Exploring the Essential Medicines List Concept

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Master of Philosophy

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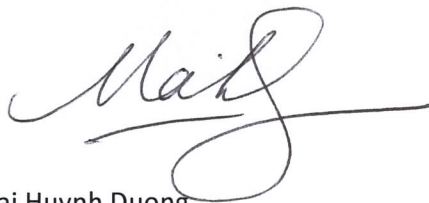
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Declaration

This thesis describes research carried out in the Faculty of Pharmacy, The University of Sydney, under the supervision of Associate Professor Timothy F. Chen, Dr. Rebekah J. Moles, and Dr. Betty Chaar, and with the permission of the Dean of the Faculty of Pharmacy, Professor Iqbal Ramzan.

The research presented in this thesis is, to the best of my knowledge, original and except as acknowledged in the text, is entirely the product of my own scholarly work. No part of this work has been submitted in part or in whole for the award of a degree at any other university. Full acknowledgement has been made where the work of others has been cited or used.

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Acknowledgements

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Tables and Figures

List of Abbreviations

Active Pharmaceutical Ingredient	API
Antiretroviral Therapy	ARV
Artemisinin-based Combination Therapy	ACT
Central Medical Stores	CMS
Disability Adjusted Life Years	DALY
Declaration of Health Action	DOHA
Drug Related Problem	DRP
Essential Medicine	EM
Essential Medicines List	EML
European Federation of Pharmaceutical Industries and Associations	EFPIA
Food and Drug Administration	FDA
Health Action International	HAI
Health Technology Assessment	HTA
High Income Country	HIC
Human Research Ethics Committee	HREC
Hydrochlorothiazide	HCTZ
International Network for Rational Use of Drugs	INRUD
International Non-proprietary Name	INN
International Procurement Reference Price	IPR
Low to Middle Income Country	LMIC
Lowest Priced Generic	LPG

Market Authorisation Holder	MAH
Médecins Sans Frontières	MSF
Millennium Development Goals	MDG
National Essential Medicines List	NEML
National Institute for Health and Care Excellence	NICE
Non-communicable Disease	NCD
Non-Governmental Organisation	NGO
Non-Profit Organisation	NPO
Oral Rehydration Salts	ORS
Pharmaceutical Benefits Advisory Committee	PBAC
Pharmaceutical Benefits Scheme	PBS
Pharmaceutical Management Agency, New Zealand	Pharmac
Preferred Drug List	PDL
Quality Adjusted Life Years	QALY
Quality Use of Medicines	QUM
Research and Development	R&D
Scottish Intercollegiate Guidelines Network	SIGN
Section 100 Program	S100
Standard Treatment Guideline	STG
Therapeutics Goods Administration	TGA
Trade Related Aspects of International Property Rights	TRIPS
United Nations	UN
United States Food and Drug Administration	US FDA

United Nations Fund for Population Activities   UNFPA

Vital, Essential, Non-Essential Medicines Model   VEN Model

World Health Organization   WHO

World Health Organization Model List of Essential Medicines   WHO EML

World Health Organization and Health Action International   WHO/HAI

World Trade Organization   WTO

List of Definitions

i) Drug Shortage

    a) Thesis Definition:
The inability to dispense a medicine at any point in time which may result in potential patient harm.

    b) The United States Food and Drug Administration (US FDA):

"A period of time when the demand or projected demand for a drug within the United States exceeds the supply of the drug" (FDA 2011, FDA 2013, Thakur 2013).

    c) The European Public Health Alliances:

"A situation in which the total supply of an authorised medicine or of a medicine used on a compassionate basis is inadequate to meet the current or projected demand at the patient level. The shortage may be local, national, European or international. This common position prioritises supply shortages that affect medically necessary medicines (also called essential medicines)" (Charnay-Sonnek et al. 2013).

    d) The European Federation of Pharmaceutical Industries and Associations (EFPIA):

"A crisis situation caused by the inability of any market authorisation holder to supply a medicine with a specific active pharmaceutical ingredient (API) to a market over an extended period of time resulting in the unavailability of this medication for patients" (Bogaert et al. 2015, EFPIA 2013).

ii) Formulary

"A list of medications stocked in the organisation or easily obtainable from an outside source" (Glossary-of-Terms 2009).

iii) Low to Middle Income Country (LMIC)

The World Bank defines country economies using the World Bank Atlas method measured in US dollars. The World Bank defines: low income economies as, "those with a Gross National Income (GNI) per capita of $1,045 or less in 2014; middle-income economies are those with a GNI per capita of more than $1,045 but less than $12,736; and lower-middle-income and upper-middle-income economies are separated at a GNI per capita of $4,125." (2016)

iv) High Income Country (HIC)

The World Bank defines high income economies as, "those with a GNI per capita of $12,736 US dollars or more." (2016)

ii) Reimbursement List

A list of medicines approved for use in the healthcare system by authorised prescribers that provide payment for pharmaceutical expenditure or costs (Culyer and Newhouse 2000).

i) The WHO definition of Essential Medicines:

"Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative cost effectiveness. Essential medicines are intended to be available within the context of a functioning health systems at all times, in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford" (WHO 2002).

v) Stock-Out

"A stock out is when a pharmacy (in a medical store or health facility) temporarily has no medicine on the shelf. It may affect one medicine or many medicines, or in the worst case, all medicines. A stock-out can be documented at one point-in-time or over a period of days, weeks or months. When there are good stock management systems in place, the stock-out duration will be minimal or, ideally, never" (Stop-Stock-Outs 2015).

Peer Reviewed Publications and Abstracts

ORIGINAL PEER REVIEWED PUBLICATIONS

Duong M, Moles RJ, Chaar B, Chen TF. (2015) Essential Medicines in a High Income Country: Essential to Whom? PLoS ONE 10(12):e0143654 doi: 10.1371/journal.pone.0143654. (Chapter 3)

PEER REVIEWED SCIENTIFIC CONFERENCE ABSTRACTS

I. Duong, M, Moles RJ, Chaar B, Chen TF. United Nations Secretary-General's High-Level Panel on Access to Medicines: List of Contributions. London, United Kingdom. March 10-17, 2016. Online at: http://www.unsgaccessmeds.org/list-of-contribution/

II. Duong M, Moles R, Chen TF. Dealing with Drug Shortages: How Can Wholesalers Ease the Problem? Global Experiences. Oral Presentation at the International Pharmaceutical Federation (FIP) Centennial Congress. Amsterdam, Netherlands. October 5, 2012: 5C.

III. Duong M, Moles R, Chaar B, Chen TF. The Supply and Management of Essential Medicines. Does Australia Prioritise Essential Medicines? Poster Presentation at the Annual Society of Hospital Pharmacists Association Conference. Cairns, Queensland. September 19-22, 2013

IV. Duong M, Moles R, Chaar B, Chen TF. The Supply and Management of Essential Medicines. Does Australia Prioritise Essential Medicines? Oral Presentation at the Global Health and Law Conference, The University of Sydney. October 1, 2013.

V. Duong M, Moles R, Chaar B, Chen TF. Applying the Essential Medicines Concept to Drug Shortages. Poster Presentation at the International Pharmaceutical Federation (FIP) Congress. Bangkok, Thailand. September 2, 2014: Social and Administrative Pharmacy Section.

VI. Duong M, Moles R, Chaar B, Chen TF. Global Perspectives on the Supply of Essential Medicines. Oral Presentation at the International Pharmaceutical Federation (FIP) Congress. Bangkok, Thailand. August 31- September 4, 2014: A3.

Abstract

Background:

Access to medicines is a basic human right. The World Health Organization (WHO) Model List of Essential Medicines was created in 1977, to promote access to essential medicines that satisfy the priority health care needs of the population. In this day and age, access to safe and affordable medicines is not guaranteed to all. There exists global inequality of access to lifesaving or essential medicines. This is referred to by the WHO as the 'global drug gap', in which approximately one third of the global population still does not have access to basic medicines.

Contributing to the disparity in access, are rising pharmaceutical expenditures and globalisation of complex pharmaceutical supply chain networks. This has resulted in countries of all economies and geographical regions sourcing their medicines from common sources. Therefore, challenges accessing unavailable medicines have become a shared experience, as demonstrated by the relatively recent emergence and recurrence of global drug shortage crises. The WHO framework for access to essential medicines, which considers rational selection of medicines, affordable prices, sustainable financing, and reliable health and supply systems, was used as a theoretical framework to explore the gap in access to medicines.

Aims and Objectives:

Aim: To explore stakeholder views about the concept of essential medicines.

Objectives: (1) To explore the application of the Essential Medicines List (EML) concept and how this was associated with access to essential medicines. (2) To explore the factors that influence access to essential medicines, and understand the roles of international key stakeholders involved in this process. (3) To explore what constitutes an "essential" medicine, and how the EML concept functions in a high income country (HIC) context.

Content of This Thesis

This thesis is made up of 4 chapters. Chapter 1 contains the background and a review of the literature on access to essential medicines. The challenges identified in chapter 1 lead to the exploration of global perspectives on the supply and management of essential medicines in chapter 2. The qualitative study in chapter 3 describes what constitutes an essential medicine for stakeholders in a high income country (HIC). Lastly, chapter 4 contains general discussions and conclusions from the work described in this thesis.

Methods:

A narrative literature review (chapter 1) was performed to explore how the application of the EML concept is associated with access to essential medicines. A search strategy developed from the principles of the WHO access to medicines framework was used to identify primary studies from Medline, Embase and PubMed.

A qualitative study was conducted to explore perspectives of international (chapter 2) and Australian (chapter 3) key stakeholders about the pharmaceutical supply chain, on the application

and relevance of EML concept and what makes a medicine essential. Snowball sampling was used to recruit decision makers, leaders or senior managers involved in medicines decision making across seven stakeholder groups. Stakeholders included: government, health care providers, academics, consumer groups, non-profit organisations, pharmaceutical manufacturers and wholesaler/distributors.

Forty-seven semi structured interviews were conducted face-to-face, via Skype or telephone, audio-recorded and transcribed verbatim. Interviews were conducted until thematic saturation was achieved. Data were analysed using a grounded theory approach. The comprehensive theory of collaboration was applied after the grounded theory analysis to organise and understand results within a management context. In addition, chapter 2 used the Ishikawa fishbone diagram to illustrate the complexities of the pharmaceutical supply chain. Meanwhile, chapter 3 illustrated the conceptual model derived from the results.

Key Findings:

Chapter 1- A literature review showed that there has been improved access to essential medicines for many populations. Findings showed EMLs help promote advocacy and provide reliable evidence at the health systems level. However, there was variable use of EMLs at the health services delivery level (i.e. for a patient at the point of care). Decision making around standard treatment guidelines and EMLs were often not aligned with procurement and management strategies within the supply chain. The literature review showed that accessing medicines was complex. Studies were often not well-designed, had narrow research objectives and few qualitative studies were conducted. Studies focused on resource limited settings in LMICs and scarce data was available for EMLs in HICs.

Chapter 2- Qualitative interviews with international stakeholders described the complexities involved in managing the global pharmaceutical supply chain. While stakeholders' roles and responsibilities were inter-connected, therapeutic decision making was often separated from logistic management of the pharmaceutical supply chain due to potential conflicts of interest. This created many gaps and inconsistencies around pricing and costs, planning and reactivity, communication and transparency, and contributed to difficulties building trust and consistency between stakeholders.

Adding to this complexity, individualised or patient-centred care approaches have emphasised the need for consumer choice and demand a wide range of products that has become increasingly challenging to manage. Therefore, drug shortages have highlighted the opportunity for collaborative alliances to identify, prioritise, and manage vulnerabilities in the supply chain to prevent or mitigate patient harm as a result of restricted access to medicines. In particular, wholesalers and distributors were identified as potentially having more valuable roles in managing supply disruptions (e.g. redistribution) and facilitating information exchange between stakeholders (e.g. forecasting or confirming at what level of the system a shortage occurs). Participants also suggested designating drug shortage experts or liaison to manage and communicate shortages, especially to consumers and health providers.

Chapter 3- Qualitative interviews with Australian stakeholders demonstrated that the different perceived functions of EMLs seemed to be stratified depending on whether the decision making context was at a health systems level or at an individual level (i.e., for a patient at the point of care). EMLs can function as reimbursement lists at the health systems level, or hospital formularies at the health services level. Meanwhile, non-reimbursed or off-formulary medicines were available to consumers who were willing and able to pay if they were deemed essential to individuals. Conversely, some medicines can be deemed essential but were not available or affordable to individuals. The wide range of views in this study, highlight the complexities of decision-making processes involved in developing and managing EMLs, which has been compounded by the expanding consumer need to have a range of therapeutic options. These findings emphasise the context within the health system determines for whom a medicine is deemed essential.

Conclusion:

Prior to this thesis, EMLs have been studied with narrow research objectives and mainly in LMICs. This body of research was the first to explore how the application and management of EMLs effected access to medicines, from a broad range of stakeholder views involved in both therapeutic decision making and logistics management. Furthermore, it was also a rare study that examined the EML concept within HIC contexts.

Findings from this body of work demonstrated different perceived functions of the EML. Furthermore, it also questioned whether the term 'essential' was appropriate and reflected how the EML was used. While EMLs can be useful to guide evidence based decision making for reimbursement at the systems level, the variations in the notion of essential at the individual level is influenced by an individual's choice. Therefore, this highlights the importance of guiding (or limiting) consumer choice with appropriate and accessible information, to help individuals make informed and responsible decisions.

This research confirmed that the access to medicines gap continues to be problematic. The pharmaceutical supply chain has been unable to handle drug shortages adequately. Therefore, in order to sustain patient-centred care practices, concessions by all stakeholders must be made if the supply chain is to withstand global economic, political, and ecological instability. Multi-stakeholder engagement, transparent processes, innovative communication pathways, and EML approaches offer potential solutions to mitigate supply chain disruptions. Future approaches should align decision making priorities with procurement practices. Decision makers and supply chain managers have a valuable opportunity to reflect and understand how the current system is functioning, in order to develop foundations for improved processes, and innovative and cooperative platforms to interact and network.

Thesis Overview

1 • Performed a literature review to identify key studies and gaps

2 • Conducted qualitative interviews with international stakeholders based on gaps identified in the literature

3 • Conducted qualitative interviews with Australian stakeholders to explore understanding and application of essential medicines lists in a high income country

4 • Discussed significance of findings, conclusions, and future research
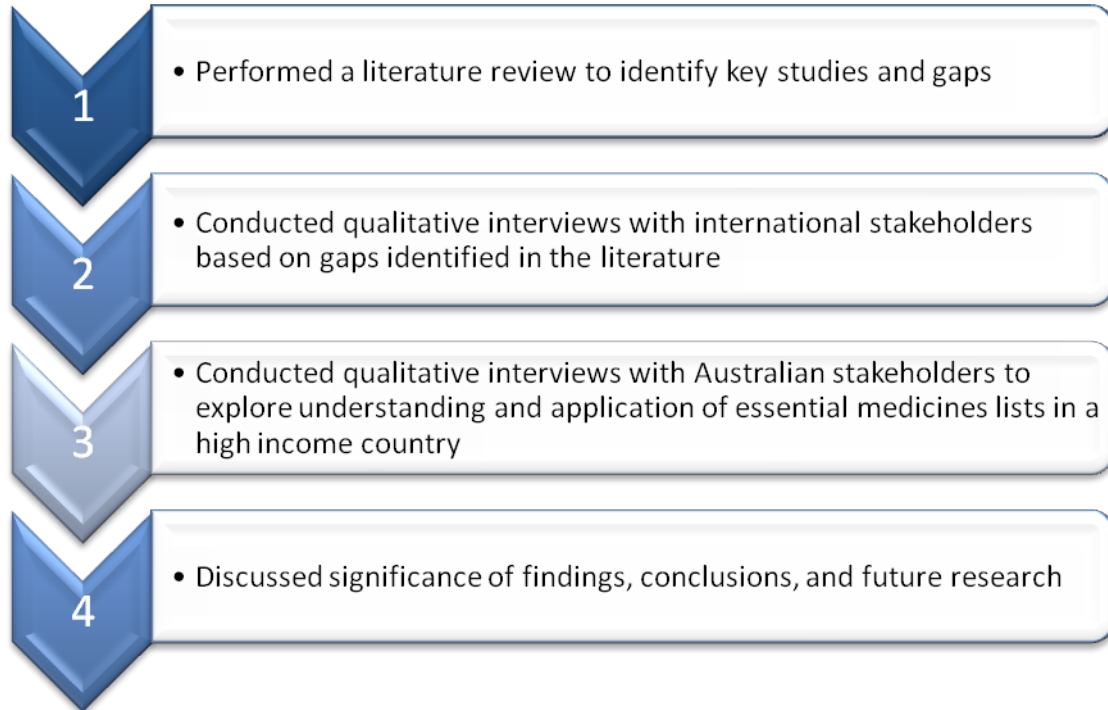
CHAPTER 1

BACKGROUND AND LITERATURE REVIEW ON ACCESS TO ESSENTIAL MEDICINES

CHAPTER 1: BACKGROUND AND LITERATURE REVIEW ON ACCESS TO ESSENTIAL MEDICINES

1.1 INTRODUCTION

1.1.1 Access to Medicines

Access to medicines is a basic human right, in line with food, water, housing, clothing and education. Medicines that are lifesaving and commonly used to improve individuals' quality of life should be available, affordable, of safe quality and appropriately used for all people (UN 1948). According to the 1978 Geneva Alma Ata Declaration on Health for all, medicines should be accessible worldwide to people of all gender, race, sexual orientation, socioeconomic status, political beliefs and religion (WHO 1978, Hogerzeil 2006). The responsibility to ensure the provision of basic health care and access to medicines has been entrusted to policy makers globally. As a result, medicines policies are critical components of all health care systems (Perehudoff, Laing and Hogerzeil 2010). As the global population continues to age and pharmaceutical expenditure rises, access to medicines has become a high priority on government health care agendas worldwide.

1.1.2 The Essential Medicines List Concept

The Essential Medicines List (EML) concept dates back to military tradition, where therapeutic supplies were essential to be carried by soldiers, field medics, and camp infirmaries into combat zones (Greene 2011). This concept was also applied to the rationalising of therapeutic restrictions necessary during wartime economy. Following the industrial revolution and after the invention of penicillin, which was used in World War II by military and aide organisations, governments began considering the importance of making lifesaving medicines available to the population (Greene 2011). In accordance with the Geneva 1978 Alma Ata Declaration on Health for all, access to

essential medicines was a human right that needed to be acknowledged and upheld by society and governments (UN 1948, Hogerzeil 2006).

In 1977, the WHO created the Model List of Essential Medicines (WHO EML) to establish international pharmaceutical standards and guidelines to improve access to medicines. The WHO defined essential medicines as:

> *"those that satisfy the priority health care needs of the population. They are selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative cost effectiveness. Essential medicines are intended to be available within the context of a functioning health system, at all times, in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford"* (WHO 2002, WHO 2015b).

Modeled after hospital formularies that aligned with standard treatment guidelines (STGs), the WHO EML started with 186 lifesaving medicines (Greene 2011). Nowadays, the WHO EML contains 409 active substances that are lifesaving and/or improve the quality of life for individuals (WHO 2015b). It consists of medicines needed for basic health care systems and also medicines that require specialised health facilities, services or are costly. The WHO EML has expanded over the years with updates made every two years. It now includes generic and patented high cost medicines, and has integrated EMLs for children and palliative care. It has been applied in both low and high income settings in 156 countries (WHO 2015b, WHO 2015a).

The WHO EML was intended to provide a flexible framework to guide national medicines policy (Hogerzeil 2006). The WHO advocated that each country take responsibility for the selection, implementation and evaluation of their EML, and governments were encouraged to adapt the EML to their population's health needs (WHO 2000). The EML was an especially useful tool for low to middle income countries (LMICs), defined by the World Bank as those economies with a gross national income (GNI) per capita less than $12,736 US dollars, who have difficulty accessing unbiased information about medicines (Brundtland 2002, WorldBank 2016). However, the EML principles are universal and should benefit health systems in all economic settings to promote

cost-effective, sustainable and affordable access to medicines (Hogerzeil 2004, Stolk, Willemen and Leufkens 2006). This includes high income countries (HICs) with a GNI per capita greater than $12,736 US dollars (WorldBank 2011, WorldBank 2016).

1.1.3 The Global Drug Gap

 While the practice and use of medicines varies by culture, in today's age it seems unimaginable that people should die from lack of access to basic medical treatments or medicines. Yet in the 21st century, access to safe and affordable medicines is not guaranteed to all. Global inequality of access to lifesaving or essential medicines still exists (WHO 2015b). The disparity of access to medicines has been referred to by the World Health Organization (WHO) as the 'global drug gap'(WHO 2000). According to the WHO, approximately one third of the global population still does not have access to basic medicines. This number rose to 50% in the poorest parts of Asia and Africa (WHO 2004). Adding to this complexity is the globalisation of pharmaceutical supply chain networks which has resulted in countries of all economies and geographical regions sourcing their medicines from common sources. This is accompanied by rising pharmaceutical expenditure (Schumock et al. 2014, Majchrzak–Smith et al. 2012, Knaul et al. , Lee et al. 2014). Therefore, challenges accessing unavailable medicines have become a shared experience, as demonstrated by the relatively recent emergence of global drug shortage crises (Fox, Sweet and Jensen 2014, Gray and Manasse 2012, Bogaert et al. 2015, Wilson 2012, Schulman and Sweet 2011, Cherici C 2011).

To address this wide gap in access to medicines, and in line with the Alma Ata Declaration to promote equitable access to medicines, the WHO has developed the framework for access to essential medicines (Hogerzeil 2006). This framework considers rational selection of medicines, affordable prices, sustainable financing, and reliable health and supply systems (WHO 2004, Wiffen et al. 2003). Therefore, the WHO Access to Essential Medicines Framework (characterised

as appropriate, available, affordable and safe quality medicines) was applied as a theoretical framework to conduct a critical review of the literature. The aim of this literature review was to explore how the application of the EML concept was associated with access to essential medicines.

1.2 METHODS

A narrative literature review was conducted to provide a broad and comprehensive background on the EML concept, which was useful in the development of a conceptual framework, discussed later in chapter three. This narrative review was performed in accordance with Green et al.'s (Green, Johnson and Adams 2006) guidelines and follows the overview rating scale and narrative review checklist, described in Appendix A (Green et al. 2006, 2016). However, this type of approach has been criticised as more biased compared to systematic reviews, due to subjective selection of information from primary articles, lack of systematic critical appraisal of each study, and differences between study designs (Green et al. 2006). Therefore, to address some of the potential biases associated with narrative reviews, a search strategy was developed from the principles of the WHO Access to Medicines Framework (WHO 2004, WHO 2002, Hogerzeil 2006).

The literature review was commenced in August 2012 and updated in October 2015, prior to thesis submission. The search for relevant literature was performed in Medline, Embase and PubMed. Search terms included 'essential medicine/drug' (OR related terms), AND 'access to medicines' (OR related terms), as described in Table 1.1. Primary studies included: those that were conducted in humans,published in peer-reviewed journals in English, and afterthe WHO EML was created in 1977. Additional searches included reference lists and grey literature from WHO archives, Health Action International (HAI), World Bank, USAID: Deliver Project and government and non-government organisation reports. Abstracts were used to screen non-empiric data or studies that were not relevant to the application of EML in improving access. Although a search

for literature pertaining to general access to medicines found many studies conducted in HIC, few were identified when searched in context of the EML concept (Table 1.1).   Summaries of the literature reviews and primary studies included in this review are available as supplementary material in Appendix B. These summary tables describe study designs and relevance to the EML.

Table 1.1: Database Search Terms

Concept 1	AND	Concept 2
Essential Medicines Concept		*Access to Medicines*
OR		OR
Essential medicines		Rational use of medicines
Essential Medicines List		Quality use of medicines
Essential Drug		Selection of medicines
Essential drugs list		Drug affordability
National formulary		Affordability of drug
Preferred drug		Drug pricing
Preferred drug list		Cost effectiveness
Vital medicines		Health technology assessment
Prioritised medicines		Cost benefit analysis
Priority medicines		Availability of medicines
		Reimbursement
		Evidence-based medicine
		Availability of medicines
		Disinvestment

1.3. RESULTS

A review of the literature was conducted to explore the EML concept and the relationship to access to medicines. This review found that limited evidence was available to evaluate the impact of the EML concept on access to essential medicines, through national EML policies. While there has been improved access to essential medicines in some LMICs, there remain challenges to using EMLs, and few studies conducted in HICs. Furthermore, variations in accessibility of medicines between countries made it difficult to generalise whether having an EML was associated with better access, since implementation and governance of EMLs differed for each country and health facility.

1.3.1 Appropriate Selection of Essential Medicines

 The literature supports that the concept of essential medicines has evolved and broadened in scope, making it difficult to select and assess the appropriate use of essential medicines (Appendix B, Table B1). Vargas-Peláez et al. (Vargas-Peláez et al. 2014) argued that EMLs supported the basic human right to medicine and improved stakeholder accountability to improve access. This aligned with Greene's (Greene 2011) historical description of how the evolution of societal needs, medical practices, and pharmaceutical markets have improved access to essential medicines. Although, he also argued that what medicines are deemed essential has become more difficult to define. Meanwhile, in the context of poor access to medicines, Van der Geest (Van der Geest 1982) argued that adequate education and training was needed to improve the inefficient delivery of essential medicines policies. Similarly, a global study conducted by Holloway & Henry (Holloway and Henry 2014), suggested EML policies were associated with improved appropriate use of medicines in LMICs, especially in terms of following standard treatment guidelines (STGs) in education and training sectors.

Furthermore, some studies examined specialty classifications in EMLs that addressed neglected populations and conditions (i.e. maternal and child health or palliative care) (Robertson and Hill 2007, Hill, Yang and Bero 2012, Wang et al. 2014, Anson et al. 2012, Bazargani et al. 2014, De Lima 2007). These studies showed low inclusion of these priority medicines on EMLs and low availability in health facilities; therefore, recognising the need for increased advocacy to support access at the patient level of care. This also drew attention to the challenges surrounding the development and provision of specialised treatments often excluded from EMLs, including orphan medicines for neglected diseases. These lifesaving treatments often affected either neglected populations in LMICs or highly expensive individualised treatments. In contrast, Vargas-Peláez et al. (Vargas-Peláez et al. 2014) cautioned that in some circumstances, the right to access essential medicines also deepened the existing inequality to accessing health care, focused on non-priority

demands, and threatened sustainable financing of the health system. For example, this occurred through judicial hearings that focused on individuals' rights (mostly those with wealth) to obtain expensive non-reimbursed medicines that overlooked the common wealth of the population.

This review included studies from HICs such as Croatia and Italy, where the EML concept helped apply appropriate use of evidence to guide reimbursement decisions; although, these processes were shown to be fragmented at different levels of the health care system (Kadić et al. 2014, Jommi et al. 2013, WorldBank 2011). Mahmić-Kaknjo and Marušić (Mahmić-Kaknjo and Marušić 2015) and Kadić et al. (Kadić et al. 2014) showed that the WHO EML provided strong evidence for decision makers and acted as a quality assurance tool to ensure that selection of medicines for national reimbursement were appropriate. The use of the WHO EML offered a fair and transparent process for reimbursement decisions. In a study by Hettihewa and Jayarthna (Hettihewa and Jayarathna 2010) knowledge of the content and selection process of the EML was helpful in guiding evidence-based prescribing. Therefore, these studies demonstrated that EMLs serve as powerful advocacy and evidence-based tools to influence policy makers.

