JPHSR Journal of Pharmaceutical Health Services Research

ROYAL PHARMACEUTICAL SOCIETY

Review Article

JPHS 2020, 11; 321–333

Received June 9, 2020
Accepted July 15, 2020
DOI 10.1111/jphs.12379
ISSN 1759-8885

Why healthcare market needs government intervention to improve access to essential medicines and healthcare efficiency: a scoping review from pharmaceutical price regulation perspective

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Abstract

Background Access to quality essential medicines at affordable price to patients in the healthcare market is one of the main goals of universal health coverage and health-related sustainable development goals. Healthcare market is imperfect, and the government cannot ensure access to essential medicines if the market is left to operate under invisible hand control. This scoping review was conducted with intention to provide the clear picture on impact of pharmaceutical price regulation on access to essential medicines, drug innovation and launching.

Methods We searched articles written in the English language since January 2000 from PubMed, Embase, Scopus, Ovid/Medline and Google scholar with systematic search query.

Results Access to essential medicines, which is defined in terms of availability, affordability, accessibility, acceptability and quality of drugs, can be improved by pharmaceutical price regulation. Countries can use different price regulation strategies based on their healthcare objectives and priority healthcare needs. Country-specific pharmaceutical price regulation could not significantly affect drug innovation and launching. However, supportive strategies such as open public funding for drug innovation research, providing innovation awards and strong patent rights can counterbalance the effect of price regulation on innovation and drug development research in developed countries.

Conclusion Regulating pharmaceutical pricing system is one of the key strategies to ensure access to essential medicines. Countries that have implemented pharmaceutical price regulation system (Germany, the UK, Canada and Iran) have achieved better access to essential medicines. However, the US and Ethiopian health systems that are unregulated concerning pharmaceutical pricing had a great challenge of affordability of essential medicines. Therefore, setting country-specific pharmaceutical price regulation system along with additional strategies to improve drug innovation is critical to ensure access to essential medicines.

Keywords access to essential medicines; drug innovation and launching; healthcare market; pharmaceutical price regulations; pharmaceutical pricing

Background

Health is defined as physical, mental and social well-being of an individual. A good health system delivers quality services to all people, when and where they need it. Equity and access to essential medicines of genuine quality at prices that are affordable to patients are dependent on price regulation and financing systems.[1,2] The role of the health system is to prevent disease and other ill health and injury and to maintain health not just to treat illness so that people remain as healthy as possible for as long as possible.[3] About 60% of healthcare budget spent on medicines in developing countries. Most of the costs of medicines in these counties are directly from out of patient's pocket, making medicines the largest family expenditure item after food.[4]

Ensuring equitable access to quality medicines requires efficiency in healthcare budget utilization, as we are operating in the budget-constrained environment.[5] Inefficiency in

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health systems is a global problem, and approximately 20–40% of all resources spent on health were wastage.[6] For example, $760 billion to $935 billion, accounting for approximately 25% of total healthcare spending in the US health system, is wastage.[7] Similar study conducted in 2016 among primary health centres in Ethiopia showed that 54% of health centres were technically inefficient.[8]

Achievement of health-related sustainable development goal and universal health coverage is highly dependent on population access to quality essential medicines.[4,9,10] Access to essential medicines is defined in terms of physical availability, geographic accessibility, affordability, acceptability and quality of medicines.[11,12] There are five core challenges for access to essential medicines policies. These include inadequate financing, unaffordability, assuring the quality and safety of essential medicines, irrational use and lack of availability of some important medicines.[13–15]. Therefore, it requires involvement of a number of stakeholders including the Ministry of Health, national drug regulatory agencies, pharmaceutical manufacturing industries, importers and distributors, international trade organizations and other bilateral organizations.[16–19]

Imperfect nature of healthcare market and failure of government to intervene in this market contribute to lack of access to quality medicines.[20] There is continuous debate on pharmaceutical price regulation due to imperfect nature of healthcare market, presence of evidences on adverse effects of price regulation and unregulated drug pricing contribution to unaffordability medicines.[20] Therefore, this scoping review was conducted based on standard protocol,[21] with intention to provide the clear picture on impact of pharmaceutical price regulation on access to essential medicines, drug innovation and launching.

Methods

Data sources and search strategy

We searched articles written in the English language since January 2000 to May 2020 from the following databases: PubMed/MEDLINE, Embase, Scopus, Ovid/MEDLINE and Google Scholar with systematic search query (available in Data S1).

We selected six different countries based on their healthcare delivery policy and pharmaceutical management system. The included countries were Germany, the UK, Canada, the USA, Islamic republic of Iran and Ethiopia. Countries were selected based on the following criteria[22–28]:

1 Ethiopia is selected to represent low-income countries with no pharmaceutical price regulation system.
2 Iran is selected to represent upper middle-income countries with pharmaceutical price regulation system.
3 The USA is selected to represent capitalism-based health system with no pharmaceutical price regulation system.
4 Germany is selected to represent high-income countries with social insurance-based health system and pharmaceutical price regulation system.
5 The UK is selected to represent high-income countries with social insurance-based health system and specific pharmaceutical price control system (profit sharing).
6 Canada is selected to represent high-income countries with social insurance-based health system and with a mixture of pharmaceutical price regulation systems.

