Too Costly & Too Scarce

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Chapter 8

Discussion and conclusions

This chapter firstly presents the findings of the research and how they address the study questions. Then the validity of the research is discussed, followed by key policy recommendations to improve the availability and affordability of medicines. The chapter concludes with issues for future research.

8.1 SUMMARY OF FINDINGS IN RELATION TO THE STUDY QUESTIONS

The study questions have been answered in detail in their respective chapters (in the form of articles). This section provides a brief summary of the key findings and conclusions, and how they answer the study questions.

(1) In LMICs, what is the availability, price, affordability and price components of medicines used to treat communicable diseases and NCDs?

The study in Chapter 2 answers research question 1. The findings have, for the first time, shown the average availability of medicines in a large number of LMICs (38.4% and 64.2% in the public and private sectors, respectively), the price governments pay for medicines (11% above international reference prices), and the price people pay for medicines (nine-25 times the reference prices for lowest-priced generics in the private sector, and over 20 times the reference prices for originator brands). Originator brands were 260% higher priced than the lowest-priced generics. As well, the study showed that standard treatments

are largely unaffordable for those on low wages. For example, across six African countries, 2.5 days' wages were required to purchase one salbutamol inhaler in the private sector. Even in the public sector, 1.6 days' wages would be needed to purchase this treatment for asthma. These finding were consistent with other studies showing poor availability and high patient prices in LMICs (74-76). A further finding was that mark-ups and other charges in the pharmaceutical supply chain can result in patients paying substantially more (even double) the manufacturer's selling price.

This study sheds light on three factors that have not been described previously in the literature:

(1) Whether or not governments buy medicines at competitive prices

As mentioned, the study found that median government procurement prices for lowest-priced generics were only 11% above international reference prices. This is a watershed finding, and dispels the widely held belief that governments in LMICs are inefficient when buying medicines. That said, purchasing is not efficient in all the countries eg. the Nigerian government was paying over 400% above international reference prices. Within a number of countries, some individual medicines (generics) are procured at far higher prices than are available on the international market and sometimes higher priced originator brands of off-patent medicines are being procured rather than generics. Governments need to be vigilant when it comes to buying medicines, especially as the international pharmaceutical market is so dynamic. But, in light of the evidence, it is wrong to assume that all governments in LMICs are doing a poor job when buying medicines.

(2) Medicine availability in outlets

When developing the WHO/HAI methodology, measuring medicine availability was initially not considered. However, when collecting prices in outlets in the first few pilot studies, it became apparent that many common medicines were not in stock. Hence an indicator for medicine availability was introduced into the methodology, which proved to be invaluable in understanding barriers to accessing medicines.

The study shows that the availability of medicines in outlets in LMICs is highly variable. In the public sector, it ranged from less than 10% in Yemen to about 90% in Mongolia. In the private sector availability was better, but still suboptimal. Public access to the WHO/HAI database has allowed a number of secondary analyses for specific disease groups, including commonly used medicines to treat cardiovascular disease, diabetes and epilepsy (77-79). Medicine availability was less than 80% for all three therapeutic groups

in both the public and private sectors. Cameron and colleagues (2011) found that generic medicines to treat chronic conditions were significantly less available than generics for acute conditions, but both groups had suboptimal availability in the public sector (36% versus 53%, respectively) and in the private sector (55% versus 66%, respectively) (80).

To date, eleven countries have conducted more than one WHO/HAI survey which allows comparisons over time. In the public sector, availability increased in five countries, showed little change in three countries, and decreased in two countries. In the most recent surveys, only three countries had 80% or more availability in the public sector (81).

A mixed picture was also seen in private pharmacies, with improved availability in three countries, little change in four countries and decreased availability in four countries. Six of the eleven countries had 80% or more availability in the private sector for the most recent survey (81). Clearly, more needs to be done in many countries to improve medicine availability.

In response to the evidence, a number of groups campaigned on medicine availability issues including HAI Africa (in Kenya, Malawi and Uganda) and the Southern Africa Regional Programme on Access to Medicines and Diagnostics (SARPAM). Since 2014, the South African Monitoring Essential Medicines Consortium's 'Stop Stock Outs' initiative has used crowdsourcing and sentinel surveyors to map stock-outs, track specific issues, and advocate for improved medicine availability[1].

(3) Mark-ups and taxes in the pharmaceutical supply chain

When prices are high, attention tends to focus on the pharmaceutical companies that supply the medicines. This is not surprising as new medicines are usually extremely high priced and multinational companies, in particular, can make multi-billion dollar profits (82-84). But focusing on the manufacturer's selling price overlooks all the other charges that contribute to the final patient price. A clear understanding of all elements in the pharmaceutical value chain, and how they contribute to the final patient price, is needed to understand determinants of high prices and appropriate policy responses.