In contrast, application of EML concepts can be fragmented and variable. Jommi et al. (Jommi et al. 2013) demonstrated that decision-making and the medicine assessment process in HICs like Italy, was multi-tiered, fragmented, and offered poor transparency of decisions. Similarly, in LMICs such as Tanzania, Mori et al. (Mori et al. 2014) showed that decision-making favoured experience and discretionary judgment over evidence. These studies showed that wider gaps in decision making became more apparent at the local health facility level of care. According to studies by Bertoldi et al. (Bertoldi et al. 2012, Bertoldi et al. 2008) and Mori et al. (Mori et al. 2014), local formularies were favoured over national EMLs at the health facility level. Furthermore, in a study by Rico-Alba and Figueras (Rico-Alba and Figueras 2013), some EMLs were considered highly irrational, containing a wide range of treatments in some therapeutic areas, yet excluded some essential medicines. In line with these results, findings from a study by Dal Pizzol

et al. (Dal Pizzol et al. 2010b) supported that non-essential medicines were needed because there was inadequate supply of essential medicines, with stakeholders believing the EML was not adequate at meeting all local concerns. Therefore, this demonstrated that the EML was not useful in supply chain operations and logistics management, where decision making at the point of care was focused on individuals' needs and less on population priorities (Albert, Fretheim and Maiga 2007)

In line with the fragmented use of EMLs at the health facility level, Chen et.al's (Chen et al. 2010) findings showed that listing on the EML did not influence manufacturers' production or retail pharmacy procurement decisions. Instead, factors influencing procurement were market demand, production costs, price, profit margins, and market share. Even in hospitals, low purchasing of essential medicines was due to lack of clinical use and availability of clinical alternatives. Hence, a study by Chen et al. (Chen et al. 2014), showed there were no changes in prescribing patterns after the implementation of a national essential medicines list (NEML) in China. Although, researchers did not determine whether this was a result of poor awareness and training around the EML, needing more time for integration into practice, or whether it was perceived as not useful. Therefore, the evidence available to policy makers showed that EML policies had not shown significant impact on quality use of medicines, questioning whether continued investment and support required to maintain and update EMLs were of value.

1.3.2 Availability and Affordability of Essential Medicines

The search strategy applied in this literature review found that there have been many medicines availability and affordability studies conducted in LMIC settings, but few in HICs. Appendix B, Table B2, described variable access to essential medicines ranging from very poor to adequate access. Since 2001, the WHO and Health Action International (HAI) developed a survey protocol to evaluate access to medicines within a country setting, referred to as the WHO/HAI survey

(Madden et al. 2010, Cameron et al. 2009, Niëns et al. 2010, Niens et al. 2012). Studies using the WHO/HAI survey methodology comprise a significant proportion of the availability and affordability studies in the field of EML research (Cameron et al. 2009, Cameron et al. 2011, Mendis et al. 2007, van Mourik et al. 2010, Cameron et al. 2012, Babar et al. 2013).

Many WHO/HAI studies found that EML policies increased affordability of medicines, especially in terms of pricing of generic medicines, providing medicines to individuals in the public sector at no or low cost, and bulk procurement (Wagner et al. 2011, Carapinha et al. 2011, Moon et al. 2011, Saleh and Ibrahim 2005, Dabare, Wanigatunge and Beneragama 2014). These WHO/HAI studies were in line with other studies, which found adherence to the WHO EML provided good evidence for decision-making and offered greater procurement cost savings (Mahmić-Kaknjo and Marušić 2015, Burapadaja and Chinawong 2010, Gitanjali and Manikandan 2011, Ganga Senarathna, Mannapperuma and Rohini Fernandopulle 2011, Cheraghali and Idries 2009, Cheraghali et al. 2004a, Carasso et al. 2009, Mouala, Abeye and Goumba 2009, Bertoldi et al. 2012, Kadić et al. 2014, Logez et al. 2004, Burapadaja et al. 2007, Zhu et al. 2008). However, results were highly variable across countries due to differences such as governance, EML implementation policies, distribution and workforce capacity. Therefore, global studies generally showed low availability and lack of affordability of medicines in public sectors (Cameron et al. 2009, Cameron et al. 2011, Cameron et al. 2012, Mendis et al. 2007, van Mourik et al. 2010, Srivastava and McGuire 2014, Babar et al. 2013, Yang et al. 2010, Kotwani 2013). These studies highlighted that access was especially low in resource limited settings such as LMICs (Babar et al. 2007, Jiang et al. 2013, Khan et al. 2011, Kotwani et al. 2007, Kotwani 2009). In addition, Nakyanzi et al (Nakyanzi et al. 2010) demonstrated that poor management of supplies may also lead to expiry and waste of medicines (Magadzire et al. 2014, Mikkelsen-Lopez et al. 2014).

This review found several approaches have been applied to measure the affordability of medicines. For example, Niens et Al. (Niëns et al. 2010, Niens et al. 2012) measured the

affordability of medicines using expenditure data, based on the proportion of the population that would be pushed below the poverty level, or the proportion of the population whose resources would be catastrophically reduced by spending on medicines. Therefore, these studies suggested that the purchase of medicines by individuals in LMICs could lead to impoverishment of a high proportion of the population.

Alternatively, Maiga and Williams-Jones (Maiga and Williams-Jones, 2010) and Van Der Geest et al.'s (Van Der Geest et al. 2000) work on cost sharing and price regulation indicated that these approaches did not improve the availability of essential medicines. Therefore, due to poor availability of free or low cost medicines in the public sector, many individuals had to seek medicines in the private sector in which prices were higher, and incurred out-of-pocket expenditure (Wagner et al. 2011, Santos Pinto et al. 2010). In addition to these challenges to make medicines affordable, international trade agreements, like the Trade Related Aspects of International Property Rights (TRIPS), threatened to hinder access to affordable medicines. TRIPS protected company patents, which keep essential medicine prices high and make them unaffordable to most LMICs, inhibiting population access (Akaleephan et al. 2009). In contrast, studies on the availability and affordability of essential medicines in HICs were not found. Instead, some literature examined the role of HICs (i.e. Canada), to facilitate access to lower cost essential medicines for LMICs through providing or advocating for compulsory licensing (Goodwin 2008).

1.3.3 Quality of Essential Medicines

This review also explored the t EML impact on quality of medicines (Appendix B, Table B3). Caudron et al. (Caudron et al., 2008), Khan et al. (Khan et al. 2011), and Lauffenburger et al. (Lauffenburger et al. 2011) found that there was an alarming presence of poor quality medicines available on the global market. These products were found in the form of substandard or counterfeit medicines, particularly in LMICs. In a study by Bevilacqua et al. (Bevilacqua, Farias and

Blatt 2011), bio-equivalency testing policy in Brazil led the number of registered products to fall from 98% to 25%. This prompted another round of bidding and resulted in dropping the test to prevent the health care system from collapsing. This signaled that there may be a high proportion of medicines in the system that are substandard, and kept within the system because they are low cost despite their poor quality. In contrast, Patel et al. (Patel et al. 2012) argued that perception of quality was not always reflective of actual quality of medicines and required more consumer education.

Overall, this literature search strategy did not identify many studies conducted in HIC countries, and none which investigated the quality of essential medicines. This could possibly be attributed to these countries having rigorous regulatory and quality assurance programs that prevent poor quality medicines from reaching the population. However, in recent years, there has been a rise in the incidence of drug shortages in HICs (Bogaert et al. 2015). This phenomenon has occurred concurrently with the prevalence of poor quality medicines in the supply chain of LMICs. Therefore, results from Bevilacqua et al. (Bevilacqua et al. 2011) and drug shortage crises in HICs raise concerns about the security and sustainability of global pharmaceutical supply chains.

1.4 DISCUSSION

This review found that limited evidence was available to evaluate the impact of the EML concept on access to essential medicines. While there has been improved access to essential medicines in some LMICs, there remain challenges to using EMLs and few studies conducted in HICs. Furthermore, variations in accessibility of medicines between countries made it difficult to generalise whether having an EML was associated with better access, since implementation and governance of EMLs differed for each country and health facility. Furthermore, this review found that limited qualitative studies were conducted in this field, but offered in-depth insights into decision making around essential medicines and the challenges to using EMLs. Additionally, while

research was intended to target the access to medicines gap, findings highlighted that studies conducted in this field were biased to LMIC settings and lacked HIC data, despite the challenges in HICs to access medicines in rural and remote areas.(WHO 2004, Kadić et al. 2014, Jommi et al. 2013, Hogerzeil 2004).

This review showed the use of EMLs improved population access to essential medicines. In line with Holloway and Henry (Holloway and Henry 2014), EML policies improved quality use of medicines through the use of standard treatment guidelines in education and training sectors, provided good evidence for decision-making, offered greater procurement cost savings, and functioned as a powerful advocacy tool to influence policy makers (Hogerzeil 2006, Reidenberg 2007, Magrini N 2014, Stolk et al. 2006, Shaw and Cook 2012, Kishore, Vedanthan and Fuster 2011, Hettihewa and Jayarathna 2010, Hettihewa, Dadallage and Wimalasena 2013). An example of improved population access to essential medicines was demonstrated by multi-stakeholder advocacy, engagement and delivery of HIV/AIDs anti-retroviral medicines in LMICs like Brazil and many African countries (Nunn, Fonseca and Gruskin 2009, Gilliam et al. 2012). Furthermore, EMLs also provided a tool to evaluate whether accessible medicines in a country adhered to global standards.

Conversely, specialised treatments and orphan medicines were shown to have low inclusion on EMLs. In most circumstances, orphan medicines were difficult to procure and sustain in the supply chain due to limited and sometimes unpredictable demand (Stolk et al. 2006). Therefore, this challenged whether special funding arrangements are required to ensure availability and affordability of these medicines. An example of specialised funding programs available in HICs like Australia include the lifesaving drugs program, Special Access Scheme, and Section 100-highly specialised drugs program (TGA 2015, PBS 2015b, PBS 2015a, Cohen and Milne 2013). Unfortunately, due to the high costs of some of these medicines, they are often not listed on EMLs, thus unavailable to the individuals that need them in resource poor settings, particularly in

LMICs. However, as raised by Vargas-Peláez et al. (Vargas-Peláez et al. 2014), policies must be in place to protect population access to essential medicines and individuals whilst preventing inequalities of spending of scarce resources.

Findings from this review demonstrated the challenges and complexities associated with EMLs. Firstly, the appropriate use of essential medicines was challenged with gaps in addressing neglected populations and conditions, lack of transparency around decision making, and fragmented processes. Furthermore, EMLs were often not perceived as being useful at the health services delivery level, not adequate at meeting local concerns, and did not influence prescribing patterns in some countries. In contrast to Holloway and Henry (Holloway and Henry 2014), Vargas-Peláez (Vargas-Peláez et al. 2014) claimed that EMLs had limited influence at the health facility level and patient point of care. Therefore, fragmented prescribing practices and implementation of policies has left many critics to question whether EMLs were useful. Particularly, when essential medicines were not available to individuals at the point of care, stakeholders preferred and used "non-essential" medicines (Bertoldi et al. 2012, Mori et al. 2014). This review found that much work remained to improve issues such as standardisation of processes, quality and interpretation of evidence, trust between stakeholders, logistics management and procurement practices.

Secondly, low availability and affordability of essential medicines were found in some public sectors, especially in LMICs. Poor management of supplies often led to waste and expiry of medicines which could not be used by individuals and exacerbated in resource scarce situations. A high proportion of the population in LMICs was at higher risk of impoverishment due to purchasing medicines. Meanwhile, cost sharing and price regulation did not improve the availability of essential medicines, and international laws threatened to keep prices of essential medicines high and inaccessible to LMIC populations.

Furthermore, this review suggested that financial and ethical issues act as barriers to accessing essential medicines. Researchers, such as Akaleephan et al. (Akaleephan et al. 2009), have claimed that international trade laws have created challenges to access affordable medicines. Agreements surrounding intellectual property rights, such as the World Trade Organizations (WTO) Declaration of Health Action (DOHA Declaration) and the TRIPS agreement, have enforced patent laws to protect international property rights held by pharmaceutical companies (Gregson et al. 2005, Akaleephan et al. 2009, Cohen 2006, Grootendorst et al. 2011). Unfortunately, this has created barriers to accessing affordable essential medicines, notably in LMICs, by keeping prices high (Martin, Sorenson and Faunce 2007). The HIV/AIDS epidemic in the 1980s and 1990s, was a key example of high prices of medicines that was mostly unaffordable for populations in parts of Africa, Asia and South America. Instead, these countries benefitted from compulsory licensing agreements, which allowed contracts to be given to generic companies to manufacture medicines while a medicine was on patent. Without the ability to create generic alternatives for these populations to access, results may otherwise have been catastrophic (Nunn et al. 2009, Cohen 2006).

Lastly, this review also raised concerns around the quality of medicines, highlighting the high proportion of low cost substandard and counterfeit medicines in the system and drug shortages. In contrast quality use of essential medicines focused perspectives, consideration of pharmaceutical supply chains also contribute to improved access to medicines (Caudron et al. 2008, Pazirandeh 2011, Jahre et al. 2012, Meijboom, Schmidt-Bakx and Westert 2011, Homedes and Ugalde 2005). The advancements in technology and communication have facilitated transportation, storage, Internet access, tele-communication, reporting, and manufacturing capacity. While not perfect, there have been many benefits that have improved access to medicines. However, globalisation has formed a new landscape for managing the pharmaceutical supply chain. Many processes, solutions, and challenges are shared throughout a complex and

intricate network. According to Caudron et al. (Caudron et al. 2008), substandard and even counterfeit medicines can permeate a supply chain, causing serious risks to individuals within a population. With the rise of manufacturing issues that have caused drug shortages in HICs, these supply chain issue needs to be addressed and further investigated (Bogaert et al. 2015).

1.4.1 Types of Research on Essential Medicines

To date, the range of evidence available to decision makers is limited in the field of essential medicines. Of the primary studies available, most have applied quantitative methods. However, few systematic literature reviews, qualitative and mixed methods studies were also identified. This review found an abundance of grey literature, but found few primary studies relevant to EMLs, and even fewer conducted with well-defined study designs. These findings were reinforced by Ratanawijitrasin et al. (Ratanawijitrasin et al., 2001), Nunan and Duke (Nunan and Duke, 2011), and Nguyen et al. (Nguyen et al., 2012), all of whom criticised the quality, lack of standardised approaches and methods conducted in essential medicines policy research.

Systematic reviews have been useful in identifying guidelines and assessment tools that can be used to guide EML policy. This was demonstrated through Newton et al's (Newton et al. 2009) work on a medicine quality assessment reporting guidelines (MEDQUARG) checklist, used to guide quality assurance practices. Meanwhile, Tran and Bero (Tran and Bero, 2015) and Ridge et al. (Ridge et al., 2010) identified barriers and facilitators to quality use of medicine from the literature, and applied visual models like the Ishikawa framework approach to organise results. In addition, Wilson et al. (Wilson et al. 2014) and Rico-Alba and Figureras (Rico-Alba and Figueras 2013) have applied qualitative constant comparative approaches to systemic reviews to assess the rationality of decisions to list or de-list medicines.

Meanwhile, the range of primary studies in this review applied quantitative, qualitative or mixed methods approaches to describe, explain or triangulate data (Khan et al. 2011, Magadzire et al.

2014, Patel and Pichardo 2012, Nakyanzi et al. 2010, Nilseng et al. 2014, Mujinja et al. 2014). This

review found that studies mostly applied quantitative methods, such as surveys. There were some

key studies that used validated methods to evaluate global access to essential medicines. For

example, Cameron et al. (Cameron et al. 2009, Cameron et al. 2011) conducted WHO/HAI survey

studies on global availability and affordability of medicines in a large number of LMICs. Whereas,

Holloway and Henry (Holloway and Henry 2014) used surveys to evaluate whether WHO EML

policies were associated with better quality use of medicines (QUM). To address the gaps in the

literature from quantitative studies, particularly the variations at the local level, qualitative

research has been recently included amongst the literature to enrich the depth of understanding

in country specific settings (Chen et al. 2010, Van Der Geest et al. 2000, Mori et al. 2014, Wilson,

Kohler and Ovtcharenko 2012, Albert et al. 2007, Mackintosh, Chaudhuri and Mujinja 2011).

Results from these studies were often in contrast to the survey studies, which showed improved

(albeit variable) population access and quality use of medicines. Instead, the views from these

qualitative studies revealed that EMLs did not function adequately at addressing local needs at

the patient point of care.

This review found that quantitative studies were conducted with limited focus on one or two

principles of the WHO access to medicines framework. These studies also had limited utility in

reporting access unless information could be provided continuously and seamlessly. Therefore,

wide variability in the reporting of how EMLs have been utilised in different health systems have

made it difficult to determine the impact of EML policies. Most notably, quantitative studies

following the WHO/HAI survey methodology accounted for a significant proportion of the

availability and affordability knowledge in the field of EML research. This survey methodology was

meant to serve as a standard protocol for measuring availability, price and affordability of

medicines, and has been conducted in over 70 countries (Madden et al. 2010). Therefore, this

review considered these studies to be a prominent body of work that offered a snapshot of the

global access to medicines situation. Although performing these studies was costly and required funding and local endorsement, they helped quantify the gap in access to medicines and inform policy (Mendis et al. 2007).

On the other hand, these WHO/HAI studies had limitations that only offered a description of the availability of medicines at one moment of time. This limitation was attributed to the dynamic nature of the pharmaceutical supply chain, where demand and supply can fluctuate seasonally and annually, Some of these design limitations included: limited generalisability of results, descriptive summary of a country's availability and pricing of a drug on only one day of data collection in each facility, and poor consideration of logistical variations. Examples of logistical variations include the likelier availability of malaria treatments (i.e. Artemesin base combination therapy (ACT)) during high risk wet versus dry season, or dwindled stocks closer to scheduled delivery dates from central medical store (e.g. monthly, or quarterly). Furthermore, geographic representation was variable, often restricted to urban centre proximity or systematically excluded remote areas and pharmacies, and included small samples of deliberately selected facilities (i.e. ranging from 6 to 129 health outlets). Therefore, this resource-intense approach had a limited ability to reflect the availability and affordability of medicines, other than at the time the study was conducted.

Furthermore, these WHO/HAI survey studies offered limited understanding of the decision making process at the point of care that may have led to medicines becoming available or unavailable.   For example, data collection was restricted to originator brand and lowest priced generic (LPG) products, and products were limited to medicines within one therapeutic class according to standard treatment guidelines (STGs), which could not account for patients with co-morbidities or prescriber preferences for other generic brands. Also, surveys did not consider differences in quality of medicines across products, patent status between countries, nor consideration of alternative dosage forms, products, or therapeutic alternatives which may have

influenced the decision to provide medicines at health facilities. Finally, the affordability of medicines at the point of care was potentially skewed based on the point of references used. For example, the daily wage of the lowest paid government worker used in calculations risked overestimation of affordability. Furthermore, the reliability of the median price ratios as a metric was used to determine median international reference price for each medicine and can be skewed high or low, which varied depending on the average income of the population in each country. In summary, these many limitations warrant alternative methods to investigate the challenges and variations in decisions to utilise EMLs at the point of care.

Lastly, medicines decision-making and communication throughout the pharmaceutical supply chain can be influenced by many subjective factors such as cultural, behavioural, sociological, environmental, and psychological experiences. These influences can be explored through different research approaches. Most notably, qualitative methods have been recently adapted in the literature to explore the cultural and social variations within a country. While results from qualitative studies are not considered generalisable, they offer deeper exploration of the challenges to access essential medicines, especially in specific settings. Hence, qualitative methods have been shown to add to the richness of understanding in the field of essential medicines research by considering valuable stakeholder perspectives. This may enhance our understanding of the impact of EMLs and what causes variations across health systems.

1.4.2 Strengths and Limitations

This review was the first to offer a broad comprehensive review of the literature, which included all four principles of the WHO access to medicines framework. Previously, study designs focused on only one or two principles of the WHO Access to Medicines Framework (e.g. availability and affordability), due to the challenges and complexity of implementing EML policies. Under this broad search strategy, this review identified a lack of studies evaluating the impact of EMLs in

HICs. While HICs are generally perceived to have good access to medicines, rural and remote areas in these countries may also experience challenges to access (Fletcher and Guttmann 2013).

Alternatively, the literature for HICs commonly showed studies on reimbursement lists, drug shortages, the role of evidence based medicine in decision making, drug formulary decisions, the cost-effectiveness of high cost medicines, upholding regulatory standards and good manufacturing practices. Although these terms seemed synonymous with the essential medicines concept, the search strategy did not locate these studies. This may imply that there were different descriptions for similar concepts within different country contexts, or the perception that EMLs were not used in HICs. Therefore, this review was unable to identify studies to offer comparison of how LMICs and HICs implement their EML policies.

Furthermore, while some researchers recommend that without explicit critical appraisal criteria, a narrative review would be extremely subjective and biased, others suggest they are not required. Instead, some researchers argued that, "since the narrative overview already includes the biases of the author, there is a limit to how much more bias may actually enhance the credibility of the overview" (Green et al. 2006). The aim of this literature review was to gain a broad comprehensive overview on the topic of EMLs, which was supported by a well defined search strategy. Therefore, a critical appraisal of each study was not deemed to enhance the credibility of the narrative review. However, summaries of the papers included were made available as supplementary material, included in Appendix B. These tables described study designs and relevance to the EML.

1.5 CONCLUSION

The universal EML concept has evolved and expanded since the inception of the WHO EML nearly 40 years ago. While there have been improvements in global access to essential medicines, there remains a disparity in access by individuals and across populations. This review showed that the

access to medicines gap has been predominantly investigated in LMICs, which similarly reported

low availability and affordability of essential medicines. Hence, perspectives and solutions to

access issues appeared limited and repetitive. Instead, investigation in settings with higher access

rates, such as HICs, could offer insight into how challenges are overcome and managed. The

literature confirms that the use of EMLs was not consistent at all levels of the health system, and

there was variation of needs at the health facility level which EMLs were unable to meet.

Although the EML was shown to be a useful advocacy tool to influence policies, it appeared poorly

applied and fragmented throughout the pharmaceutical supply chain, falling short in guiding

procurement practices. Therefore, further investigation with qualitative methods is needed to

determine what makes a medicine essential and the influences on stakeholders that facilitate or

hinder access to these medicines. This exploration would help define what variables contribute to

access at different levels of the health system, and how EML policies can be supported

throughout the pharmaceutical supply chain to support patient access at the point of care.

CHAPTER 2

GLOBAL PERSPECTIVES ON THE SUPPLY AND MANAGEMENT OF ESSENTIAL MEDICINES

"You can save a life for less than you pay for a Mars Bar"

—Health Provider, Physican, Western Pacific

CHAPTER 2- GLOBAL PERSPECTIVES ON THE SUPPLY AND MANAGEMENT OF ESSENTIAL MEDICINES

2.1: INTRODUCTION

2.1.1: The Pharmaceutical Supply Chain

The vital role of essential medicines in society necessitates a reliable and sustainable

pharmaceutical supply and distribution system (supply chain) (WHO 2003). However, the

pharmaceutical supply chain is a complex network of multiple stakeholders and management

systems (Rossetti, Handfield and Dooley 2011). The provision of medicines involve an array of

stakeholders (Lee and Whang 2000, Shah 2004). For example, consumers, health care providers,

wholesalers, distributors, government, third party insurers, procurement agencies, non-profit

organisations, academic institutions, advocacy groups and the pharmaceutical industry participate

in ensuring reliable, safe and efficient processes in delivering medicines to individuals.

Meanwhile, the processes involved in the provision of medicines are complex. Prior to production,

medicines innovation involves research and development (R&D) driven by advocacy, academic

research and industry investment. After discovery, medicines pass through intense economic

analysis, clinical trials, regulatory approvals, and third party reimbursement assessments. Once

these requirements have been met, medicines can be approved for production through the

pharmaceutical supply chain (Greene 2011). Afterwards, medicines enter manufacturing

processes which begin with active pharmaceutical ingredients (API) and inactive ingredients,

along with their chemical components, supplied to manufacturers who create the finished

medicine product (Thaul 2013). This product then goes through packaging (sometimes

repackaging), regulatory requirements to ensure quality, wholesale, distribution (sometimes

redistribution to secondary warehouses), storage and dispensing at health facilities. In brief,

medicines travel through the pharmaceutical supply chain starting from raw materials, to

manufacturing, filing and packaging, to international and local distribution centres, wholesalers, and then delivered to health care facilities to dispense to patients (Figure 2.1) (McBeath 2012).

Figure 2.1: The Pharmaceutical Supply Chain

Complexity of the pharmaceutical supply chain can also challenge access to medicines. The processes and systems involved in delivering medicines has become more complex due to more products and therapeutic options available on the market, accommodation of broader individual needs, and the expansion of markets due to globalisation (Bhatia, Lane and Wain 2013). Globalisation in particular, has created many issues for all supply chains worldwide, and has led to volatility in supply chains caused by environmental, geopolitical, economic and technological disruptions (Bhatia et al. 2013, Hogerzeil and Laing 2009). Hence, many things can go wrong along the way. For example, a range of risks include: supplier failures (e.g. financial, production, design, facility, standards), delivery delays (e.g. customs, accessible roads or repair); counterfeiting; theft; poor packaging; spoilage; improper handling or cargo placement; diversion or gray markets; and unanticipated demand surge or drop-off (McBeath 2012). In addition, unpredictable events may also cause supply disruptions in an already vulnerable supply chain. These can include: unanticipated supply constraints, allocation, or price increases; price, currency and interest rate fluctuations; political upheaval; infrastructure outages (e.g. fire in plant, power grid down); natural disasters; pandemic, work stoppages and labour disputes (McBeath 2012, Bhatia et al. 2013). Hence, these risks have become increasingly challenging to coordinate amongst multiple stakeholders (Craighead et al. 2007, Papageorgiou 2009, Koh et al. 2003).

Contributing further to these risks, were the recent management trends in global supply chains across all sectors. These trends include specialisation of services, complexity in processes and systems, decisions toward lean processes to improve efficiency (e.g. "just in time model"), information sharing or availability, and government legislation such as international trade agreements or change to regulatory requirements (Bhatia et al. 2013, Sousa et al. 2011). Therefore, global and local systemic risks flow down the supply chain, in which problems become magnified and can lead to supply disruptions such as drug shortages, recalls, and discontinuations of medicines by manufacturers (Bogaert et al. 2015, de Vries et al. 2011, Jahre et al. 2012, Fox et al. 2014, Abramowitz P.W. 2013, Wilson 2012, Woodend, Poston and Weir 2005, Lee Ventola 2011, Quilty et al. 2011, Cherici C 2011). These supply chain vulnerabilities impact health systems and risk consumer safety.

2.1.2: Unavailable Medicines in the Pharmaceutical Supply Chain

Supply disruptions can result in unavailable medicines at the point of care. One third of the global population does not have access to essential medicines, rising to 50% in low to middle income countries (LMICs) (WHO 2004). These health systems face resource, capacity, political, and infrastructure challenges, resulting in lower availability of medicines such as insulin, anti-retrovirals (ARVs), tuberculosis medicines, magnesium sulphate, doxycycline, and hydrochlorthiazide (Stop-Stock-Outs 2015, Cameron et al. 2009). Until recently, access to essential medicines in high income countries (HICs), has not received much focus; however, the drug shortage crises in the last few years have raised many concerns regarding the stability of the pharmaceutical supply chain (Gray and Manasse 2012, Jahre et al. 2012, Bogaert et al. 2015, Yu et al. 2010, Koh et al. 2003, Craighead et al. 2007). For example, in the United States, the number of new drug shortages quadrupled from approximately 60 in 2005, to more than 250 in 2011; and by the end of 2012, more than 300 shortages remained active (FDA 2013).

