmacists will be deployed to provide clinical pharmacy services using the pharmaceutical care approach outside of the pharmacy units¹⁹.

The visibility of pharmacy academics, their deliberate engaging strategies with stakeholders, coupled with an active College's Continuing Professional Pharmacy Development (CPPD) program and an organized Structured Practical Experience Program (SPEP) that allows students to spend supervised training time in community and hospital pharmacies during their undergraduate course are all important factors that maximize the chances of advancing pharmacy practice in Qatar.

Pharmacy practice in Qatar's strategic plans

At a National level, the identity and leadership of pharmacy practice in Qatar received a boost from the National Health Strategy 2011-2016⁷. The strategy describes its goal of developing a comprehensive world-class healthcare system, such as the introduction of disease management, health insurance

and greater integration between government and the private sector⁷. The document advocated 'a community pharmacy network supported by appropriate policy and process, decreasing the reliance on hospitals for filling drug prescriptions, leading to increased efficiency and enhanced access²⁰. These policies and plans exemplify the national leadership that will be necessary to provide the impetus for a transformation of pharmacy practice to being an effective patient-centered service provided by pharmacists and supported by technicians and automation.

Pharmacy leadership

At the practice level, leadership has come from Hamad Medical Corporation (HMC). HMC is a Joint Commission International Accredited health system that currently includes seven hospitals. In 2009, the managing director revised and re-launched a pharmacy leadership group known as the Pharmacy Practice Committee (PCC), which is comprised of both pharmacy leaders from within HMC and educational leaders from the College of Pharmacy and CNA-Q. Key objectives of the Pharmacy Practice Committee include (a) To provide governance and leadership on professional pharmacy issues; (b) To identify and develop good pharmacy practice models for HMC; (c) To support and encourage these models to be applied across all HMC facilities; (d) To ensure that the pharmacy profession is structured and maintained to meet the needs of the citizens of Qatar; and (e) To provide timely scientific, technical and administrative advice and recommendations regarding pharmacy practice to the HMC Executive.

In June 2011, the bar was raised even further when HMC leadership announced that it was committed to creating an Academic Health System. It is clear that the pharmacy practice Committee must seek to develop pharmacy services that meet the needs of the patient and the expectations and demands of a world class Academic Health System. This together with the Corporate Executive announcing that Medication Safety was one of the key priorities has helped to ensure that pharmacy is highly valued as a clinical service at the highest levels in the organization, not simply as a drug distribution service.

Frameworks such as the "High Performance Pharmacy" framework developed in the USA represent excellent tools for planning and prioritizing efforts²¹. These are exciting times and another initiative that will help to transform medicines management in HMC will be the introduction of a Clinical Information System that will provide an integrated electronic medical record across the majority of government providers, including Computerized Physician Order entry.

One major initiative that is hoped to help in the transformation of pharmaceutical services and practices in Qatar is the fact that a revised and progressive pharmacy and medicines law is under review and should be published in the near future. This law, and its associated regulations, will enforce professional standards and encourage the development of patient (not product) focused services. It is therefore anticipated that the new pharmacy law and regulations will provide the basis for a contemporary

pharmacy practice in Qatar, where pharmacists will be expected to demonstrate a professional attitude, be capable to show an understanding of the cultural and professional requirements in a Qatari pharmacy environment, and can be held accountable for their performance.

In conclusion, the State of Qatar is in the middle of a revolutionary expansion of health services and, thanks to pioneering educational initiatives and strong leadership at the national and practice level, there is a very good chance that pharmacy will emerge transformed into a highly respected, and progressive clinical service.

Authors' contribution

Nadir Kheir conceived the idea and both authors contributed in writing the commentary. This commentary reflects the opinions of the authors and not necessarily that of any organization in the State of Qatar.

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No conflict of interest to declare

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What determines the duration of patient medication compliance in patients with chronic disease: are we looking in the wrong place?

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Abstract

Objectives: The objective of this study was to do a pilot inquiry, to determine whether physicians with similar practices in the same neighborhood demonstrated any difference in the duration of compliance among their patients.

Methods: Through a cooperating urban community pharmacy, patients with prescriptions for hypertension and type II diabetes were identified for this pilot study. Patients refill medication records were searched to determine the average number of months of drug regimen compliance. The patient data of the four local physicians were separated and compared.

Results: One physician was able to generate refill durations nearly double that of the average duration of medication refills seen in the patients consulting the several other nearby physicians.