Study types

The different study types are as follows: systematic reviews, clinical trials, cohort studies, and observational and cross-sectional studies related to healthcare market, healthcare efficiency, and access to essential medicines, drug launching and market entry, drug research and development, and pharmaceutical price regulation.

Inclusion and exclusion criteria

1 Systematic reviews, clinical trials, cohort studies, and observational and cross-sectional studies related to healthcare market, healthcare efficiency, and access to essential medicines, drug launching and market entry, drug research and development, and pharmaceutical price regulation are included.
2 Studies conducted before January 2000 are excluded.
3 Articles that are not related to healthcare market, healthcare efficiency, and access to essential medicines, drug launching and market entry, drug research and development, and pharmaceutical price regulation are excluded.

Study selection

From a total of 225 articles identified by literature search, 171 potentially relevant articles were selected, and after applying the inclusion–exclusion criteria listed above, 92 articles were found to be relevant (Figure 1). Two investigators (MD and MM) independently reviewed each study's abstract against prespecified inclusion and exclusion criteria. In case of disagreement on quality of the article, two authors discussed in front of table in the presence of the third and fourth authors (AA and FS).

Data extraction

Two investigators abstracted healthcare market, healthcare efficiency, and access to essential medicines, drug launching and market entry, drug research and development, and pharmaceutical price regulation data from all included studies. A second investigator checked these data for accuracy. Disagreements among us are managed through discussion in the presence of other authors.

Data synthesis and analysis

We qualitatively described and summarized the evidence related to impact of pharmaceutical price regulation on access to essential medicines, healthcare efficiency, drug launching and market entry, drug development and research.

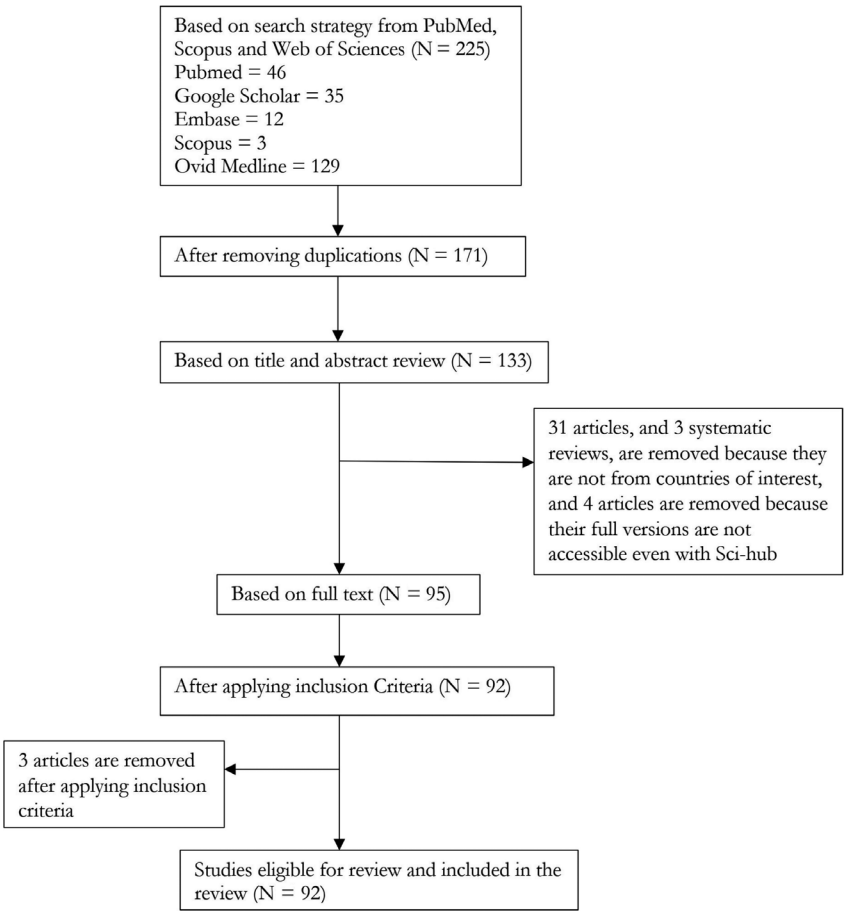

Figure 1 PRISMA flow chart representing the result of search and the number of articles excluded and eligible for review.

We also described approaches to improve access to essential medicines to ensure universal health coverage and sustainable development goals in low-income countries such as Ethiopia.

Results

Overview of healthcare market

Under the 'general equilibrium theory' of economics, a perfect market has the following characteristics: there is a availability of large numbers of buyers and sellers of a homogeneous product, all consumers and producers have complete knowledge of price and quality of services, buyer purchase goods or services that increase their economic utility, there are no barriers to entry and leave, and both buyer and seller have no power to set prices. This equilibrium is called a 'Pareto optimum', meaning that nobody can be made better off by exchange without making someone else worse off.[20]

However, healthcare market does not fulfil the perfect market criteria because of the following reasons. These reasons include the following: health is consumption and investment good, information asymmetry, agent selects for principal, third party pays for the service, patient co-pays a price much less than full price, and the customer buys surrogate need (health care) not the direct need (health).[20,29,30]