Drug shortages have been defined differently across health systems. According to the United States (US) Food and Drug Administration (FDA) a drug shortage is as, "a period of time when the demand or projected demand for a drug within the United States exceeds the supply of the drug" (FDA 2011, FDA 2013, Thakur 2013). Similarly, the European Public Health Alliances defined supply shortage as, "a situation in which the total supply of an authorised medicine or of a medicine used on a compassionate basis is inadequate to meet the current or projected demand at the patient level. The shortage may be local, national, European or international. This common position prioritises supply shortages that affect medically necessary medicines (also called essential medicines)" (Charnay-Sonnek et al. 2013). Whereas, the European Federation of Pharmaceutical Industries and Associations (EFPIA) describes a drug shortage as, "a crisis situation caused by the inability of any market authorisation holder (MAH) to supply a medicine with a specific active pharmaceutical ingredient (API) to a market over an extended period of time resulting in the unavailability of this medication for patients" (Bogaert et al. 2015, EFPIA 2013). Time frames stipulating a shortage were variable among European countries, ranging from a minimum of 48 to 96 hours, and without mention of a maximum limit. Similarly, a stock-out, "is when a pharmacy (in a medical store or health facility) temporarily has no medicine on the shelf" (Stop-Stock-Outs 2015). For the purposes of this thesis, drug shortages and stock-outs have not been differentiated; and drug shortages refer to the inability to dispense a medicine for an individual at any point of time, which may result in potential patient harm.

The risks of drug shortages pose significant health threats to the provision of patient care, strain resources needed to manage medicine supplies, and corrupt systems by driving prices up with emerging grey markets (Akaleephan et al. 2009, Cherici C 2011, Lee Ventola 2011, Bogaert et al. 2015, Gray and Manasse 2012, McBride et al. 2013, TGA 2013, GaBI 2012, Schulman and Sweet 2011). Drug shortages can result in delaying or denying needed care to individuals and may cause health practitioners to prescribe an alternative therapy that may be less effective for the patient

or that poses greater risk. This has even disrupted clinical trials, potentially delaying research on important new therapies (FDA 2013). In HICs, even though clinically interchangeable substitutes were mostly available, the FDA reported 89% of drug shortages caused a safety issue or drug related problem (DRP) and 80% resulted in the delay or cancellation of a patient care intervention (FDA 2011). This was most concerning when essential medicines for life-threatening diseases, including some treatments for cancer and serious infections, were affected by drug shortages (e.g. morphine, gentamycin, naloxone, frusemide, cytarabine, adrenalin, and noradrenalin) (FDA 2011).

In light of these issues, the integrity and reliability of the pharmaceutical supply chain needs reinforcement. Ongoing supply disruptions threaten global access to medicines in the short and long term. Therefore, response to these significant supply disruptions, requires a coordinated approach between multiple stakeholders (Rossetti et al. 2011). However, the pharmaceutical supply chain is extremely complex. While there has been research on the supply chain, it has been studied in silos and focused on specific areas or practice settings (Bhakoo, Singh and Sohal 2012, Meijboom et al. 2011, Jahre et al. 2012, Ford and Hughes 2007). Therefore, further understanding is needed on how the different elements of the pharmaceutical supply chain and health systems operate and interact. Investigation is required to explore how multiple stakeholders within the medicine supply continuum respond to supply disruptions, how these responses change depending on the context and work environment of each stakeholder, and how stakeholders interact or collaborate. Exploring the dynamics of how stakeholders interact throughout the pharmaceutical supply chain could highlight management strategies that may reinforce and protect the supply of essential medicines.

The objective of this qualitative study was two-fold. Firstly, this study aimed to explore key stakeholders' perspectives of the factors that influence access to essential medicines; and

secondly, to understand the roles of international key stakeholders involved in access to essential medicines.

2.2 METHODS

2.2.1: Qualitative Semi-Structured Interview Framework

Ethics approval was obtained from the University of Sydney Human Research Ethics Committee (HREC) (Appendix C). Participant consent was obtained, and confidentiality and anonymity was guaranteed (Appendix C,E). Research objectives and literature were used to design a qualitative semi-structured interview protocol based on the WHO access to medicines framework to address issues around access to essential medicines (WHO 2004). The interview guide was pilot tested with a hospital pharmacist and researcher. As part of the consent process, the interview guide was provided to participants prior and during interviews. Reporting of the study adhered to the Coreq-32 checklist guidelines, included in Appendix F. The interview guide, included in Appendix G, contained questions pertaining to participants familiarity and experiences with the EML concept, what their thoughts were on what made a medicine essential, facilitators and barriers to the provision of essential medicines, collaborations involved in delivering EMLs, and key issues surrounding essential medicines. Each area of appropriateness, affordability, availability and quality were explored according to each participant's background and expertise. The data pertaining to Australian stakeholders only, have been published in a peer-reviewed journal, described in Chapter 3 (Duong et al. 2015). Subsequently, parts of the methods section overlap and have been repeated. This chapter included all interviewed stakeholders.

2.2.2: Sampling

Between October 2012 and January 2015, 47 stakeholders were recruited worldwide for in-depth interviews through purposive and snowball sampling approaches (Heckathorn 2011, Goodman 1961). Key stakeholders had experience in multiple country settings, including: Canada, United

States, Columbia, Netherlands, Denmark, Estonia, Latvia (and other Baltic countries), Tanzania, Zimbabwe, South Africa, Nigeria, Uganda, Namibia, Cameroon (and neighbouring French speaking African countries), India, Pakistan, Afghanistan, Bangladesh, Sri Lanka, Australia, New Zealand, Philippines, Fiji, Tonga, and Papua New Guinea. The broad range of expertise was representative of each WHO region, including: Pan America, Western Pacific, South East Asia, Africa, Eastern Mediterranean and Europe (WHO 2015c). While representation was highest in the western pacific region due to the nature of the snowball technique, at least one stakeholder was interviewed from each region. Of the 96 participants contacted to participate in the study, 23 declined to participate either due to perceived limitation of expertise or time constraints. Ten of those who declined to participate referred a colleague, and a further 24 failed to respond to the invitation to participate.

Stakeholders represented in this study were working in government, regulatory bodies, hospital practice, primary health care settings, the pharmaceutical industry, wholesale/distribution companies, medicines non-profit organisations, academia and consumer health groups. The study targeted individuals with EML experience, medicines reimbursement and selection knowledge, or those with experience managing drug shortages. Participants included were recognised as leaders, advisors and/or experts amongst colleagues or professional organisations in the area of quality use of medicines, medicines policy, medicine distribution, procurement management, manufacturing, or health economics. Most participants had professional backgrounds as physicians or pharmacists. In addition, consumer representatives, chief executive officers, supply chain managers, and health economists were also included. Most participants had broad experiences across multiple and overlapping sectors in high or low income countries, and often both settings. A summary of participant demographics is illustrated in Table 2.1.

Table 2.1: Summary of Participant Demographics

Demographic	# of Participants (Total n=47)
Region*	
Africa	4
Europe	2
Pan America	5
South East Asia	1
Western Pacific	35
Profession*	
Physician	12
Pharmacist	26
Business Management	3
Other: e.g. Sociologist, Psychologist, Scientist, Teacher	6
Gender	
Male	33
Female	14
Stakeholder Group*	
Government	10
Consumer Group	4
Health Provider	7
Academia	11
Pharmaceutical Industry	6
Wholesaler/Distributer	5
Nonprofit	4

*There was overlap between participants, but for the purpose of Table 2.1, participants have been allocated to prioritised to region, profession and stakeholder groups

2.2.3: Data Collection

In-depth, face-to-face, teleconference and Skype interviews were conducted with participants. Audio recordings of the interviews were de-identified, transcribed verbatim, and secondary verification of the transcripts was conducted by the researcher to ensure accuracy. De-identified supplementary field notes were included in the data analysis.   Interviews were conducted until thematic saturation was achieved (when several participants repeated similar or recurrent concepts in their response), as described by Bazeley (Bazeley 2013). Interviews lasted a median time of 60 minutes (IQR: 45 – 69).

2.2.4: Data Analysis

Interview transcripts and field notes were imported into the qualitative data analysis software program N-Vivo 10 for coding and data management (Welsh 2002). Sequential analysis was used to explore relevant issues according to participants' responses (Pope, Ziebland and Mays 2000). A grounded theory approach was applied in data analysis to extract themes and key concepts using iterative constant comparative techniques (Strauss 1998). This well-established research method has been widely accepted and supported as a high standard of analysis used in interpreting and reporting qualitative research (Strauss 1998, Miles and Huberman 1994, Patton 2002, Creswell 2013, Bazeley 2013).

Additionally, to understand how multiple stakeholders engaged within the pharmaceutical supply chain, the comprehensive theory of collaboration was applied to assist in explaining results (Wood and Gray 1991, Bazeley 2013). In other words, this underpinning theory provided a management context for themes to be considered as control mechanisms or contributing to the complexity of the situation (Wood and Gray 1991). While the theory of collaboration provided a management context, thematic data analysis adhered to the grounded theory approach. Therefore, open, axial and selective coding methods were used to identify and interpret emerging themes (Bazeley

2013). One researcher independently conducted the axial and open coding thematic content analysis to identify themes and concepts, which were then discussed and validated by the rest of the research team. Final selective coding was performed as a team.

To display the significance of stakeholders' roles, themes were applied to the Ishikawa Fishbone diagram to explain the factors that contributed to access to medicines. The comprehensive theory of collaboration contextualised results according to control mechanisms and complexities faced by multiple stakeholders throughout the supply. The iterative consultative approach offered reflexivity and explored relationships between these themes and concepts. As described by Patton (Patton 2002), reflexivity of data collection, interpretation and analysis was offered by the researchers' broad experiences working across multiple pharmacy, patient care and administrative settings, with international experiences in both HICs and LMICs.

2.3 RESULTS

Results demonstrated perceived factors that influenced access to medicines (section 2.3.1) and explained stakeholder roles in the medicine supply chain (section 2.3.2).

2.3.1: Factors and Influences Affecting Access to Medicines

Participants had a broad range of views of what factors influenced access to essential medicines. Results demonstrated that fragmented management of essential medicines was driven by the underpinning principle of choice. Four main concepts demonstrated this by illustrating the complexities involved in managing the pharmaceutical supply chain. Firstly, both international and local disruptions contributed to vulnerabilities in the pharmaceutical supply chain; there were gaps in communication between multiple stakeholders throughout the continuum of the pharmaceutical supply chain; there lacked a coordinated approach between stakeholders to manage supply disruptions throughout the pharmaceutical supply chain; and lastly, the current consumer driven "just-in-time" supply model must meet a wide range of individual needs that has

become increasingly difficult to sustain. The following themes and quotes supported these

concepts.

2.3.1.1: Theme 1- Both international and local disruptions contributed to vulnerabilities in the supply chain.

Many stakeholders felt they had no control of supply disruptions, especially when they were

caused outside their country.

> *"The current inventory that's out there is dwindling. They haven't come back online yet. Doctors are starting to talk to their patients about, "we'll, start doing half-dosing. The MS will probably come back, or the Crohn's disease will start getting some severe symptoms. But I have nothing to do for you until they fix this." Participant 42-Academic/ Government-Pharmacist-Pan America*

> *"...something like morphine, you'd think there'd be companies all around the world making the stuff? But there was a problem looming. The TGA [Therapeutics and Goods Administration, regulatory body], was able to enable a different preparation of morphine but we found it had an additive in it; and therefore, people [could not use this] into the spinal canal for epidurals. This represents a safety issue. I'm still concerned that there may be an adverse event with this [new] morphine. But there's nothing we can do about that factory." Participant 20-Government-Physician-Western Pacific*

Most participants viewed that supply disruptions were caused by manufacturing and distribution

issues.

> *"Supply chain issues tend to be more of a problem from the manufacturing perspective than from the user end… producing enough or having the [drug] shortages based on contamination, [manufacturing plants] going down, supplies along the way being intercepted, and grafting corruption." Participant 42-Academic/ Government-Pharmacist-Pan America*

Many participants viewed that stakeholders had the capacity to address direct risks associated

with their immediate work environments rather than the continuum of the supply chain.

> *"The national department co-ordinates policy and then the provinces are where policy is implemented. Some of the provinces have people other than pharmacists responsible for the pharmaceutical supply chain. You have efficiencies in some instances because those are finance people that might be efficient in ensuring that medicines are paid for in time. [They] do not order unless [there's] money in the budget. [However], they do not understand the seasonal changes that will lead to a particular product being used more*

than for the rest of the year and tend to react very slowly to those kinds of changes."
Participant 8-Non-profit-Pharmacist-Africa

Some stakeholders described how sudden regulatory decisions and changes in requirements

contributed to drug shortages.

> *"We basically make no API [active pharmaceutical ingredient] in Australia. We make a lot of our finished products overseas. They have different quality standards. The TGA [Therapeutic Goods and Administration] have very high standards. We don't want to change them, but we want to be able to get some pro-activity around where they live. So TGA is integral in this process. Globally, we're raising our quality requirements, as soon as you get any variation from regulatory authorities and if it doesn't get through quality there's a batch that you write off and you have to make a new batch. Go back to the API and you're chewing through wastage at that end. There's a massive amount of wastage driven by quality. Participant 18–Pharmaceutical Industry-Pharmacist-Western Pacific*

Many stakeholders discussed that governance and enforcement of ethical practices were variable

and lacked transparency. Most notably in LMICs, concerns of corruption and financial

inducements were hindrances to collaborative alliances.

> *"Prescribers get financial incentives from pharmaceutical companies. Companies, [mostly] from India, come and induce through sponsorship, sometimes outright financial inducement; which is very unethical. Participant 6-Distributor-Pharmacist-Africa*

> *"We have the national tender system where every province is invited to submit the list of requirements with the numbers. But you also have provincial tender boards. Provinces have the freedom to decide not to procure a particular item on national tender and get it instead on provisional tender. We've seen many examples of the price of medicines doubling because they acquire it at the provisional tender. The difference obviously goes into people's pockets. So you have a lot of corruption in the procurement system. [And no] amount of consultancy or technical assistance is going to improve things if that continues. So it's a huge problem." Participant 8-Non-profit–Pharmacist-Africa*

2.3.1.2: Theme 2: There were gaps in communication between multiple stakeholders throughout the continuum of the pharmaceutical supply chain.

According to some participants, wholesalers and distributors had the capacity and supply chain

knowledge that could potentially facilitate or boost access to essential medicines.

> *"One of the problems we have here [in Australia] because we're such a big country, is you might have an out-of-stock situation at the manufacturing level but there's plenty in the wholesale chain. There's 50% of it [in Western Australia] and they use 5% of it a year. And*

then none of its [in New South Wales] and you need a lot of it. You can get imperfections in the supply chain that creates artificial shortages, and similarly you've got 5,000 pharmacies. Everyone has pharmacies [where they] might have one that they outsource stopped product. But how do they get it to the place where it's needed?" Participant 26– Pharmaceutical Industry-Pharmacist-Western Pacific

"Availability is an issue because of underfunding, [and] management issues, [such as], late procurement, or deliveries. [Even] if the drugs are there in the country in sufficient quantities; distribution inside the country is an issue sometimes. [For example], Uganda and Tanzania migrated from a push system to a pull system. Push system means that the pre-determined quantity you get [is] based on a number of parameter. The reality is, morbidity is not evenly distributed and in every region there are so many factors that influence the requirements. You have districts where you have an oversupply and a district where you have under supply. It's so difficult to re-distribute from one district to another because of the administrative and logistic complications. Availability is and going to remain an issue as long as we haven't solved these management issues and the budget limitations." Participant 2-Nonprofit-Pharmacist-Africa/Europe

Wholesalers and distributors were identified by many stakeholders as not consulted in the decision making process, or lacked input in the process of managing and improving supply disruptions.

"Looking back on it now particularly, with the experiences I've gained around the AIDS, the ACTs and the anti-malarial medicines; if I had my time again, I would have been much more active in involving the distributors and the local wholesalers for them to know what was the change [in therapeutic guidelines or procurement decisions]." Participant 43-Academic/Government–Physician-Africa/Pan America.

"When morphine was an issue, we [the wholesalers] were restricting morphine sales and drip feeding it out to stop people stockpiling. *More and more manufacturers are asking us to restrict the supply out to hospitals because they know there's going to be a shortage. They think we should have to do it based on our current fees which are being squeezed dramatically over the last five years. I don't have an issue with the wholesaler doing it, because we're the ones that deal with hospitals, so we're the logical people to do it, but somebody's got to pay for us to do it. At the moment, nobody wants to pay us to do it and that's the problem."* Participant 29-Wholesaler/Distributor-Business Management-Western Pacific

All stakeholders expressed concern that there was poor communication between stakeholders and fragmented approaches within the system.

"In practice, [the EML] is really not working effectively, but in theory it is. Because of changing governments, various governments come and go and there is no consistency in policy implementation. Because of that, you have a lot of problems in trying to get those

policies implemented. So you don't see the policy changes, the change of government or new minister comes with new ideas." Participant 6-Distributor-Pharmacist-Africa

"If you don't communicate about that quality [of medicines] it will stay in the minds of people [that] cheap medicines are bad quality." Participant 7-Distributor-Pharmacist-Africa

Additionally, many stakeholders described how tensions between stakeholders were caused by pricing of medicines and costs of services for a wide range of products; therein, putting much pressure on the system.

"Most of the old generic drugs are being forced to become cheaper. And that's causing the problem. [Today], ceftriaxone costs $1 per vial. So you can life-save for meningitis for less than you pay for a Mars Bar." Participant 15-Health Provider-Physician-Western Pacific

"I think Australia is a disastrous example as far as the generic market is concerned. The prices paid compared to New Zealand and compared to just about every other country, middle and high income country in the world, is disastrous." Participant 43–Academic/Government-Physician-Africa/Pan America

Most participants demonstrated that stakeholders had limited knowledge of how others managed supply disruptions.

"People worry drug shortages must be the company's fault? Sometimes it is. Sometimes companies screw up. But then other times there are actually drugs out there. The supply is there but it's not in that hospital's formulary. So is that the company's problem? Or is that the hospital formulary manager not anticipating, or he/she only realised the company wrote to them six months ago [saying], 'you might want to start stocking up on your formularies', and they didn't do it." Participant 14-Pharmaceutical Industry-Business Management-Western Pacific

Meanwhile, all stakeholders agreed information sharing was limited and inconsistent, sometimes due to the lack of trust or communication between stakeholders.

"In the past, the manufacturers association was a member of the committee and it was a major battle. [They were] removed from the committee because of that conflict of interest. I don't see any conflict of interest with the public sector procurement agency because they have a responsibility for providing for the public sector. The distributors were a much more difficult issue. How we handled that was we shared the changes in the treatment guidelines in advance with the distributors and told them what the new treatment guidelines were and to be aware that there will be a change in the market." Participant 43-Academic/Government-Physician-Africa/Pan America

"Industry wants decision-making more transparent. Transparency is a flexible term. Sometimes what that translates into is industry wants more of an ability to influence the decision makers. [For example], they want the ability to make direct presentations to committees, or an appeal mechanism if they've been turned down. It's fair to industry to have a set of principles [for the] evidence that you have to provide, [and] the way we're going to evaluate the evidence. That's okay. [But] when industry talks about transparency as the ability to influence decisions, I'm not supportive of that." Participant 41 - Academic/Health Provider/Government-Physician-Pan America

"It's particularly a challenge when the places you're trying to harmonise are at different levels of development. [For example], harmonising within Latin America is proving a lot easier with Anvisa in Brazil as the core, along with a few fairly similar regulators to share information and do joint inspections. The Southern African development community has 14 countries, including the Democratic Republic of Congo who hasn't got a regulator. [South Africa] has got some regulatory capacity, [but] how do you work with a place that has nothing, and how do you harmonise that? It's easier for us to harmonise with other PIC/S [Pharmaceutical Inspection Corporation Scheme] countries and share our inspections. That's the nature of PIC/S. It's about GMP inspection, recognising one another's inspection reports and sharing inspection reports. So you can all be at the same standard, applying the same rules, and then share results." Participant 3– Academic/Government–Pharmacist-Africa

Most participants claimed that prescribing practices did not provide a consistent pattern for

procurement to follow due to many preferences and therapeutic options.

"They came together as a committee to complain about stock-outs. The [cancer] specialists, wanted to treat everything, but were dealing with repeated stock-outs and shortages. They would initiate a patient on anti-leukaemia, lymphoma or Burkitts [treatment], but would run out and then the child would relapse and be resistant. They identified which were the priority conditions to start with. I said [to] look at the budget, you cannot have everything, and some medicines are more essential than others. Some medicines were better than others and you have to recognise it, and tell me what those medicines are so I can help you do the cost effectiveness analysis. That moment, they could see that treating one patient with high-cost medicine, [meant] there were ten that were deprived of treatment under those circumstances. The essential medicines principles came across in a very effective way. And, the chair of this committee was very successful in motivating all the specialists." Participant 43–Academic/Government-Physician-Africa/Pan America

"I remember one person from one of the hospitals from the province saying, 'You're putting a cost on survival?' And I said, 'a cost on life? Absolutely.' That's a public health approach, and this is what the essential medicines approach is. They came onboard because we convinced them that it was the stock-outs and [drug] shortages that were killing them." Participant 43–Academic/Government-Physician-Africa/Pan America

2.3.1.3: Theme 3: Lack of a coordinated approach between stakeholders to manage supply disruptions throughout the pharmaceutical supply chain.

All participants reported that supply chain stakeholders fixed their own problems instead of a

cohesive approach with clear leadership.

> *"Health professionals can be extremely good at getting stuff for their patients. To what extent do health professionals either ignore or actually circumvent the EMLs because their concern isn't so much about the politics or the financing of drugs for their country? Their concern is helping this person who's in front of them."   Participant 42-Academic/ Government-Pharmacist-Europe/Pan America*

> *"If there's a supply issue and it's a company that can't supply, then the government should have in place alternative supply, particularly for essential medicines. We're not talking about every medicine; we're talking about penicillins and morphines. They should be able to access alternative suppliers and have that as a backup." Participant 44-Consumer-teacher-Western Pacific*

Some participants showed that timing and reducing the impact of short and long term shortages

was a priority for stakeholders involved at the point of care.

> *"We use mostly prednisone 5mg tablets in South Africa. The reason [suppliers] give is that the API is very expensive, it's not worth producing [because] the market is not big enough for it. The other one is chloramphenicol eye drops and eye ointment. It's those medicines that appear not to be very important because they are not used to treat the big disease categories. But, when they are not there, you really feel it because people just can't get access to those. Sometimes manufacturers will deliberately decide not to continue producing something." Participant 8-Nonprofit-Pharmacist-Africa*

Some stakeholders discussed that accountability of supply disruptions required more clearly

defined stakeholder roles and responsibilities in order to improve engagement and collaboration.

> *"If nobody's in charge, it's going to be a big issue, that thorn in your side every day. But if you dedicate a 0.1 FTE [full time employee] staff member for example, in your pharmacy, pharmacy group or organisation you can refer to the expert in drug shortages. That way the message is being delivered consistently all the time, and the patient [or physician] won't get mixed messages of what was available. [Otherwise, this] can be very draining on people. So it's about knowing your work environment, being able to have that organisational structure that says who's responsible for what, and then having the CEO ensure that proper training is done so that the people know who, when and how to do the referral piece." Participant 1-Health Provider/Nonprofit-Pharmacist-Pan America/Africa*

Meanwhile, participants showed there were different (at times conflicting) priorities amongst

stakeholders. For example, most stakeholders demonstrated isolated management according to

the specific needs and capacity of each practice setting, sometimes resulting in duplication of

activities

> *"The purchasing people in hospitals are working like many wholesalers and we don't see that as necessary to do. We think there's an opportunity to be more efficient with sharing data at the hospital level, the hospital to the wholesalers. They can get more consistency back to the manufacturer, so they could manage the supply chain better." Participant 29-Wholesale/Distributor-Business Management-Western Pacific*

> *"There are a lot of people who sell medicines. People import medicines and sometimes there's no pharmacist. Sometimes, [people] trust medicines but then they hear about the counterfeits, or something has happened. After this, they don't trust the system anymore. They will trust only the people they know, the pharmacies they know, to resolve their medical problem." Participant 7-Distributor-Pharmacist-Africa*

However, most participants demonstrated that shared priorities were not identified or

communicated between stakeholders.

> *"When you talk to individuals who are coming from a clinic or small hospitals in rural areas, they know [there's an] EML but it doesn't mean much to them. They're working from their formulary. There are many countries that don't even have EMLs. Should they? That ties into national drug policies that many countries don't have. Participant 42-Academic/Government-Pharmacist-Europe/Pan America*

> *"The EML was never meant to support innovation in any sense. The idea [was] to provide access to medicines that were needed by the population." Participant 41-Academic/Government/Health Provider-Physician-Pan America*

> *"Eighty percent of people that die of non-communicable diseases live in developing countries. The EML may not efficiently and effectively, with the limited resources available, [offer] these treatment options to help people, and prioritise [medicines]. [For example] insulin [is on the EML], but funding levels are so low, [so] you then prioritise within your priorities. [With] the EML you'll find that they stratify according to categories of vital, essential, and non-essential. So first, if your resources are limited you drop the non-essential ones, then the essential ones, and the vitals you never touch. But I've never seen a well organised approach towards dealing with limited resources, by having a fair composed group of people, committee, determining what [to] buy, what [not to] buy. As soon as you have an EML [where] you have to make selections within a selection, then it seems to be done at random." Participant 2-Nonprofit-Pharmacist-Europe/Africa*

2.3.1.4: Theme 4: The current consumer driven "just-in-time" pharmaceutical supply chain model must meet a wide range of individual needs that has become increasingly difficult to sustain.

Many participants were uncertain whether consumers played a role in managing the supply chain.

"The more you look at the supply chain, the more vulnerability you see. We create some of our own vulnerabilities here with our just-in-time medication, and with our contracting processes. " Participant 20-Government–Physician-Western Pacific

"For low [income individuals], and the lowest possible incomes are those who live on services from the state, up to one-fourth [25%] had said they can't always afford the medicines from the doctor." Participant 16-Academic-Pharmacist-Europe

Some participants acknowledged health provider concerns were unable to accommodate

consumer demands. This also draws attention to the importance of well trained health providers

who can communicate and advocate appropriate or cost-effective therapeutic options, despite

pressures, in order to empower consumer choice.

"To some extent, we now influence non-essential medicines coming in. When a patient says, this is the prescription from my doctor and this is what I want, what would you do? You just have to find a way of getting it for them. People go to the private sector for medicines if it's not covered under essential medicines. I know some government hospitals still insist on getting essential medicines, but the doctor will tell you this is what I want for my patient. And when he says that, there's nothing you can do, you have to look for it or you lose your customer, you lose your patients." Participant 6-Distributor-Pharmacist-Africa

In contrast, some participants viewed that ordering, poor quantification and forecasting practices,

especially from the health facilities, as major limitations to providing fluid and reliable supply.