Conclusion: In this pilot study, it was determined that there are differences in the compliance behavior of patients attending different physicians. We can conclude that some communication or personality characteristics of some physicians appear to be more successful in achieving higher compliance. Subsequent studies should identify those which may be at least partially responsible for this finding.

Keywords: Medicines compliance, medicines concordance, patients, physicians

Introduction

The importance of patient compliance was mentioned 2000 years ago by Hippocrates and after all of this time, the issue of non-compliance has still not been definitively solved¹. Numerous studies have been conducted on the topic of patient medication compliance^{2,3}. Patients' income, co-payment levels, tablet or capsule shape or color and patient age, gender and numerous other socio-demographic variables have been considered some of the factors which could help or aid towards patient compliance. For many years, pharmacists have attempted to understand how they can improve patient adherence. Time spent by pharmacists undertaking consultation, and the communication skills learned by pharmacists have been found to be important issues⁴. However, studies are incomplete and inconsistent regarding the benefits of printed leaflets, follow-up telephone calls, colorful labels, special boxes for pills, reminder

alarm boxes, printed personalized instructions and in-person encouragement at the prescription counter in the pharmacy.

Each new research project has endeavored to understand and explain at least one aspect of the overall compliance problem. But nearly all of these studies^{4,5} have focused on the patient or in a few cases, on the pharmacist and nevertheless they do not seem to help in aid in solving and understanding the dilemma of lack of compliance with prescribed therapeutic medication regimens. One may speculate that the pharmacist and the patient are not the only directions to look for answers regarding patient medication compliance behavior. It is rather obvious that the first person who comes in contact with the written prescription for a patient is the physician. And usually, physicians inform patients about their illness and about the importance of the drug being prescribed. Physicians are the ones who would be expected to motivate, encourage and persuade patients

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about the medication schedule necessity as prescribed. It is well-known that physicians have a powerful effect on patient knowledge regarding their therapy as well as patient behavior. Following on from Tamblyn⁶ et al., the authors suspect that there is a possibility that physicians who usually possess great proficiency in communication and/or medical management will achieve better medication adherence among their patients, but that this has not been examined definitively².

It is estimated that only one half of patients with chronic diseases are compliant over time⁷. Lack of compliance with prescribed medication is likely to influence numerous medication related outcomes such as: unnecessary suffering, hospitalization, decreased quality of life and increased costs for both the individual and society⁸. Findings from qualitative-oriented compliance research have been used to build behavioral models to overcome and improve compliance with medication deficits. The Health Belief Model and Health Decision Model are examples of such efforts⁹. Based on reports about these models, questionnaires were developed. The Beliefs about Medicines questionnaire (BMQ) is one of the surveys that have been studied based upon several qualitative and quantitative inquiries. These studies show that both general and specific beliefs have an effect on compliance. Also, health professionals' beliefs affect patients and their own beliefs, opinions and attitudes. Health professionals, primarily doctors, nurses and pharmacists reflect their own beliefs to patients while they are communicating. Patients' and health care providers' cultural backgrounds have also been found to have an influence on patient adherence behavior¹⁰. Moreover, it has been shown that demographic variables such as gender, age, education, income and clinical variables such as disease severity or culture variations have a relationship with compliance. There are also multiple other reasons for patients' failure to comply with medication regimens. Patient unwillingness to accept the therapy, lack of motivation, early recovery and forgetting about physician advice are also some other factors^{11,12}.

Britten¹³ suggested that noncompliance can be avoided through five prerequisites undertaken by physicians during patient consultations. Britten believed that willingness to share power and a commitment to giving appropriate weight to patient values and goals, open discussion of the options with explicit inquiry to patient views without making assumptions, adequate sharing of information, including uncertainties to arrive at a decision, listening as much as talking, and time allocated to patients are vital prerequisites the physician should include in any consultation.

Cushing and Metcalfe¹⁴ found that patients could remember only about 60% of what they had been told. Patients remembered the first things that the physician had said. And also, it was found that patient' prior knowledge and consistency aid in recall when the health professionals' explanations are not very clear. In essence, this means that if the message from the physician is not entirely clear, that patients will continue believing their own ideas and much of this prevents them from being totally compliant.

In accordance with data on this topic in the literature, Huntenburg¹⁵ also found that most of the patients for whom long term drug therapy was prescribed, ceased using their medications after a brief period of time. About 50% of patients who have been prescribed maintenance medication for chronic conditions for the first time, stop using their medications within a matter of months. Perceived side effects, ineffectiveness of medications and personal considerations were related to the use, as well as lack of need of treatment. These were the main reasons for discontinuing maintenance drug therapy¹⁶. Also, in another study, it was declared that one third of chronic patients' beliefs were that long-term effects of medications could be dangerous. The same study strongly emphasized that medication beliefs were more powerful predictors than were clinical and socio-demographic factors¹⁷.