The process of decision-making in normal market and healthcare market varies due to difference in stakeholders involved. Main players in normal good market are buyer and seller, while in healthcare market, patients, physicians, insurance companies and health facilities play an important role. Due to these differences, the healthcare market will not maximize the utility or welfare of the people if left to operate in free market principle. Therefore, government involvement to control healthcare market is important (Figure 2).[20,29,30]

Healthcare outcomes of selected countries

The USA has greater healthcare expenditure as percentage of GDP per capita than other OECD countries, with less life expectancy, higher maternal mortality ratio, higher under-five mortality, probability of dying from chronic illnesses and higher suicide mortality rate (Table 1).[31,32] We made a simple comparison of healthcare efficiency based on total expenditure on heath as percentage of GDP per life expectancy at birth. Based on this simple comparison, the US health system spends more dollars to attain one extra life

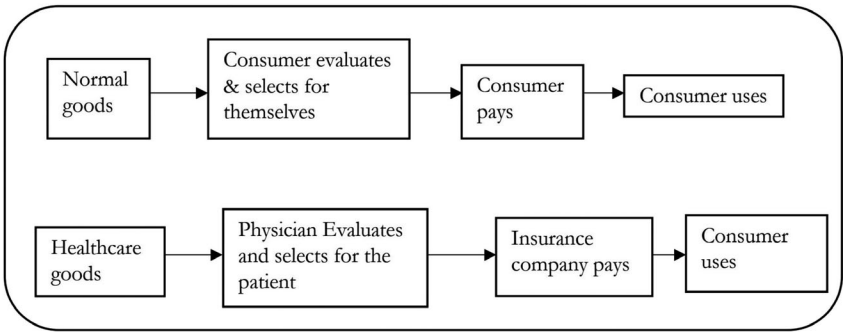

Figure 2 Simple process flow for decision and use of normal goods and healthcare goods.

years than others (i.e. least efficient).[10] The uncorrelated healthcare expenditure and healthcare outcome in the US health system tells us that there are non-medical health determinants that can improve healthcare outcomes in addition to clinical care. Studies indicated that health care only accounts 20% share on improving health outcomes and the greater majority goes to health behaviours (30%), socio-economic status (20%) and environmental factors (10%) (Figure 3).[33]

Pharmaceutical price regulation global health agenda

Universal health coverage (UHC) is ensuring access to the healthcare services for people at affordable price. Core components of UHC are as follows: mandatory population coverage; range of services made available; and extent of financial protection. Providing universal coverage for all without controlling the healthcare market is difficult, since the healthcare system is operating in the budget-constrained environment. In addition to this, services that are necessary such as health care have inelastic market and consumers have little freedom of choice, and if unregulated, they can lead to serious financial catastrophe that will disturb the whole community.[4]

As evidenced by different studies, there is a negative relationship between out-of-pocket (OOP) payments and life expectancy. These hold true irrespective of the economic status of countries with little variation in the magnitude of effects of these factors. For example, income and education were found to have a much larger effect in low- to middle-income countries. Doubling GDP is believed to increase life expectancy by 2.4 years at age of 40 years and 5.4 years at age of 60 years. Increasing health spending is associated with 1-year increase in life expectancy. Similarly, doubling drug spending is associated with 1 year and 0.8 years at age 40 and 2.4 years at age 60 years. This is because increased OOP payments lead to financial catastrophe or reduced healthcare utilization.[4,20,34]

Strong political commitment and vigilant healthcare system are required to achieve universal health coverage. Sustainable achievement of UHC requires action in the following areas: prioritizing adequate financial coverage for cost-effective services, across the whole population; building financial sustainability; and innovating service delivery looking for ways to maximize the efficiency of health spending.[4,35,36]

Universal health coverage relays on financial protection and equity of basic health services. Improving financial protection to improve access to medicines will have paramount importance, since about 20% of health dollars goes on purchasing pharmaceuticals.[37–39] Containing pharmaceutical spending by price regulation, developing policies to promote the use of generics and improving procurement procedures are important to ensure access to medicines.[4]

Pooling the risk from sick to healthy through mandatory health insurance system and providing subsidization for individuals who cannot afford are important to reduce

Table 1 Health-related SDG statistics of selected 15 countries, WHO region and globally (2015)

Country	Total population (000)	Life expectancy at birth (years)	Current health expenditure as GDP (%)	Maternal mortality ratio/100 000 live births	Under-five mortality rate/1000 live births	Neonatal mortality rate/1000 live births	Probability of dying from NCDs, B/n 30-70 years (%)	Suicide mortality rate/100, 000	Healthcare efficiency index
Germany	81 915	81	11.2	6	3.8	2.3	12.1	13.6	7.23
USA	322 180	78.5	16.8	14	6.5	3.7	14.6	15.3	4.67
UK	65 789	81.4	9.9	9	4.3	2.6	10.9	8.9	8.22
Canada	36 290	82.8	10.4	7	4.9	3.2	9.8	12.5	7.96
IRI	80 277	75.7	7.6	25	15.1	9.6	14.8	4.1	9.96
Ethiopia	102 403	65.5	5.2	353	58.4	27.6	18.3	7.2	12.5

Note: IRI, Islamic Republic of Iran; NCDs, non-communicable diseases.