"The reasons for stock-outs in the Pacific are almost entirely due to bad management. They don't have a culture of keeping records. In Cambodia, in the public sector, if they order something from the CMS [central medical store], they're only likely to get half of it [even though] you may know that in the CMS it's all there. The reason is that the CMS staff believed that the minister [of health] liked the CMS to [always] be full." Participant 38-Academic/Nonprofit-Pharmacist-Western Pacific

"Generally, most medicines are available in the country. Every province has its own medicines depot. But availability in the medicines depot does not equate to availability in the facilities. The problem is that because of poor quantification, or poor forecasting [on

the part of] the facilities, other facilities will not have a drug, even if it's available at the medicines depot. They don't have enough skilled, experienced, qualified people to run the drug supply management chain. Of course, you do have companies that do not supply as they are supposed to. But in the system, there's been no provision for follow-ups for monitoring of the performance of the companies." Participant 8-Nonprofit-Pharmacist-Africa

Many stakeholders expressed that there lacked cohesive and inclusive consultation between

stakeholders regarding solutions to fix drug shortages or offer sustainable supply solutions.

"You've got to get the six states and two territories to agree on the list. If they don't agree on the list, they'll tend to do their own thing. If they want consistency when there are shortages, they have to have a national approach how they'll allow products to be drip fed out to the market nationally. If they don't get to a national arrangement and get those states to agree, they'll all go do their own thing because there'll be each state with one thing of their own essential product listing, which they essentially do now. They're all different, but 80-90% of it can be a combined list. Unless you get all the states together, nothing's going to change." Participant 29-Wholesaler/Distributor-Business Management-Western Pacific

"In the public sector it's very difficult not to adhere [to EMLs] because other medicines just simply aren't there. In South Africa and at primary care level, all medicines are free to uninsured patients, so there's no co-payers, no consulting fee. But you can't prescribe what's not available, it's quite simple. On the private side you can deviate from those algorithms, and even if the insurer refuses to pay, the patient picks up the co-pay." Participant 3-Academic/Government-Pharmacist-Africa

Moreover, some highlighted that the availability of too many therapeutic options and market

competition driven to meet a broad range of individual needs has consumed large amounts of

resources.

"Think about relativity. There's a valuation and people make those decisions. People say that medicines are expensive, and I'll grant you that there are some medicines that are very expensive and I don't understand why they're so expensive. But are they affordable? [I think] you can do anything you want to do, you just have to face the consequences." Participant 1-Health provider/Nonprofit–Pharmacist-Pan America/Africa

"I find the essence of the EML is defeated. It's not that they're not competent. Definitely those EMLs are there, but you see pressure coming from outside to use these products [and] a lot of irrational prescriptions coming from the prescribers, because the pharmaceutical companies are coming up with innovations, ideas, and puts pressure on them. [Some] doctors [might] say, 'okay let me see how this [new medicine] is?' In the private sector, they can make use of any medicine they want to use. But in the public sector, there's policy on essential medicines, and preference to essential medicines in

tenders in government hospitals. [But] policy is not implemented to the letter, so there's still room for non-essential medicines coming in, which is compounding the system."
Participant 6–Distributor–Pharmacist-Africa

"We're reimbursing sometimes because of political pressure. What becomes essential, cost effectiveness? The culture will influence what you think is essential to some degree. The other thing that influences essential is moral attitudes. [If] it's quality of life, then how far do you want to go with that in terms of essential and not essential? Does that make enough difference to your quality of life that it should be on the list?" Participant 41-Academic/Government/Health Provider–Physician-Pan America

In addition, some participants explained the expiry and waste of medicines were costly

consequences to providing essential medicine stockpiles or emergency use only medicines.

"Everybody should adhere to the essential medicines concept, because we don't need a lot of waste in the healthcare system even if you're in a high resource place. Also, if this is strictly adhered, to as far as judging efficacy and safety in comparing one drug to another, making sure that you don't need every alternative available but the best alternative, anyone [and] any country could benefit from that." Participant 40-Academic/Government–Scientist-Pan America

"Stockpiling is extremely dangerous. Stockpiling has [only] worked for anti-retrovirals in Africa. IDA [International Dispensary Association] or the SCMS, [Supply Chain Management Systems] has stockpiles in South Africa that are able to supply to SCMS projects. It's a single payer. The US Government is paying for all those medicines, whichever country it goes to, so they are able to shift funds around." Participant 43-Academic/Government-Physician-Africa/Pan America

2.3.2: The Roles of Stakeholders in the Pharmaceutical Supply Chain

In addition to these influences, this study also explored the roles of supply chain stakeholders to

understand how they interacted and engaged in decision making. The Ishikawa fishbone diagram

has been used in studies to display barriers and facilitators (Ridge, Bero and Hill 2010, Tran and

Bero 2015). In line with the comprehensive theory of collaboration, the themes displayed in

Figure 2.2 and 2.3 highlighted control mechanisms and complex challenges involved with each

stakeholder's role. Results showed that sometimes stakeholders' intended control mechanism

contributed to the complexity of the supply chain, and stakeholder roles sometimes overlapped.

For example, providing quantification of medicine stock is a critical control mechanism needed for

the supply chain to run smoothly. Meanwhile, poor quantification frequently occurred due to capacity, resource or time limitations, resulting in complexities such as stockpiling, expiry of medicines, unavailable medicines, and delivery delays.

Thematic analysis showed that logistics management and therapeutic decision making were managed separately by stakeholders in the supply chain. As a result, these were displayed in two separate diagrams. The first fishbone diagram (Figure 2.2) shows stakeholders involved in decision making to facilitate access to medicines. The second fishbone diagram (Figure 2.3) shows stakeholders involved in pharmaceutical logistics to deliver access to medicines.
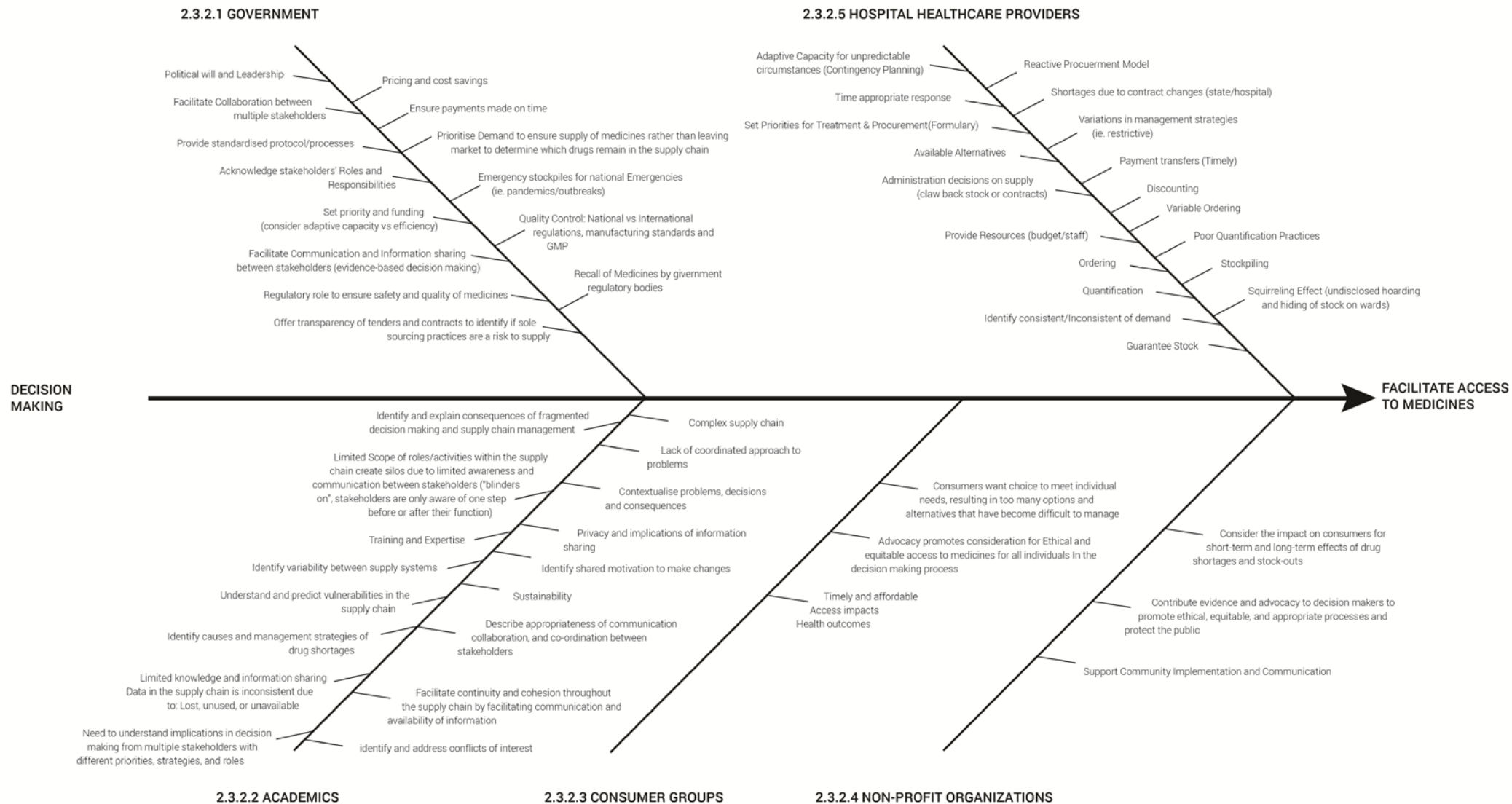
2.3.2.1 GOVERNMENT

Political will and Leadership
Facilitate Collaboration between multiple stakeholders
Provide standardised protocol/processes
Acknowledge stakeholders' Roles and Responsibilities
Set priority and funding (consider adaptive capacity vs efficiency)
Facilitate Communication and Information sharing between stakeholders (evidence-based decision making)
Regulatory role to ensure safety and quality of medicines
Offer transparency of tenders and contracts to identify if sole sourcing practices are a risk to supply

Pricing and cost savings
Ensure payments made on time
Prioritise Demand to ensure supply of medicines rather than leaving market to determine which drugs remain in the supply chain
Emergency stockpiles for national Emergencies (ie. pandemics/outbreaks)
Quality Control: National vs International regulations, manufacturing standards and GMP
Recall of Medicines by givernment regulatory bodies

2.3.2.5 HOSPITAL HEALTHCARE PROVIDERS

Adaptive Capacity for unpredictable circumstances (Contingency Planning)
Time appropriate response
Set Priorities for Treatment & Procurement(Formulary)
Available Alternatives
Administration decisions on supply (claw back stock or contracts)
Provide Resources (budget/staff)
Ordering
Quantification
Identify consistent/Inconsistent of demand
Guarantee Stock

Reactive Procurement Model
Shortages due to contract changes (state/hospital)
Variations in management strategies (ie. restrictive)
Payment transfers (Timely)
Discounting
Variable Ordering
Poor Quantification Practices
Stockpiling
Squirreling Effect (undisclosed hoarding and hiding of stock on wards)

DECISION MAKING → **FACILITATE ACCESS TO MEDICINES**

Identify and explain consequences of fragmented decision making and supply chain management
Limited Scope of roles/activities within the supply chain create silos due to limited awareness and communication between stakeholders ("blinders on", stakeholders are only aware of one step before or after their function)
Training and Expertise
Identify variability between supply systems
Understand and predict vulnerabilities in the supply chain
Identify causes and management strategies of drug shortages
Limited knowledge and information sharing Data in the supply chain is inconsistent due to: Lost, unused, or unavailable
Need to understand implications in decision making from multiple stakeholders with different priorities, strategies, and roles

Complex supply chain
Lack of coordinated approach to problems
Contextualise problems, decisions and consequences
Privacy and implications of information sharing
Identify shared motivation to make changes
Sustainability
Describe appropriateness of communication collaboration, and co-ordination between stakeholders
Facilitate continuity and cohesion throughout the supply chain by facilitating communication and availability of information
identify and address conflicts of interest

Consumers want choice to meet individual needs, resulting in too many options and alternatives that have become difficult to manage
Advocacy promotes consideration for Ethical and equitable access to medicines for all individuals In the decision making process
Timely and affordable Access impacts Health outcomes

Consider the impact on consumers for short-term and long-term effects of drug shortages and stock-outs
Contribute evidence and advocacy to decision makers to promote ethical, equitable, and appropriate processes and protect the public
Support Community Implementation and Communication

2.3.2.2 ACADEMICS

2.3.2.3 CONSUMER GROUPS

2.3.2.4 NON-PROFIT ORGANIZATIONS

Figure 2.2: Stakeholders involved in decision making to facilitate access to medicines.
Logistics management and therapeutic decision making were managed separately and displayed in separate diagrams. To simplify reporting of results, repetition of themes were not displayed in the fishbone diagram. Instead, themes were arranged according to the stakeholder who was perceived to have the most influence (control) on the issue.   Furthermore, since managing drug shortages was explored in interviews, the analysis often reflected how unavailable medicines were managed in the supply chain.

2.3.2.1: Government Roles

Stakeholders perceived that governments had significant leadership, facilitating, regulatory, enforcement, provision and funding roles.

"People in leadership [positions] have the charisma and preparedness, to bring people together and share a combined vision. At a national political level, it can make such a dramatic difference how a minister of health is appreciated, how much he /she advocates and [stands] behind these kinds of ideas to impact the willingness and preparedness to follow [through]. [However], knowing is different from doing. [For example], the Budget Declaration is a commitment by countries in Africa to spend at least 15% of the national budget on health care. Almost none of the African countries, except Botswana and Namibia, even reach 10%. Governments have to [set] their priorities right." Participant 2-Nonprofit-Pharmacist-Europe/Africa

"[Nowadays], government hospitals have medicines available, [with] patients lining up for the services. [This did not happen] before, because there were no medicines [at the facility]. When the president made the mandate, the corresponding logistics, structure, and monitoring logistics were also done, [through the] political will of the insurance company, of the head of the department of health, and the regulatory agencies. I could not work well with them before, because our ideas clashed. [Since] these administrative and executive orders [were passed within] a legal frame, [it allowed] everybody to really work [together]." Participant 4-Health Provider/Government–Pharmacist-Western Pacific

Meanwhile, government involvement created complex environments and were challenged with issues around pricing, ensuring payments, regulatory changes, monitoring quality and safety of medicines and market influences.

"The major reason for stock-outs is nearly always a failure or delay in paying for the medicines. In the US, the increasing quality standards [have created] a very competitive, very tight generic market where the insurers are ratcheting down the reimbursement price for products, while at the same time the FDA [US Food and Drug Administration] has raised standards. And so the cost of manufacturing has increased for what are often low-volume products, and that's the most frequent cause of shortages in middle and high income countries. In the low income countries, the vast majority of stock-outs and shortages have related to inadequate financing or inadequate financial management." Participant 43–Academic/Government-Physician-Africa/Pan America

"Eighty percent of API for both brands and generics come from China or India. It doesn't matter what country you're in. In the US, the market competition drives the price for generics down extremely low. If you're deciding what's on the list just on the basis of price, than you may end up with shortages. If you pick a single supplier, this is typically if you're tendering, you tender to the lowest bidder, but then something happens. [For example], the situation with the fire in the Sandoz plant in Quebec [Canada]. If that happens, then you could be in

trouble with shortages of what you deemed an essential drug because you've only got the one supplier." Participant 41-Academic/Government/Health Provider-Physician-Pan America

"If a regulatory authority such as the FDA has Okayed a particular product, some people will say why doesn't South Africa simply take their [decision] into consideration and give approval. To some extent, I think it happens on some of the medicines. But much [as] our regulatory authority is quite strong, certainly the strongest on the African continent, it's not efficient enough. [Therefore], companies complain that it can take up to five years, those are extreme cases, to have a product's registration go through. Our government agreed to fast tracking the registration of certain medicines, if they are found essential and therefore required. [Regulatory requirements are] quite strict, but takes a long time, and companies complain they lose a lot of money waiting for registration to go through. If a company wants to register a drug in South Africa they have to have a presence in the country, even if it means initially opening an office and employ a pharmacist who's going to look after their interests. So [companies] start spending money long before the product is registered." Participant 8-Nonprofit-PharmacistAfrica

Furthermore, decisions around prioritising health needs and contingency planning were complex.

"We assume that nothing is going to come to the committee unless there is at least marginal public health need. But I don't think committees grapple very well with differentiating between something that's going to be used by everybody versus a very small segment of the population." Participant 40–Academic/Government–Scientist-Pan America

At the same time, government roles were viewed as susceptible to coercion and corruption due to

lack of transparency around decision making and handling of public funds.

"In one province, the company that was supplying this only drug was not paid. The company then withheld supplies. But the province was given money to do a buyout, meaning buying that same product from the same company outside the tender process by paying a lot more money. The suspicion in fact was that officials in the department are paid to make sure that the companies are not paid so that they can sell them at the higher prices. So [companies] have all sorts of ways of ensuring that they make a lot more money, especially when they are single source suppliers." Participant 8-Nonprofit–Pharmacist-Africa

2.3.2.2: Academic Roles

Academic stakeholders had a pivotal role in providing unbiased information that identified, and

explained information sharing and interaction between stakeholders in the supply chain.

"I think there is a sort of myth that the EML is for second class medicines, [as in] they're not the best medicines. Really, they are the best medicines." Participant 40-Academic/Government–Scientist-Pan America

"Consistent statistics management - it all boils down to components of information in the supply chain system. In Kenya for example, in spite of insurmountable situations, local staff have come up with a logistics information system where somebody sitting in the capital city, Nairobi, in real time, can know what is going on in Nyanza province or anywhere else in Kenya. [They know] the consumption level and what the situation is there. They have time to even act upon any redistribution that may be needed from one province to another in case there's a shortage over there. So when all that information comes upstream that can help them plan for a procurement cycle." Participant 9-Nonprofit-Pharmacist-South East Asia/Africa

"So a good example of how to deal [with] simple things and do them consistently is Namibia. They gather simple indicator data every six months and they report it every year, and they can see a percentage antibiotic use or what proportions of the population who leave a primary care facility have had an injection and they can track it over time." Participant 3-Academic/Government-Pharmacist-Africa

However, some challenges academics faced were around providing and communicating information from different levels of the health care system to different stakeholders, engaging collaboratively with different stakeholders, and sharing and coordinating information in a timely and ethical manner.

"I find it pointless when researchers try to have a consistent measure. You just can't do that and studies cost money, time and resources. The availability data that you might see from studies five years ago, well it changes. Even last year will change this year because it all boils down to pricing, supply chain information, quantification, and forecasting." Participant 9-Nonprofit-Pharmacist-South East Asia/Africa

"We are gradually moving towards bringing about a connection between the procurement system and the selection system. You have the people on the [EML] committee simply choosing medicines based on efficacy, on suitability for treating the particular ailment or disease. The procurement people on the other hand, will look at the price. If the procurement [and] the selection processes did all of this together, then they'd be able to look at two [products] for the same ailment and then bring into the whole equation, availability, wide availability of the product. There are instances where other products which might not be as efficacious, but which is readily available and is produced by more than one company. That product could have been used and would have had better success." Participant 8-Nonprofit-Pharmacist-Africa.

Further challenges that academics faced, included the lack of trust and conflict of interests between stakeholders.

"They won't talk about the process, there's a complete lack of transparency. It corrupts the whole system, because then you're moving the medicines that are available to the practitioner further away from what's on the EML, because you've had all these financial dealings behind the scenes. I mean why have an EML if you know people are going to go make these behind door deals and wind up with a small number of companies whose products are on their list?" Participant 40-Academic/Government-Scientist-Pan America

These issues also raised concerns about the importance of training and qualified staff to interpret

and disseminate evidence.

"[Available] people who are able to interpret this and challenge poor quality modeling is scary. Think of industry providing modeling to NICE [the National institute for Health and Care Excellence], how many times does NICE say we ran another model and we disagree with the one that was submitted to us? The capacity do to that and to distinguish between good and bad public economic data is very limited." Participant 3-Academic/Government–Pharmacist-Africa

"There's this notion [of] providing treatment to the poor and treatment to the affluent. I think education is core, it's essential. In medical schools they have to include this in the curriculum, to medical doctors, pharmacists, and nurses. But, if these tools are out dated, it loses its value. It depends on so many elements. What is the culture in an institution, the university, the school of medicine in the university? How much do people interact with each other and have faith and trust in each other? That varies over time." Participant 2-Nonprofit-Pharmacist-Europe/Africa

"I think the main difference is the [Health Technology Assessment] HTA process does have the formal cost effectiveness analysis. In the evidence review, they're very similar in terms of efficacy and harm, but when we get to the cost data the HTA is a more formal process. Also the HTA doesn't necessarily take into account public health need." Participant 40-Academic/Government –Scientist-Pan America

2.3.2.3: Consumer Group Roles

Consumers were most concerned with having timely and affordable medicines available when they

needed them.

"What am I going to do? [The patient thinks] I need my pink pills or I go crazy, or I get hot flushes or I get this or that, or my kids are going to shoot me. I have to focus on managing that process. So every ounce of energy that I spend away from that focus is waste. So from a patient perspective, they may see that I'm really trying to help them. I'm their advocate. On the other hand, they could well be saying, 'you're an idiot, I came last week and you didn't have them either'." Participant 1-Health Provider/Nonprofit–Pharmacist-Pan America/Africa

There was emphasis on advocacy for access and the importance of having choices to meet their individual needs.

> *"I think choice is very important and having as much information as possible in order to make an informed choice is actually more important. For consumers we have to think much more about the trade off in paying for very expensive medicines that don't cure. That means other medicines that might be able to cure the people of other diseases may not be as affordable because we're paying so much for these medicines that extend life. Or it might mean that we can't put as much money into other things like preschool education." Participant 44-Consumer-Teacher-Western Pacific*

> *"The industry argues innovation in the sense that every new drug is to some degree innovative because it's a new molecule. It provides extra choice." Participant 41-Academic/Health Provider/Government-Physician-Pan America*

> *"It depends on people's choice. Some people will want to not have medicines that prolong their lives for a short time because the side effects are so debilitating. They'd rather forego the treatment. Participant 44-Consumer-Teacher-Western Pacific*

While consumers provided demand, they were not seen to contribute to the supply chain management process.

> *"If you pay for a service you have the right to demand something in return. So you give a voice to people who have no voice. If you get something for free in Africa, in a country like Tanzania; if you get health care for free, people, patients have no voice. And the dynamics change if people have to pay for services. That changes the dynamics in the system too. That's not happening nowadays. So free services for free, is never providing an incentive unless you have people with this intrinsic motivation out of their personal value system. But reality tells you that as people, we all are in our own way, very selfish." Participant 2–Nonprofit-Pharmacist-Europe/Africa*

> *"I don't know what [consumers] can do about [drug shortages]? Put pressure on the purchases of medicines? [Not having medicines available] can be devastating to people. But they have to know about it, and I don't know who would take responsibility for informing people." Participant 44-Consumer–Teacher-Western Pacific*

2.3.2.4: Non-Profit Organisation Roles

Non-profit organisations had a role in providing advocacy for consumers and unbiased information to all stakeholders.

> *"[There is a need] to disseminate information to the public, what is a medicine, why is it being used, what are the things you need to be careful about, and what information you are*

to ask when you use this, because medicines are viewed as an ordinary commodity."
Participant 4-Health provider/Government–Pharmacist-Western Pacific

Their involvement in various contexts offered reflection of challenges implementing policies on the

ground level.

> *"When people talk about all these policy things, the national drug policy and EMLs, it's the politicians and the NGO [non-government organisations] directors who are envisioning all these wonderful things. Then when you see what happens on the ground, in the field in some small village, it's a completely different world. Oftentimes I think WHO, Ministers of Health, NGOs, trainers, academics, don't do a very good job of educating people in those lower levels mostly in community settings or specific health settings, clinics and so forth. Both the providers and the patients, [need education] about essential medicines, and what this means, how are you going to implement it and use it in your particular setting?" Participant 42-Academic/Government-Pharmacist-Pan America*

Non-profit organisations' roles sometimes overlapped with other stakeholders in LMICs, when

involved with the provision of care or managing donated or sponsored medicines; however, this was

not addressed in these results.

2.3.2.5: Hospital Health Care Provider Roles

At the therapeutic decision making level, health providers determined health need priorities and

processes based at the patient level, managed standard treatment guidelines (STGs) and

procurement processes, and were at the front lines of managing therapeutic options for drug

shortages.

> *"The larger an EML gets, the larger and more complicated the procurement process and storage becomes. The prescribing can become more complicated as well. Then you've got to look at the different dose forms and strengths that are available too. For example, pregabalin is available as 25mg, 75mg, 150mg and 300mg capsules. You need to have shelf space for four different strengths of the one drug if you're going to have all four drug strengths on your hospital formulary. The cost of that has to be taken into account. So access is affected by the different levels of the supply chain. You've got impressed in the hospital, versus prescribing, versus supply as well. Participant 10-Health Provider-Pharmacist-Western Pacific*

> *"The only way we'll substitute a product is if the pharmacist from the hospital tells us what they want to buy. [The wholesalers] don't have clinical people. Whatever they tell us we'll do. Whatever the alternatives we've got in stock, we will supply that at the contract price if*

it's on tender and then charge the difference to the manufacturer. That is totally embedded in our system." Participant 29-Wholesaler/Distributor-Business Management-Western Pacific

"The main thing that affects prescribing is what's available to people to prescribe. If the EML was guiding purchasing and management of the supply more directly then maybe that could prevent some of those shortages particularly since the EML is focused on the medicines where we do know there's a high public health need." Participant 40-Academic/Government-Scientist-Pan America

However, these stakeholders felt the consequences of unavailable medicines through their inability

to deliver patient care, and were crucial to relaying patient needs to other stakeholders. Therefore,

the therapeutic decisions made at the patient level of care, mostly reflected the consumer demand

in the supply chain.

"Just because it's on the EML doesn't mean the company's going to keep providing it." Participant 12-Health provider-Pharmacist-Western Pacific

"Health professionals are people who want to help their patients. They care less about politics and lists and what WHO says. [The EML] is good guidance, especially if one doesn't have time to maintain their knowledge level for all the changes in medicine. But for the most part, they're just focusing on what my patients need from us as providers of healthcare. I remember where the government deemed [a medicine] to be an essential medicine and focusing on that word 'essential' and how loaded it is. But we can never get any at our clinic. So how essential is it really if they have it on a list but it's never or rarely available? Or when we can get it, it's really expensive?" Participant 42-Academic/Government-Pharmacist-Europe/Pan America

On the other hand, high variation in administration and management strategies, procurement,

capacity, resources, budget constraints, variations in contracts and tenders, and payment practices

created a high degree of inconsistencies throughout the supply chain.