In Horne and Weinman's research, patients who had stronger concerns about side effects reported having lower adherence rates. This should remind us that patient education via the media and direct marketing may have unwanted effects, especially on patients with chronic conditions, and elderly patients. Patients who believe in themselves more than health professionals are seen to be more noncompliant according to qualitative semi structured interviews. Many chronic condition patients declared: "I hate taking medicines." This is an important statement that we learn from many societies. At this point, the role of the health professional, especially the physician, is the most important role for patients¹⁸. These declarations and statements by patients lead us to think that physicians' affect and role should be measured. The study and the analysis of the generated data describe and prove the statements to be true.

Physicians' effect on compliance has been investigated in many different illnesses, both chronic and acute, and it is obvious that if communication is to be effective between patient and physician, the patient is more likely to adhere¹⁹⁻²². These background studies and their results lead us to speculate that patient compliance with prescribed medication may differ according to physician characteristics and variables.

One of the important variables of noncompliance is the patient's cultural difference with the physician. The world is globalizing and in both developed and in lesser developed areas, people are moving and migrating. Communicating on health issues with the physician is becoming more complicated for patients. In a study, interviews with diabetic patients related to compliance show that food has different meanings for various ethnic groups. Patients were not compliant with the nutrient regimen that physicians had asked them to adhere to and some patients did not even comply with described future consultation visits because of this²³. The study has also been replicated in various ethnic neighborhoods.

In order to measure patient compliance with prescribed medication, numerous different methods have been used: pill counts, physical tests, medical and pharmacy records, self-reporting, electronic monitoring, health behavior testing and

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appointment keeping²⁴. In this context, the objective of this study was to determine whether different physicians are associated with different patient compliance results. In this study patient compliance was measured using a different approach, involving pharmacy refill records. The objective was then to determine whether physicians in similar practices had differences in the medication compliance rates of their respective patients. The variable responsible for differing levels of patient compliance with prescribed medication to physician characteristics was postulated.

Methodology

Recent research has shown that structured self-reported measures can yield adherence estimates that have moderate to strong concordance with objective measures such as computerized pharmacy records, insurance claims records and electronic monitoring. Such reports support a high correlation between self-reported measures and pharmacy records²⁵. As Rickles and Svarstad²⁶ showed in their study, patients' written and oral information strongly paralleled pharmacy records. Given these conclusions it was decided to use only pharmacy records and not to engage individual patients in this study.

New and refill prescription records were obtained from an urban, independent community pharmacy located in Philadelphia, Pennsylvania on a crowded, busy, shopping street. The neighborhood is comprised of lower social/economic strata patients, many of whom are from ethnic minorities. Very close to this community pharmacy are the solo offices of four different general practitioner physicians. All of them treat the full range of patient medical problems and most of the prescriptions written by these four physicians are brought to the study pharmacy since it is the closest community pharmacy to their offices. Many of these lower income patients do not own automobiles, so convenience and proximity are important considerations in community pharmacy choice.

The study data regarding patient and physician identifications was blinded to the researchers, an assumption was made that the 154 patients included in the study were in many ways homogeneous, from the same neighborhood, similar educational attainment and probably the same general range when typical chronic diseases such as diabetes and hypertension are first recognized. This assumption was accepted as basically accurate by the pharmacists at the study pharmacy. Patient medication records in the pharmacy's computerized management and information system were searched for patients with an index prescription for a chronic medication. The date that the patient should collect follow-up medication was calculated by using the prescribed dosage and the number of medication units. This was matched with the number of days of actual supply. Chronic medications were assumed to be taken regularly all year. The number of months that the patient had medication prescribed and collected from the pharmacy was calculated and recorded. Some patients had concomitant chronic illnesses and medicines,

but only drugs for cardiac conditions and diabetes were included in the study. The medications for these conditions when found in the pharmacy records were noted and analyzed. The outcome for each patient was only a number and the total number of months that the chronic condition medication was refilled was also recorded. Prescriptions were recorded from January to December 2010. The computer service monitored these patients and follow-up medication refills were provided anonymously with patient code numbers during the one-year study period. The medication practices of patients of four physicians were recorded. The difference between the compliance periods for patients of the four physicians was evaluated.