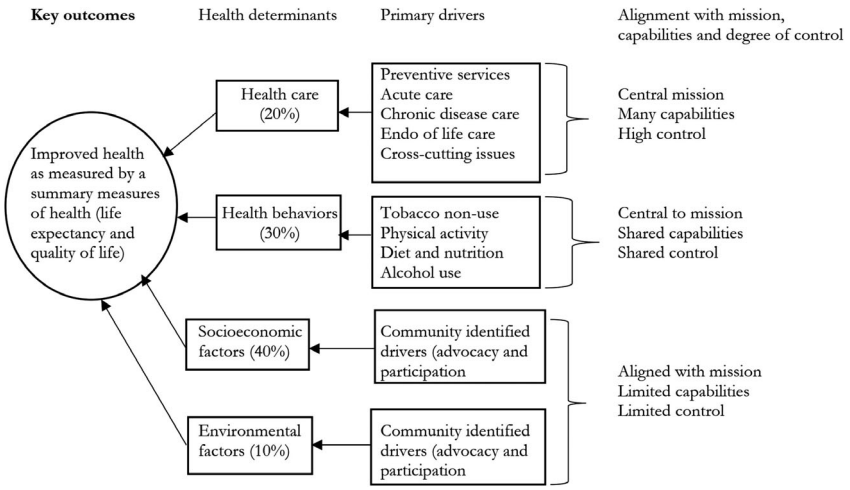

Figure 3 Conceptual framework depicting measurement domains of a system within a system approach and the drivers of health determinants. SOURCE: Isha.

out-of-pocket payment.[30,40–42] Another important strategy for achieving UHC is maximizing the efficiency of healthcare spending. This is to minimize significant wastage in health resources (20-49%) due to inefficiency in health systems.[6] Some important and innovative ways in which countries can maximize their healthcare efficiency include investing on health promotion and disease prevention, shifting services from hospitals to primary care and the community; expanding the role of non-physicians and using health information technology.[43]

Investing in health promotive and preventive services outside hospital environment is backbone for every healthcare system. This because most of chronic illnesses the world is fighting today are not curable and their management should focus on socio-economic, health behaviour and environmental protection.[44] Globally, today's healthcare spending is not proportional to associated healthcare outcomes.[35,45,46] This can be explained by the fact that clinical care contributes only 10–20% to health outcomes, while socio-economic, health behaviour and physical environment-related factors are estimated to account for up to 80% of health outcomes.[46]

In addition to UHC, access to essential medicines is the concern of another health agenda 'Sustainable Development Goals' – Sustainable Development Goal (SDG) 3.8: 'Achieve universal health coverage, including financial risk protection, access to quality essential health-care services, and access to safe, effective, quality and affordable essential medicines and vaccines for all'; and SDG 3.b: 'Support research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines'.[9,10]

Access to essential medicines and pharmaceutical market control

Pharmaceutical industry has unpredictable return from investment, because of extensive research work required and number of regulatory standards to comply with before marketing. Pharmaceutical business today is also affected by set of different interests from regulators, patients, payers, policymakers and providers.[47,48]

Medicines account for 20–60% of health spending in low- and middle-income countries. Up to 90% of the population in developing countries purchase medicines through out-of-pocket payments. Higher cost essential medicines are unaffordable for large sections of the global population.[49] Affordability measures the financial capacity of consumer to buy the medicine, usually measured by using daily wage of the lowest paid government worker.[50]

High cost of health care is a barrier to access for many Americans. About 22% of the population skipped consultations; 18% did not purchase prescribed medicines due to cost in 2016, and 8% American adults import medication to save money. The access problem is particularly marked for poorer families, with 43% of low-income adults reporting unmet care needs because of the cost of care.[51]

Prescription drugs cost more in the USA than in anywhere else in the world. As a result, Americans are illegally importing drugs from other countries. Drugs sold in the USA cost an average of 56% less in other high-income countries (Table 2).[52,53] A number of factors can impact drug pricing, such as the costs of research and development and the amount of competition in the marketplace, direct-to-consumer advertising, and lack of transparency, country's free pricing system and a ban on federal negotiation of drug prices.[54–58]

Similarly, medicines for treatment of chronic diseases and paediatrics use are not affordable in Ethiopia. For example, treatment of type II diabetes with hypertension using metformin 500 mg and atenolol 50 mg would require days' wages ranging from 3.56 to 6.87 in private health facilities.[59,60]

Affordability of essential medicines can be ensured by using combination of different pharmaceutical pricing, making transparent pricing policies, supporting pricing policies with an appropriate legislative framework, regular

Table 2 Comparison of drug prices manufactured by the same manufacturer in the USA and other countries

Drug	Drug company	Drug use	Price (2017)				
			USA	Canada	UK, Australia	India	Turkey
Benicar, Olmetec, 20 mg	Daiichi Sankyo	Hypertension	$5.07	$1.37	$0.82	$1.07	$1.83
Benicar HCT, Olmetec, 40 mg/25 mg	Daiichi Sankyo	Hypertension	$8.37	$1.88	$1.44	Not available	$1.48
Paxil, 20 mg	Bristol-Myers Squibb	Depression	$6.83	$2.98	$0.98	NA	$0.7
Viagra, 100 mg	Pfizer	Erectile dysfunction	$58.72	$10.77	$8.31	$4.44	$9.27
Nexium, 40 mg	AstraZeneca	Peptic ulcer	$7.78	$3.37	$2.21	<37 cents	<37 cents

