



Review

Policies to promote use of generic medicines in low and middle income countries: A review of published literature, 2000–2010

Warren A. Kaplan^a, Lindsay Sarah Ritz^b, Marie Vitello^c, Veronika J. Wirtz^{d,*}

^a Center for Global Health & Development/Department of International Health, Boston University School of Public Health, Boston, USA

^b Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, 1620 Tremont Street, Suite 3030, Boston, MA 02116, USA

^c Children's Hospital, 300 Longwood Avenue, Pavilion 269, Boston, MA 02116, USA

^d Center for Health Systems Research, National Institute of Public Health, Av. Universidad 655, Cuernavaca, C.P. 62100, Morelos, Mexico

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ABSTRACT

Objective: Review the literature on the impact of policies designed to enhance uptake of generic medicines in low and middle income countries (LMICs).

Methods: We searched for publications related to generic medicines policies (January 2000–March 2010) and did a bibliometric, descriptive analysis of the dataset in addition to an analysis of studies evaluating the impact of pro-generic policies. We repeated a subset of this larger search in January 2012.

Results: Of the 4994 articles screened, 315 (6.3%) full-text publications were related to generic medicines policies. Of these 315, 236 (75%) dealt with generic medicine policies in high-income countries, and 79 (25%) with policies in LMICs. In total, we found only 10 evaluation studies looking at the impact of competition, trade, pricing and prescribing policies on generic medicine price and/or volume. Key barriers to implementing generic medicine policies in LMICs are negative perceptions of stakeholders (e.g., generics are of lower quality) plus perverse private sector financial incentives to sell products with the highest profit margin. Other relevant barriers are legal/regulatory, such as the absence of generic substitution regulations. There also exists a general difficulty in promoting generics due to a lack of transparency in the pharmaceutical supply and distribution system, for example, a lack of price information provided by health care provider organizations to physicians.

Conclusion: There is little policy evaluation to determine which pro-generic policies increase generic medicines utilization in LMICs. Ensuring a functioning medicines regulation authority, creating a reasonably robust market of generic medicines and aligning incentives for physicians, consumers and drug sellers are necessary prerequisites for increasing the uptake and use of generic medicines.

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1. Introduction

With the rising costs of healthcare and the uncertain global economic situation, governments and payers in many countries will require the increased usage of generic

medicines. Data from price surveys in 36 low and middle-income countries (LMICs) show that in the private sector, prices of the lowest cost generic medicines were on average 2.6 times less expensive than the corresponding originator medicines [1]. By using generic medicines, potential savings can be quite large [2]. For example, in the private sector of 17 countries, the average percentage savings for individual medicines ($n = 4$ –12 medicines) ranged from 9% to 89% if private sector purchasers would switch from originator

* Corresponding author. Tel.: +52 777 329 3040.

E-mail address: veronika.wirtz@insp.mx (V.J. Wirtz).

brands to the lowest-priced generic equivalents [2]. Savings would not, however, be confined to the private sector. For example, in public hospitals in China, over US\$86 million (2008 dollars) could be saved from switching only 4 medicines, saving patients an average of 65% [2].

Given the actual and perceived need for increased usage and promotion of low-price, assured-quality generic medicines, it is important for countries to gather evidence as to what pro-generic medicines policies actually work in their countries' context. There is a large body of research on pro-generic medicine pharmaceutical policies in the United States and Europe, see e.g., [3–6]. In contrast, impact evaluation of pro-generic medicine interventions in LMICs appears much less systematized.

Therefore, the objective of this study was to inquire into the nature, extent and strength of the evidence for successful implementation of pro-generic medicines policies in LMICs. We further attempt to characterize barriers to increasing the uptake of generic medicines in LMICs that are related to “supply side” (e.g., trade, competition, pricing, regulation, intellectual property, reimbursement) and “demand side” (physician, dispenser, consumer) policies. Finally, we attempt to also identify a minimum set of pro-generic medicine “enabling” policies that most LMICs could implement to help policy makers prioritize actions.

2. Materials and methods

2.1. Search strategies

To the extent possible, the literature review followed the PRIMSA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The study protocol is available upon request from the authors. We searched the following databases for publications between 1 January 2000 to 31 March 2010 in English, French, Spanish and Portuguese: PubMed via the US National Library of Medicine, Excerpta Medica Database (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Political Science Abstracts of CSA Worldwide (the Public Affairs Information System (PAIS)), Thomson Reuters (formerly ISI) Web of Science, POPLINE (One Source), and the Latin American Literature on Health Sciences (LILACS). For the ISI Web of Science database, we searched for “generic” or “generics” in the title and/or abstract. We searched for topics and keywords using MeSH terms for PubMed. Major subject headings were used for CINAHL, EMBASE, CSA/PAIS, POPLINE and LILACS (i.e., “medicamento” and “generic”). The search strategies were meant to capture high-income countries (e.g., United States, Europe, Canada, Japan, New Zealand, Australia and the like) and “low and middle income” countries. A detailed description of the search terms can be found in [Electronic supplementary documents](#). We defined “policies” as laws, rules, financial and administrative orders made by governments, non-government organizations or private insurers [5]. We tested whether we may have missed literature by using alternate terms for “generic” by just searching PubMed using the terms “interchangeable or interchangeability” plus the term “policy” or “policies”. We then compared our

results with those from our larger search using “generic” or “generics”.

In January 2012, we repeated two broad PubMed searches originally done in March 2010 (i.e., “generic drugs” and “health policy” with, and without, the MeSH designation) as a validity check on the method and to obtain any references after 2010 that might be considered impact evaluation. The results of these two searches (March 2010 and January 2012), were identical between the two dates, aside from new references post-March 2010. The additional references for impact evaluation studies were included in [Tables 2 and 4](#). Other studies from this January PubMed search were not included in the aggregate bibliometric analyses because we only searched PubMed and not any of the other databases.