Only a few medicine price components studies have been undertaken, which indicate the challenge in collecting such information in opaque settings. Measuring medicine price components is strongly encouraged in the WHO/HAI manual and detailed guidance is given on how to collect and analyse the data. In the study (Chapter 2) these 'add-on' charges were reported in a few countries. Cumulative mark-ups in the public sector for individual medicines ranged from 17% (Tanzania) to 84% (Mali). In the private sector, they ranged

[1] http://www.stockouts.org/

from 11% to 6894% (El Salvador). Hence, in some settings and for some medicines, mark-ups in the supply chain contribute more to the final patient price than the manufacturer's selling price. But this is not always the case. For example, across the medicines tracked in the private sector in Pakistan, the manufacturer's selling price was 65% to 72% of the final patient price.

Substantive mark-ups were seen in the public sector of several countries. In Shangdong Province in China, mark-ups were higher in the public sector compared to the private sector. This suggests that some governments are generating revenue from medicine sales to subsidise other parts of the health care system. Seven of eight provincial surveys in China, undertaken using the WHO/HAI methodology, have shown higher patient prices in the public sector compared to the private sector for originator brands and/or generics (85,41). In China, approximately 41% of an institution's revenue is thought to come from medicine sales (86). The Chinese government has now introduced a zero mark-ups policy in primary level facilities in the public sector (87). This is a welcome development but its success will rely on the ability of the government to procure medicines at low prices. This was not the case in a 2016 study looking at insulin prices in Hubei and Shaanxi Provinces, China. While the zero mark-up policy was evident, the Chinese government was paying up to ten times what other governments were paying for human insulin (88).

Mark-ups on generics were generally higher than on originator brands, which is consistent with the findings of Kotwani and Levison (89). This may be justified for low priced products (whether generics or originator brands) to ensure adequate returns, and acts as an incentive to stock and sell them. A 2011 WHO/HAI review of mark-up regulations found a few LMICs set higher mark-up levels for lower priced medicines to promote their use (52). Careful consideration is needed, particularly in rural areas where turnover can be lower, to balance the viability of the pharmacy with treatment affordability for patients. In a study of a not-for-profit pharmacy network in rural Kyrgyzstan, Waning and colleagues (2010) found mark-ups of 32% to 244% were needed across products to ensure sustainability. Mark-ups needed by private pharmacies would be even higher in the absence of government subsidies (90).

This study also shows that many LMICs apply value added tax (VAT) and other taxes and tariffs on medicines. This confirms findings from previous research on tariffs and taxes on medicines (91-93). A 2011 WHO/HAI review of sales taxes on medicines concluded such taxes are regressive and reduce utilisation, particularly by the poor and elderly, and reduce compliance with cost-effective preventive and chronic disease treatment regimes. It makes political, economic, and social sense to advocate for a "healthy tax strategy"

combining the elimination of taxes on essential medicines with increases in taxes on unhealthy products and behaviour (54).

Not all add-on costs should be eliminated, such as the cost of testing the quality of products (55). But those that are unjustifiable (such as taxes on essential medicines) should be removed, and those that are unjustifiably high (some mark-ups) should be reduced. Our study shows the importance of understanding the entire pharmaceutical supply chain in order to identify drivers of high patient prices.

(2) In LMICs, what is the price, availability, and affordability of insulin?

Almost a century after its discovery, access to insulin is poor in LMICs. Life-expectancy is as low as one year for a child with type 1 diabetes in sub-Saharan Africa, whereas in the USA people with type 1 diabetes have only a 4–6 year difference in life expectancy compared to that of the general population (64,94).

The study in Chapter 3 answers research question 2. The study found the availability of insulin was poor (56% and 39% in the public and private sector, respectively), insulin prices were high (annual patient prices were USD$35.40 in the public sector and USD$95.71 in the private sector) and insulin was unaffordable in some settings (eg. the lowest-paid unskilled government worker in Mexico City would have to work five days to purchase a vial of human insulin in private pharmacies). This mirrored the findings from an earlier study by Mendis and colleagues (2007) where insulin affordability ranged from 2.8 days' wages in Brazil to 19.6 days' wages in Malawi (74).

Insulin is one of the growing number of large-molecule biological medicines that are now used to treat various conditions. Factors thought to be contributing to high insulin prices differ to those hindering access to most small-molecule chemical medicines. The most notable is the market domination by only three companies. As reported in Chapter 3, over 90% of the global insulin market is dominated by Eli Lilly, Novo Nordisk, and Sanofi in terms of both value and volume. A 2015 review of the global insulin market identified 30 or so additional manufacturers of generic insulin (or biosimilar insulin as it is referred to), mainly in India, China, and other parts of Asia (95). They mostly sell domestically and in neighbouring countries; few have insulin products with marketing consent in more than 10 countries.

Dylst and Simoens (2011) found high generic market share countries have larger decreases in medicine prices than countries with low generic market share (96). A US study showed prices dropped significantly when five generics are on the market (97). Few national

markets have this level of competition for insulin, therefore, a lack of competition is thought to be a major barrier to more affordable insulin.