Note: $, US dollar; HCT, hydrochlorothiazide.

monitoring, promoting the use of affordable medicines, effective implementation of pricing policies to ensure compliance, adopting policies to promote the use of quality-assured generic medicines, promoting collaboration to exchange of information about policies, their impacts and pharmaceutical prices.[49]

The demand for essential drugs depends on the interaction between patients' demand for health care and the choices of physicians who prescribe and pharmacists who dispense drugs. Regulating prices define the incentives and constraints on these choices. For non-prescription drugs, the patient is the primary decision-maker, but regulation of retail pharmacies may affect the prices and choice available. Government can intervene on pharmaceutical market to improve access and affordability of essential medicines by price and profit control, using reference pricing and brand premiums, eliminating tariffs and taxes, fixing margins, using digressive markups and capitation systems.[61]

Pharmaceutical price regulation is variable globally due to variation in political and health policy issues, objectives of pharmaceutical sector and pharmaceutical manufacturing industries. For example, the US and Ethiopian healthcare systems rely on capitalism, where market governs itself under invisible hand control and pharmaceutical pricing is unregulated. Privatization of the healthcare system has profound impact on health by emphasizing private management of healthcare quality and reform, rather than public funding, thereby limiting access to quality care for some economic classes (i.e. health inequality).[62–64] On the other hand, Germany, Canada, the UK and Islamic republic of Iran health policies rely on social democratic ideology with social egalitarian principles. All of these countries regulate pharmaceutical pricing differently based on their respective healthcare needs. For example, the UK follows profit sharing and reference system, Canada uses mixed pricing system, Germany uses internal and external reference pricing system, and Iran uses reference and cost plus pricing system (Table 3).[22,65–75]

Drug innovation and drug launching

Studies indicated that 36% of all new medicine entities (NMEs) were developed in the USA followed by the UK, 10.4%.[76] Another study indicated that most of new drugs come from the USA, 57%, followed by Switzerland, 13%; Japan, 13%; the UK, 8%; Germany, 6%; and France, 6%. Interestingly, some countries with direct price control, profit control or reference drug pricing appeared to innovate proportionally more than their contribution to the global GDP or prescription drug spending.[77]

Many countries with significant price regulation were important innovators of pharmaceuticals. The country-specific pricing policies probably do not affect country-specific innovation. For example, although prices in the UK are much less than in the USA, the industry continues to be very profitable and innovative. In Canada, income from domestic sales of brand companies is on average about 10 times greater than its research and development costs, even in the face of prices that are approximately 40% lower than in the USA. Despite the above-average profitability of the US-based companies, the higher prices paid by the US consumers are not rewarded by more than expected domestic innovation.[78–82]

A study indicated that weak price control and stronger intellectual property right would improve drug entry and launching by virtue covering fixed costs associated with launching from increased firm profit. However, patents indeed make local markets more attractive, and they also convey control over launch decisions to multinational firms with global interests. Multinationals may delay or avoid launching drugs in lower-priced countries because they are concerned about the implications for pricing in other markets. If they hesitate, and patent rights block otherwise willing local entrants, then strong patent rights actually reduce product entry.[83]

Analysis of the timing of launches of 642 new drugs in 76 countries during 1983–2002 shows that price regulation delays launch, while longer and more extensive patent rights accelerate it.[84] A study evaluated the impact of price regulation on the launch of new drugs, which showed that the US-based companies were leading in drug launching followed by Germany, the UK and New Zealand. This is because a low price in one market may 'spillover' to other markets, through parallel trade and external referencing, manufacturers may rationally prefer longer delay or not launch to accept a relatively low price.[61,85]

Modelling study conducted to evaluate launch prices for new pharmaceuticals in the heavily regulated and subsidized Spanish market, 1995–2007, showed that, unlike in the USA and Sweden, therapeutically 'innovative' products are not overpriced relative to 'imitative' ones after having

Table 3 Pricing system and cost containment strategies of pharmaceuticals in selected countries

S.no	Country	Drug pricing system	Payment system	Price control system
1	Germany	Internal and external reference price.	• SHI and co-payment. a. Outpatient care co-payments. b. Essential medicines, 100% reimbursement, c. No co-payment for inpatient cases. • Free pricing for OTC.	Regulate the maximum pharmacy remuneration. • VAT = reimbursement, 6%; and non-reimbursement, 18%. • Regressive pharmacy margins to disincentivize dispensing expensive products.Generic: volume: 81.0%; and value: 36.2%.
2	USA	Pricing is arbiter of competition and success.	• Private and public insurance. • 13% uninsured. • Most of drug expenditure is out of pocket.	FDA is involved in the testing of new drug candidates for patient safety. Affordable care act is working to increase the insurance coverage.
3	UK	Reference price. Profit share pricing agreement b/n pharmaceutical industry and MOH. Free pricing to OTC.	NHS and co-payment. • Outpatient care co-payments. • Essential medicines, 100% reimbursement. • No co-payment for inpatient cases.	Regulate the maximum pharmacy remuneration. • VAT = NHS= 0% and non-NHS = 20%. • Generic: volume: 84.3%; and value: 34.9%.
4	Canada	Mixed pricing. Different pricing among provinces. Reference pricing. Lowest price. Maximum allowable cost price.	Private and public insurance. • Deductibles at cost CAN $25 for individuals or cost CAN $50 per family. • Co-payments at 20% (0–30%).	Canada allows the import of active ingredients through a *compulsory licence (TRIPS)*. • To encourage competition and lower the price for brand-name drugs.
5	Iran	Cost plus method and Reference Pricing. • Different markups at Pharmacy, Distributor and importer level are used. • Lower markups for high price drugs.Pricing is done by Pricing commission	Government and private insurance and co-payment. • Co-payment in outpatient cases, 10%. • No co-payment for specific diseases (transplantation, haemophilia, dialysis). Disadvantaged groups pay low	Iran FDA also uses import tariff rate as a measure to control importation level. Tariff rate about 30% is considered for the products in which its domestic equivalent generic has at least 50% of total market share.
6	Ethiopia	Centralized open tender. • Pharmaceutical prices are not controlled by the government.	100% out of pocket (except for Malaria, TB, HIV/AIDS). Duties and taxes are contributing to increased prices.	• EFDA regulates quality of pharmaceuticals and promotes generic prescription.