We created the following policy domains as adopted from the literature [7,8]: regulation (market authorization and labeling), competition (e.g., timing of entry onto the market, balancing interests of originator and generic), trade related aspects/intellectual property right(s) (e.g., Trade-Related aspects of Intellectual Property Rights (TRIPS), free trade agreements, patents), pricing (e.g., reference pricing, tendering and other fiscal policies), reimbursement, prescribing, dispensing and consumer/patient. Publications in the database were classified according to these policy domains for each high-income and LMIC country.

We assumed that a rigorous study of pro-generic policies in LMICs would likely be published in database-indexed journals so our literature review was primarily focused on peer reviewed articles as opposed to the so-called “grey literature” (i.e., written material that is published and/or not widely accessible such as from technical reports from government agencies or scientific research groups, working papers from research groups or committees and so-called “white papers”). We do note, nonetheless, that there is a large amount of “grey” literature on this subject. To capture some of this grey literature, we limited our search to the electronic databases of the following organizations: World Bank, World Health Organization, Health Action International, Pan American Health Organization. If the website of these organizations allowed, the search was done using the same key words as for the database-indexed journals. If the website did not allow searching, or the searches did not result in any hits, we searched the sections (if any) of the website directed to “pharmaceutical policy”, “medicines”, and/or “pharmaceuticals”.

2.2. Data review and exclusion criteria

The original searches from all the databases were combined in an EndNote® library (EndNote® version 8, San Francisco, CA, USA) and all duplicates removed. References lacking abstracts or studies with ONLY abstracts were excluded. We excluded any study that did not relate to pharmaceuticals (e.g., studies dealing with devices and vaccines) or if it was clearly unrelated to generic medicines (i.e., a study about “generic” administrative policies or “generic” factors related to water purification) or if the reference evaluated the use of generic medicines or was in some way not related to generic medicines policies (e.g., bioequivalency studies). Two independent teams of

authors (WAK plus LSR and MV plus VJW) reviewed each of the titles and abstracts independently. The cases of disagreement were resolved on an individual basis via detailed discussion of the justification for exclusion.

2.3. Data analysis

We performed a simple descriptive bibliometric analysis of this dataset to map the research available about generic medicines of LMIC and high-income countries. Relevant articles from Endnote® were placed in a series of Excel® tables. For each publication, extracted data included: year of publication, author name(s), publication title, country of first author's affiliation and of the corresponding author, and funding organization. If no funding source was specifically mentioned, we inferred that it came from the organization of the corresponding author. We calculated frequency of country(ies) (region) of focus and policy domains. Country or countries of focus, theme, type of study (e.g., narrative, observational, survey) were assessed by reading the full text. Countries were classified into “low and middle income” countries (including “upper middle income” countries) according to the World Bank classification: low income, \$995 or less; lower middle income, \$996–\$3945; upper middle income, \$3946–\$12,195 [9]. All other countries according to the World Bank scheme are considered high-income countries (Gross National Income (GNI) per capita \$12,196 or more). We note that in some search engines, these terms did not correspond exactly to the LMIC groupings. For instance, in EMBASE, the search term “developing country” includes Hungary, which the World Bank considers a “high-income” country. We corrected these discrepancies when we reviewed each of the references.

2.4. Impact evaluation

We carried out a second type of analysis for selected publications which focused on one or more LMICs to describe in-depth those that presented an impact evaluation of a pro-generic policy using at least one of the following study designs: interrupted time series analysis, repeated measures studies, and/or controlled or uncontrolled before and after studies, and/or a predictive economic or other model such as a multivariate regression. The study had to include appropriate outcome measures: for instance, change in generic medicines volume market share over time to demonstrate changes in prescription or sales. Other outcome measures could be price change and/or costs (expenditure) in combination with volume and price change. We extracted information on the method, outcome measure(s), and effect size of the policy (e.g., the amount of savings, the magnitude of price reduction, or the magnitude of market share increase of generic medicines).

2.5. Barriers to implementation of generic medicines policies

Finally, of the large number of included articles that did not fall into our sub-category of impact evaluation, we reviewed all of them for a discussion of the factors that act

Table 1

Geographic focus of policy literature: top ten league table.

Country or region focus	Total
United States of America	76 (32.6%)
Multiple (high-income + LMIC)	50 (21.4%)
Multiple (LMIC only)	29 (12.4%)
Australia	17 (7.3%)
Canada	14 (6.0%)
Spain	12 (5.1%)
France	11 (4.7%)
Sweden	8 (3.4%)
Brazil	8 (3.4%)
India	8 (3.4%)

as a barrier to implementation of pro-generic medicines policies in LMICs. Specifically, we looked for barriers with respect to enhancing access to medicines (i.e., affordability and availability). We made no attempt to “grade” the evidence presented in these primarily descriptive documents [10].

3. Results

3.1. Bibliometric analysis

Of the 4994 articles screened, 686 references (13.7%) contained “generic” in the title or in the abstract (Fig. 1). Out of those 686 references, we identified 313 full text publications (45.9%) whose overall subject matter was related to generic medicines and pro-generic medicines policies in high-income and LMICs.

Many geographic regions and countries were represented in these references, but the top ten most common countries/regions (representing $n=233$ references) are shown in Table 1. More than 32% of these 233 references concern generic medicines and medicines policies in the United States and an equal percentage of these total references deal with groups of countries in the aggregate (“global”). The LMIC economies of India and Brazil are the primary representatives of the LMICs (nearly 7% of the 233 references).

We also categorized the publications from both high-income countries and LMICs into the eight, pre-defined policy domains. Slightly more than half (50.4%) of all these total publications concerned price, prescribing and competition-based generic medicine policies (Table 2). Forty percent ($95/236=40.2\%$) of policy domain topics for high-income countries and about 32% of the identified literature in LMICs dealt with these same three policy domains. Thirty two percent of LMIC references emphasized trade/IP policies compared to just three percent of high-income references. Proportionally, twice the high-income literature emphasized regulation as compared with the LMIC literature (Table 2). For LMICs, information about pro-generic medicine policies related to reimbursement, or the consumer/patient/end-user were the least common domains (6.5% of total LMIC literature).