"I think they mostly budget properly. It's the budget allocation that's a problem, lack of skills to [prepare] proper forecasting or quantification, and the irrational failure to pay suppliers. But most medicines are generally available in the country. So it's the logistics system that leads to what we refer to as artificial stock-outs." Participant 8-Nonprofit-Pharmacist-Africa

"There's no pro-activity when we get past the wholesaler, and this is down to the end user perspective. Stock control is a site-by-site level and only for those organisations that see it as a financial enabler, but there's no sharing of that information system-wide. So when you hear [government] say we need to create a reserve of essential medicines, I completely and utterly disagree, because we need to actually understand where this resource is within the country so that we can best use it." Participant 18-Industry-Pharmacist-Western Pacific
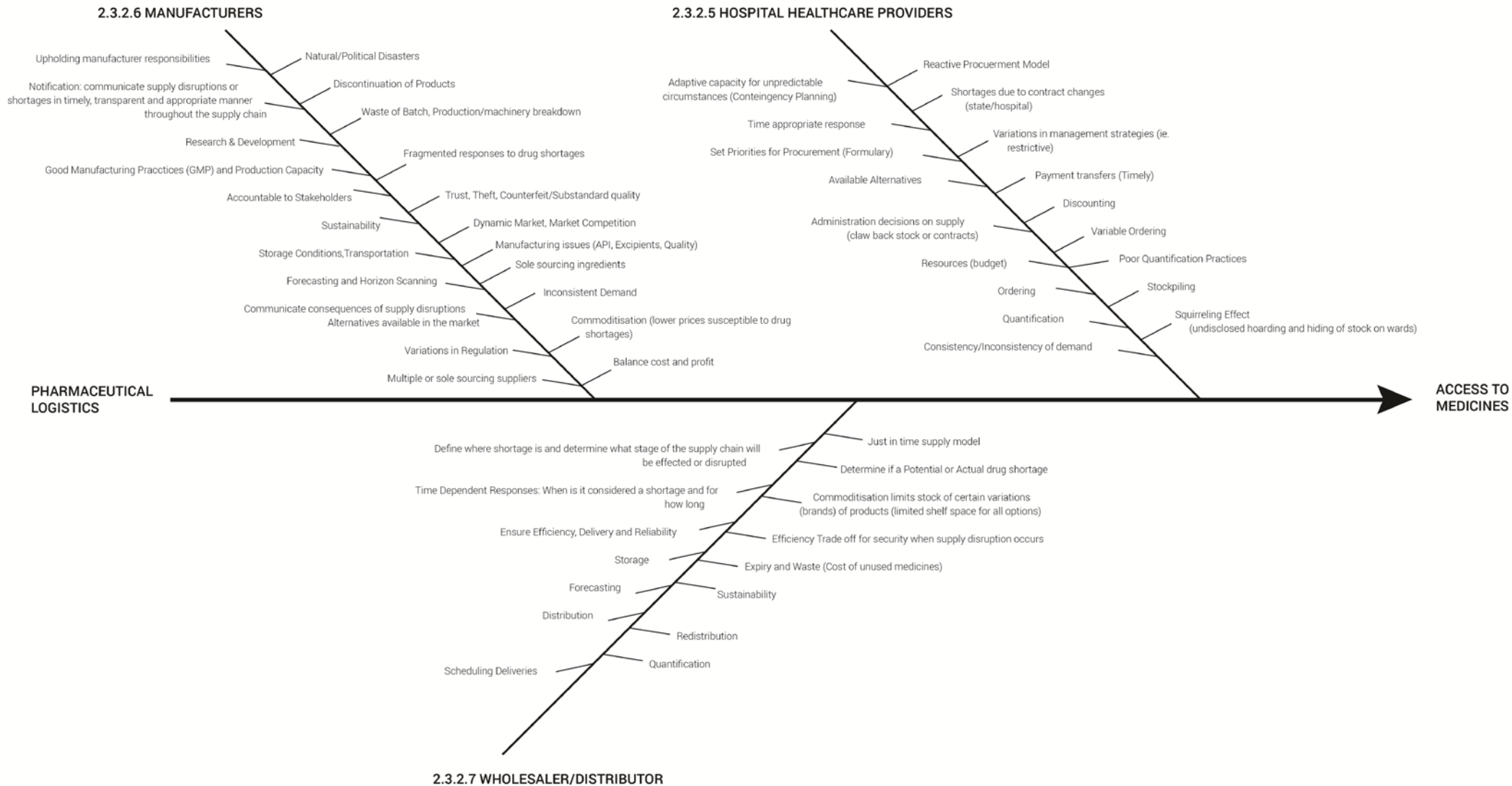
2.3.2.6 MANUFACTURERS

- Upholding manufacturer responsibilities
- Notification: communicate supply disruptions or shortages in timely, transparent and appropriate manner throughout the supply chain
- Research & Development
- Good Manufacturing Pracctices (GMP) and Production Capacity
- Accountable to Stakeholders
- Sustainability
- Storage Conditions,Transportation
- Forecasting and Horizon Scanning
- Communicate consequences of supply disruptions Alternatives available in the market
- Variations in Regulation
- Multiple or sole sourcing suppliers

- Natural/Political Disasters
- Discontinuation of Products
- Waste of Batch, Production/machinery breakdown
- Fragmented responses to drug shortages
- Trust, Theft, Counterfeit/Substandard quality
- Dynamic Market, Market Competition
- Manufacturing issues (API, Excipients, Quality)
- Sole sourcing ingredients
- Inconsistent Demand
- Commoditisation (lower prices susceptible to drug shortages)
- Balance cost and profit

2.3.2.5 HOSPITAL HEALTHCARE PROVIDERS

- Adaptive capacity for unpredictable circumstances (Conteingency Planning)
- Time appropriate response
- Set Priorities for Procurement (Formulary)
- Available Alternatives
- Administration decisions on supply (claw back stock or contracts)
- Resources (budget)
- Ordering
- Quantification
- Consistency/Inconsistency of demand

- Reactive Procuerment Model
- Shortages due to contract changes (state/hospital)
- Variations in management strategies (ie. restrictive)
- Payment transfers (Timely)
- Discounting
- Variable Ordering
- Poor Quantification Practices
- Stockpiling
- Squirreling Effect (undisclosed hoarding and hiding of stock on wards)

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2.3.2.7 WHOLESALER/DISTRIBUTOR

- Define where shortage is and determine what stage of the supply chain will be effected or disrupted
- Time Dependent Responses: When is it considered a shortage and for how long
- Ensure Efficiency, Delivery and Reliability
- Storage
- Forecasting
- Distribution
- Scheduling Deliveries

- Just in time supply model
- Determine if a Potential or Actual drug shortage
- Commoditisation limits stock of certain variations (brands) of products (limited shelf space for all options)
- Efficiency Trade off for security when supply disruption occurs
- Expiry and Waste (Cost of unused medicines)
- Sustainability
- Redistribution
- Quantification

Figure 2.3: Stakeholders involved in pharmaceutical logistics to deliver access to medicines.
Logistics management and therapeutic decision making were managed separately and displayed in separate diagrams. To simplify reporting of results, repetition of themes were not displayed in the fishbone diagram. Instead, themes were arranged according to the stakeholder who was perceived to have the most influence (control) on the issue. Furthermore, since managing drug shortages was explored in interviews, the analysis often reflected how unavailable medicines were managed in the supply chain.

2.3.2.6: Manufacturer Roles

Manufacturers were accountable to stakeholders nationally and globally. They provided capacity, ensured reliability of supply, upheld quality standards, and communicated supply disruptions throughout the supply chain.

> *"The system we've had in Australia has worked well for the last 50 years or more. Even though there have been drug shortages, you haven't heard about it, because the system worked." Participant 14-Pharmaceutical Industry-Business Management-Western Pacific*

> *"[Medicines] are commodities. The people who sell the commodity play all the games they play in sales and marketing to make money with these commodities." Participant 42-Academic/Government-Pharmacist-Pan America/Europe*

Due to globalisation, medicines were predominantly sourced out of country, and companies were expected to provide safe, reliable, and appropriate supplies of medicines.

> *"Eighty percent of all those drugs are being manufactured out of India, so if something goes wrong with the Indian manufacturing system; it's going to have a massive issue with the shortage. On top of that, any drugs, even these generic drugs, get solely listed on a tender even though they've got these issues, [and] they can broker by the brand one. There's more and more generic providers [that] get on the tender and they don't have stock here. They cause all sorts of issues with out-of-stocks. It's more time consuming when you have product substitution and claim back the dollars." Participant 29-Wholesaler/Distributor–Business Management-Western Pacific*

> *"About 90 percent of the medicines we use are imported, and the local production is not very effective. So a company importing this product wants their products to be sold, bring in new products, and to introduce new molecules." Participant 6–Distributor–Pharmacist-Africa*

> *"The differences between little generic firms in developing countries and the big firms are beginning to merge." Participant 3-Academic/Government–Pharmacist-Africa*

The ability to perform these roles made them the drivers of the medicine supply chain. However, unexpected natural or political disasters, manufacturing and delivery issues, international laws, and profit margins created volatility in the supply chain.

> *"Low prices may also contribute to shortages because there's less profit margin. The generic companies are looking at their range of products that they're offering, and discontinue selling the ones they're making [less] on to focus on the ones that they're*

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making a higher profit margin." Participant 41-Academic/Government/Health Provider–Physician-Pan America

"There's an example where a company in Australia will have responsibility [as] the only company that imports in Australia. Not that they've got an exclusive contract, they just happen to be the only company. They rely on another separate company to supply the main board for that company there. If that first company doesn't tell the second company, then there's one example where they go raise the talk. Where company x is relying on company y overseas to do it in Europe. Company x bought it off company y. Company y had decided to refurbish its factory or do something but they didn't bother telling company x. So company x who is operating here in Australia suddenly goes what do you mean you can't supply anymore? So company x had to deal with company y's [issue] - anyway that happens." Participant 14-Pharmaceutical Industry-Business Management-Western Pacific

Furthermore, the provision within the supply chain was complicated by market competition, manufacturing issues or disruptions, meeting regulators quality requirements, fragmented management and response, operational costs, profit targets, investment costs and the discontinuation of products.

"Where we have a single source product, as in a product that's produced by just one company, what happens quite often is that the company will decide not to make the medicine available for the tender system. Thereby, [providers would] be forced to buy at a high price because it's not on tender. They will simply remove it knowing that there's no other medicine." Participant 8-Nonprofit-Pharmacist-Africa

*"The company that becomes the sole supplier for prescribed medicines basically has such an enormous proportion of the market that other suppliers might decide it's not worth it and not supply. That's something that Pharmac (*Pharmaceutical Management Agency, New Zealand) *has to take into account when they do sole supply agreements; to make sure their sole supplier is actually in a position to guarantee supply. There was a problem with that, about paracetamol. People weren't very happy with the paracetamol that got the sole supply. It wasn't very pleasant to take, difficult to swallow, and didn't have the coating on it that would make it easier [to swallow]. The other kinds of paracetamol became more difficult to get because the sole supply went to that particular company. Participant 22-Academic-Sociologist-Western Pacific*

2.3.2.7: Wholesaler/Distributor Roles

Wholesalers and distributors had an important role in ensuring the fluidity and reliability of the pharmaceutical supply chain. They had knowledge of the demand and usage of medicines that contributed to the national and international supply and distribution of medicines.

"You just see the lack of supply at one end, the price changing at the other end, and that's the end of it. There are a lot of things happening." Participant 30-Wholesaler-Business Management-Western Pacific

"We [the wholesaler/distributor] see the [entire] supply chain market." Participant 29– Wholesaler/Distributor-Business Management-Western Pacific

"[Distributors] have supply chain knowledge, by going country to country, town to town, village to village. But it has some costs. It's normal that in some countries where they have insurance, things are easier, because insurances can pay back the effort of a distributor. [But they] need the supply chain to have transportation, material, employees, and [provide for] their own lives. The [distributors] can use their experiences [so that] people may [access] more medicines." Participant 7-Distributor-Pharmacist-Africa

They helped determine and manage supply disruptions in short and long term drug shortages.

"What is the process when there are shortages and how do the wholesalers and manufacturers then restrict stock so that everybody gets a fair share of the stock? That's part of trying to change the supply chain. At the moment, there's no industry standard of how to treat shortages. Each manufacturer does it their own way, all separately. There's no industry motivation. There's a hospital pharmacist society in Australia but it's more of a clinical front. There's no real industry body on the supply chain side." Participant 29– Wholesaler/Distributor–Business Management-Western Pacific

On the other hand, the just-in-time supply model did not allow for flexibility in forecasting.

"The more you look at the supply chain, the more vulnerability you see. We create some of our own vulnerabilities here with our just-in-time medication, and with our contracting processes. " Participant 20-Government–Physician-Western Pacific

"[With] distribution into Australia, there are long lead times because we're importing a lot of stuff. We've got distribution challenges: how are we distributing, are we holding stock here? No we can't hold stock here. Why not? Because we're actually being asked to squeeze our margins because there's less money, because it's a commoditised market. So in the system map flow, we've actually put efficiencies in there in an attempt to save money that [instead] has created inefficiency because now we are unable to react. We've gone too deep and the elasticity is too far." Participant 18–Pharmaceutical Industry-Pharmacist-Western Pacific

Furthermore, expiry and waste of medicines were unaccounted for and often led to profit losses.

"[There is limited] space on the shelf in the warehouse. Expiry [of products and] cash tied up [are big challenges] because [wholesalers] have to pay the manufacturer, and [medicines] just sit there and we're paying interest on that cash tied up. We've got sheds [of products] but the big two costs is the interest on the product tied up and expiry." Participant 29–Wholesaler/Distributor-Business Management-Western Pacific

"The market actually works against [EMLs]. As drugs get more scarce and drives less sales dollars, you have less priority on them, and that's what some of these essential medicines do. Something's got to give, so you hold less stock because you can't make the dollars, so you have less investment." Participant 30-Wholesale/Distributor-Business Management-Western Pacific

"The hospital's [purchaser] looks at the price [of the medicine], even if it's one or two cents the price [of what] the wholesaler is paying. They don't look at it from what we can see as most public hospitals probably hold about 15 to 30 days worth of stock. [Hospitals] write a lot of expired stock off." Participant 29–Wholesaler/Distributor-Business Management-Western Pacific

2.4 DISCUSSION

This study showed the intricate inter-connectivity of stakeholders' roles and responsibilities throughout the pharmaceutical supply chain. It identified gaps and vulnerabilities in the management of the pharmaceutical supply chain due to how key stakeholders interacted. This demonstrated that therapeutic decision making was often separated from logistic management within the pharmaceutical supply chain, which was likely due to potential conflicts of interest. Results showed that inconsistencies (variability) in the supply chain were linked to stakeholders' value of having choice. Meanwhile, differences between LMIC and HICs demonstrated the impact of governance on supporting resources and processes throughout the pharmaceutical supply chain. Therefore, stakeholders involved in the provision of medicines were challenged with complex decisions requiring significant collaborative effort.

2.4.1: Stakeholder Roles

This study showed that the interconnectivity of stakeholders' roles and responsibilities highlighted the importance of engagement and accountability by stakeholders. Stakeholders relied on processes along each part of the supply chain to run smoothly in order to achieve their own goals and perform their functions. Along this continuum, all stakeholders were valuable (Ellram 1991). For example, quantification and forecasting to determine the amount of supply needed to meet

demand was a function that health providers, wholesalers, and manufacturers all performed. Stakeholders at one end of the supply chain relied on information at the other end (e.g. health facility needs or government epidemic planning targets, manufacturer production), in order to forecast supply requirements. On the other hand, evidence-based decisions to reimburse medicines could facilitate or inhibit prescribing, effect patient access, and determine whether companies would invest in providing a medicine.

This study demonstrated that selection committees could involve wholesalers and distributors in their decision making process to enhance access and information sharing within the pharmaceutical supply chain. These wholesalers and distributors offered expertise and capacity that could help predict and facilitate supply distribution and disruptions (e.g. forecasting or confirming at what level of the system a shortage occurs, redistribution). Whilst the management of each stakeholder's practice environment was their own responsibility, their decisions and actions could influence other areas along the supply chain (Jahre et al. 2012). Unfortunately, stakeholders within health systems tend to operate in silos and lack coherence and transparency between them (Meteos 2013, Bigdeli et al. 2013a, Crowe et al. 2013). Participants described some of these instances as when medicines were discontinued at the manufacturer level, medicines were taken off hospital formularies, there were changes to tendering or contract agreements, or there were changes in prescriber preference for another therapeutic option. As a result, fragmented decisions and responses occurred throughout the pharmaceutical supply chain.

As displayed in Figure 2.2 and 2.3, results showed there were many gaps and vulnerabilities in the pharmaceutical supply chain involving multiple stakeholders. Stakeholders considered numerous risks and advantages, both independently and collectively. However, unpredictable obstacles acted as barriers that permeated through the supply chain, warranting reactivity from each member (Jahre et al. 2012, Shah 2004, McBeath 2012). Similarly, many participants' confirmed that the decisions to improve efficiencies in the supply chain, such as minimising stock holdings or

sole supplier contracts, also contributed to the increased reactivity to supply disruptions due to less buffers available in the system. Management strategies therefore, have limited advantage when made in isolation or without consultation with other stakeholders. For example, participants explained that some stakeholders at the patient level of care felt pressured by the timeliness and urgency of supply disruptions, compared to stakeholders who made decisions at the policy and manufacturing level. Some stakeholders felt they were poorly informed or told too late about supply disruptions, resulting in risks to patient care or incurred costs. Their decisions needed immediate resolutions for patients at the point of care whether it be for emergency situations, result in treatment interruptions of critical therapies, or loss of trust in the system (Wilson 2012). Contributing to this dilemma, was the emphasis on advocacy for new or individualised patient therapies, which strained suppliers' capacity to cautiously keep stock. As a result, some stakeholders viewed that strategies to strengthen and ensure capacity throughout the overall supply chain was often neglected.

Another critical gap between stakeholders was the issues of pricing and costs of medicines. Stakeholders had highly skewed views around what was considered reasonable cost savings for public tenders and individual patients, versus what was considered appropriate profit margins and sustainable financial structures. Meanwhile, even though a medicine was approved for reimbursement, frequent changing between suppliers, created gaps along the pharmaceutical supply chain. This was compounded by isolated and fragmented management by different stakeholders. This was further complicated by the spike in costs incurred due to unforeseen disruptions. In contrast, some participants' described the mismanagement of funding by government workers, sometimes due to corruption, that resulted in failed or late payments to suppliers. This caused instability and a cascade of other problems. Adding to this discourse, stakeholders highlighted the high incidence of waste in the pharmaceutical sector. Medicines often went expired on the shelf, or manufacturing batches were thrown away if they did not meet

regulatory quality assurance standards. This in turn, eroded the global supply of active

pharmaceutical ingredients (APIs), and consumed substantial financial and material resources by

suppliers. These events perpetuated waste and could lead to drug shortages.

This study showed that in some circumstances, there was deliberate avoidance of some

collaborative alliances. Results demonstrated that therapeutic decision making and logistics

management of the pharmaceutical supply chain were often separated, mainly due to conflict of

interests. This would be in line with criticisms of pharmaceutical companies' influence on

physician prescribing (Campbell 2007). While it was valuable to acknowledge this potential

conflict of interest, separating these processes came with a cost. Therapeutic and supply

decisions made in isolation or without consultation, resulted in fragmentation and continued

uncertainty in the pharmaceutical supply chain. Meanwhile, an inclusive and transparent model

would be difficult to achieve, unless engagement between these two processes were facilitated

and protected from coercion. In contrast, results showed that health providers were the common

interface (overlap) between decision making and pharmaceutical logistic systems; highlighting the

significance of their role in engaging and communicating with other stakeholders. Furthermore,

some participants suggested designating drug shortage experts or liaisons to manage and

communicate shortages, especially to consumers. Thus, challenges to collaborative engagements

needed further investigation.

2.4.2: Factors Influencing Access to Medicines

The wide range of views surrounding the management and supply of essential medicines showed

that stakeholders valued choice. Choice was demonstrated to be a significant driver for the

demand to provide multiple therapeutic options. A high degree of choice; therein, contributed to

inconsistencies and increased complexity and vulnerability in the pharmaceutical supply chain.

When supply disruptions like drug shortages occurred, it risked patient care, increased costs and

consumed additional resources. On the other hand, where an alternative therapeutic option was

available, it disputed whether a medicine was accepted as "essential", or to whom it was essential

for. A prescriber may have therapeutic preferences that can change as guidelines or patient

experiences shape their practice. Thus, when individuals have choice, it confounds the notion of

essential.

Building on the comprehensive theory of collaboration, choice has created inconsistency and

complexity throughout the pharmaceutical supply chain which has been challenging to manage.

This was in line with Wood and Gray (Wood and Gray 1991), who argued that increased

complexity due to individualism and autonomy decreased an organisation's control over a

domain. Meanwhile some features of collaboration suggest that collaborative alliances were also

likely to make systems more complex (Bresser 1988). Hence, providing many therapeutic choices

in the supply chain decreased a health system's ability to control formularies, keep up the supply

of a wide range of products, waste stock, and store adequate supplies in dispensaries and

warehouses of all products. This disparity demonstrated the change of focus from utilitarian value

to accommodating individuals' needs. This phenomenon may occur in any health system. While a

health system may respect an individual's choice to determine whether a medicine is essential for

them; each individual should also be accountable for these decisions and share responsibility for

having these choices provided. Particularly, when they do not serve public health needs. On the

other hand, equitable access to essential medicines should include those that suffer from

neglected diseases or require specialised care (Reich 2000). For example, orphan essential

medicines and treatments for rare diseases may risk neglect of some individuals. Therefore,

subsidisation schemes need to carefully consider how to provide alternative funding to ensure

that public health needs are met and that individuals are supported.

Participants described significant advantages of having complex systems. For example, multiple

suppliers for generic products offered governments opportunities to negotiate lower prices for

medicines, even in monopsony markets such as the United Kingdom, Australia, Canada, and New

Zealand (Lexchin and Mintzes 2008, Clement et al. 2009, Manning 2011, Tordoff, Norris and Reith

2008, Morgan et al. 2006). Additionally, reliable and responsible management of company

portfolios to meet population needs fostered trust and relations with other stakeholders and

global markets. Furthermore, access to alternative supply sources offered solutions and resilient

strategies to manage unpredictable supply disruptions. Meanwhile, at the point of care, the

availability of therapeutic alternatives acknowledged the importance and dynamics of patient-

centred care. In line with Wood and Gray (Wood and Gray 1991), collaboration between

stakeholders involved in the pharmaceutical supply chain was considered foundational to

reducing inconsistencies and enhancing fluid management of the system in order to guarantee

supply of essential medicines. Hence, the impact of drug shortages offered a collaborative

opportunity and motivation for stakeholders in the pharmaceutical supply chain to provide

solutions and improve processes that ensure the provision of critical health services.

While choice is a human right and an empowering attribute; these choices must be governed

respectfully, ethically, and fairly. Many stakeholders discussed the importance of trust and

accountability involved in pharmaceutical supply chain collaborations. Some stakeholders

suggested difficulty engaging with other stakeholders. For example, relationships between

stakeholders took time to develop. Some participants highlighted that governments were often

elected every few years, which affected the dynamics of collaborative engagement. Participants

explained this was further complicated, when governing bodies themselves were involved in or

accused of unethical conduct by government workers or pharmaceutical companies, resulting in

loss of trust by the public and collaborating stakeholders. Similarly, these relationships were

strained when pharmaceutical companies set exorbitantly high prices for medicines. Stakeholders

working in LMICs mostly reported concerns regarding unethical conduct and corruption in

governance and financial interactions as major barriers. However, HIC settings also grappled with

transparency around pharmaceutical industry involvement and influences in decision making, and disparities in pricing. Therefore, in order to improve collaboration between stakeholders, transparency, communication and accountability must be further addressed.

As described by participants, situations where the decisions to have many therapeutic choices available for treatments were perpetuating constant drug shortages. This was resolved through multi-lateral discussions that encouraged prescribers to prioritise their choices, in order to ensure supply of the treatments that were critical for the majority of their patient population. Stakeholders acknowledged that concessions due to financial restrictions, allowed decision makers to establish pathways and management strategies that facilitated consensus amongst stakeholders. While these tough decisions cannot align for all individuals' needs; decision-makers, including governments, industry, health providers and consumers, must responsibly support and sustain the health system. In accordance to improving collaborative alliances, linking this to communication pathways and understanding of the supply chain may facilitate acceptance of these decisions.

2.4.3: Strengths and Limitations

This study described the views of multiple stakeholders from a wide range of countries and regions worldwide. While it explored global perspectives, it did not represent views from every country and sector. For example, public and private procurement agencies, as well as wider range of health work force staff who also provide consumers medicines (e.g. nurses and pharmacy technicians), were not included in this study but could be considered in future investigations. In line with qualitative methodology, this study was not intended to be representative of the global population. Rather, an in-depth look at the issues considered by international key opinion leaders and the context of their roles and environments were explored and compared. This study included perspectives from multiple disciplines, in both developed and developing countries.

Recruitment of global participants proved to be challenging and time consuming as leaders were often very busy and unavailable for correspondence or participation, compounded by coordination of different time zones. This study acknowledged that some participant views were of international stakeholders that resided in high income countries, but provide support and training in developing countries. Therefore, they may have applied their paradigm onto these settings, rather than culturally developed. Future investigations within regions or a country context may provide understanding of different cultural and social interactions between stakeholders. Furthermore, future research may explore shared priorities and practical collaborative approaches or models.

2.5 CONCLUSION

This was the first study to explore the management of essential medicines from a broad range of stakeholder views involved in both therapeutic decision making and logistics management. Furthermore, it was also one of very few studies to include a HIC context. It showed that the complex global pharmaceutical supply chain was vulnerable to shortages and crisis. Findings also revealed there were more similarities than differences between health systems in accessing medicines in a vulnerable supply chain. Results showed the concepts of EMLs had relevance to HICs in promoting multi-stakeholder engagement. In line with Hogerzeil (Hogerzeil 2004), no country has unlimited resources. Therefore, value was demonstrated in aligning medicine selection decisions with procurement strategies. Results highlighted the need for engagement and accountability by stakeholders to involve integrative and transparent strategies. This study showed that global and national strategies needed to improve communication, supply chain management capacity, information sharing, harmonisation of roles between stakeholders, and collaborative alliances. Therefore, further investigation was needed to establish a clear understanding of what shared priorities were foundational to facilitate collaboration between stakeholders that ensured utilisation and access to essential medicines.

CHAPTER 3

QUALITATIVE INTERVIEWS EXPLORING WHAT MAKES MEDICINES ESSENTIAL FOR KEY STAKEHOLDERS IN A HIGH INCOME COUNTRY

CHAPTER 3- QUALITATIVE INTERVIEWS EXPLORING WHAT MAKES MEDICINES ESSENTIAL FOR STAKEHOLDERS IN A HIGH INCOME COUNTRY

3.1: INTRODUCTION

The review of the literature in chapter one demonstrated there was inequality of access to essential medicines. On the other hand, EMLs have been shown to provide reliable evidence to guide reimbursement decisions, guide education and training, and be useful tools to promote advocacy to influence policies and lower prices of medicines for individuals and the population. However, findings showed variation of patient access to essential medicines at the health facility level. EMLs have not been strictly adhered to at the prescribing level due to the expanded scope of patient needs, and fragmented decision making and procurement practices. This has contributed to drug shortages, which have made guaranteeing supply of medicines challenging. Furthermore, problems with access to essential medicines have been mainly examined in LMIC, and few studies have explored access in HICs, which also experience access challenges in rural and remote areas, such as in Australia. Similarly, primary studies in the area of EMLs have predominantly applied quantitative methods. Few qualitative studies have been conducted to explore the different influences between stakeholders involved in medicines decision making, which caused the inequality of access to essential medicines.

Findings from chapter two revealed that there were similarities between health systems in accessing medicines in a vulnerable global pharmaceutical supply chain. It also demonstrated that there was reason to believe that stakeholders involved in therapeutic decision making and logistics management of the supply chain were unwilling to collaborate. Yet at the same time, their collaboration was necessary to align medicines selection with procurement management.

In line with Hogerzeil (Hogerzeil 2004), although the Essential Medicines List (EML) concept was rarely studied in high income country settings, no country has unlimited resources. Therefore,

there was relevance, in a country like Australia, to explore how the EML concept may be used to promote access to medicines through multi-stakeholder engagement. In particular, the drug shortage situation requires transparency and stakeholder engagement in order to share information and solutions between stakeholders. Therefore, further investigation was needed to understand what factors were foundational to facilitate collaboration between stakeholders to prevent and manage access to medicines.