Note: Flexibilities under the TRIPS agreement allow countries to gain access to medicines that in other countries may still be under patent, in the interest of public health.

CAN $, Canadian dollar; EFDA, Ethiopian Food and Drug Administration; FDA, Food and Drug Administration; MOH, Ministry of Health; NHS, National Health System; OTC, over the counter; SHI, Social Health Insurance; TRIPS, Trade-Related Aspects of Intellectual Property Rights; VAT, value added Tax.

controlled for other factors. Price setting is mainly used as a mechanism to adjust for inflation independently of the degree of innovation.[86]

Study conducted to evaluate diffusion of new drugs in the post-TRIPS Era showed that even after controlling for drug characteristics and variation in national health expenditure, there were substantial differences across countries in the probability of a drug being commercially available. It is lowest in countries such as Brazil, China and India with historically weak patent protection. Sellers of new drugs are much less likely to have market exclusivity in these countries. Conditional upon being launched, a drug is five to 25 times more likely to be generic/multisource in these countries than in, for example, Spain.[87]

For many large pharmaceutical firms that sell branded drugs, the successful launch of new therapies remains the key to profitable growth. As the patents of older drugs in their portfolios expire, generic drugs enter the market at much lower prices compared with the original brand and an original brand typically loses half of its market share 1 year after patent expiration. Pharmaceutical firms that produce brand-name drugs fight the trend of generic substitution by owning their own generic subsidiaries, offering diagnostics and other types of services in addition to their drugs, trying to convince patients or physicians to be brand-loyal through social media.[88]

Pharmaceutical manufacturers argue that the current patent system is crucial for stimulating research and

development (R&D), leading to new products that improve medical care. Patents could conceivably reduce the total cost of care if new patented medicines turn out to be cheaper than existing medical interventions. But patents are delaying biomedical research by preventing researchers from accessing patented materials or methods they need for their studies.[89]

There is a complicated debate about whether patents impede 'downstream' medical care and 'upstream' medical innovation is ultimately about *access* to such care and innovation. Access to medicines is inhibited by high prices of patented products, particularly in low- and middle-income countries.[83] Patent is not the only barrier to medical care, but other factors such as demand for a product and market size (e.g. a large market and high demand for a product might lead to considerable revenue for the company even at a lower price) can also influence medical care.[83,89]

Net impact of price regulations on societal welfare

Benefits of the introduction of price regulation are obtained through reducing excess profits earned by suppliers of medicines. These include increased affordability of essential medicine, reduced healthcare cost to insurers; reduced government healthcare expenditure; and indirect increase on expenditure non-health-related development goals. However, strict targets in terms of price control may cause great economic risk without a comparative advantage. This is because businesses would seek to be more productive by considering more efficient capital replacement decisions that may result in perverse health effects.[90,91]

The relationship between access, quality and cost of health care is one of the most debatable topics in health policy. Price control may be wrong tool if the goal is to increase healthcare quality and improve healthcare affordability. This is because some quality improvement areas may require adaptation of high-cost technologies. On the other hand, improvements in quality could lower costs by reducing complications or hospital readmissions. Policymakers should be vigilant enough to identify comprehensive evidence-based care needs and use different cost containment methods.[92,93] The debate of 'Iron Triangle' continues, and knowing where to spend the money is critical for health policymaking (Figure 4).

The net impact of price regulations on societal welfare is still debatable. Society loses from delayed introductions of cost-effective innovations, but gains efficiency from reducing markups over marginal cost. However, price controls have negative implications on dynamic efficiency by reducing incentives for timely entry and the extent of competition. Delays in adoption reduce the net present value of research & development (R&D) investments by delaying cash flows and shortening the exclusivity period, which has been observed to reduce future R&D outlays and innovation.[94,95]

Discussion

In this review, we described the role of government involvement in healthcare market from pharmaceutical price regulation perspective in developed and developing countries to achieve UHC and SDGs. The impact of pharmaceutical price regulation on access to essential medicines, drug launching and market entry, drug research and development, and healthcare efficiency was also addressed.[9]

Pharmaceutical price regulation can improve access to essential medicines in low- and middle-income countries, and it can delay new drug launching and market entry and drug launching, as well as research and development unless supported by other strategies. Approaches to improving access to essential medicines without causing significant harm to new drug launching and drug development research will be discussed in detail below.