The lack of competition is influencing the insulin market in various ways. In 2004, the Central Medical Store in Mali purchased insulin for the first time in two to three years (98). This lapse was attributed to an inability to find a supplier of generic insulin (Mali promotes the use of generics) and the requirement for tender quotes from three potential suppliers (which was not possible because of the small number of insulin suppliers). This shows the need for purchasers to understand that the pharmaceutical market is not homogeneous, and to adjust their procurement practices when needed to ensure an uninterrupted supply, particularly for life-saving medicines such as insulin.

In this study (Chapter 3), the impact of formulations and presentations on patient prices was not assessed. However, a 2015 study found human insulin was lower priced than the newer analogue insulin in both the public sector (US$7.64 versus USD$45.03) and private sectors (USD$16.65 versus USD$39.95). All formulations of human insulin in vials were lower priced than when supplied in pens and cartridges, but this was not the case for all analogue insulin formulations (99). To improve access to insulin in resource-constrained settings, it is vital that lower priced human insulin in vials continue to be manufactured.

(3) In LMICs, what is the combined availability and affordability of medicines used to treat cardiovascular diseases, diabetes, chronic obstructive pulmonary diseases and central nervous disease conditions?

The study in Chapter 4 answers research question 3. The approach of analysing availability and affordability in combination is innovative, as previous surveys analysed medicine availability and affordability separately. The study showed that for each of the four NCDs, few medicines were both available and affordable. In low- and lower-middle income countries, less than 20% of lowest-priced generics across the four NCDs met WHO's target in the public and private sectors. In upper-middle income countries, the situation was also far from satisfactory as only 32.3% and 37.4% met the target in public and private sectors, respectively.

A target of 80% availability of affordable medicines, including generics, in the public and private sectors by 2025 was adopted in WHO's Global Action Plan (57). To assess the impact of initiatives against this target, a baseline is needed. This study establishes a baseline.

Analyzing availability and affordability separately, and then in combination, gave very different results. For example, the availability of generics in low-income countries was 40.7% and 51.0% in the public and private sectors, respectively. But when affordability

was factored in, the percentages of medicines that were both available and affordable fell to 15.9% and 16.7% in the two sectors. This combined assessment more accurately reflects the reality for people accessing medicines. By publishing this article, it is hoped that findings from future medicine availability and affordability surveys will be analysed in this way.

(4) In LMICs, what is the influence of inclusion of medicines in national EMLs on their availability in outlets

The study in Chapter 5 answers research question 4, that is, in LMICs the inclusion of medicines in national EMLs results in improved availability of these medicines in medicine outlets. The availability of essential medicines was 40% and 78% in the public and private sectors respectively, compared to 7% and 57% for other medicines. The difference in availability between essential and other medicines was smaller in the private sector compared to the public sector, suggesting a less prioritised and closer to free market environment. While the essential medicines concept was primarily targeted at the public sector, it has influenced the private sector as well. One explanation may be the increased demand for essential medicines in private pharmacies due to their poor availability in public sector outlets.

According to WHO, the availability of medicines in outlets in LMICs is undermined by several factors, including poor medicine supply and distribution systems (100). WHO's Model List is used to help countries develop national EMLs in order to rationalise the purchasing and distribution of medicines, thereby reducing costs to the health system and improving access to important medicines. This has resulted in four out of five countries worldwide now having EMLs (101).

Of the countries with a national EML, 94% use the list as a basis for public procurement of medicines (13). In these countries it would be expected that the availability of medicines on the national EML would be high, particularly in public sector outlets. While some previous surveys of medicines on national EMLs reported adequate average availability (42,102,103), this was not always the case (104,105).

This analysis confirms that efforts over the last 40 years to promote the essential medicines concept, and the development and implementation of national EMLs in particular, have positively influenced the provision of essential medicines. However, the availability of essential medicines in outlets is far from optimal, especially in the public sector. This is hampering access, especially for the poor who rely on outlets in this sector to stock essential medicines.

(5) In LMICs, what is the influence of price transparency and comparisons on procurement prices?

The study in Chapter 6 answers research question 5, that is, comparing public sector procurement prices and quantities can positively influence procurement processes and prices. Identifying prices paid by others empowered UNRWA to negotiate a lower price for its top medicine by value (premixed insulin). However, a key limitation identified in the study was the difficulty in accessing comparator data.

For more than 60 years UNRWA has been the primary health care provider for Palestine refugees in the Middle East, which has resulted in significant improvements in their health status, in particular in the reduction of maternal and child mortality. This has been achieved despite the poor living conditions and high levels of unemployment of refugees, political instability and frequent conflict in the region (66,106). Access to medicines and other services are vital, especially where refugees are unable to access any government health services in host countries (such as Lebanon).