3.2. Funding

Of the 79 references from LMICs, 35 (44.3%) specifically stipulated the funding source for the research, and

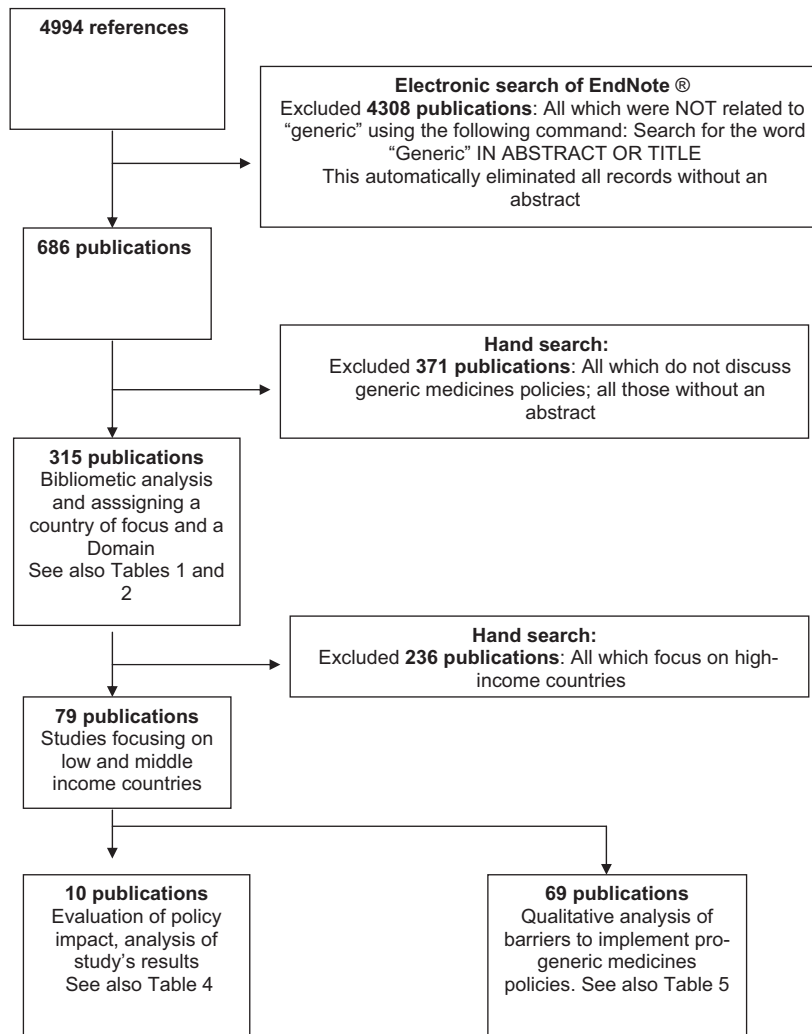


Fig. 1. Search algorithm.

Table 2

Literature review: policy domain analysis-number and geographic location.

Overall rank	Domain	Total (% of grand total)	High-income (% of high-income grand total)	LMIC (% of LMIC grand total)
1	Price	50 (15)	39 (17)	11 (14)
2	Various domains	48 (15)	37 (16)	11 (14)
3	Competition	39 (12)	30 (13)	9 (11)
4	Prescribing	33 (11)	26 (11)	7 (9)
5	Dispensing	33 (11)	27 (11)	6 (8)
6	Trade/patents	35 (11)	8 (3)	27 (34)
7	Reimbursement	30 (10)	29 (12)	1 (1)
8	Regulation	26 (8)	22 (9)	4 (5)
9	Consumer/patient	21 (7)	18 (8)	3 (4)
Grand total		315 ^a	236	79 ^b

^a The total includes only two additional evaluation studies identified in a second search for literature; other description studies identified in the second search have not been added.

^b Ten of these studies are evaluations of the impact of policies (see Table 4).

Table 3
Number of LMIC studies by funding source.

Funding source	Known funder	Not stated but inferred from corresponding author affiliation
University	2	26
Government	14	2
IGO/NGO/donor	5	1
Private sector	6	5
Multiple funders	8	0
Total	35	34

IGO = Intergovernmental organizations; NGO = Non-governmental organizations.

of these only 14 (14/79 = 17.7%) were funded by a government or governmental authority. We inferred a funder for 34 of the remaining references that did not stipulate any funding source. The majority of these “inferred funders” (26/34 = 76.5%) were academic institutions (Table 3). Ten references had no information at all in this regard.

3.3. Impact evaluation of generic policies in LMICs

Of the LMIC papers found in our 2010 search, only eight studies matched inclusion criteria. Of the 12 additional LMIC references we found in the PubMed searches of January 2012, two were impact evaluations (Tables 2 and 4: both searches yielded ten studies in total: one on competition, four on trade, three on prices and two on prescribing).

3.3.1. Competition

There is good quality evidence from high income countries that competition can reduce prices for medicines. Indeed, even for patented medicines, competitive pressure from close therapeutic substitutes, or “me-too’s”, can place downward pressure on prices. Competition policy is a potentially important policy space to improve use of generics in LMICs.

A single study met our inclusion criteria for the competition policy domain. Waning et al. [11] estimated via regression analysis the impact of various global strategies to reduce antiretroviral (ARV) prices using data on procurement transactions from databases hosted by the WHO (World Health Organization) and the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM). Significantly, generics were less expensive than differentially priced branded ARVs, except where little generic competition existed, which was the case for generic protease inhibitors. In this case, the generic protease inhibitors were more expensive than their branded counterparts (e.g., lopinavir 133 mg plus ritonavir 33 mg as originator product purchased under a differential pricing scheme was 73% less expensive than the generic product purchased). For the majority of solid ARV dosage forms, they detected no association at all between price and volume purchased. In this market dominated by donor funding and relatively few producers (including many Indian manufacturers), large purchase volumes did not necessarily result in lower ARV prices.

From this reference, the key messages for generic medicines policies are: prices of generic medicines are lower compared to originator products if there is “enough” competition (not defined), and higher volume purchases are not, by themselves, sufficient to reduce prices of generic medicines.