Healthcare market is different from other perfect market structures because of the following reasons. These include the following: health is consumption and investment good, information asymmetry, the agent selects for principal, party pays for the service, patient co-pays significantly less than actual price, and the surrogate of the final need is bought by customer.[20,29,30,96–99] Both universal health coverage and sustainable development require access to essential

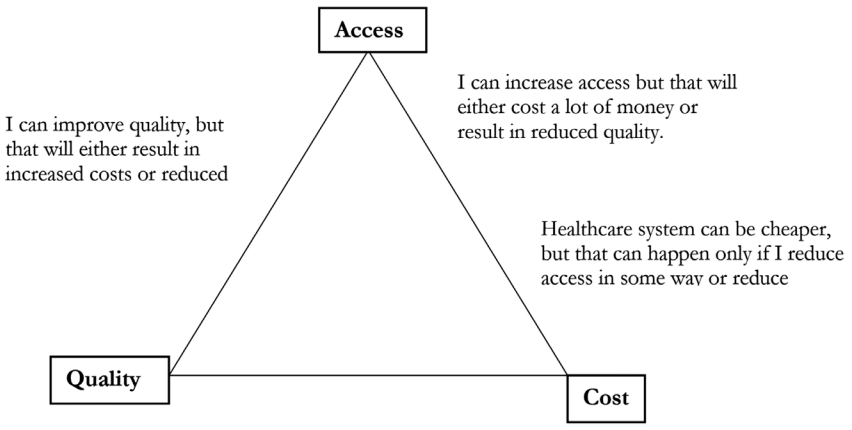

Figure 4 Iron triangle of healthcare access, cost and quality (trade-off one or two for other).

medicines that satisfy the priority healthcare needs of the population. Movement towards UHC and SDG have associated increase in healthcare demand. Therefore, it is important to understand the nature of healthcare market from both demand and supply sides.

Access is defined in terms of physical availability, affordability, geographic accessibility, acceptability and quality. Access to medicines is at the core of universal health coverage and the Sustainable Development Goals.[11,12] There are five core challenges for essential medicines policies. These include lack of adequate financing to pay for an appropriate set of essential medicines, affordability of essential medicines, assuring the quality and safety of essential medicines, irrational use and lack of availability of some important medicines.[13–15]

Demand side factors that could increase the need for essential medicines include moral hazard, ageing population and information asymmetry. From supply/provider side, expanded service coverage to achieve universal health coverage is major potential contributor for increased need of essential medicines. Appropriate co-payment mechanisms include alternative provider payment methods, reforming drug procurement systems and strengthening the application of standard clinical paths in treating patients at hospitals.[100]

A healthcare provider can take the following actions to improve access to essential medicines: maintain national medicines policies and essential medicines lists, strengthen procurement systems, pricing and regulation of medical products, make appropriate use of Trade in Intellectual Property Rights Agreement (TRIPS) flexibility, improve rational use of medicines, improve local production, increase mandatory social insurance coverage, share information on medicines prices and quality of medicines, and bilateral and multicounty collaboration on procurement of lifesaving drugs, and monitor access to medicines.[15,100]

The TRIPS agreement provides compulsory licensing, which allows a government to force a drug company to license its patent to a local generic producer who must pay a royalty to the patent holder. But a government is allowed to issue a compulsory license only after price negotiations with the patent holder have failed.[101] In addition to this, WHO should support inter-country and regional cooperation in procurement, pricing and regulation of medical products, and provide technical support to build capacity as needed.[15] Other innovative approaches such as strategic public funding to attract the private sector to create R&D innovations that effectively address priority global health needs should be implemented. However, using patents as the financial incentive to encourage the pharmaceutical industry to develop drugs for the world's poor is of limited use where the market is nonexistent because neither governments nor patients can afford the end product.[89,102,103]

Unaffordability of medicines leads patients to substitute the drugs less costly once, which may be over the counter and counterfeit. Patients with no substitutable options will reduce or omit therapy and develop adverse health outcomes (worsening, death or drug resistance) from untreated indication.[20] Affordability issues can be addressed by removing taxes and duties on essential medicines and control markups, using pooled procurement often with more competitive methods (such as open tender), establishing efficient procurement period and frequency, enhancing local production and improving health insurance system to include a basic package of financial protection, and providing incentives for pharmaceutical manufacturers to invest in quality medicine production. Accessibility of health services can be addressed by increasing operational hours of clinics providing free or subsidized care, decreasing waiting times by streamlining organizational processes and changes in regulations, and increasing perceived quality of care.[9,11,12]

Acceptability can be improved by providing fixed-dose combination (FDC) medications (poly-pill), and performing large population-based studies to demonstrate efficacy, safety and acceptability of FDCs. Quality of medicines can be ensured by strengthening the capacity of the National Medicines Regulatory Authorities (NMRA), promoting the prequalification programme, creating a business environment that is favourable for the private sector to invest in secure supply chains, regular quality testing at procurement and sales sites, and consumer short message service (SMS) and mobile application verification of product authenticity.[9,11,12]