Increasing numbers of refugees, an aging population, and increasing numbers of refugees with NCDs was resulting in rising medicine expenditure (from USD$13.8 in 2009 to USD$18.31 in 2010) and a looming budget deficit. The top 10 medicines procured cost USD$6.7 million, with premixed soluble/isophane insulin having the highest expenditure at approximately USD$1.5 million (106).

The study showed that overall there was little difference between UNRWA procurement prices and the comparator prices across the medicines where there were matches. However, there were some wide variations for individual medicines, indicating possible opportunities for UNRWA to buy at lower prices. For example, UNRWA paid USD$3.10 per vial for premixed insulin and purchased about 500,000 vials. Buying from the same pharmaceutical company, GCC paid USD$2.12 per vial and purchased nearly two million vials.

UNRWA acted on the study findings, and in the following years negotiated a price reduction for insulin. Despite its reduced purchasing power, UNRWA now pays $2.92 per vial only marginally higher than the price paid by GCC ($2.82) (99). The savings allowed UNRWA to purchase statins, which they previously did not buy due to insufficient funds.

(6) In LMICs, what is the influence of local medicine production on prices and availability?

The study in Chapter 7 answers research question 6. The key finding of the study was the mixed influence of local production on prices in the two study countries. In Ethiopia, local

production did not result in lower tender prices or lower patient prices in the public sector. A different picture was seen in Tanzania. Local production did result in lower tender prices although it did not result in lower patient prices in the public sector.

The methodology used in this study is innovative, with the findings providing insight as to how local production can impact availability and patient prices, and how it can be influenced by governments through preferential purchasing and variable mark-ups in the public sector.

In Ethiopia, a higher proportion of products purchased by the government were locally made, but at higher prices (45% more) than imports. For nine of the 25 medicines, one or more locally made products and one import were purchased, at varying prices and quantities. The reasons for this purchasing practice warrant further study. The 25% local preference policy was being exceeded for some medicines, and significant savings would result if only lower-priced products (imports) were purchased. The situation was different in Tanzania where the government was only buying one product per medicine. About half the products purchased by the government were made locally, and overall these products were 50% lower priced than imports.

Both governments were applying variable public sector mark-ups which further support local producers. The Ethiopian government applied a 17% mark-up on higher-priced local products and a 53% mark-up on lower-priced imported products, which reduced the difference in patient prices between local and imported products to 22% (but local products were still higher priced). The Tanzanian government charged a 135% mark-up on lower-priced local products and 65% for higher-priced imports. This resulted in only a 7% difference in patient prices between local and imported products.

In the private sector in Tanzania, patient prices were similar for imports and local products while in Ethiopia, patients were paying 193% more for imports. This shows the willingness of consumers to pay higher prices for imported products.

In mid-2015, Ethiopia launched a 10-year strategy and plan of action for pharmaceutical manufacturing (107). The objectives include improving access to medicines through the local production of quality-assured pharmaceuticals, strengthening the regulatory authority, promoting the production of active pharmaceutical ingredients, and creating a research and development platform. Our survey establishes a baseline for measuring whether the plan of action results in improved access to medicines through greater availability and lower prices.

8.2 VALIDITY OF THE RESEARCH

Despite its strengths, the WHO/HAI methodology has some limitations. First, data is collected only for products with marketing authorisation in the country, so product-quality assurance is assumed. But it is not measured. Second, availability and price are determined for the specific list of survey medicines, and do not account for alternate strengths and dosage forms of these products or therapeutic alternatives. Third, the reliability of median price ratios as a metric for comparison depends on the number of supplier prices used to determine the median international reference price for each medicine. When few supplier prices are available or when the buyer price is used as a proxy, median price ratio results can be skewed by a particularly high or low international reference price.

Availability data only refer to the day of data collection at each facility and might not indicate average availability of medicines over time. However, since surveys are done in several facilities over a period of time, the data provide a reasonable estimate of the overall situation and are indicative of the real-life situation faced by patients on a daily basis.

In the study of availability and prices across 36 countries (Chapter 2), availability in public sector outlets did not take into account the level of care of the outlet (primary, secondary, or tertiary facilities) and whether or not each level was permitted to stock and sell each survey medicine. Information on the level of care was not collected in surveys at that time. Collecting this data became a requirement in the second edition of the WHO/HAI methodology manual, published in 2008. Hence this is taken into consideration in the studies on insulin availability (Chapter 3) and the combined availability and affordability of NCD medicines (Chapter 4).

The daily wage of the lowest-paid unskilled government worker is used to estimate treatment affordability. However, in many countries a large proportion of the population earns less than this worker. Moreover, the need for other non-discretionary expenditures (eg. housing), the seasonal fluctuations in income, the number of dependents who live on this wage, potentially being treated with multiple medications, and the full costs of treatment (such as diagnostic and consultation costs) are not accounted for. Nevertheless, this wage is a universally available metric to assess the affordability of medicines. In 2010, two alternate measures of treatment affordability were proposed (108) but their use in national surveys has not been reported.