The issues discussed in the previous chapters have demonstrated fragmented application of the EML concept between a large number of stakeholders, and continued challenges and inequality to accessing essential medicines. Furthermore, essential medicines studies have continually been examined in LMICs, and few have explored the essential medicines access situation and/or solutions to access challenges in HICs. Therefore, this led to the study outlined in chapter three, to explore the perspectives of a diverse group of stakeholders engaged in medicines decision making around what constitutes an 'essential' medicine, and how the EML concept functions in a high income country context (Australia).
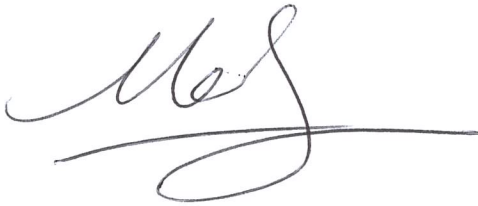
This chapter, published in Plos One, a peer reviewed journal, showed that there were differing views of what medicines were deemed essential between stakeholders. Furthermore, these different views also contributed to tensions between stakeholders and aversion to some collaboration. The notion of essential becomes more fragmented and complex, when moving from the health system perspective towards the point of care, where there are variable and broader patient needs. Since stakeholders held different views of what was considered essential, this reflected inconsistent management of essential medicines throughout the supply chain and willingness to collaborate. These issues will continue to perpetuate the drug shortage and access to medicines situation, and calls for innovative and cooperative approaches to managing a sustainable global supply chain.

3.2: Essential Medicines in a High Income Country: Essential to Whom?

Author Contributions:
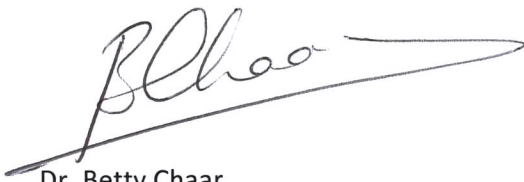
Mai Duong (MD), Timothy F Chen (TFC), and Rebekah J Moles (RJM) conceived and designed the qualitative study. MD conducted the interviews, collected the data and conducted the data coding. Betty Chaar (BC) contributed to final stages of coding. MD, TFC, RJM, and BC analysed the data. MD drafted the manuscript. TFC, RJM, and BC reviewed and approved the final version for submission.

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RESEARCH ARTICLE

Essential Medicines in a High Income Country: Essential to Whom?

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Abstract

Objective

To explore the perspectives of a diverse group of stakeholders engaged in medicines decision making around what constitutes an "essential" medicine, and how the Essential Medicines List (EML) concept functions in a high income country context.

Methods

In-depth qualitative semi-structured interviews were conducted with 32 Australian stakeholders, recognised as decision makers, leaders or advisors in the area of medicines reimbursement or supply chain management. Participants were recruited from government, pharmaceutical industry, pharmaceutical wholesale/distribution companies, medicines non-profit organisations, academic health disciplines, hospitals, and consumer groups. Perspectives on the definition and application of the EML concept in a high income country context were thematically analysed using grounded theory approach.

Findings

Stakeholders found it challenging to describe the EML concept in the Australian context because many perceived it was generally used in resource scarce settings. Stakeholders were unable to distinguish whether nationally reimbursed medicines were essential medicines in Australia. Despite frequent generic drug shortages and high prices paid by consumers, many struggled to describe how the EML concept applied to Australia. Instead, broad inclusion of consumer needs, such as rare and high cost medicines, and consumer involvement in the decision making process, has led to expansive lists of nationally subsidised medicines. Therefore, improved communication and coordination is needed around shared interests between stakeholders regarding how medicines are prioritised and guaranteed in the supply chain.

Conclusions

This study showed that decision-making in Australia around reimbursement of medicines has strayed from the fundamental utilitarian concept of essential medicines. Many stakeholders involved in medicine reimbursement decisions and management of the supply chain did not consider the EML concept in their approach. The wide range of views of what stakeholders considered were essential medicines, challenges whether the EML concept is out-dated or underutilised in high income countries.

Introduction

The concept of "essential medicines" dates back to military tradition, in which therapeutic supplies (such as penicillin) were essential to be carried by soldiers, field medics, and camp infirmaries, into combat zones. This was also applied to the rationalising of therapeutic restrictions necessary during wartime economy [1]. Ensuring access to essential medicines has been considered a basic human right, in line with access to food, water, shelter and education [2]. The Essential Medicines List (EML) was introduced by the World Health Organization (WHO) in 1977, as a core list of 186 pharmaceuticals deemed necessary to manage the disease burden and basic health needs of a population (Box 1) [1,3]. Today, the WHO's Model List of Essential Medicines (WHO EML) includes 409 active substances, is updated every two years, includes low and high cost medicines, and is applied to all income settings in 156 countries [4–6].

Nearly forty years since the introduction of the WHO EML, few studies have investigated the impact of EML policies on access to medicines [7,8]. Although the EML concept appears simple, it can be complex to implement and maintain. Therefore, the intention of having access to essential medicines within the context of a functioning health care system remains a work in progress for many countries [6]. Challenges in managing EMLs are most apparent in low-to-middle income countries (LMICs), compared to high-income countries (HICs) with sophisticated health care systems and national health insurance schemes [9,10]. Furthermore, the Access to Medicines Gap reported by the WHO states that one third of the world's population still does not have access to medicines, which rises to up to half of the population in some LMICs [11,12].

A study by Cameron et al [9] showed that despite national EML policies, LMICs still experience low availability of generic medicines and high prices paid by consumers. Within LMIC settings these challenges are further complicated by scarce resources, limited availability and substandard and/or counterfeit products which pose safety risks to consumers [9,13]. Meanwhile, studies have also shown discrepancies between the WHO EML and national medicines lists in middle to high income countries [14,15]. Whilst disparities exist between how countries

> ## Box 1. The WHO Definition of Essential Medicines [3]
>
> "Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative cost effectiveness. Essential medicines are intended to be available within the context of a functioning health systems at all times, in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford."

amongst colleagues or professional organisations in the area of quality use of medicines, medicines policy, medicine distribution, procurement management, manufacturing, or health economics. Most participants had professional backgrounds as physicians or pharmacists. However, consumer representatives, chief executive officers, supply chain managers, and health economists were also included. Some had broad experiences across multiple and overlapping sectors, and/or had international experience working with EMLs in LMICs.

In-depth face-to-face, teleconference and Skype interviews were conducted with participants. Interviews were conducted prior to the 19th WHO EML, published in May 2015 [4]. Audio recordings of the interviews were de-identified, transcribed verbatim and secondary verification of the transcripts was conducted to ensure accuracy. De-identified supplementary field notes were included in the data analysis. Interviews were conducted until thematic saturation was achieved (when several participants repeated similar or recurrent concepts in their response), as described by Bazeley [32]. Interviews lasted a median time of 63 minutes (IQR: 50–71).

Transcripts and field notes were imported into the qualitative analysis software program N-Vivo 10 for coding and data management [33]. Sequential analysis was used to explore relevant issues according to participants' responses [34]. A grounded theory approach was applied in data analysis to extract themes and key concepts using iterative constant comparative techniques [35]. The grounded theory approach is a well-established research method which has been widely accepted and supported as a high standard of analysis used in interpreting and reporting qualitative research [32,35–38]. Accordingly, open, axial and selective coding methods were used to identify and interpret topics, themes, and concepts [32].

One researcher independently conducted the open coding thematic content analysis to identify themes and concepts, followed by two researchers conducting axial coding together that was validated by the rest of the research team. Final selective coding was performed as a team. While the initial thematic content analysis was performed by one researcher, the continuous consultative approach offered reflexivity and explored relationships between these themes and concepts. Results derived from the grounded theory approach were applied to the comprehensive theory of collaboration to build a conceptual model [39]. As described by Patton [37], reflexivity of data collection, interpretation and analysis was offered by the researchers' broad experiences working across multiple pharmacy, patient care and administrative settings, with international experiences in both HICs and LMICs. Participants were offered the opportunity to validate the accuracy and interpretation of their views expressed in selected quotes.

Results

Participants had a broad range of views on the notion of what is meant by an "essential" medicine. Three main concepts were derived from the views of multiple stakeholders on what constituted an essential medicine and how the EML concept applied in the Australian context. Table 1 illustrates the corresponding quotes reported in the results.

1. The definition and function of an EML in Australia was interpreted differently amongst stakeholders

All participants considered access to essential medicines as a basic human right that should be upheld by society [Q1]. However, most participants noted that in principle, the notion of an "essential" medicine in a HIC like Australia has evolved in terms of the definition and intended application of an EML [Q2]. Some participants considered the reimbursement of medicines through the Australian PBS was akin to a functioning EML [Q3]. However, many participants argued they could not distinguish between reimbursed medicines and essential medicines [Q4]

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Table 1. Stakeholder Comments on the Aim and Function of an EML in Australia.

Concept	Significance	Quotations
1) The definition and function of an EML in Australia is interpreted differently amongst stakeholders.	Access to essential medicines is a basic human right	[Q1] "No one should live with infection, serious pain, {or} a disability that can be treated. The essential elements of healthcare should be available to everyone whether you live in rural Australia, the city, on a good wage or without a job. Everybody has a right to that basic level of healthcare. That includes access to drugs." (Participant 31- Consumer)
	The notion of an "essential" medicine has evolved	[Q2] "When the EML was created, it was about the aspirin (s), {and the} penicillins. . . things that really were going to make a difference. These days, it's no longer the case. You have to consider is this good value for money? I think the essential medicines list has evolved and changed. (Participant 25- Academic)
	National reimbursement of medicines through the Australian PBS is a functioning EML	[Q3] "Ours {PBS list} is bigger than the WHO list, but that's appropriate for a wealthy country like Australia. . . yet it certainly does only encompass a fraction of all the drugs available. It {the PBS} is a limited list, selected on the basis of diseases in the country and cost effectiveness, and that's the principle of the WHO list."(Participant 22-Government)
	There lacks a clear distinction between reimbursed medicines and essential medicines.	[Q4] "I would like to think {the PBS} is an EML, otherwise why are we funding them? One of the things we need to do better in Australia is to remove drugs which have been superseded by other drugs as far as their effectiveness or cost effectiveness is concerned." (Participant 30-Consumer)
		[Q5] "You tend to get a wish list, and then it becomes difficult to sort through what really is essential and what's would be nice to have. (Participant 23- Non-profit)
	An EML can support stakeholders to sustain fundamental health services.	[Q6] "Today, the EML is the PBS by default. It's far from essential. . . When securing supplies, we really need to identify what is essential, and why it's essential. If it's not essential then acknowledge that it's not. So that in my day-to-day practice, drugs that I rely on to keep patients alive are available." (Participant 6, Healthcare Provider)
	Focus on medicines cost and cost-effectiveness diverts from the notion of essential	[Q7] "The WHO defines essential medicines in such a way that cost effectiveness is one of the criteria. I think that's a perversion of the idea of an essential medicines list. A medicine is intrinsically essential. You either need it or you don't. The cost of that medicine is not a dimension of your need or the potential benefit you may derive from that medicine." (Participant 14– Government)
2) The selection criteria of medicines and the context to which the EML concept is applied are dynamic variables which influence decision making.	A medicine is essential at the point of care for the individual	[Q8] "{Essential medicines} are life-saving, {or} enable management of a difficult, chronic condition. The individual consumer of course wants access to the drugs which will help their individual conditions and needs." (Participant 30- Consumer)
	A reimbursement system assesses cost effectiveness and additional benefit of a medicine for some individuals not the essential need of a medicine for a population.	[Q9] "The PBS is different, because they're not essential by definition. They are {medicines} that have been proven to be cost effective and the government is willing to pay to give their citizens access to these medications. Some could be lifesaving, high-cost drugs, and then that's a different program. The structure in a country like Australia is different because it's how much you're willing to pay for an extra innovation. So the concept is different from an EML." (Participant 25-Academic)
	Perception that an EML is only used in low middle income settings	[Q10] "The danger is that you end up saying that an EML is what less well-off countries have and reimbursement lists are what wealthier countries have. "(Participant 20-Academic)

(Continued)

Table 1. (*Continued*)

Concept	Significance	Quotations
	The supply of essential medicines is vulnerable to disruptions in all country settings.	[Q11] *"We live in a complex world where some pharmaceutical supplies are not guaranteed to any nation. There's a lot of politics and economics involved in healthcare decisions that are not necessarily directed at mutual utilitarian benefits of pharmaceuticals, in terms of patient outcomes. But having a list of essential medicines acknowledged can help direct our society to develop infrastructure and supply chains to protect the most important medicines."* (Participant 6, Healthcare Provider)
	Stakeholders involved in providing medicines in the supply chain prioritise medicines according to different principles	[Q12] *"1) Medical relevance. Is this product a life-saving {medicine} versus {a medicine for} long-term disease improvement {or} symptomatic relief issue? The more life-saving {the medicine}, it becomes more essential. 2) Demand. If {a medicine} has either a sporadic or responsive demand, it becomes an essential product we need to plan for. Flu vaccines are an essential medicine. It improves health outcomes, but because {of} it's sporadic demand you need to plan for its use. 3) Supply. Who else can deliver this product? If there's four competitors of a product we don't see it as an essential medicine as a pharma company. It may be an essential medicine for a practising pharmacist but that's where the differentiation starts to occur. 4) To deliver value to shareholders {as} a publicly listed company {and to} sell {medicine} at a positive margin. Some items within our portfolio we sell a lot of which makes a lot of money, and therefore it's a commercially essential medicine."* (Participant 8 – Pharmaceutical Industry)
3) Tensions amongst stakeholders are created by differing views on the function of an EML and conflicting interests surrounding the selection of medicines.	The notion of essential medicines is highly confounded.	[Q13] *"What makes a drug essential? You can lay down some criteria, but they're not absolute and definitive. You can prioritise and heavily weigh them with a declining degree of weight. Then there's a transition between at what point {is} something essential or non-essential. That is highly confounded. {Clotrimazole for treating} candidiasis is an example. Not essential. Damn! Who says it's not essential? Someone has made that determination —in this case, other than the consumer. The government made the decision they were available over the counter, therefore we {society} wouldn't pay for them. Does that make them non-essential? Or they're available over the counter? What is the link between subsidy and essential medicines?"* (Participant 11-Government)
	The influence of cost containment is interpreted differently amongst stakeholders. Lowering costs of some medicines allow for expansion of the PBS to include more medicines	[Q14] *"One of the reasons the industry has supported all the price cut policies they renegotiated with government. . . is that they are designed to drive down the price of old drugs so that the health system could afford to list the new drugs coming through in the future. The Government {has} got the savings, now we can afford to bring {other} things on."* (Participant 5, Pharmaceutical Industry)
	The PBS keeps medicine costs affordable for Australians despite high prices set by pharmaceutical companies	[Q15] *"The PBS has helped {so Australians} can afford all these new medicines. Drug companies might complain that the {price listed on the} PBS is too cheap, that they can't afford to sell medicines to {consumers at such a price}. It doesn't seem to stop them from registering their products and listing them on the PBS."* (Participant 1-Healthcare provider)
	Demand for improved transparency around the pharmaceutical industry's role and influence in the decision making process	[Q16] *"{The PBS has} got too many alternatives. . . You have to look at the make-up of the Pharmaceutical Benefits Advisory Committee (PBAC). I believe the current PBAC membership has the necessary expertise and looks appropriately comprehensive. {But} drug companies can exert influence directly or through consumers who then pressure MPs (Members of Parliament). I believe they could be under a lot of pressure to put new things on the list which probably should not be on the PBS. It is important that there are mechanisms to deal with that pressure."* (Participant 27,Academic)

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[Q5]. While some believed an EML approach could support stakeholders in the supply chain to sustain fundamental health services [Q6], one participant highlighted that the consideration of a medicines' cost and cost-effectiveness were contentious issues that undermined the notion of essential [Q7].

2. The selection criteria of medicines and the context to which the EML concept was applied were dynamic variables that influence decision making

Some participants reflected the selection of medicines for reimbursement has been increasingly driven by consumer needs [Q8]. Furthermore, some participants explained reimbursement decisions were driven by cost effectiveness and additional benefit of a medicine for some individuals rather than the essential need of a medicine by the population [Q9]. Many participants found it challenging to apply the concept of EML to the Australian context because EMLs were perceived to be useful for resource scarce settings [Q10]. However, some participants regarded essential medicines as part of a complex pharmaceutical supply chain. Even in HICs, access cannot always be guaranteed [Q11]. One participant described the characteristics of medicines that are categorised as "essential" by the pharmaceutical industry within the supply chain [Q12].

3. Tensions amongst stakeholders were created by differing views on the role of an EML and conflicting interests surrounding the selection of medicines

The selection and supply of reimbursed medicines were complex issues. One participant reflected that the notion of essential medicines was highly confounded [Q13]. The influence of cost containment was interpreted differently amongst stakeholders. Some participants thought decisions about whether a medicine was listed on the PBS included consideration of cost containment by lowering prices of generic medicines in order to expand the PBS to list new medicines [Q14]. While some participants felt that despite high prices set by pharmaceutical companies, the PBS has helped keep medicine costs affordable for Australians [Q15]. Many participants encouraged more transparency around the pharmaceutical industry's role and influence in the decision making process [Q16].

Discussion

This study found that stakeholders had a broad range of views surrounding the application and/or relevance of the EML concept within the Australian context. The findings illustrated a diversity of perspectives amongst stakeholders, often reflecting their position within the health care system. Views held by consumers and health professionals with respect to what was "essential" and what medicines should therefore be accessible and reimbursed, were sometimes in contrast to the views of supply chain managers or policy makers. This demonstrated the tussle between perceptions of an EML based on a utilitarian approach in the health system for a population versus an EML established to meet individuals' needs.

Stakeholders' opinions of what constituted an 'essential medicine' differed depending on whether they were being tasked with making decisions for the population or they were considering a medicine to be 'essential' for an individual. From a consumer's perspective, a medicine is considered essential at the point of care. Education can empower consumers to request access to medicines they deem essential. Individuals want access to the right drug, at an affordable price, of safe quality and available at all times within close proximity [40]. On the other

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hand, policy makers within the health system consider medicines to be essential based on a country's priority health care needs and cost effectiveness, in order to facilitate wider access to medicines by the population [12]. Although the notion of 'essential' for an individual or health system is often used interchangeably, results showed that the two perspectives are often divergent and therefore applied as different concepts.

While participants in this study supported the EML concept and were able to explain its general function, most found it difficult to determine what constituted an essential medicine due to the confounding nature of individual or utilitarian needs, as described above. Historically, an EML was once a basic formulary of survival and emergency medicines that adhered to utilitarian principles [41]. Today, the EML concept has evolved, influenced by human rights' movements, disease specific epidemics and societal values, to become a much more complex list used to save and also improve the quality of life for many more individuals [1,41]. Furthermore, the evolution in pharmacotherapy from prescribing for a disease to prescribing for an individual includes consideration of those with multiple conditions. This could mean that standard treatment guidelines, which are usually limited to the treatment of a single condition and informed by data gathered in clinical trials, may not be applicable for patients with multiple co-morbidities. Adding to this complexity is the continual development of pharmaceutical products in the market, leading to more choices and alternatives available. This expansion and evolution of the "EML concept" has led to the development of extensive lists of publicly subsidised medicines in HICs, such as Australia. These lists often have multiple pharmacotherapy choices available to manage conditions [42,43]. While in some health systems, lists can be sub-categorised using "vital", "essential", or "non-essential" medicine (VEN) models of procurement to identify priority medicines [44]. In line with this trend of list expansion, the 19th WHO EML includes a range of high cost medicines that address priority diseases in a variety of settings [4]. For example, Trastuzumab in breast cancer and Sofosbuvir for Hepatitis C [4,5]. Therefore, in HICs like Australia, it remains unclear if the decisions to add and manage medicines on these lists still adhere to the foundational utilitarian principles that were once crucial to its inception.

Study participants described the PBS accommodated broader individual needs than EMLs. Some highlighted that consumer engagement in the decision-making process has contributed to the wide breadth of the PBS to include sometimes rare and costly medicines to meet individual needs and expand access. The tussle between policy makers and consumer driven decisions may be explained by the Comprehensive Theory of Collaboration which describes three types of self-interest: shared, differing, and opposing [39]. **Shared self-interests** provide clear conditions for a health system to identify and manage national priority medicines. For example, the utilitarian-type public health program around influenza pandemic planning manages and ensures continued supply of vaccines and medicines to all Australians. Meanwhile, participants' discussed how **differing interests** contributed to the wide breadth of reimbursement under the PBS, which can include multiple options within the same drug class. Lastly, tensions between stakeholders may result from individuals having **opposing interests**. Participants described these tensions in the deliberations involved in the selection of high cost medicines for reimbursement, and negotiations to lower prices of generic medicines. For example, cost containment may prevent few individuals from accessing rare high cost medicines through public subsidised funding. At the same time, pharmaceutical companies may have opposing interests to governments and consumers regarding pricing of their medicines, and may be pressured to lower the cost of products in order to have them listed and utilised. This demonstrates how individuals' opposing and differing interests contribute to the expansion and costs of reimbursement lists in HICs, in contrast to shared (utilitarian) interests around priority medicines.

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It is often assumed that an EML ensures access to prioritised medicines. Therefore, stakeholders perceived that applying the EML concept provided access to affordable medicines to individuals and the health system. Yet, even in a HIC like Australia, access to medicines can be hindered. Two examples of vulnerabilities highlighted by stakeholders include unforseen drug shortages and high costs of medicines. Despite reimbursement, essential medicines are part of a complex global supply network, in which supply cannot always be guaranteed during unpredictable drug shortages [45–47]. This was demonstrated during worldwide shortages of injectable benzyl penicillin in 2011 and morphine in 2013, causing much strain on the health system and consumers [48,49].

Secondly, participants described the affordability of medicines for consumers and health systems was a growing concern as pharmaceutical expenditures continue to rise [17]. Health systems may need to pay high prices for these medicines and governments must make difficult decisions as to how these medicines will be paid for. As a national reimbursement scheme, the PBS negotiates lower prices with manufacturers to provide, "timely access to medicines that Australians need, at a cost individuals and the community can afford" [26]. There are a range of therapeutic options available through the PBS, including rare and high cost medicines. Additional arrangements provide funding and restricted supply for medicines under: the Life Saving Drugs program, Section 100 (S100) program, or Special Access Scheme for rare or specialised conditions [50–53]. Despite this, Australia still pays some of the highest prices for generic medicines compared to other countries, and up to twenty times more than its neighbouring country New Zealand, where sole-sourcing and pooled procurement strategies have been applied to obtain lower prices [17,54,55].

Furthermore, consumers' inability to afford out-of-pocket expenses can hinder access to medicines, sometimes leading to "catastrophic drug costs" [56,57]. Although Australia is a HIC, there is disparity of wealth across the population [58]. Therefore, whilst catastrophic drug costs are rare due to PBS subsidisation, out-of-pocket expenses (ie. co-payment of $37.70 AUD for general patients in 2015 [59], which increases annually), can become too much for some individuals to afford, especially for those on regular multiple medicines [17,60]. Meanwhile, some medicines deemed essential to individuals and listed on the WHO EML, but may not be reimbursed under the PBS, leading to out-of-pocket payments by consumers. It should be noted that in Australia, PBS listed medicines are indirectly paid for by all individuals through the government income-based taxation system. Additionally, individuals requiring medicines can pay for them through direct out-of-pocket payments (usually for medicines not listed on the PBS or those that are priced under the co-payment amount), or through co-payments for government subsidised medicines. Some may also receive partial reimbursement for high cost, non-listed medicines through private health insurance. Similar to Cameron et al. [9], HICs also face challenges to guarantee supply of generic medicines and high prices. Therefore solutions and approaches in HICs may provide useful to LMIC settings.

All participants acknowledged the PBS as a national reimbursement scheme generally effective at meeting Australians' health needs. However, the issues raised above, led them to explore strategies from the EML concept to prioritise medicines in the supply chain. In line with Hogerzeil [6] and Wood & Gray [39], applying collective (utilitarian) interests to identify a core list of medicines needed to maintain the basic functions of a health system, can improve resilience to supply disruptions and manage rising medicine expenditure. Furthermore, in a US study, Millar et al. [61] found that WHO EML medicines appeared on most Preferred Drug Lists (PDLs), suggesting that the EML could function as a core list for PDL development to guide procurement and decrease prices of medicines.

The comprehensive theory of collaboration was applied as the underpinning theory to explain the variability in the notion of what is meant by an essential medicine. "Self-interests"

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in collaboration surrounding EMLs influence stakeholders' views of what they deemed essential. Hence, multiple factors may influence these self interests which guide individuals to choose medicines, as represented in S1 Fig. This conceptual model supports that an EML is used at a health system level, for most people, most of the time. However, for individuals at the point of care with many options, an EML is often viewed as not relevant. Although, a specific drug on the EML may be appropriate. The layers in S1 Fig demonstrated the influence of self interest at different levels of care. As one moves through the levels of the health system from government policies towards the point of care, the notion of self-interest becomes more focused on the individual and less utilitarian. This phenomenon has contributed to the expansion of reimbursement lists. In contrast, when a medicine becomes unavailable, where there are no alternatives or options are unaffordable for individuals or governments, then this focus shifts back towards shared priorities in order to ensure the delivery of health services. Hence, this conceptual model demonstrates the concept of EML becomes fragmented as it moves through the pharmaceutical supply chain towards the point of care.

A health system is unable to meet every need of all individuals within a population. Thus, S1 Fig illustrates the disparity between health systems that focus reimbursement schemes on utilitarian population needs versus meeting the expanding needs of individuals. This is most apparent between LMIC and HIC approaches to reimbursing medicines. When consumers absorb the difference in out-of-pocket medicine costs outside of government reimbursement programs, it can sometimes become exorbitantly unaffordable [57]. Therefore, consumers' opposing interests remaining outside population wide reimbursement schemes may need alternative funding assistance or education programs to address ongoing tensions.

Strengths and Limitations

The results in this study were not meant to be generalisable. Instead, the use of qualitative methodology allowed researchers the opportunity to explore issues facing decision makers when creating national medicines lists. The strength of this study lies in offering an in-depth exploration of a broad range of key stakeholder views through rich qualitative data. This study gathered the perspectives of leaders and senior management throughout the continuum of a complex supply chain involved in decision-making surrounding medicines management in HICs. The study however, did not explore perspectives of primary health care workers, which should be pursued in future studies. It showed there were a variety of views as to what the term EML really means and how it relates to policy in a HIC context. While not included in the scope of this study, future studies could examine how this can be applied in LMICs. Additionally, future studies could examine further each individuals work environment and its effect on their views.

Conclusions

The EML concept is simple, idealistic, and has been widely received. However, this study showed that the notion of "essential" is not implicit. Although beneficial in theory, Australian stakeholders struggled to identify how the EML concept functioned in practice. In Australia, decision making around reimbursement of medicines has strayed from the fundamental utilitarian concept of essential medicines. Instead, focus is on cost-effectiveness of new technologies and meeting unmet individual needs through expansive reimbursement lists. Interestingly, many of those involved in medicine reimbursement decisions and management of the pharmaceutical supply chain did not consider the EML concept in their approach. Moreover, the results of this study challenge for whom we consider essential medicines for, and if the term essential is currently appropriate. Therefore, this challenged whether the EML concept was

out-dated or underutilised in HICs such as Australia. As medicine expenditures continue to rise worldwide and global drug shortages remain frequent and problematic, the EML concept can potentially play a role in managing health resources. Therefore, further investigation is required to address innovative ways to apply EML concepts in HICs to support population wide access to prioritised medicines, while strengthening collaborations between pharmaceutical supply chain stakeholders. Transitioning the EML concept from policy to practice continues to be a work in progress.