A recent study focused on investigating the role of the USA in global pharmaceutical innovation showed that the USA still dominates in the global pharmaceutical innovation network, especially when it comes to essential core inventions.[104] Modelling studies also associated this leading role in drug innovation with unregulated pharmaceutical pricing. However, the average profitability of companies was not directly translated to more domestic innovation.[105–107]

However, many countries with significant price regulation were important innovators of pharmaceuticals. Emerging countries are developing at an accelerated pace in the domain of science, technology and innovation in the pharmaceutical sector.[108] For example, it is predicted that China will be the second largest pharmaceutical market after the USA by 2015.[104] In addition to this, countries such as the UK, Germany and Canada, which have price regulation system, were playing significant role in drug innovation.[61,84,85]

The country-specific pricing policies probably do not affect country-specific innovation. For example, although prices in the UK are much less than in the USA, the industry continues to be very profitable and innovative. In Canada, income from domestic sales of brand companies is on average about 10 times greater than its research and development costs, even in the face of prices that are approximately 40% lower than in the USA.[78–82] Therefore, unregulated pharmaceutical pricing system is not the only contributor to drug innovation and launching. Setting different pricing strategies like the UK can help to ensure access to essential medicines and maintain or improve drug innovation and launching.

Pharmaceutical price control affects entry of new products into market.[83,84] This is because a low price in one market may 'spillover' to other markets, through parallel trade and external referencing, and manufacturers may rationally prefer longer delay or not launch to accept a relatively low price.[61,85] Therefore, it is important to consider

additional strategies to maintain or improve drug innovation and new drug market entry. The recently introduced promising approach is open public funding to motivate private sector involvement in drug development and innovation.[104]

Almost all countries regulate prices of pharmaceutical products to ensure access to essential medicines. Countries could have a number of different pricing strategies based on the health policy objectives and public health priority needs. Popular measures include international referencing to set prices, internal reference pricing systems to promote price competition in domestic markets, and positive lists for reimbursement to promote consumption of generics.[109]

The issue of pharmaceutical pricing is a persistent problem, and essential medicines were unaffordable to majority of global population. Unaffordability could be related to patent of product, weak health insurance system, manufacturer monopoly, poor procurement system, irrational use of medicines and companies' profit interest. In response to pharmaceutical company greater profit interest, United Nations Educational, Scientific, and Cultural Organization's Universal Declaration on Bioethics and Human Rights (UDBHR) has established socially responsible capitalism in which pharmaceutical companies continue as profit-making ventures, yet establish moral concern for the welfare of all their stakeholders, including the healthcare consumer.[110]

Patent-related factors can be addressed through TRIPS flexibility option.[101] Health insurance system issue can be addressed by introducing mandatory social insurance for risk pooling. Procurement-related issues can be addressed at national and facility level by re-evaluating the drug selection, and procurement process.[15] Irrational use of medicines is another problem contributing to unaffordability of medicines. Both underuse and overuse can contribute unaffordability. Promoting rational use of medicines requires collaboration of manufacturers, distributors, health professionals, drug regulatory bodies, patients and public.[111,112]

In addition to this, differential retail pricing of a drug among countries and within a country is considered to ensure affordability of medicines for different segment of population particularly in LMICs. Factors such as import tariffs, taxes and various markups if the drug is sold retail or wholesale also contribute to these differences.[110] Pharmaceutical business models are gradually changing to incorporate aspects of social responsibility that include affordable pricing. Therefore, transparent data about just how affordable a company's products are in a LMIC are needed.[110]

Conclusion

Regulating pharmaceutical pricing system is important tool to improve access to essential medicines. Countries that have implemented pharmaceutical price regulation system (Germany, the UK, Canada and Iran) have achieved better access to essential medicines. The US and Ethiopian health systems that are unregulated concerning pharmaceutical pricing had a great challenge of affordability of essential medicines. In addition to this, the USA is not benefiting proportionally from its high profitable pharmaceutical companies in drug development and innovation. Patients with chronic illness in Ethiopia are suffering from lack of affordable essential medicines, which could be reduced by setting country-specific pharmaceutical price regulation.

For countries contributing to new drug development and providing public research and development funds, innovation awards and patent protection to encourage private investors in involvement in development of essential drugs are important to improve innovation and drug launching. Using TRIPS flexibility options for patented products can enhance new drug entry into the market in developing countries.

Based on findings of this scoping review, we provide the following recommendations for countries with unregulated pharmaceutical pricing system. Both the Ethiopian and the US healthcare systems could benefit from pharmaceutical price regulation, to reduce problem of unaffordability of essential medicines. Therefore, setting country-specific price regulation system along with additional strategies such as open funding for drug innovation is critical to ensure access to essential medicines without significantly affecting drug development and launching.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

Funding

This review received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Acknowledgements

We would like to thank all Tehran University of Medical Sciences, Department of Pharmacoeconomics and Pharmaceutical Administration staffs for their technical and material support during our review including access to Internet.

Authors' contributions

All authors read and approved the manuscript. MM has conceived the review project and framed the format design. AA and MD have conducted the review and developed the manuscript for publication. SN and AK participated in literature review and format design, participated in literature review and polished the language of the manuscript. All Authors state that they had complete access to the study data that support the publication.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable. This is a systematic review, and we have used only published articles.

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