A limitation of the study looking at the influence of the national EML on availability (Chapter 5) was the lower number of non-essential medicines in the analysis (average 11 per survey) compared to the number of essential medicines (average 39 per survey). This is partly due to the encouragement of including essential medicines in WHO/HAI surveys. The analysis in Chapter 6 was representative as it included the top 80 medicines purchased by UNRWA by value, accounting for 93% of pharmaceutical expenditure from their General Fund. However, the number of comparators was limited. Efforts to obtain data from other governments in the region (Egypt, Syria, and Lebanon) were unsuccessful.

Limitations of the methodology to measure prices and availability of locally produced and imported medicines (Chapter 7) include: the relatively low number of survey medicines (although over 2500 data points were generated per country), measuring availability only on the survey day, not identifying clearance costs for imports purchased by the Ethiopian government, and not measuring all price components in the pharmaceutical supply chain. However, none of these individual limitations detract from the overall picture of access to essential medicines that emerge from these studies compared to the situation in 2001 when this body of work began. There is now far more knowledge on the subject which provides a basis for policy recommendations.

8.3 CONCLUSIONS AND POLICY RECOMMENDATIONS

In the introduction, a number of hypotheses were proposed. Based on the findings in Chapters 2-7, it is now possible to say whether the hypotheses are supported or not.

H1 **A robust methodology allows for the collection, analysis and reporting of prices, availability, affordability and price components as a basis for developing policies and responses that will improve access**

The WHO/HAI methodology has been used in over 100 national and sub-national surveys since it was published in 2003. The findings have resulted in policy reforms in many countries. As well, the WHO/HAI database of survey findings has been used in various secondary analyses (many of which are reported in, or referenced to, in this thesis).

H1.1 **Medicine availability is suboptimal and affordability is poor in LMICs, and availability and affordability cannot be considered in isolation**

The findings in Chapter 2 support the hypothesis that availability is suboptimal, and affordability is poor for those on low wages, in LMICs. The findings in Chapter 4 support the hypothesis that availability and affordability need to be considered in combination. This reflects the significance of both determinants as barriers to accessing medicines, and more accurately reflects the reality for people when accessing medicines.

A range of policy options and interventions are available to governments to address issues of low availability, high medicine prices, and poor affordability. The most appropriate action to follow depends on a country's survey results and underlying determinants (eg. poor government procurement practices, not permitting generic substitution, and high mark-ups in the private sector). Existing pharmaceutical policies and market situations also need to be considered. Hence the choice of interventions will be contextualised, and a range of interventions will likely be needed.

Once chosen, the interventions may have to be prioritised, with consideration given to what will yield greatest health benefits and lowest economic and socio-political cost of policy implementation. Consideration should be given to focusing on a limited number of measures at any one time, ensuring they are fully implemented and enforced. Many countries have good policies and regulations but implementation and enforcement is poor, resulting in no improvement in availability and affordability (109).

WHO's World Medicines Situation Report (2011) lists a number of policy options to improve medicine availability and affordability (110) (Table 1). Low availability and improved affordability in the public sector can be addressed through adequate, equitable and sustainable financing, adequate selection (eg. limiting purchases to medicines on the national EML, with quantities based on need), improved purchasing efficiency (eg. competitive tenders using the INN name, price negotiation), timely distribution to facilities, and providing medicines free-of-charge or passing on procurement prices to patients. Differential pricing schemes that offer reduced prices in poorer countries should be considered, particularly for essential medicines that are under patent or where there is very limited competition. For any differential pricing scheme it is important to check there are no unacceptable conditions, such as market exclusivity for medicines that are off patent which impacts competition.

Mark-ups and other costs in the supply chain need to be regulated to avoid excessive add-on costs. A zero mark-up policy in the public sector is needed. In the private sector, the remuneration of pharmacies via dispensing fees should be considered to encourage

Table 1: Policy options to improve medicine affordability and availability (109)