3.3.2. Intellectual property/trade

There is a vast literature on public health aspects of intellectual property rights (IPR) and the opportunities to overcome the monopoly advantage of patents via TRIPS [12–15] and references cited therein. Nonetheless, four references fit our inclusion criteria related to the policy domain of IPR and trade. The rest of the many other studies were descriptive in nature. Ford et al. [12] used a time series analysis of antiretroviral (ARV) prices before and after key policy implementations in Brazil and Thailand to create case studies of ARV prices in these countries. Policies to improve access to medicines generally included: local production of off-patent medicines, challenging patents before they were granted (pre-grant “oppositions” – a TRIPS “flexibility”), challenging existing patents, and the threat of, or actual issuance of, compulsory licensing (a TRIPS “flexibility”). Local production in Brazil of non-patented first line medicines, coupled with the threat and issuance of compulsory licenses for patent medicines, ultimately proved successful in reducing ARV prices. By itself, price negotiations with originator companies were not sufficient to develop optimal ARV prices in both Brazil and Thailand. Brazil paid up to four times more for second-line ARV medicines as compared with international prices. For Thailand, the authors concluded that compulsory licenses and aggressive patent challenges were promoting generic medicines uptake.

Akalephan et al. [13] attempted to quantify the impact of the US–Thai Free Trade Agreement (FTA) on medicines access. According to the model, the “TRIPS-plus” provisions of this FTA were estimated to increase medicine expenses by a minimum of \$US806.4 million to \$US5.2 billion and also delay generic accessibility [13].

Kessomboon et al. [14] used a model developed and tested previously by the WHO and the Pan-American Health Organization (PAHO) jointly [15] to calculate the impact of the US–Thailand FTA on the pharmaceutical market. They made various assumptions of the impact of this FTA and determined that medicine prices would increase by 32% due to delays in generic entry based on a 10 year patent extension. We note that Akalephan et al. [13] and Kessomboon et al. [14] suggested that FTAs may increase the prices of medicines, although this conclusion still remains to be empirically tested in a methodologically rigorous manner.

Supakankunti et al. [16] analyzed the temporal changes of medicine volume and price after the 1992 Thai Patent Act and the proportion of patented and generic medicines on the pharmaceutical market. Since the 1992 Patent Act went into effect, the share of original drugs in the Thai market increased by 1–6% per year, reaching a peak in 1997, when the shares of generic and original products were 33% and 67%, respectively. However, the Thai financial crisis of 1997 complicated this analysis.

Table 4
Summary of the LMIC “implementation” studies.

Country	Author/year	Objective	Study design	Study sample	Outcome measures	Main results	Funding source
<i>Competition</i>							
Global	Waning et al. (2009)	Estimate impact of global strategies on reducing price of ARVs ^a	Cross sectional/regression analysis using original ARV price data from Global Price Recording Mechanism database	7253 procurement transactions (July 2002–October 2007) from databases hosted by WHO ^b and Global Fund to Fight AIDS, Tuberculosis, and Malaria	ARV prices, impact of differential pricing, generic vs. originator and Clinton Foundation HIV/AIDS Initiative (CHAI) negotiations on price	CHAI negotiations useful to lower prices for generic ARV's. Where generic competition is lacking (e.g., Kaletra), differential pricing by originators can lead to prices \ll generic versions. Provides some suggestions: ease generic entry into the market/tech transfer	United Kingdom Department for International Development through the Medicines Transparency Alliance (MeTA Project)
<i>Patent and IP</i>							
Thailand	Akaleephan et al. (2009)	To quantify the impact on medicine expense and medicine accessibility including access to generic medicines	Simulation study: 2000–2003 time series of national data	74 INNs ^c accounting for 49.9% of sales value (9938.7 million Baht)	Estimated consumption, estimated savings from using generics, estimated loss in savings due to extension of market exclusivity	In 2003, the availability of generics helped to save 104.5% of actual expense. TRIPS ^d -Plus proposal in the Thai–US FTA ^e negotiation would bring about a significant increase in the medicine expense as well as the delay in improved accessibility from the generics	Fiscal Policy Research Institute, Ministry of Finance
Thailand	Ford et al. (2007)	Examine strategies employed to improve access to key ARV's in Thailand and Brazil and identify factors for future success	Time series of ARV prices in Thailand; history of price negotiations in Brazil; Case study approach	Drug prices, disease rates, and legal provisions as recorded by each countries MOH ^f	Overview of strategies to improve affordable access to medicines in Brazil/Thailand	Three factors were critical to this success: legislation for free access to treatment; public sector capacity to manufacture medicines; and strong civil society action to support government initiatives to improve access	World Bank, Joint United Nations Programme on HIV/AIDS, WHO
Thailand	Kessomboon et al. (2010)	Assessed the impact of the Thai–US FTA on access to medicines	Economic simulation model Baseline condition (TRIPS) vs. US/Thai FTA TRIPS Plus provisions	Model ran from 1992 (product patent regime started) to 2002	Price index for medicines, spending for medicines	Introduction of generics delayed due to patent linkages, data exclusivity and/or patent extensions, thus total expenditures on medicines increase	Food and Drug Administration, Ministry of Health, Thailand

Table 4 (Continued)