Supporting Information

S1 Fig. Conceptual Model. A core list of medicines reflects shared stakeholder interests to support the fundamental basic needs of a country's health system. Bearing in mind that all medicines on the WHO EML are not assumed to be included on a country's EML, since they are adapted to meet each health system's needs. In contrast, broader reimbursement schemes have wider inclusion of differing and opposing interests between stakeholders. The extent of out-of-pocket expenses individuals may incur beyond the shared priorities supported by the health system are illustrated by the difference in area from the outer layer. This model does not take into consideration that a health system with broader reimbursement may also be at risk of reimbursing inappropriate medicines. Also, countries without a national EML (ie. the US) are not illustrated in this model despite high out-of-pocket expenses, due to the high variability of private insurance schemes. And while some health systems do not have EMLs, people can still access medicines if they are willing and able to pay-out-of pocket or have alternative funding assistance available such as private insurance.
(TIF)

S1 Text. Qualitative Semi-structured Interview Protocol.
(PDF)

S2 Text. COREQ-32 item checklist for reporting qualitative studies.
(PDF)

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Author Contributions

Conceived and designed the experiments: MD TFC RJM. Performed the experiments: MD. Analyzed the data: MD TFC RJM BC. Wrote the paper: MD TFC RJM BC. Collected the data and conducted the coding: MD. Contributed to coding: MD BC. Wrote the paper: MD. Provided comments to guide the writing of the paper: TFC RJM BC.

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Figure 3.1: Conceptual Model

Consumer Need

High Income Country Reimbursement Scheme
(e.g., Pharmaceutical Benefit Scheme (PBS))

Low Middle Income Country EML

Core List of Medicines
(e.g., WHO EML Core list)
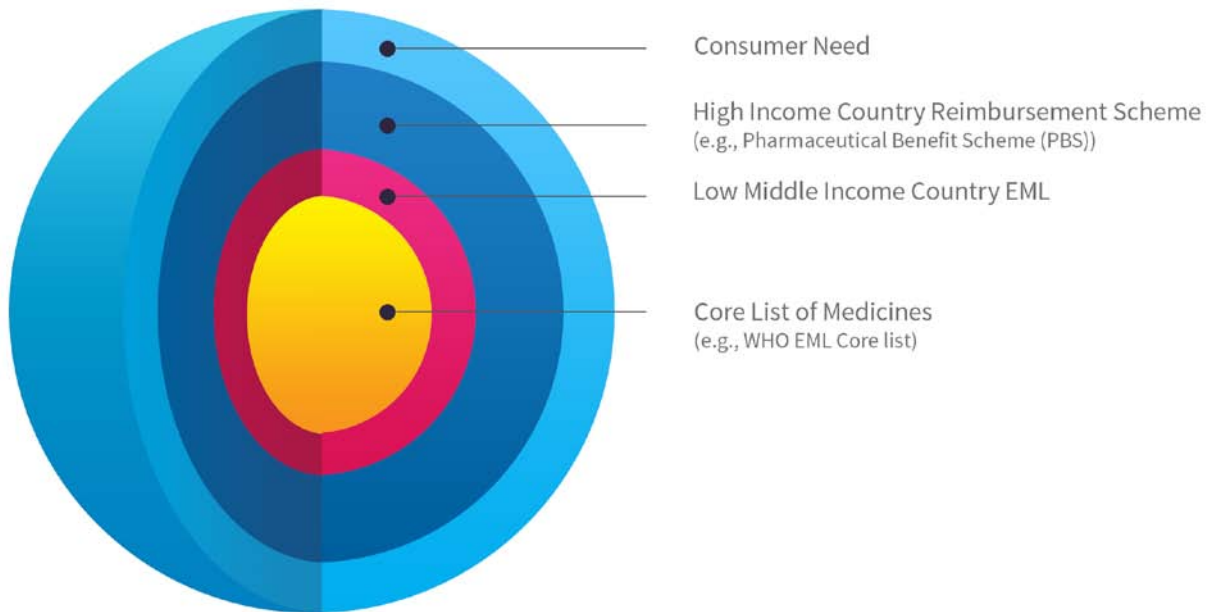
CHAPTER 4

DISCUSSION AND CONCLUSION

CHAPTER 4- DISCUSSION AND CONCLUSION

DISCUSSION

The body of research reported in this thesis suggests that there are different perceived functions of Essential Medicines Lists (EMLs). These perceived functions seem to be stratified depending on whether the decision making context was at a health systems level or at an individual level (i.e. for a patient at the point of care). The differing views of diverse stakeholders regarding access to essential medicines, highlighted within this research, showcased the complexities of decision-making processes involved in developing and managing EMLs.

In contrast to the work conducted by Holloway & Henry (Holloway and Henry 2014) and Cameron et al. (Cameron et al. 2009), this study explored a broader context of stakeholders involved in decision making processes affecting access to medicines. This involved stakeholders from government or policy decision makers through to healthcare providers and consumer groups; as well as stakeholders involved in the logistics of the pharmaceutical supply chain, such as manufactures and wholesalers. It offered a variety of opinions regarding what constituted an essential medicine and how an EML for reimbursement and procurement should be utilised. Building on previous literature (Hogerzeil 2004, Millar et al. 2011, Patel and Pichardo 2012, Meteos 2013), this research revealed that the challenges of balancing individual choice and system priorities requires innovative and plausible collaborative approaches to achieve concessions that minimize supply disruptions and meet individuals' health needs.

It was found that the notion of an EML was usually perceived as a systems concept, intended as a reimbursement list to increase access to affordable therapeutic options based on utilitarian population health needs and evidence based guidelines (WHO 2003). The literature review supported that EMLs have provided effective advocacy and evidence at the systems level to select

and list medicines with the intention of trying to improve access for a population (Mahmić-Kaknjo and Marušić 2015, Burapadaja and Chinawong 2010, Gitanjali and Manikandan 2011, Cheraghali and Idries 2009, Cheraghali et al. 2004b). However, EML studies have mainly focused on low to middle income countries (LMICs), and little research has examined their use in high income countries (HICs), as discussed in chapter 3 (Duong et al. 2015, Kadić et al. 2014, Jommi et al. 2013). No country has unlimited resources. High prices paid for medicines and rising pharmaceutical expenditure are challenges across all health systems (Duckett et al. 2013, Bigdeli et al. 2013a, Bigdeli et al. 2013b). Therefore, the importance of applying evidence, experience, communication, and individual choice to decision-making and provision of essential medicines is equally relevant to both HIC and LMIC health systems.

As stated, it has traditionally been the utilitarian approach of the "greatest good for the greatest number of people" (Roberts and Reich 2002), that has driven decision making regarding listing of medicines on EMLs (mainly utilised as national reimbursement lists). This research highlighted however, that this utilitarian approach could often be in contrast to how an individual would define an "essential medicine". Many participants, particularly consumers and health care providers, considered an essential medicine as a medicine that was needed by an individual at the point of care (regardless of cost or listing on a reimbursement list). This is in line with patient-centred care approaches (Greene 2011, Barry and Edgman-Levitan 2012). Adding to the complexity of semantics, the findings from this body of work supported the notion that the EML concept has been evolving away from its utilitarian principles, in order to meet broader individual needs (Greene 2011, Barry and Edgman-Levitan 2012). EMLs have therefore expanded from basic lists of life-saving medicines to reimbursement lists that encompass many medicines for more complex diseases. Hence, balancing this evolution with limited resources has perhaps left many EMLs ambitiously designed to be something to everyone; and therefore, falling short at the

implementation and utilisation phases. This has added to the complexity of the notion of who

stands to benefit most from an EML.

In addition, many participants agreed that the logistic complexities of the pharmaceutical supply

chain, has fed tensions between stakeholders surrounding selection and management of essential

medicines. These findings were supported by the literature review which showed huge variability

of EML policy implementation and suggested EMLs were difficult to use at the point of care due to

different local priorities (Bertoldi et al. 2012, Mori et al. 2014, Dal Pizzol et al. 2010a).

Qualitative interviews however, showed that many stakeholders (particularly health providers

and consumers) valued choice. Some stakeholders stressed that providing more choices could

lead to more difficulty in managing lists requiring more responsibility and accountability.

Conversely, this could allow for more tailored care for individuals as well as contingency or

"backup" options during drug shortages. It was evident that choice seemed directly related to

wealth, with HICs such as Australia possessing many more medicines on their reimbursement lists.

Some qualitative interviews voiced that restricting choice was perceived as taking away an

individual's "voice" or their autonomy to choose and influence decisions. Therefore, multilateral

agreements and communications need to rationalise individuals' choices and the capacity to pay

for those choices. Furthermore, consumer education and empowerment may help individuals

make more appropriate decisions regarding their care based on evidence of effectiveness

balanced with price (Barry and Edgman-Levitan 2012, Patel and Pichardo 2012).

This body of work explored how different health systems focused on or supported priorities of

access through reimbursement (Millar et al. 2011, Wilson 2012, Morgan et al. 2006, Carapinha et

al. 2011, Zerda, Salud and Salud 2002). These examples ranged from the expectation of out-of-

pocket expenses in a free market environment with no EML (e.g. US), to broader (albeit limited)

reimbursement schemes such as those in HICs (e.g. Australia), or to restricted reimbursement and

access in resource limited settings like LMICs with EMLs. In line with Hogerzeil (Hogerzeil 2004), managing limited choices rather than emphasising restrictions was needed as many stakeholders were still of the view that cheap medicines and prioritised reimbursement lists were for poorer countries, and expensive medicines and long reimbursement lists were for richer countries.

A contemporary finding of this work suggests that consumers have a powerful stakeholder voice that can drive pharmaceutical market demand. According to stakeholders, if consumer demand and willingness to pay supported the need for a medicine, it will probably be made available to them. Again this supports the notion that an "essential medicine" is deemed essential to the individual at the point of care, regardless of listing on a reimbursement list. Coincidentally, this draws attention to what sources of information are available to the public and how direct to consumer advertising influences consumers. In some instances, consumers have been successful in lobbying governments to add highly expensive medicines to such lists for rare conditions (Nunn et al. 2009, WHO 2015a, PBS 2015b, PBS 2015a, Edwards et al. 2015, Vargas-Peláez et al. 2014). However, even if lobbying was unsuccessful, many consumers will still access non-reimbursed medicines through out-of-pocket payment if they are deemed "essential" to the individual (Wagner et al. 2011, Phillips 2009, Knaul et al.). It is therefore apparent that reimbursement of medicines has become even more complex with the rise of consumer stakeholder voice in the decision making process.

In short, managing the differences between individual choices and health system priorities has proven challenging. These challenges have been further compounded by the complex, multi-tiered, and elaborate global supply chain (Rossetti et al. 2011). On one hand, complexities such as multiple suppliers, manufacturers, wholesalers, and retailers have been systematically added into the supply chain to offer considerable advantages and resilience in the form of lower pricing, therapeutic substitutions and backup suppliers (Lexchin and Mintzes 2008, Tordoff et al. 2008, Morgan, McMahon and Greyson 2008).   On the other hand, inconsistencies and complex

interactions between stakeholders have made the logistics and timely access to medicines sometimes difficult to achieve (Quilty et al. 2011, Bresser 1988). Thus, communication between systems may be more likely to fail. In such cases, participants described that improved supply chain resilience would entail concessions made by all stakeholders and willingness to pay for contingency planning. That is, system buffers or resilience planning must account for the cost and provision of unpredictable supply disruptions, extra shelf space in pharmacies and warehouses, and national redistribution strategies to reduce waste and expiry to rotate or move around supply; meanwhile, still meeting consumer needs. Strategies to mitigate or prevent all "eggs in one basket" situations must be supported by all stakeholders and considered sustainable, which may be in contrast to current trends towards lean processes to improve efficiency (Bhatia et al. 2013, Sousa et al. 2011).

Gaps and vulnerabilities in the supply chain have risked supply disruptions (e.g. drug shortages) that have threatened patient care and increased costs (Cherici C 2011, McBeath 2012, FDA 2013, Bogaert et al. 2015). It has been cited that improved supply chain management can facilitate access to essential medicines by reducing drug shortages (Bogaert et al. 2015, Gray and Manasse 2012, Quilty et al. 2011). This research found that drug shortages were a common management challenge in both LMIC and HIC settings, which in turn threatened patient care and strained resources. Although governments feel empowered by the ability to negotiate lower prices for medicines, governments and consumers no longer "get a better deal" when medicines supply is not guaranteed (Huff-Rousselle 2012, Tordoff et al. 2008, Cherici C 2011, FDA 2013, Duckett et al. 2013). Therefore, reactivity in the system has resulted in higher incurred costs of medicines, use of resources, and susceptibility to coercion and corruption (Cherici C 2011, Bogaert et al. 2015, FDA 2013, Bevilacqua et al. 2011, Dal Pizzol et al. 2010b, Bertoldi et al. 2012). In response to these challenges, many participants explored the benefits of the EML approach (e.g. applying utilitarian principles to prioritise vital, essential or non-essential medicines) to better manage supply

disruptions or secure high priority medicines within the supply chain (Millar et al. 2011, Hogerzeil 2004). However, this approach would necessitate improved collaboration, communication, transparency and coordination between stakeholders throughout the continuum of the pharmaceutical supply chain and decision making processes (Meteos 2013).

This body of knowledge proposed that addressing medicine supply chain problems demanded improved collaborative alliances. In line with the comprehensive theory of collaboration and Pharma Futures report, management of these supply chain challenges requires collaboration, building strategies, identifying shared priorities and establishing agreements on how to manage different values (Wood and Gray 1991, Meteos 2013). However, according to qualitative results discussed in chapter two of this thesis, the interconnected stakeholder roles and responsibilities lacked cohesion. Furthermore, it also showed deliberate avoidance of some collaborative alliances due to conflicts of interests. Similarly, qualitative interviews discussed in chapter three, demonstrated this caused tensions between stakeholders around the function of EMLs and conflicting interests around the selection of medicines. Additionally, the literature review described financial and ethical barriers to accessing medicines (Akaleephan et al. 2009, Cohen 2006). For example, divergent views on pricing and cost savings of medicines were highly skewed and international trade agreements like the Trade Related Intellectual Property Rights (TRIPS) agreement further contributed to these tensions. In line with the comprehensive theory of collaboration, the research reported in this thesis demonstrated that identifying and understanding stakeholders' self-interests could facilitate solutions involving multilateral agreement and action. This could be achieved through the alignment of selection and procurement of medicines. Hence, challenges to the supply and use of EMLs offer an opportunity to align the values of health system priorities with individual choice.

Strengths and Limitations

This thesis gathered a broad range of views of many stakeholders from multiple levels of the health system. While other studies have focused on one segment of access to medicines, this study offered a rare global overview of the access to medicines framework demonstrated in both the literature review and qualitative interviews. In line with qualitative method objectives, the results of this study were not intended to be generalisable.   Rather, they were able to explore gaps in the literature regarding the influences on access to medicines and report perceived challenges that stakeholders experienced. Furthermore, this unique study highlighted the interaction of different stakeholder's views and gave insight into factors that influenced decision makers surrounding the supply and access to medicines.

Although not all countries, range of health systems, and individual circumstances were represented in this study; it was still able to compare views of stakeholders from many HICs and LMICs through the vast and overlapping experiences of the participants recruited. This study also acknowledged that while participants had rich experiences across different health systems, many were from HICs but worked in LMICs. Therefore, their paradigm of health may have been imposed onto their views of the situation in LMICs rather than culturally developed. Despite this, results showed the views of participants from LMICs were aligned with views of participants from HICs when describing the situations in LMICs. Lastly, complex overlapping stakeholder functions and activities were not depicted in this study. Instead, this was presented as simplistic diagrams and selected quotes to describe major stakeholder roles and challenges. Other specific strengths and limitations have been discussed in previous chapters.

CONCLUSION

This is the first body of research to use a qualitative approach in exploring the global use of EMLs through comprehensive stakeholder views. The divergence of perspectives gathered in this research reflected the complex decision making processes involved in developing and managing

national reimbursement lists. Therefore, findings from this body of work challenged whether the term "essential" was appropriate to describe national lists, and if "reimbursement" lists were more reflective of how lists were used. This research also confirmed that decision making processes around access to medicines are extremely complex. Adding to this complexity, consumer demand for therapeutic choices to accommodate individualised care has resulted in more logistics to manage and pressure decision makers to add medicines to expanding reimbursement lists. This has put increasing pressure on governments to balance what consumer demands they are willing to reimburse with the limited available resources. Therefore, empowering consumers with information to responsibly and safely guide these decisions could direct the provision of medicines within the supply chain.

Findings confirmed that the access to medicine gap continues to be problematic, and explored potential solutions to mitigating supply chain disruptions through multi-stakeholder engagement and EML approaches. This is relevant within the climate of globalisation, economic crisis, political conflicts, and natural disasters (Bhatia et al. 2013). This research also demonstrated that health systems and individuals can look to EMLs to guide advocacy, prioritisation and provision of the most "essential" medicines. Therefore, building on Hogerzeil (Hogerzeil 2004) and Wood and Gray (Wood and Gray 1991), these solutions demand innovative and plausible collaborative approaches to achieve concession that improve supply disruptions and meet individuals' health needs. In brief, it is recommended that all stakeholders must work together to carve communication pathways that encourage and sustain patient-centred care. In line with the Pharma Futures report (Meteos 2013), we recommend improved stakeholder engagement through absolute commitment to participate, increased communication, improved transparency, timely co-ordination of responses, and practical concessions. Furthermore, this research suggests aligning decision making priorities with procurement practices. This should be considered in committee decisions or applied to evaluative measures to determine for whom essential

medicines are for; stratifying the priority for vital, essential and non-essential medicines; how

they are managed and communicated throughout the supply chain; contingency planning to

ensure provision of priority medicines; and consumer communication. In summary, the

challenges in this current climate offer decision makers and supply chain managers a valuable

opportunity to reflect and understand how the current system is functioning, and develop

foundations for improved processes, and innovative and cooperative platforms to interact and

network.

Future Research

Future investigations within regions or a country context may provide understanding of different

cultural and social interactions between stakeholders. Furthermore, future research may explore

how shared priorities identified in collaborative alliances have been successful in providing access.

Additionally, further research could examine each individual's work environments and how that

effects their views. Finally, an extension of this body of work for future investigations could

identify and test causal variables that determine what makes a medicine essential to

stakeholders. This would help identify self-interest variables that could be applied to improving

collaborative alliances and offer insight into how stakeholders weigh evidence, experience,

choice, and political pressure.

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APPENDICES

Appendix A: Narrative Literature Review Checklist (chapter 1)

Narrative Review Checklist

Developed from:
Elsevier. 2016. Information for Authors - Narrative Review Checklist. Journal of the Academy of Nutrition and Dietetics. Available at: http://www.andjrnl.org/content/authorinfo#nar

Section/Topic	#	Checklist	Reported on chapter or page #
TITLE			
Title*	1	Identify the report as a Narrative Review of …	Statement included in Chapter 1: Methods page 5
ABSTRACT			
Unstructured summary*	2	Provide an unstructured summary including, as applicable: background, objective, brief summary of narrative review and implications for future research, and clinical practice or policy development.	Abstract, page xii-xiv
INTRODUCTION			
Rationale/Background	3	Describe the rationale for the review in the context of what is already known.	Chapter 1: Introduction
Objectives	4	Specify the key question(s) identified for the review topic.	Chapter 1: Introduction
METHODS			
Research selection	5	Specify the process for identifying the literature search (eg, years considered, language, publication status, study design, and databases of coverage).	Chapter 1: Methods,
Discussion/Summary			
Narrative	6	Discuss: 1) research reviewed including fundamental or key findings, 2) limitations and/or quality of research reviewed, and 3) need for future research.	Chapter 1: Results Discussion
Summary**	7	Provide an overall interpretation of the narrative review in the context of clinical practice, policy development and implementation, or future research.	Chapter 1: Conclusion

*adapted from the "journal of the academy of nutrition and dietetics" publication standard to thesis format (2016)

**adapted from the discipline of nutrition for medicine

Narrative Overview Rating Scale

Green, BN, Johnson CD, Adams A. 2006. Writing narrative literature reviews for peer-reviewed journals: secrets of the trade. Journal of Chiropractic Medicine.5(3)**:**101-117.

Circle the number that you feel is appropriate for the paper that you are reading:
1 = Absent 2 = Present but not complete 3 = Present and complete
Initial Impression
1 2 3 Does the review appear to be relevant to an issue of interest (18, 30)?

Abstract
1 2 3 Is the specific purpose of the review stated (3, 15)?
1 2 3 Is context for the overview provided?
1 2 3 Is the type of research design stated?
1 2 3 Are the search methods clearly summarized?
1 2 3 Are the important findings clearly discussed?
1 2 3 Are the major conclusions and recommendations clearly outlined?

Introduction
1 2 3 Is the specific purpose of the review clearly stated based upon a brief review of the literature (1, 3, 18, 24)?
1 2 3 Is the need/importance and context of this study established (2, 11, 24)?
1 2 3 Are novel terms defined (10, 29)?

Methods
1 2 3 Were the electronic databases used to conduct the literature searches identified (MEDLINE, CINAHL, etc.) (3, 13, 17)?
1 2 3 Were the search years stated?
1 2 3 Were the search terms stated (3)?
1 2 3 Were standard terms used as search terms, including Medical Subject Headings (17)?
1 2 3 Were the guidelines for including and excluding articles in the literature review clearly identified (10, 18, 22)?

Discussion
1 2 3 Were the results summarized in a comprehensible manner (3, 10)?
1 2 3 Was the critical appraisal of each study the same and reproducible (11, 13, 22)?
1 2 3 Was the quality of the included articles assessed objectively (3, 11, 13)?
1 2 3 Was the variation in the findings of the studies critically analyzed (1, 10, 13, 22)?
1 2 3 Were the meaning of the results addressed (3)?
1 2 3 Do the authors tie in the results of the study with previous research in a meaningful manner (1, 3, 10)?
1 2 3 Were the weak points and untoward events that occurred during the course of the study addressed by the authors (1, 3)?

Conclusions
1 2 3 Was a clear summary of pertinent findings provided (10)?
1 2 3 Were the authors' conclusions supported by the evidence provided (1, 3, 13, 18)?
1 2 3 Were specific directives for new research initiatives proposed?
1 2 3 Specific implications to the practice environment are addressed (3).

References
1 2 3 Are references relevant, current and appropriate in number (11)?
1 2 3 Are all papers reviewed cited in the references (1)?

Overall Impressions
1 2 3 Do the merits of this review of the literature outweigh the flaws?
1 2 3 Were the authors unbiased in their approach to the review (11, 18)?
1 2 3 Will the results of the paper help me in my philosophical or evidence based approach to patient care (11,18)?

Appendix B – Literature on Essential Medicines (chapter 1)

Studies were organised according to the WHO Access to Essential Medicines Framework under

appropriate selection (Table B1), availability and affordability of medicines (Table B2) and quality

of medicines (Table B3). Studies were displayed in order of methodology, country (multiple to

individual countries), WHO region (Europe, Western Pacific, South East Asia, Africa, Americas),

and author. Where some studies evaluated more than one outcome measure, they were

described in one section only. Notably, studies and reviews categorised under multiple countries

were generally conducted in LMICs, since HICs were not reported in the sample. Facilitators and

barriers to EML implementation were identified.

Table B1: Appropriate Selection of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML?	Comments
Greene (Greene 2011)	Making medicines essential: The emergent centrality of pharmaceuticals in global health	Multiple countries	To understand what practices render a medicine essential.	Literature Review	Historical narrative review.	Appropriate use of EML could not be determined and questions what renders a medicine essential. The evolution of practice and politics has led to the expansion of the EML.	Describe the origin, evolution, goals, perceptions, progress, challenges and changes in the concept of essential medicines and access.
Ratanawijitrasin et al. (Ratanawijitrasin, Soumerai and Weerasuriya 2001)	Do national medicinal drug policies and essential drug programs improve drug use?: A review of experiences in developing countries	Multiple countries	To define the available knowledge regarding drug policy effects on drug use, identify evidence important for future policy and research.	Literature Review	Systematic literature review, regulatory interventions evaluated. Reviewed 36 published works (18 journal articles, 13 reports, 1 book chapter, 1 booklet, 2 theses, 1 conference presentation).	Could not determine if EML improved quality use of medicine due to poor quality of studies and few categories of policy assessed.	Variability in quality of studies using different methodologies; stronger research designs required.
Tran & Bero (Tran and Bero 2015)	Barriers and facilitators to the quality use of essential medicines for maternal health in low-resource countries: An Ishikawa framework	Multiple countries	To identify barriers & facilitators to availability & use of oxytocin, ergometrine and magnesium sulphate in pre-eclampsia and eclampsia.	Literature Review	Ishikawa Framework Approach applied as analytical framework to identify barriers and facilitators. Analysed UNFPA/WHO reports. 4 health system levels: government, pharmaceutical supply, health facility and health professional.	Appropriate use and availability of magnesium sulphate was low despite EML listing.	This study identified barriers and facilitators to quality use of medicines including: STGs, forecasting and procurement, availability of antidote, storage. Useful tool for rapid assessment to guide quality use of medicine.

Table B1: Appropriate Selection of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML?	Comments
Vargas-Peláez et al. (Vargas-Peláez et al. 2014)	Right to health, essential medicines, and lawsuits for access to medicines - A scoping study	Multiple countries	Examined the approach to judicialisation of access to medicines and its possible impacts.	Literature Review	A scoping literature review with through qualitative thematic analysis of 65 articles to evaluate social approach to judicialisation.	EML improved right to health to support appropriate use, however, policies were distorted during implementation resulting in poor availability of medicines.	Judicial intervention can be a useful mechanism for promoting the right to health and pushing governments to fulfil their constitutional obligations. However it induces distortion in the implementation of policies which can compromise health systems sustainability. Have limited impact on operations of health services. Judicial system in Europe prioritises common wealth over individual rights. Whereas in Latin America, judicial decisions favour individual lawsuits without considering the impact on the health system and the rest of the population.
Wilson et al. (Wilson et al. 2014)	Process, contexts, and rationale for disinvestment: a protocol for a critical interpretive synthesis	Multiple countries	To understand whether, how & under what conditions health systems decide to pursue disinvestment, how health systems have chose to undertake disinvestment, and how health systems have implemented their disinvestment approach.	Literature Review	Critical interpretive synthesis approach using qualitative constant comparative method applied to a Systematic literature review to develop a theoretical framework.	EMLs must be updated regularly in order to be used appropriately. Listing and delisting medicines can impact adherence to EMLs.	Use of constant comparative approach to identify common themes from literature to develops theoretical constructs. Used purposive sampling of papers to fill in conceptual gaps. This study design used qualitative techniques to interpret literature to design a tool that can be administered to stakeholders.