Component of medicines policy	Specific actions to influence price, availability and/or affordability
Selection of essential medicines	• Formulation/updating of EMLs and institutional formularies • Development and use of Standard Treatment Guidelines • Development of a therapeutic substitution policy
Procurement/ purchasing	• Limited to an EML by the INN name • Base quantities on reliable estimates of actual need • Base on formal written procedures and explicit, predetermined criteria to award contracts (i.e. ensure transparency of the process) • Plan properly and monitor performance (results should be made publicly available) • Base on competitive procurement from prequalified suppliers • Pool procurements at the national level • Use pharmacoeconomics or external reference pricing (international price comparisons) as a guideline for setting prices of new medicine (single-source) • For high-priced products, apply pressure for differential prices and consider use of TRIPS flexibilities for medicines under patent
Distribution system	• Maximise efficiency and transparency • Control of mark-ups with regressive margins and with effective enforcement
Generic competition	• Establish an effective quality assurance capacity • Reduce regulatory barriers to market entry of generic equivalents (e.g. early-working, fast-tracking applications, and reducing the application fee) • Permit and promote generic substitution
Prescribing and dispensing	• Introduce incentives to prescribe and dispense generic medicines • Improve health professional and public confidence in generics • Provide unbiased consumer medicine information • Strictly regulate the promotion of products by pharmaceutical companies according to WHO's Ethical Criteria for Medicinal Drug Promotion and ban direct-to-consumer advertising of prescription medicines • Separate prescribing and dispensing functions; develop and monitor good prescribing and good dispensing practices • Empower patients through the publishing of prices and availability • Establish regular monitoring of prices and availability
Financing	• Encourage pooled and prepaid financing of medicines (e.g. through social insurance schemes) • Support community-based insurance initiatives that focus on improving access to essential medicines • Establish a social health insurance system covering the whole population • Ensure that social health insurance benefits are comprehensive, using limited formularies based on cost-effective therapeutic guidelines, and that patients are not required to seek reimbursements • Abolish taxes and duties on essential medicines • Introduce minimal or no patient co-payments in the public sector or health insurance systems

the dispensing of lower-priced products, with levels set that do not result in higher prices for patients. If remuneration is based on the value of the medicine, then mark-ups need to be applied regressively (lower percentage for a higher-priced product) to encourage the dispensing of lower-priced products, as occurs in some LMICs. In both the public and private sectors, taxes and tariffs on essential medicines should be eliminated, a policy which has been implemented in many (but not all) countries.

Increasing the use of lower-priced quality-assured generic medicines is a key strategy for improving medicine affordability, as identified in Chapters 2 and 4. Use of generics is promoted at the highest levels, including by the Director General of the WHO who stated in 2011:

> "WHO not only supports generic products. We aggressively *promote* them, whether through guidelines for conducting bioequivalence studies or through the prequalification programme. Generic products serve public health in multiple ways. In terms of improving access to medicines, price and quality go hand in hand. Generic products are considerably less expensive than originator products, and competition among generic manufacturers reduces prices even further. Generics serve the logic of the pocket. An affordable price encourages good patient compliance, which improves treatment outcome and also protects against the emergence of drug resistance."
>
> Dr Margaret Chan, Director General, World Health Organization, 28 February, 2011

Switching from originator brands to lowest-priced generic equivalents can result in significant savings for governments and patients, as illustrated by Cameron and colleagues (2008). They found savings of 9%–89% would be possible in the private sector, and public hospitals in China could save USD$370 million USD from switching only four medicines (111). Indeed, a range of pro-generic medicines policies are available, although their development, implementation and enforcement in national settings can be both complex and challenging (112).

Policies to improve access to medicines can be divided into supply-side policies and demand-side policies (113). According to a review by Kaplan and colleagues in 2012 (114), key supply-side pro-generic policies include:

- Incentives for generic manufacturers to file an application for market authorization: reducing fees and granting an exclusivity period to the first generic on the market.
- Reducing the time to market authorisation: shortening the review time of applications and implementing Bolar provisions that exempt generic manufacturers from patent infringement when developing a generic of a patented product.

- Price regulation: a number of options exist, each with pros and cons, including internal reference pricing and setting generic medicine prices relative to prices of originator products.

Key demand-side pro-generic policies include:

- Promote the prescription of generics by mandating prescribing by the INN name.
- Increasing the dispensing or selling of generics by permitting or mandating generic substitution and manipulating mark-ups and/or dispensing fees.
- Campaigns to health care professionals and the public to inform and create awareness of the relative cost benefit of generic medicines. Price information needs to be accessible to all.
- Limit or ban free samples of all products as they are aimed at creating brand loyalty.

***H1.2* Barriers at various levels impact medicine availability, prices and affordability**

This hypothesis is supported as the findings in Chapter 3 identify a variety of barriers at the global and national levels impacting access to insulin.

The use of quality-assured biosimilar insulins as a cost containment measure brings additional challenges not commonly faced by generics. The process of biosimilar approval is demanding and requires substantially more data to demonstrate quality, safety, and efficacy than is required for a generic (116). Regulatory guidelines are not present in all countries, and there is heterogeneity in the definition of a biosimilar among countries. Requirements can differ across countries e.g. some national authorities require additional clinical trials in the local population which prolongs the time needed to submit applications and increases costs (117). Issues about the interchangeability of biosimilars complicate their uptake (118), which may account for some governments procuring insulin by brand name. The 90% market domination by three multinational companies, all with significant marketing capabilities, will also challenge the uptake of biosimilar insulins. Gaining market entry is essential, but it does not guarantee that biosimilar insulins will be used in sufficient quantity to recoup the large investment needed to produce them and get them approved.

Many of the policy recommendations in Chapters 2 & 4 are applicable to Chapter 3. These include the need for procurement price transparency and undertaking procurement price comparisons, tendering insulin by the INN name, controlling insulin prices, passing on low procurement prices to insulin users who must pay out-of-pocket in the public sector,

regulating mark-ups in the private sector supply chain, eliminating taxes and tariffs on insulin etc.