Regarding ethical concerns, the researchers were blinded and did not know the identity of the four physicians or of any of the patients. The researchers had no link to patients or physicians. The pharmacist provided the documents with physicians being numbered and with patients having a separate number system. All ethical considerations were adhered to and neither patients nor physicians were put into any risk at any time.

The data analysis was conducted with the use of SPSS version 15. First, the Kolmogorov Simirnov Test was applied and it was found that the distribution was asymptotic. Then with the addition of the Kruskal Wallis Test, the differences between the groups (physicians and patients) were analyzed. Following this it was found that there was a significant difference between groups (<0.05), and the Mann – Whitney U Test was used for paired groups to determine where differences existed.

Results

The study included 154 patients. The number of total patients was 210, but the number of patients that fulfilled with the study criteria of chronic coronary or diabetic diseases with prescribed maintenance medication was 154. The summary of findings may be seen in Table 1.

The concern about *seterus paribus* was taken into consideration; patient age, gender, financial, educational and clinical situations were expected and assumed to be similar and homogeneous. The Kruskal-Wallis Test showed that there is a significant difference between the physicians ($p < 0.05$). The Mann-Whitney Test was used between each pair of groups so as to define where the differences exist. There is a significant difference between physician one and both physicians three and four. There is no difference between physicians three and four in terms of patient

Table 1. Physician Compliance Results

TOTAL	Physician 1	Physician 2	Physician 3	Physician 4	Results
Number of patients	37	43	89	41	210
Number of chronic patients involved	16	33	67	38	154

Table 2. Description of data analysis

Phys. No.	No. of patients	Mean	Std. Deviation	Std. Error	Mini.	Max.
1	16	5.7500	3.19374	.79844	2.00	12.00
2	33	4.3333	2.68871	.46804	1.00	12.00
3	67	3.0000	1.63299	.19950	1.00	7.00
4	38	3.3158	1.33771	.21701	1.00	6.00
Total	154	3.6494	2.20674	.17782	1.00	12.00

compliance. The difference is mainly coming from physician one's patients ($p < 0.05$), as seen in Table 2.

Physician 1's patients have nearly 6 months of compliance, on average. This is the highest duration compared to the other physicians' patients. The least compliant group is that of physician four's patients. Their average compliance is three months with the most compliant patient demonstrating only seven months adherence with prescribed medication. There is no difference between physician three and physician four's patient compliance. Their minimum and maximum compliance are similar, even though the numbers of patients the individual doctors are substantially different. ($n=67$ vs. $n=38$). Physician 2's patients have average compliance duration of 4.3. There is a difference between the numbers of compliance months between the four physicians' patients.

Physician 1's patients are the most compliant group. It is obvious that some characteristics of physician one lead to his/her patients having followed their drug regimen longer than those of the other physicians.

Discussion

We believe that a major part of persuading a patient is to "touch" his or her needs. No matter what one thinks about the illness or drug, if you believe in the doctor, you obey what he has instructed. The important thing in compliance, more than technical and medical knowledge, is communication. All the communication barriers should be eliminated to persuade and lead the patient to compliance.

It is advised that barriers between health professionals and patients should be eradicated. These barriers could be summarized as: time, communication skills and medical training. Physicians are motivated to tell the medicine name, what it does to the patient, to ask the patient's opinion, to talk more about the side effects and benefits of the medicine, and to listen more²⁷.

As Homedes and Ugalde declared a decade ago, modifying the behaviour of all the actors in the medication cycle (manufacturers, health professionals, retailers, consumers and government) is needed. A meaningful change is necessary to improve the pharmaceutical management as it has a very precious economic value²⁸. Managing pharmaceuticals is in a way like managing economics. All health professionals in all arenas of the health system have to take care of clinical, humanistic and also economic outcomes. The cost of non-compliance affects all society. Especially, chronic diseases need long term medication treatment. Both in diabetes and hypertension, patients misusing medicines cause more severe health problems, complications, suffering and expenditures. So, to allocate and share resources properly, compliance is an important issue for health economists. Non compliance also is a criterion for negative effects of health investments.

In the last five decades many studies have looked at compliance. It is obvious that the term compliance is used for adherence, concordance, cooperation and partnership in different parts of this paper. The foundation for compliance is a health profession-patient relationship, good communication and shared decision-making. Patients' health beliefs and the patient perspective should be incorporated also in doctor-patient encounters. However, health care providers can change themselves faster than the patients and it is necessary to continue to revise professional relationships as this paper has shown that physicians are a major factor.