Country	Author/year	Objective	Study design	Study sample	Outcome measures	Main results	Funding source
Thailand	Supakankunti et al. (2001)	Proposes a strategy for alleviating the potentially negative impact of TRIPS in Thailand	Pre/post data analysis of Thai pharmaceutical sector (originator and generic) before 1992 and after	Empirical studies on procurement systems and drug prices; several impact assessments; surveys to complete situational analysis	FDI, ^g total medicine supply, GNP ^h /cap, total medicine value, prices since 1992	No price changes in originators due to patent act. No data pre 1992 and little data post 1992 for generics	WHO's South-East Asia Regional Office
<i>Pricing</i> South Africa	Rothberg et al. (2004)	To measure the impact of a medicines reference pricing program covering items for which appropriate generic equivalents are available.	2273 products on reference pricing list	Interrupted time series, no control	Medicine price; cost savings	A clearly positive impact of a medicines reference pricing program covering items for which appropriate generic equivalents are available. Most of the downward price pressure due to generics trying to improve their position	No disclosure
Global	Holmes et al. (2010)	To evaluate the uptake of generic ARVs among PEPFAR-supported programs in Guyana, Haiti, Vietnam, and 13 countries in Africa, and changes over time in ARV use and costs.	Total procurement information between 2005 and 2008 from 16 countries (Botswana, Cote d'Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Vietnam, Zambia, and Zimbabwe)	Longitudinal study of trends of expenditure in medicines procured	Proportion of generic procurement across years and countries, and cost savings from generic procurement	The proportion of generic packs procured increased from 14.8% (95% CI, 14.79–14.84%) in 2005 to 89.33% (95% CI, 89.32–89.34%) in 2008 ($P < 0.01$)	The President's Emergency Plan for AIDS Relief (PEPFAR) of the US government
Brazil	Bevilacqua et al. (2011)	To analyze the financial impact of medicine procurement with the required bioavailability and or bioequivalence tests for the basic pharmaceutical services component.	Santa Catarina state, Southern Brazil	Before and after study (2007 procurement without the requirement of bioequivalence and 2008 with the requirement of bioequivalence for all purchased medicines)	Percentage out of total procurements not completed because of lack of bidders, percentage of price changed in 2008 when compared with unit price in 2007	In the first procurement in 2007, 2.6% of items could not be procured, while in the first procurement round in 2008 56.9% items could not be bought. Among medicine purchases, 60.0% were increased and 29.3% decreased from 2008 to 2007	No funding source provided
<i>Prescribing</i> South Africa	Meyer et al. (2001)	Assesses the effect of a prescribing training intervention for primary health care nurses.	Controlled trial	N = 11 clinics control/intervention; 340 prescriptions in each group	Percent increase in generic prescribing	24% increase compared to control group	Health Systems Trust (HST), Durban, South Africa, Grant # 186/97

Table 4 (Continued)

Country	Author/year	Objective	Study design	Study sample	Outcome measures	Main results	Funding source
Global	[22]Lim (2009)	Systematically and comparatively appraise the research evidence related to the practices of dispensing doctors	Literature review	21 studies included	Quantitative data comparing practices of dispensing doctors and non-dispensing doctors	Dispensing doctors prescribed more often than non-dispensing doctors	Primary Health Care Research, Evaluation and Development (PHCREd)/Research Development Fellowship: 2007

^a Antiretroviral.

^b World Health Organization.

^c International Non-proprietary Name.

^d Trade related aspects of international property rights agreement.

^e Free Trade Agreement.

^f Ministry of Health.

^g Foreign Direct Investment.

^h Gross National Product.

3.3.3. Pricing including reference pricing and tendering

Pricing policies use strategies to influence reimbursement as well as market prices of pharmaceutical products. Particularly, with regard to situations where several medicines have relatively similar characteristics (i.e., therapeutic properties) reference pricing is used such that for a related medicine group, a single reimbursement level or reference price is set. Medicines above the reference price require part or total payment by the patient. This, in principle, acts to cap prices. The tendering process should promote the procurement of low price but quality products. Three studies in the pricing policy domain met our inclusion criteria.

Rothberg et al. [17] (2004) measured the impact of a South African medicines reference-pricing program covering items for which appropriate generic equivalents were available. The reference pricing program had an “immediate effect” [17] on slowing the rate of medicines price inflation after implementation because the scheme switched from original or branded products to generic medicines, or switched from higher-priced to lower-priced generic equivalents.

Holmes et al. [18] examined time series from 2005 to 2008 of volume, costs, and types of ARVs purchased for 16 LMICs with PEPFAR funds and estimated cost savings achieved through the use of generic ARVs. Reported annual spending on ARVs increased from \$116.8 million to \$202.2 over this period. Estimated yearly savings because of generic usage increased from \$8.1 million to \$214.6 million. According to the authors, the savings attributable to generic ARV use has “. . . allowed PEPFAR country programs to shift funds from their ARV budget categories and invest further in other priority activities. . .” [18].

Bevilacqua et al. [19] studied medicines procurement in a municipal health system in Brazil which in 2008 required tests for bioequivalence and/or bioavailability. They attempted to estimate the financial impact of this procurement. The total procurement costs for 150 medicines, considering per unit costs and average annual consumption, doubled between the 2 years. This was related to two significant issues: (a) the “high percentage of failed [tests] in the first and second [procurement] bids of 2008. . .”; and (b) the fact that brand name “similar”¹ medicines were procured in 2007 as opposed to generics in 2008 [19]. Brand name “similar” medicines were actually less expensive than generic versions.

3.3.4. Prescribing/dispensing

Incentives for physicians, pharmacies and patients to prescribe, dispense and ask for generic medicines can be considered demand side policies. The range of prescribing options available goes from permitting, encouraging and making mandatory the use of the INN or generic name to providing them with financial and non-financial incentives. Only two papers matched the inclusion criteria.

¹ “Similar” are common in Central and Latin America and are pharmaceutical products that are off patent but lack proof of bioequivalence [21].

Meyer et al. [20] conducted a controlled trial in South Africa which evaluated the effect of a training course to promote generic medicine prescribing by nurses. This educational intervention was quite labor intensive and both its medium/long-term impact and cost was unclear.

Lim et al. [22] conducted a systematic review of the literature on dispensing and non-dispensing prescribers that included 21 studies from developed and developing countries. Prescribers who also dispensed medicines were more likely to prescribe originator products than prescribers who did not also dispense medicines.

3.4. Barriers to implementation of generic medicines policies in LMIC

Table 5 summarizes the implementation barriers that we have extracted from the descriptive LMIC publications. Legal barriers to implementation are primarily associated with regulatory and intellectual property policies that tend to slow the market entry of generic versions of originator medicines (lack of harmonized regulatory provisions among stakeholders, data exclusivity, patent linkage, patent extensions). Other legal barriers such as regulations on pricing, purchasing, and dispensing help create disincentives to providing generic medicines. Managerial and other institutional barriers include the low availability of high quality generics in certain public sectors, poorly managed generic advocacy programs, lack of prospective monitoring and retrospective evaluation of the impact of generic medicine policies, and informational asymmetry between producers and consumers of medicines regarding price and quality. Behavioral and perceptual barriers often involve the notion that “low price equals low quality”. Financial barriers to the uptake of generic medicines are those which similarly cause or augment existing misalignments among stakeholders, such as low salaries for prescribers and dispensers, ownership of pharmacies by physicians, perverse economic incentives caused by low mark ups for the dispensing of generic medicines, or dispensing fees as a fixed percentage of price.