However, because of the specificities of insulin, regulatory issues for biosimilar insulin, and market domination, a number of specific interventions are recommended based on the study findings. These include standardizing national regulatory requirements for insulin, including insulin in WHO's prequalification programme, splitting government tenders across insulin manufacturers to support competition, education on the cost-benefits of human versus analogue insulins, and clinical audits to ensure people with type 2 diabetes are not unnecessarily on insulin when oral antidiabetes medicines (which are more affordable) could be used.

H1.3 **Governments in LMICs are procuring medicines at prices far above international reference prices**

The findings in Chapter 2 do not support this hypothesis. Overall, governments in LMICs were paying only 11% more than international reference prices. However, some individual countries were paying substantially higher prices than reference prices.

Policy recommendations include:

- Reviewing the medicine procurement process in countries where procurement prices are found to be high compared to international reference prices. This will identify the reasons for the high prices. This includes reviewing the supplier prequalification process, what general approach is taken (international open tenders or some other process), how tenders are compiled and advertised, the appropriateness of any conditionalities, how bids are evaluated and awarded, and the extent to which emergency purchases are needed and the prices paid in such situations compared to the tender prices etc.
- Reviewing high procurement prices of individual medicines. Again, causes need to be identified. Identifying new potential suppliers of these medicines should be undertaken, particularly those where the products are registered with competent regulatory authorities and are likely to have competitive prices. Such suppliers should be encouraged to apply for pre-qualification and to bid for tenders.
- Conducting regular procurement price monitoring, against MSH prices and prices paid by other governments and agencies.

- ***H2* Identified policy interventions will influence medicine prices and availability**

  ***H2.1* Essential medicines lists have a positive effect on availability**

The findings in Chapter 5 support this hypothesis as the availability of medicines on national EMLs, in public and private sector outlets, was higher than the availability of medicines absent from the list. However, the availability of medicines was suboptimal in both sectors, including those on national EMLs.

Policy recommendations to improve the availability of medicines on the national EML, in public sector outlets, include:

- Limiting government procurement to medicines on the EML
- Procuring by the INN name
- Basing quantities on reliable estimates of actual need
- Pooled national procurement in order to benefit from economy of scale, with savings used to procure essential medicines
- Timely distribution to outlets
- Monitoring supplier performance

***H2.2* Analysing procurement prices can lead to positive outcomes for the procurement process**

The findings in Chapter 6 support the hypothesis for UNRWA, but the hypothesis may not be supported in other settings. By comparing procurement prices and identifying potential savings, UNRWA negotiated a price reduction for its top medicine by value, with the savings used to procure an essential medicine for cardiovascular disease that they formerly were unable to afford.

Policy recommendations include:

- Comparing national procurement prices with prices in MSH's Guide on an annual basis. Such an analysis will identify whether or not tender bids are competitive compared to the international market.
- Publishing government procurement prices (and related information, including quantities) on a publicly-accessible website so that price comparisons are possible with neighbouring and/or other countries. WHO's Western Pacific Regional Office established a database for sharing procurement prices paid by Member States in the region (www.piemeds.com) but it is not regularly updated. WHO regional offices have a key role to play in facilitating price sharing in their region, and should establish regional price exchanges that are comprehensive and current.

- Considering various procurement processes, including price negotiation, for high value essential medicines with little or no competition.

H2.3 **Local production results in lower prices and improved availability**

Based on the findings in Chapter 7, this hypothesis cannot be supported. While local production improved availability, the findings puncture the myth that local production always results in lower prices. That said, more studies are needed to confirm this finding. It is fashionable to champion local production in terms of health security, and development and economic policy, but the overall impact on health is still unclear. Local medicine production (Chapter 7) is an issue where it is critical that health, trade and industrial policies are balanced. It is the view of the author that the primary focus should always be on improved health through improved access to medicines (greater availability and improved affordability through lower prices). Therefore it is recommended that governments supporting local medicine manufacturers should regularly monitor prices and availability, and ensure patients do not pay higher prices because of this policy.

8.4 FUTURE RESEARCH

There are many areas where future research is needed on medicine prices, availability, and affordability issues. In this section those of most relevance and importance that have emerged from the studies will be considered.

In 2011/12, WHO and HAI reviewed several pharmaceutical pricing policies in LMIC, based on refereed journal articles and grey literature. The subsequent reviews were on external reference pricing (50), the role of health insurance in the cost-effective use of medicines (51), mark-up regulations (52), competition policy (53), taxes on medicines (54), and the role of health technology assessment in medicine pricing and reimbursement (55). In addition, a review on policies to promote the use of generics, when governments and patients buy medicines, found little evidence of the use and impact of the selected range of policies in LMICs, despite evidence of pricing policies and regulations in place, particularly in middle-income countries (113). Where studies do exist, they tend to be descriptive and/or cross-sectional and do not evaluate the impact of policy changes. The paucity of policy analysis suggests that LMICs should evaluate the impact of any pricing policies employed, and make the findings publicly-accessible so others can learn from their experiences.