This pilot study was not designed to determine what physician variables might be related to patient compliance differences, but only to ascertain whether such differences might exist. Having found that, future research is now needed to help determine what features or physician attributes are critical and related to the differences found in this pilot study.

One may consider the situation of the office: professional or shabby, or physician dress, the number of minutes spent with each patient, the nature of the communication, the opportunity for the patient to ask questions, eye contact, a handshake or pat on the back as possible key features. As a subnote, the reader has probably already recognized that the duration of compliance for even the patients of "the best" doctor in this study are not ones to brag about. Clearly there is still a void or vacuum which translates into an opportunity for the dispensing pharmacist to reinforce the message about the importance of serious efforts toward long-term compliance with the prescribed therapeutic regimen.

Conclusion

What may be concluded from this pilot study is that there were major differences in the average compliance rates of several physicians. Physician characteristics and features should be studied in a greater sample sized investigation and accompanied

What determines the duration of patient medication compliance

by the collection of physician practice information. Perhaps we have been looking in the wrong place far too long in the search for the key to high levels of patient medication compliance.

Limitations

This study has several imitations. First of all, as only a small sample of patients was involved and only one pharmacy data were used, findings may not be generalizable to other patient populations. Also physician characteristics and specifications cannot be generalized. They can all be similar or totally different both in character and professionalism. Other potential predictors of medication use such as side effects, disability, costs, polypharmacy were not evaluated and thought to affect all participants similarly. Third, we did not collect oral or written data from patients. We do not know the reasons for not obtaining the refill. Finally, pharmacy records may have limitations as a data source but it is assumed that patients usually patronize the same pharmacy for refills and that records are maintained accurately.

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Impact of pharmacist recruitment on ADR reporting: Malaysian experience

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Adverse drug reactions (ADRs) pose a serious risk to the achievement of positive therapeutic outcomes¹. Spontaneous ADR reporting, a key component of pharmacovigilance systems is not only an excellent means to document uncommon ADRs, but also allows the risk-benefit assessment for old and new medications^{2,3}. Despite ADR reporting being a professional obligation, underreporting by healthcare professionals is commonplace and it is estimated that only 6% of all ADRs are reported globally⁴. Whether pharmacists have a role in national drug monitoring programmes varies by country. For example, in the United States, 70% of the ADR reports submitted to the Medical Watch programme were generated by pharmacists⁵. However, in Nordic Countries pharmacists are not in a position to directly report ADRs⁶.

Malaysia has a well-organized spontaneous ADR reporting system and a postage-paid "Blue Card" is used to document and report ADRs. The blue card is accepted as the best for both ease of use and for capturing maximum data⁷. All ADR reports across Malaysia are received and screened by the Malaysian Adverse Drug Reaction Advisory Committee (MADRAC), within the National Center for Adverse Drug Reaction Monitoring⁸. The center was one of the earliest members of the World Health Drug (WHO) Safety Monitoring Program in Asia (1990), before Singapore (1993), India, and China (1998)⁹. Recently, a mechanism has been introduced to allow patient reporting of ADRs directly to MADRAC. Reports can also be submitted online via MADRAC website.

Historically, underreporting of ADRs has been a serious problem in Malaysia¹¹. However, the number of reports received by MADRAC has increased from 2363 in 2005 to 5850 in 2009, fulfilling WHO criteria for a reporting centre (200 reports per million of population) for first time in 2009¹⁰. The sharp rise in

reporting rate is mainly due to reporting by pharmacists working in the public sector. Adverse drug reaction reports generated by pharmacists increased from 726 (28.5%) in 2006 to 3357 (57.4%) in 2009¹¹. On the other hand, the contribution by physicians towards ADR reporting was 22.9% in 2009¹¹. The increase in the number of reports submitted by pharmacists could be a reflection of the increase in pharmacists working in public hospitals. In Malaysia, the number of pharmacists working in the public sector increased from 889 in 2005 to 3877 in 2009¹¹. This is likely to be due to the Malaysian Ministry of Health's requirement that before registration with the Pharmacy Board of Malaysia, all pharmacist must complete a 4-year compulsory service in public sector. The aim of this initiative was to enhance clinical pharmacy services in public hospitals and health clinics in Malaysia. The involvement of hospital pharmacists in direct patient care appears to have triggered better detection, documentation and reporting of ADRs. The contribution of community pharmacists in ADR detection and reporting remains suboptimal and necessitates further education and training.

Authors' contribution

MAH did the literature review and wrote the initial draft. LCM provided the data related to pharmacovigilance in Malaysia and proof read the final draft.

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Conflict of Interest

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