4. Discussion

4.1. Bibliometric analysis

One key message is that a large majority (81.9%) of the literature in our database is directed toward pro-generic medicines policies in high-income countries. Of the LMIC literature, the primary countries of focus are Brazil and India with particular emphasis on trade and intellectual property-related issues. Nonetheless, this literature is primarily descriptive.

A second point is that certain policy areas in the LMIC literature (see Table 2) are not well represented. There are fewer references (as a fraction of the total) regarding regulation, dispensing, reimbursement and consumer-oriented policies in LMICs than in high-income countries. That the reimbursement literature is weak can be explained by the relative lack of insurance systems in LMICs, although this is changing [23].

Our third point is that many health systems in LMICs have technical, financial and political constraints which result in less effective medicines regulation [25–27] and this is possibly reflected as a relative lack of literature on the “regulatory” policy domain compared to high-income countries (Table 2).

Finally, we think the “demand side” of health systems is important, but largely neglected in terms of policy and evaluations [24]. This is problematic as policies designed to align the interests of all the relevant stakeholders (prescribers, dispensers and patients) are important, particularly in countries where the large majority of funding for medicines is out-of-pocket. As the poor in LMICs frequently use private providers (formal and informal), it is very relevant to bring the informal sector into an overall public policy net. Clearly, consumers have a much more important role in settings with high out-of-pocket expenditure than in many developed countries where insurance is the main agent financing medicines and hence, the main driver of the type of medicines consumed.

Of the funders that were specifically mentioned, very few of them were governmental agencies (13 out of 77). Indeed, the only LMIC authorities funding such work appear to be the governments of Brazil, South Africa, Zimbabwe and Thailand (Electronic supplementary data). This is unfortunate as governments have the most at stake with respect to improving market share of generic medicines and should be funding this sort of policy analyses. Importantly, we cannot exclude a publication bias (of unknown magnitude) that prevents most governmentally funded studies from being published.

4.2. Impact evaluation of pro-generic medicines policies

The results of the review show that only a small proportion of all LMIC references used a suitable design to evaluate policy impact. Thus, with such a small sample size we are limited in generalizing about whether and to what extent specific generic policies in LMICs will impact the uptake of generic medicines.

However, there is clearly a paucity of relevant impact evaluations of pro-generic policies in LMICs. Of the existing published data, much of the evidence-based research seems to be descriptive and/or cross-sectional. To evaluate whether the policy had an impact in terms of a desired outcome more robust methods need to be applied [5]. Suggested methods for impact evaluation (e.g., investigating cause-and-effect questions) of pharmaceutical policies are randomized and non-randomized controlled trials, interrupted time series analysis, controlled before–after studies [5]. A similar result has also been found for evidence-based interventions regarding rational use of medicines [28] and essential medicines programs [29]. Gilson and Raphaely [30] reviewed the literature on the process of health policy development in LMICs and also found that most of the literature was dominated by high-income countries and the majority of articles were largely descriptive.

The key messages for those studies which used a design to evaluate the impact of the generic policies implemented show that educational interventions and reference pricing can increase the consumption of generic medicines,

Table 5
Barriers to implementation of pro-generic medicines policies in low and middle-income countries.

Category	Policy domain	Barriers
Legal	Market authorization	Definition of counterfeit medicines can compromise the use of generic medicines [49]
		Lack of regulation that demands standard testing for generic medicines including the lack of harmonization [50]
		Lack of harmonized regulatory control on quality of generics among key stakeholders [51]
		Any form of delayed registration of generic medicines, such as unrealistically high standards for proving bioequivalence and “TRIPS plus” data exclusivity, linkage and patent extension provisions [52]
		Lack of regulations regarding bio-generics [53]
Pricing	Pricing	Lack of regulation to safeguard fair promotion of medicine products (including both originators and generic medicines products) [54]
		Weak patent examination and granting procedures that allow the patenting of non-inventive aspects [55]
Purchasing	Purchasing	Price regulation setting a maximum price undermines competition (for instance the price of generic medicines is set in a fixed relation to the originator product) [5]
		Regulation of tendering needs to be set up in a way that it allows choosing low-cost but good quality generic medicines [56]
Dispensing	Dispensing	Rules permitting physicians to dispense medicines can result in lower utilization rate of generic medicines [7]
		Obtaining consent from prescribers for each generic substitution done in pharmacy can lower substitution rate [57]
Management and other institutional barriers	Market authorization	Lack of clarity in the legal regulation of substitution can inhibit efficient substitution [58]
		Low availability of generic medicines of high quality in the public sector can undermine private market efficiency [59]
Pricing	Pricing	Poorly managed generic pharmaceutical industry advocacy programs [60]
		Lack of prospective monitoring and assessing of generic medicine policies when they are introduced, in order to be able to obtain the required evidence on their impact [50]
Purchasing	Purchasing	Lack of retrospective evaluation of the impact of past generic medicine policies using rigorous and well-validated methodologies, when the data required are available [50]
		Lack of price information provided by health care provider organizations to physicians to promote generic medicines [70]
Prescribing	Prescribing	Lack of financial and other incentives to procure generic medicines [61]
		Lack of obligation to take educational courses about generic medicines and their benefits [62]
Behavior, perception, knowledge	Prescribing	Lack of individualized attention/care diminishes trust in the quality of generic medicines provided
		Physicians do not like to entrust substitution to pharmacy staff [63]
Dispensing	Dispensing	Brand names are easier to memorize than INN names [64]
		Physician and consumer perceptions are interlinked: If physicians perceive generic medicines as low quality that will have an important impact on consumer choices [63]
Consumers	Consumers	Lack of professional ethics that demands use of generic medicines to provide more affordable care [59]
		Physician peers who do not prescribe generic medicines affect others who imitate their behavior [60]
Financial	Regulation of market	Equating low cost with low quality [65]
		Rejection of mandatory substitution due to lack of knowledge by pharmacy staff and drug sellers [58]
Prescribing	Prescribing	Low knowledge about generic medicines will hinder generic medicines promotion and use, lack of exposure to educational campaigns providing knowledge about generic medicines [58,62]
		Equating low cost with low quality [66]
Dispensing	Dispensing	Equating low cost with low quality [64]
		Generic medicine prices that are too low are a disincentive for generic manufacturers to enter the market [71]
Consumer	Consumer	Lack of a balanced evaluation between the overall risks, requirements and costs and the direct benefit for the poor of “local production” of medicines [12]
		Financial gains from prescribing are common in places where the salary is low and additional financial income is very important (low physicians’ salaries as cause) [67]
Dispensing	Dispensing	Owner/co-ownership of pharmacies by physicians seems to decrease the rate of generic medicines prescribing [68]
		Low mark ups for the dispensing of generic medicines create incentives not to prescribe generics [7]
Consumer	Consumer	Fixed dispensing fees create a perverse incentive that can undermine generic promotion [7]
		Financial incentives of dispensers misaligned with consumer incentives to choose generic over originator product [66,69]