Over 100 national and sub-national surveys have been undertaken using the WHO/HAI methodology. While there have been reports of policy reforms in response to survey findings (eg. in Lebanon, Tajikistan and the UAE), there is a need to systematically identify what happened after the survey was completed and what stimulates policy reforms. Research questions could include (1) were the findings disseminated? (2) were they discussed in national multi-stakeholder workshops (as recommended by WHO/HAI) or by some other means? (3) was any additional research undertaken? (4) what new/revised policies and interventions were developed? (5) were they fully implemented? (6) what was the outcome in terms of prices, availability and affordability? Such information would shed light on whether or not evidence stimulates policy reforms.

In Chapter 2 it was found that, on average, originator brands were 260% higher priced than lowest-priced generics, but in some countries the difference was over 1000%. As discussed, there are many policy options that promote the use of lower-priced quality-assured generics. However, they predominantly focus on supply-side issues. Consequently, research is needed on demand-side issues particularly at the point of dispensing. This includes:

- what products are stocked in outlets and what are their prices as compared to other equivalent products that could be stocked but are not;
- the interplay between pharmacists and patients when dispensing/buying medicines eg. do pharmacists offer lower-priced products and do patients ask for and subsequently receive lower-priced products?; and
- to what extent have policies that educate the population on the value of generics been successful and replicable.

Although some countries have undertaken medicine price component studies, more research is needed to better understand what additional costs are added to medicines in the supply chain, and what those costs contribute to the final patient price. Further research should investigate how additional costs differ depending on product type (generic or originator brand), whether the product is locally produced or imported, whether the outlet is in a rural or urban area, etc. This will naturally lead to further research on remuneration levels for wholesalers, retailers, etc. that promote medicine availability and affordability while ensuring economic viability (especially in rural areas). In LMICs, mark-ups are based on the value of the medicine. Research is needed on other remuneration options, such as dispensing fees based on service provision, and their impact on prices.

Medicine discounting, rebating and trade schemes (eg. 'buy six get one free') commonly occur, but they tend to be confidential arrangements. This may account for the scant number of studies on discounting and rebating. However, the South African government investigated discounting and rebating levels, and consequently both were banned. They now provide publicly-accessible information about the price of medicines sold in the private sector (119). Vogler and colleagues (2012) found discounting and rebating by pharmaceutical companies to European public payers was common (120). Such research is needed in other countries to better understand the extent of such practices.

It is widely believed that companies will offer lower prices for larger quantities of medicines purchased. The UNRWA analysis (Chapter 6) shows that this is not always the case. Research is needed to compare selling prices with the quantity purchased, and the significance of other factors (such as prompt payment discounts) considered by manufacturer's when they set or agree on their selling price.

The study on the impact of local production on medicine prices and availability included two countries (Ethiopia and Tanzania); both had less than 10 local medicine producers and similar levels of local preference when the government procured medicines. Further studies are needed, particularly in countries with a large number of local producers (such as Vietnam and China), where local preference exists or conversely does not exist, and where governments are actively supporting local production through other means. Such studies should include detailed analyses of add-on charges in the supply chain to ascertain differences for locally produced and imported medicines and their contribution to the final patient price. In addition, research is needed on the perceptions of health care providers and patients to prescribing, dispensing, and using locally produced medicines particularly when they are low-priced. If they perceive the quality is inferior to that of imported products, then education interventions will be needed to show the products are tested by the national medicines regulatory authority and are quality-assured.

From the findings of the study in Chapter 3, various aspects of the global insulin market, and their impact on access to insulin, need studying. Insulin price, availability, and price components studies are needed in a larger number of LMICs to add to the findings in Chapter 3. Key findings from the study were the 90% global market domination by three multinational companies, and that only a few of the 30 or so other manufacturers of biosimilar insulin have products registered in 10 or more countries. Research is needed on how these biosimilar insulin manufacturers can penetrate markets in monopoly situations and hence improve competition. Such research needs to consider manufacturers' selling prices, regulatory requirements for biosimilar insulin, government tendering processes

(some governments are known to tender by brand name), and acceptance and use of biosimilar insulin by health care providers and insulin users. It is a challenging and multi-faceted issue, but with competition, prices would be expected to fall, making insulin more affordable.

This thesis describes 15 years of work that has been a personal journey and part of an effort to transform our understanding of medicine availability, prices, and affordability in LMICs. When the work began in 2001, there was very limited understanding of the price, availability, and affordability of medicines, as well as the complexity of the issues. This thesis documents the evolution of the methods and our understanding not just of the issues but also of the policy options. Ensuring universal access to essential medicines is possible, but more work is needed to ensure it is a reality.