In square brackets the reference of the study that mentions the barrier. Usually, for each barrier there is more than one study mentioning the barrier but one was chosen as an example.

whereas free-trade agreements, and policies permitting physicians to dispense medicines can reduce the use of generics.

4.3. 'Exporting' generic medicine policies from high income countries to LMICs

Generic medicines policies in high income countries [3–6] are not the subject of this review, but it is worthwhile to broadly discuss some key policies and the relevance that they might have in LMICs. With regard to pricing policies, at least in Europe such policies can focus on reference pricing systems, "free" pricing (i.e., prices set by the manufacturers), price controls (e.g., regulatory requirement for generic prices not to be higher than some percentage of the originator price) and providing discounts to dispensers. A large number of studies focus on reimbursement pricing of generic medicines. These studies are not relevant to LMICs whose main focus is on price regulation in the market unrelated to reimbursement. Even in Europe, there does not seem to be a single approach toward developing generic medicine pricing policies [3] and we assume this will also be the case in most LMICs.

We further note that the combined result of lower generic prices and higher generic penetration should be greater savings for health insurance but reviewers suggest that these currently are not realized, as governments seem to be paying too much for generics [4]. We daresay that in LMICs at present, even those edging toward universal health coverage, this may also be the case. To be fair, it is also true that creating and implementing universal health coverage may stimulate a generic medicines market in LMICs. Further, it has been suggested that high income countries should be able to learn from each other's experiences in creating and implementing generic medicines policies [6]. There is no reason, in principle, that allowing or even mandating LMICs to similarly learn from each other could not happen among LMIC trading and regulatory partners (e.g., ASEAN, COMESA).

4.4. Overcoming barriers to implementing pro-generic medicines policies

The primarily descriptive literature on generic medicine policies in LMICs consistently mentions as principal barriers to generic uptake, an overall lack of knowledge about generics and a perception of stakeholders that generic medicines are of inferior quality. Interventions should focus on providing information and changing perceptions. Based on our review, we suggest three over-arching "enabling conditions" that might overcome these barriers. These three enabling conditions are necessary, but probably insufficient. They are: (1) creating a trusted medicines regulatory authority; (2) creating a robust market for generics; and (3) aligning the pro-generic medicine incentives of prescribers, dispensers and patients. Policies informed by these conditions should be implemented in a provisional or incremental manner and, most importantly, they ideally should be monitored and evaluated before they are implemented for the long-term.

Condition 1. A functioning and reliable medicines regulatory authority.

One "enabling" condition would be to provide stakeholders in LMICs with the knowledge that marketed generic medicines are of assured quality. Clearly, this involves sufficient political will, financial stability, and an educational and scientific commitment of a high order, but we think is the absolute requirement for any generic medicines policy to be successful [7]. We believe that the public sector (and of course, ideally the private sector) should not promote the lowest price generic per se but rather lower-priced, but quality assured generics.

A functioning and reliable Medicine Regulatory Authorities (MRA) and successful policies that allow people to trust their MRA may help de-conflate and overcome the "price = quality" barrier. Evidence suggests that consumers use the price of products as a proxy for judging its quality [31–33]. The response by research and development (R&D)-based firms to generic competition is managing the brand so as to reinforce perceptions of higher quality [34]. In our view, this psychological issue is an extremely important barrier. Remarkably, such perceptions of "price = quality" may even govern actual therapeutic efficacy [31,32]. The literature on the shortcomings of MRAs [35,36] and the ever-increasing literature on counterfeit and substandard medicines [37–39], suggest that meeting this condition in LMICs will continue to be a major challenge. Even though other policies may be proposed or even implemented concurrently, we think that unless stakeholders believe a generic medicine is a quality medicine, generic medicine policy implementation of any sort will be difficult.

It is reasonable to speculate that promoting International Non-proprietary Name (INN) generics is beneficial by itself, as this would be less confusing to consumers and prescribers. However, even if this is the case in one country, the finding may not be generalizable to other countries with different pharmaceutical markets and policy structures.

There is literature from high-income countries that suggests that insurance systems can successfully promote the use of generic medicines [40]. However, as insurance coverage is still low in many LMICs, it is important that other agencies promote the use of generic medicines. Public educational campaigns have been used in recent years to change consumer perceptions that generic medicines are of inferior quality and there seems to be a positive effect on the uptake of generic medicines [41].

Condition 2. A functioning market for generic medicines.

Another group of barriers to the successful implementation of pro-generic medicine policies involves barriers to market entry of generic medicines upon patent expiration. Intervention design must be preceded by a careful analysis of the various factors that hinder rapid generic market penetration as there are multiple, probably simultaneous and confounding policies in existence [42].

Therefore, a second "enabling" prerequisite should be a reasonably robust market (supply) of generics which is required for assured quality, low cost medicines. In addition, if governments try to control the prices of

generics at a too low level they might remove incentives for generic entry. Similarly, if prices are set in relation to the originator product, this could also undermine competition. Policies that could improve the availability of generics include effective implementation of the so-called TRIPS “flexibilities” (e.g., “Bolar” provisions, compulsory licensing, pre/post-grant opposition proceedings) [43,44] as well as regulatory policies designed to do the same thing (e.g., fast-track approval of generics, reduced fees for market authorization applications of generic medicines [36]). In the United States, the Hatch-Waxman legislation [45] (Drug Price Competition and Patent Term Restoration Act 1984) speeds the availability of generics by protecting the first generic by a market exclusivity period of 6-month market exclusivity. However, the LMIC literature does not provide examples of similar comprehensive legislation.

Condition 3. Sufficiently aligned incentives among “demand side” stakeholders.

Financial barriers, particularly related to dispensing and prescribing, were found in many LMIC markets. To implement strategies that favor the prescription and dispensing of low price, assured-quality generics is complex as there is no clear consensus as to what works best. The incentives of stakeholders in the generic medicine supply chain (e.g., funders, procurement agencies, regulatory authorities, prescribers, dispensers, end-users) to perform certain actions (e.g., forecasting demand, raising or lowering prices, prescribing, dispensing and purchasing low cost, quality assured generics) are often misaligned. Such misalignments have unintended consequences that can delay or even prevent implementation of policies with regard to generics. For example, we might expect there to be misalignments of incentives among physicians and pharmacies as influenced by different pricing policies. Each stakeholder in the pharmaceutical value chain, including, and perhaps especially, the patient, bears some of the consequences of these misalignments. Experience in Europe suggests that aligning perceptions and incentives of different users and consumers of generics can be vital when selecting policy options [46]. For example, at a minimum, it is important that pharmacy staffs are able to substitute for a less expensive generic if a physician has prescribed a branded medicine, so long as a generic is available. In addition, in case private pharmacies are reimbursed for the dispensing of medicines (which is not actually the case in many LMICs), they should be reimbursed in such a way as to encourage them to dispense less expensive generic products. Our review suggests potential value in overcoming these “demand-side” barriers as many LMICs contain large numbers of persons who pay out-of-pocket. Many of these particular barriers are perceptual and they are likely to be extremely important [7].

All this suggests a third requisite factor that would be needed, i.e., finding the most appropriate mix and alignment of financial incentives among prescribers, dispensers and consumers to support the uptake of generic medicines. Political will is necessary to re-align various incentives among key “demand side” stakeholders.

4.5. Limitations

The major limitation to this work is that the references found here are surely not the only potentially useful and reliable sources of information on this subject. Inasmuch as we have done a relatively systematic search, we can say with some confidence that while details may have been missed in our search strategy, overall, this is the general sense of the literature at the present time. An additional, although minor, limitation is that the categorization of barriers (Table 5) into four categories could be done differently. However, we believe that we captured the large majority of barriers mentioned in the literature.

Publication bias is another limitation that could lead to false conclusions. However, we think that it is very likely peer-review journals would accept sound generic medicines policy studies. Another possible bias could be introduced as we used limited inclusion criteria to define impact evaluations and might have excluded some that other authors regarded as assessment of generic policies and their impact. However, we used a definition of impact evaluation which has been used in other systematic reviews (for example, Cochrane reviews on policy evaluation). We note in addition that only two additional studies evaluating the impact of pro-generic medicines policies were retrieved from the searches in January 2012 using a very broad PubMed search. It is certainly possible that we might have missed further impact evaluations in other databases if we had repeated the entire search strategy with all databases again in January 2012, something which we chose not to do due to time constraints.

5. Conclusions

Overall, the literature on the impact of pro-generic medicines policies in LMICs suffers in comparison with the literature in high-income countries, with the possible exceptions of Brazil and India regarding trade policies. There are certain policy domains relevant for generic medicines policies that are clearly underrepresented in LMICs, notably regulation and the “demand side” of the medicine value chain, i.e., the dispensers and consumers.

On the basis of our findings from the literature we have suggested three principal prerequisites necessary for successful pro-generic medicine policies in LMICs, namely; a functioning medicines regulatory system in which all stakeholders have confidence, a competitive market for medicines, and an appropriate mix and alignment of financial incentives among prescribers, dispensers and consumers sufficient to support the uptake of generic medicines, often in the absence or paucity of health insurances.

Clearly, further work is necessary, as only a few studies in LMICs appear to have actually carried out any impact evaluation. This makes it difficult to suggest specific policy recommendations. There is a much more extensive experience of Europe in this regard but we cannot, a priori, assume those lessons will translate to LMICs. In particular many LMICs are dependent on donor funding and still lack insurance systems and we suggest that this leads to a lack of administrative and health system “channels” or

pathways for implementation and enforcement of pro-generic medicines policies.

Lack of evidence is not evidence that pro-generic medicine policies are a failure in LMICs. We are not denying that pro-generic medicines policies are successful, irrespective of whether impact evaluation has taken place. One could, however, imagine testing out generic medicine policies before they are set into legislation by doing controlled trials in selected locations in order to understand the true costs and benefits. This method is likely to be very difficult and a more reasonable approach must be based on a more realistic monitoring and evaluation methodology.

Any policy success stories in this regard cannot continue to be merely anecdotal and must have some sort of quantitative and/or qualitative evidence-based methodology [47] (including rigorous case studies [48]) that can potentially influence decision makers. The existing body of intervention research on pro-generic medicines policies in LMICs demonstrates that it is not yet contributing to an understanding of the impact of such policies on price and/or volume of generic medicines. Evaluations of generic medicines policies in LMICs are urgently needed.

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Conflict of interest

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Author contributions

WAK and VJW developed the concept and design followed by drafting of the manuscript and then critically reviewed it for important intellectual content. Both WAK, VJW, LSR and MV carried out the bibliometric analysis. All authors contributed to interpretation of the data. WAK supervised the study.

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Appendix A. Supplementary data

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