Table B1: Appropriate Selection of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML?	Comments
Nguyen et al. (Nguyen et al. 2012)	Indicators of quality use of Medicines in South-East Asian countries: a systematic review	Multiple countries in South East Asia	To identify indicators of quality use of medicines used in the South-East Asian region.	Literature Review	Systematic literature review to identify quality use of medicines indicators in South East Asia. 17 studies in 7 countries were included.	The impact of EML in south east Asia was difficult to determine as indicators of quality use of medicines were limited and lacked validity and reliability.	QUM was suboptimal and varied greatly. WHO indicators most frequently used. Existing Indicators need to consider validity, reliability, feasibility and changing health needs in the region (i.e. NCDs).
Ridge et al. (Ridge et al. 2010)	Identifying barriers to the availability and use of Magnesium Sulphate Injection in resource poor countries: A case study in Zambia	Zambia	To identify barriers to the availability and use of magnesium sulphate in the public health system in Zambia.	Literature Review	Literature review of archival data used to develop the Ishikawa Fishbone diagram to explain barriers to availability of Magnesium sulphate injections through observations from obstetric services at a health facility.	Poor availability of EML listed medicine due to poor procurement practices.	Barriers included lack of public procurement, demand by health care professionals and in-service training in using magnesium sulphate.
Van der Geest (Van der Geest 1982)	The efficiency of Inefficiency: Medicine distribution in South Cameroon	Cameroon	To explain why public health services in south Cameroon function inefficiently.	Qualitative	Participant observations, case histories, health reports/files, and financial accounts were collected.	Appropriate use of EMLs required improved education and training of health care workers, and community cooperation.	Education and training of health care workers must include the community's cooperation and meetings to disseminate values. Community is responsible for demand and use of services and also a part of the shortage cause. Health care providers need to have communication with community. Favours, gifts, and relationships are very important to understand in cultures.

Table B1: Appropriate Selection of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML?	Comments
Albert et al. (Albert et al. 2007)	Factors influencing the utilization of research findings by health policy-makers in a developing country: the selection of Mali's essential medicines	Mali	To explore policy makers views on the factors influencing medicine utilisation.	Qualitative	Qualitative semi-structured interviews and discussion with national policy makers. Data analysis used a Giorgi's Phenomenological approach.	Could not determine appropriate use of essential medicines due to poor quality of evidence and collaboration to inform EML decision making.	Emerging factors influencing the decision making process included: Access to evidence, application of information, limited resources (including staff), competency, requires time that competes with other duties, trust in research, biased views, differing priorities, and accountability. Need for more collaboration and technical support to assist policy makers to make informed decisions.
Mori et al. (Mori et al. 2014)	The role of evidence in the decision-making process of selecting essential medicines in developing countries: the case of Tanzania	Tanzania	Describe the process of updating the STGs and EML in Tanzania and further examines the criteria and the underlying evidence used in decision making.	Qualitative	Qualitative in depth interview and document reviews with 18 key informants. Analysed using thematic content analysis. Outcome Measures: described the criteria and evidence used in decision making.	Appropriate use of EML could not be determined because of the variation of what was considered evidence and how it influenced clinical judgement.	Decision making favoured experience and discretionary judgement, rather than Evidence. Cost had limited role, no consideration of cost-effectiveness due to lack of expertise. The process and organization requires improvement and more discussion. Medicines used in a hospital were assumed to have clinical evidence. Clinical experience and patient feedback was also perceived as evidence. Identified issues trusting and applying evidence balanced with experience. Clinical advice can informally come from pharmaceutical industry through colleague discussions.

Table B1: Appropriate Selection of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML?	Comments
Homedes & Ugalde (Homedes and Ugalde 2005)	Multisource drug policies in Latin America: Survey of 10 countries	Multiple countries in Latin America	To describe different country experiences in defining and implementing generic drug policies, cost & time of registering products, and government incentives to promote use of multisource drugs.	Mixed Methods	Mixed Methods: 82 Survey and qualitative questions in 10 Latin American countries. 22 participants with min 1 person in drug regulatory agency or pharmaceutical policy in each country and compared with archival data. Investigated whether definitions were appropriate in policies.	Difficult to determine EML impact because the quality of medicines could not be evaluated when the terms generic and bioequivalence were used differently.	Definition of the term "generic" has different meaning within and between countries. Length of time for drug approval in Latin America is significantly shorter than developed countries, and some can be automatically registered if no response is received (Peru). Need to harmonize vocabulary and technical procedures to ensure quality of pharmaceutical products from multiple sources.
Bazargani et al. (Bazargani et al. 2014)	Selection of Essential Medicines for Diabetes in Low and Middle Income Countries: A Survey of 32 National Essential Medicines List	Multiple countries	To examine selection of and influencing factors around essential medicines to treat diabetes.	Quantitative	Comparison of national EML of 32 countries for Insulin/analogues and blood glucose lowering drugs used in diabetes treatment.	Suboptimal and inconsistent availability of diabetes medicines despite listing on EML.	Most LMICs listed the minimum required diabetes medicines. A median of 6 medicines for diabetes treatment were listed on National EMLs. Suboptimal or inconsistent availability of some of these essential diabetes medicines require further investigation.
De Lima et al. (De Lima et al. 2007)	Ensuring Palliative Medicine Availability: The Development of the International Hospice and Palliative Care List of Essential Medicines for Palliative Care	Multiple countries	To describe how the WHO EML for Palliative Care was created.	Quantitative	Guidelines were developed and sent through a modified Delphi Process to 112 physicians in 77 developing countries, followed by working groups from 26 organizations.	Listing of Palliative medicines on WHO EML used to improve access.	33 medicines were included on the List of Essential Medicines for Palliative Care, in which 14 were already included on the WHO EML.

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Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML?	Comments
Holloway & Henry (Holloway and Henry 2014)	WHO essential medicines policies and use in developing and transitional countries: an analysis of reported policy implementation and medicines use surveys	Multiple countries	To determine if the WHO EML policies were associated with improved QUM.	Quantitative	Surveys from 56 countries, used 10 validated QUM indicators and 36 self-reported policy implementation variables from WHO databases from 2002-2008.	EML policy was associated with improved appropriate use of medicines in LMICs, especially in education around STGs.	A positive correlation was shown between EML policy and QUM in LMICs, especially in education around STGs. Regression analyses showed positive association between QUM scores and number of EML policies.
Logez et al. (Logez et al. 2004)	Could the WHO Model List of Essential Medicines Do More for the Safe and Appropriate Use of Injections?	Multiple countries	To describe injectable medicines in the WHO EML and examine how it addresses access to injection devices.	Quantitative	Database using 11th WHO EML to give 27 injectable medicines using Martindale, expected size of syringes needed, and medium price per unit.	WHO EML influenced availability and appropriate use of medicines.	Outlined the importance of injectable essential medicines and need for safe and appropriate guidelines for procurement, preparation & administration.
Mahmic-Kaknjo & Marusic (Mahmić-Kaknjo and Marušić 2015)	Analysis of evidence supporting the Federation of Bosnia and Herzegovina Reimbursement medicines lists: role of the WHO EML, Cochrane Systematic	Bosnia and Herzegovina	To compare the WHO EML with the national formulary list to evaluate the evidence supporting inclusion of additional medicines.	Quantitative	Formulary Comparison: WHO EML with national formulary list and using Cochrane review and HTA reports to support non-WHO EML drugs included on the national formulary list.	EML provided good evidence for reimbursement decisions especially when financial resources were scarce.	30% of medicines included on the national formulary list but that were not found on the WHO EML did not have good enough evidence to justify their inclusion on the national formulary list. The WHO EML, Cochrane systematic review, and HTA reports offer high quality evidence to assist circumstances with scarce resources. This aids decision making on medicine reimbursement.

Table B1: Appropriate Selection of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML?	Comments
	reviews & technology assessment reports						
Kadić et al. (Kadić et al. 2014)	Using the WHO essential medicines list to assess the appropriateness of insurance coverage decisions: a case study of the Croatian national medicine reimbursement list	Croatia	Used the WHO EML to evaluate evidence basis for medicine on the national insurance coverage list in Croatia.	Quantitative	Compared WHO EML with Croatian Institute Health Insurance (CIHI) basic list.	WHO EML was a useful quality assurance tool to ensure countries used appropriate evidence to list and reimburse medicines.	WHO EML provided useful evidence for reimbursement decision making.
Jommi et al. (Jommi et al. 2013)	Multi-tier drugs assessment in a decentralised health care system. The Italian case-study	Italy	To address gaps arising from multi-tier drug assessment processes and how these issues are dealt with.	Quantitative	Case study: structured multiple choice questionnaire for regional and hospital committee members in Italy. Described decision making process and considerations for policy makers.	Application of EML hard to determine because decision making processes were fragmented and not transparent.	The decision making process is fragmented and requires regional and local assessment. No consideration for appeals. Therapeutic committees are closed to industry and patient associations' involvement. Prioritisation is driven mostly by disease severity, clinical evidence, and absence of therapeutic alternatives. Committees demonstrated low level of transparency.

Table B1: Appropriate Selection of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML?	Comments
Chen et al. (Chen et al. 2014)	Does Economic Incentive Matter for Rational Use of Medicine? China's Experience from the Essential Medicines Program	China	To measure changes in prescribing patterns after removal of economic incentives for physicians to overprescribe after EML implementation	Quantitative	Multistage cluster sampling surveys, analysed with regression methods. Conducted in primary healthcare facilities.	EML did not improve appropriate use by prescribers.	No change in prescribing patterns after implementation of EML policy was shown. Removing prescriber economic incentives from pharmaceutical companies did not improve appropriate use of EML by prescribers.
Hettihewa & Jayarathna (Hettihewa and Jayarathna 2010)	Comparison of the Knowledge in Core Policies of Essential Drug List Among Medical Practitioners and Medical Students in Galle, Sri Lanka	Sri Lanka	To assess the knowledge of EML and the attitudes on prescribing essential medicines by medical practitioners and students.	Quantitative	Comparative cross-sectional survey with 42 medical practitioners and 120 medical students.	EML improved appropriate use by influencing prescriber knowledge.	Medical students had good knowledge of EML content, but poor knowledge of criteria. Whereas medical practitioners had good knowledge of selection criteria but were not confident about EML content especially inclusion criteria such as generic names and common ailments. Medical practitioners need repetitive service training in EMLs and Curriculum needs to include criteria for EML selection.

Table B1: Appropriate Selection of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML?	Comments
Lubinga et al. (Lubinga et al. 2014)	Impact of pharmacy worker training and deployment on access to essential medicines and health outcomes in Malawi: protocol for a cluster quasi experimental evaluation	Malawi	To measure impact of pharmacy assistant training program in LMIC on access to medicine and health outcomes.	Quantitative	Cluster Quasi Experimental Evaluation: 1) Health centre based time motion and patient survey 2) population based household survey, 3) a model-based health and economic analysis. 150 pharmacy assistants trained and worked in 18 districts. 4150 surveys. Outcome Measures: operational efficiency (patient wait times); access to ACT, antibiotic, ORS; QALY gained, DALY averted and costs of program.	The availability of essential medicines is influenced by the capacity and availability of qualified staff.	This protocol described a guide to national and regional human resource intervention that impacts cost, health outcomes and cost effectiveness.
Dal Pizzol et al. (Dal Pizzol et al. 2010a)	Adherence to essential medicines lists in municipalities of three Brazilian States	Brazil	Assessed adherence of prescribers to municipal EML.	Quantitative	Survey and Data collection of 288 prescriptions were compared to WHO EML by a multi-disciplinary committee, in 8 city municipalities in 3 states associated with tertiary educational institution.	Low availability of essential medicines due to inappropriate use of local EMLs.	Some cases showed that need for "non-essential" medicines were justified by the perceived inadequacy of the local EML and drug shortages to address therapeutic gaps. Of the 10 most prescribed medicines, 1 or more medicines were not part of the local EML. Medicines listed on the local EML were more likely to be available than unlisted medicines. Patients would go to private sector and pay out of pocket for these frequently prescribed non-essential medicines.

Table B1: Appropriate Selection of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML?	Comments
Rico-Alba & Figueras (Rico-Alba and Figueras 2013)	The fuzzy line between needs, coverage, and excess in the Mexican Formulary List: an example of qualitative market width analysis	Mexico	To evaluate coverage of basic health needs provided by drugs included in the Mexican national formulary and reference catalogue for national Mexican health services, and measure the rationality of the drugs in the list.	Quantitative	Mixed methods: Quantitative comparison of the Mexican EML to assess therapeutic rationality of medicines not included in the WHO EML. Qualitative analysis using Prescrire Classification to rate rationality of medicines and degree of usefulness. Outcome Measures: 1) Listed on WHO EML with standardised therapeutic rational, 2) Rationality of WHO EML unlisted products meet Prescrire Classification of therapeutic rationality.	Comparison of WHO EML with Mexican EML shows twice as many products and irrationality of missing essential medicines.	Used standardised tools such as WHO EML and Prescrire Classification system to compare EML and explore rationality of listing on the formulary. 236/771 (30.6%) product listed on Mexican EML perfectly matched WHO EML. Several essential products to treat prevalent diseases were missing, while there was also an oversupply of other products with little or no added therapeutic value (28%). Missing medicines were cheap, had no patent protection and of poor marketing interest.

ACT-Artemisinin-based Combination Therapy; DALY-Disability-Adjusted Life Years; EML-Essential Medicines List; HTA-Health Technology Assessment; LMIC-low to middle income country; NCD-non-communicable disease; ORS-Oral Rehydration Salts; QUM-Quality Use of Medicines; QALY-Quality Adjusted Life Years; STG-Standard Treatment Guideline; UNFPA-United Nations Fund for Population Activities; WHO-World Health Organization; WHO EML- World Health Organization Model List of Essential Medicines.

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Nunan & Duke (Nunan and Duke 2011)	Effectiveness of pharmacy interventions in improving availability of essential medicines at the primary healthcare level	Multiple countries	To assess the effectiveness of pharmaceutical system interventions in improving the availability of essential medicines at the primary care level.	Literature Review	Systematic literature review of pharmaceutical interventions' impact on availability of medicines in LMICs.	Availability of EML can be improved through local pharmacy interventions.	A standardised approach to measuring availability of medicines is needed. Pharmacy interventions at the primary health care level can potentially improve medicines availability without large scale international cooperation or global policy change.
Mackintosh et al. (Mackintosh et al. 2011)	Can NGOs regulate medicines markets? Social enterprise in wholesaling, and access to essential medicines	Multiple countries	To describe and assess the activity of NGOs and social enterprise in essential medicines wholesaling.	Qualitative	Qualitative semi-structured interviews. Senior procurement managers of NGOs and social enterprise in Europe, India and Tanzania. Analysis cross-referenced ownerships structure with aspects of reported business behaviour. Triangulated data on behaviour of competitors and the evolution of market competition.	Wholesaling improved access to good quality medicines.	Social enterprise wholesaling can improve access to good quality essential medicines in the absence of effective government activity and regulation. NGO regulatory impact can complement but not replace state action.

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Magadzire et al. (Magadzire et al. 2014)	Frontline health workers as brokers: provider perceptions, experiences and mitigating strategies to improve access to essential medicines in South Africa	Tanzania	To compare consumers' and health care providers' perceptions of the quality of generics to the actual quality of selected products.	Qualitative	Qualitative cross sectional semi-structured interviews with 36 nurses, pharmacy personnel and doctors in 6 public health centres in 2 districts both rural and urban settings. Content analysis and grounded theory approach, used five dimensional framework to illustrate connections.	Availability of EML was poor due to logistic barriers.	Barriers to available medicines include: logistic bottlenecks in the supply chain, poor transport networks, poor cohesion between disease programs and patient needs, proximity to medicine centres, stigma, and transport costs.
Van der Geest et al. (Van Der Geest et al. 2000)	User fees and drugs: what did health reforms in Zambia achieve?	Zambia	To determine what the user fee health reforms had achieved, and if there were improvements in the quality of health care.	Qualitative	35 Qualitative semi-structured interviews, 25 focus groups and observations from a checklist were conducted with consumers (community leaders and users of health centre). Conducted in 2 urban and 2 rural health centres.	Cost sharing did not improve availability of medicines.	Cost sharing was not seen to have improved the quality of care or availability of medicines. The medicine supply chain was seen as unreliable, therefore the high fees seemed unfair.
Chen et al. (Chen et al. 2010)	Availability and use of essential medicines in China: manufacturing, supply and prescribing in Shandong and Gansu provinces	China	To investigate manufacturing, purchasing and prescribing of essential medicines	Mixed Methods	Quantitative surveys of manufacturers, hospitals, and retail pharmacies. Prescription review of hospital prescriptions. Qualitative structured interviews with manufacturers CEO, hospital/retail pharmacy managers.	Inappropriate use of EML, therefore low availability and affordability of essential medicines.	There was low demand for essential medicines and price mark up controls. Proportion of essential medicines produced was not proportional to sales volume (low production). Listing on EML did not influence manufacturers production or retail pharmacy procurement decisions. Influencing factors on procurement were: market demand, production

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
							cost, price, profit margins, or market share. In hospitals, low purchasing of EML due to lack of clinical use or availability of clinical alternatives. A wide range of availability (20-80%).
Carasso et al. (Carasso et al. 2009)	Availability of essential medicines in Ethiopia: an efficiency-equity trade-off?	Ethiopia	To determine availability and cost of essential medicines in rural health centres and explore if the fee waiver system protected patients from paying.	Mixed Methods	Data was collected from 4 rural primary health centres and 7 private outlets. Availability and affordability of medicines studied through quantitative collection of number, price and type of medicines prescribed and dispensed upon exit interviews. Qualitative semi-structured interviews looked at patients' experience with accessing medicines.	Availability was high in private and public centres. Low availability was due to lack of qualified staff. Medicines were not always affordable to low income. Results described financial and social hardship on families who needed more support.	Availability of essential medicines in a rural area was high (more than 80%) in private and public facilities, and highest in public centres. Where availability was poor (specialty pharmacies), facilities reported shortage of qualified staff. Private vendors were used as complementary services if medicines not available in public sector. Qualitative results showed patients incurred financial burden such as loans from relatives/neighbours, selling livestock/assets or postponing health visits until the illness was very serious. Proposed a revolving medicine fund for purchasing in private sector. But, cautioned in creating a parallel system that may leave medicines unavailable in public sector.

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Mujinja et al. (Mujinja et al. 2014)	Local production of pharmaceuticals in Africa and access to essential medicines: "urban bias' in access to imported medicines in Tanzania and its policy implications	Tanzania	To describe the nature and benefit of local production to improve access to medicines	Mixed Methods	WHO/HAI price data on sources for 40 medicines in 96 facilities. Used NVivo and Stata for data analysis. Applied analytical framework of "urban bias". Measured price data, views on role of NGOs in medicine access	Higher availability of locally manufactured than imported medicines in both rural and urban areas.	Locally produced medicines were more accessible than local imports to rural areas. Medicines that are locally produced were more available in both urban and rural areas than imported medicines. Most available medicines were for acute conditions.
Nilseng et al. (Nilseng et al. 2014)	A cross-sectional pilot study assessing needs and attitudes to implementation of Information and Communication Technology for rational use of medicines among health care staff in rural Tanzania	Tanzania	Pilot test of new android program to assess use of information communication technology amongst health workers in relation to medicine distribution practices, stock-outs and continuing medical information.	Mixed Methods	Mixed Methods on new Android application to improve inventory management: Qualitative semi-structured interviews with 20 health care works at 13 health facilities in 2 districts. Quantitative data collected on drug access availability and stock-outs.	Low availability of essential medicines due to procurement practices.	Severe drug shortages and stock-outs were the main problem with medicine distribution in this area. Poor access to medical information. Ordering can be made more simple and automatic to improve staff capacity. There was potential for technology to improve and simplify ordering tasks but required internet and electricity, as well as improved infrastructure and transportation for distribution.

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Babar et al. (Babar et al. 2013)	The Availability, Pricing, and Affordability of Three Essential Asthma Medicines in 52 Low- and Middle-Income Countries	Multiple countries	To determine availability, price, and affordability of medicines likely to affect access to asthma medicines.	Quantitative	WHO/HAI surveys in 52 countries (85%LMIC) for 3 asthma medicines.	Variations in pricing and availability even though listed on EML. Low availability of asthma inhalers in public sector, better availability in private sector, and none at all in some countries.	Variations in pricing and availability suggest differences between countries' commitment to access health care. Low availability of inhaled corticosteroids and listing on EMLs. Salbutamol was mostly listed in EMLs, but had low availability in public sector, acceptable availability in private sector, but not available in some countries.
Cameron et al. (Cameron et al. 2009)	Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis.	Multiple countries	To describe the results of WHO/HAI surveys of availability, pricing and affordability in LMICs.	Quantitative	WHO/HAI surveys in 36 LMICs. 15 medicines presented in results and 4 individual medicines. Secondary data analysis.	Lower availability in public sector. Higher availability and Prices in private sector. Inappropriate use of EMLs. Results suggested medicines sales may be used to subsidise other parts of the health care system	Public sector has consistently low availability due to variations in products in EML and poor compliance with recommendations. Low availability in public sector due to inadequate funding, lack of incentives for maintaining stocks, inability to forecast accurately, inefficient distribution systems, or leakage of medicines for private resale. Availability in private sector was high comparably with higher prices. Low public procurement costs suggest some public facilities are using the medicine sales to subsidise other parts of the health care system.

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Cameron et al. (Cameron et al. 2011)	Differences in the availability of medicines for chronic and acute conditions in the public and private sectors of developing countries	Multiple countries	To investigate potential differences in the availability of medicines for chronic and acute conditions in LMICs.	Quantitative	WHO/HAI surveys for 15 acute and 15 chronic medicines in 40 developing countries.	Low availability in both public and private sectors. Medicines are more available for acute than chronic conditions.	Results show a gap in access, in which generic medicines for chronic conditions have significantly less availability than acute conditions, in both public and private sectors.
Cameron et al. (Cameron et al. 2012)	Mapping the availability, price and affordability of antiepileptic drugs in 46 countries	Multiple countries	To describe availability, price and affordability of antiepileptic drugs and whether these factors contribute to treatment gaps.	Quantitative	WHO/HAI surveys in 46 LMICs. Secondary data analysis. 5 antiepileptic drugs (phenytoin, carbamazepine, valproic acid, Phenobarbital, and diazepam).	Low availability and affordability (higher prices) of antiepileptic medicines.	Low Availability of antiepileptic medicines in LMIC, less than 50% except for diazepam injections. Generic prices in LMICs were higher than international reference prices in both public and private sectors. This may act as a barrier to accessing treatment for epilepsy.
Hill et al. (Hill et al. 2012)	Priority Medicines for Maternal and Child Health: A Global Survey of National Essential Medicines Lists	Multiple countries	To examine the occurrence of maternal and child health medicines on EMLs.	Quantitative	Comparison of WHO List of priority medicines for mothers and children with 89 country EMLs for 28 pharmaceuticals in 41 dosage forms.	Poor availability of essential medicines and inappropriate use of WHO EML due to low inclusion on EML. There was a lot of variation between EML and WHO EML list.	Many priority medicines are still not listed, making it difficult for policies to achieve MDGs. There was variation between lists. Recent updates promoted higher probability for inclusion of priority medicines. Paracetamol, oral rehydration salts sodium chloride and gentamicin most frequently listed (93%). Least frequently listed were anti-malarials, and injectable and rectal formulations. Half the lists had magnesium sulfate.

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
							Only 1/4 of lists had been updated recently (in last 5 years), and were more likely to include misoprosotol, zinc, cefixime, nifedipine.
Mendis et al. (Mendis et al. 2007)	The availability and affordability of selected essential medicines for chronic diseases in six low- and middle-income countries	Multiple countries	To assess the availability and affordability of medicines used to treat chronic disease.	Quantitative	WHO/HAI surveys in 6 LMICs: Brazil, Pakistan, Sri Lanka, Bangladesh, Malawi, Nepal. 32 medicines to treat cardiovascular disease, diabetes, chronic respiratory disease, glaucoma, and palliative cancer care.	Poor availability and affordability of EML listed medicines. Private more availability than public sector but both still poor.	Cost of brand up to 10 times higher than generic medicines. Medicines are free in public sector, but their availability was poor. Stock-outs may be due to poor estimates or consumption and cash-flow constraints. If patients cannot afford medicines, will forego treatment. Private more than public availability but still poor. Poor availability of most inexpensive drugs (e.g. HCTZ).
Moon et al. (Moon et al. 2011)	A win-win solution?: A critical analysis of tiered pricing to improve access to medicines in developing countries	Multiple countries	To examine how tiered pricing can make medicines affordable in LMICs, determines who should pay for R&D, and determine who and how pricing is decided.	Quantitative	Case studies of ARVs for HIV/AIDS, ACT for malaria, drug-resistant tuberculosis drugs, drugs for visceral leishmaniasis, and the pneumococcal vaccine. Used international tiered pricing to measure affordability of medicines (impoverishing effect of a medicine).	Affordability can be improved short term through tiered pricing.	Tiered pricing offered short term access to products. It does not ensure affordability and availability in the long-term. In some cases, tiered pricing resulted in lower prices than competitive production. Tiered pricing lowered prices to improve access when markets were small, highly uncertain, production capacity limited and demand low.

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Niens et al. (Niëns et al. 2010)	Quantifying the impoverishing effects of purchasing medicines: A cross country comparison of the affordability of medicines in the developing world	Multiple countries	To estimate the impoverishing effects of 4 medicines in 16 LMICs using the impoverishment method to measure affordability.	Quantitative	Measured affordability based on proportion of a population that would be pushed below a poverty line by the purchase of a medicine. 4 medicines were studied.	Affordability of medicines was considered in relation to how close they were to the poverty line. Considered the prevalence of disease and inability to fund medicines.	Analysed medicine prices, aggregated income data, and information on income distribution. Showed relative impact of medicine purchase in relation to proportion of the population above/below the poverty line before and after medicine purchase. Showed that essential medicines were unaffordable when compared against the poverty line of US$1.25 and US$2. Considered price of medicines and prevalence rate of disease in country.
Niens et al. (Niens et al. 2012)	Practical Measurement of Affordability: an application to medicines	Multiple countries	To develop two practical methods for measuring the affordability of medicines in developing countries.	Quantitative	Looked at 2 methods of measuring affordability: 1) Catastrophic Approach: Ratio of expenditures to total household resources, and 2) Impoverishment Approach: Residual income after expenditure.	Affordability of medicines considered results of out of pocket expenditure on low income households. Should be considered in how affordability is measured in other studies.	Used ratio of expenditures to total household resources and residual income after expenditure. Compared "catastrophic" with "impoverishment" approaches. Considered price of treatment of a medicine, a country's total population, the aggregate income level of a country and proportion of the total income earned across income groups. Macro and Micro data were illustrated.

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Srivastava & McGuire (Srivastava and McGuire 2014)	Analysis of prices paid by low-income countries - how price sensitive is government demand for medicines?	Multiple countries	To explore the variation in pharmaceutical prices and price mark-ups, to investigate the price sensitivity at the government level and compute price elasticity for sales to government purchasers, analyse relationship between estimated price elasticity and income.	Quantitative	WHO/HAI surveys data from 16 low income countries of 48 branded medicines in 18 therapeutic classes.	Affordability of medicines was difficult to determine due to price elasticity and variation between therapeutic classes.	Prices were variable between therapeutic classes.
Van Mourik et al. (van Mourik et al. 2010)	Availability, Price and Affordability of Cardiovascular medicines: A comparison across 36 countries using WHO/HAI data	Multiple countries	To examine availability, pricing, and affordability of cardiovascular medicines in developing countries.	Quantitative	WHO/HAI surveys in 36 LMICs. Cardiovascular medicines (atenolol, captopril, losartan, hydrochlorothiazide, nifedipine).	Low availability of cardiovascular medicines. Private more than public sector but both still poor.	Low availability of lowest priced generic in public sector. Private sector had better availability for all medicines generic and brands. High income regions had better availability than low income regions. In high income areas, low availability of generic but had high availability of brands. Poor availability of public sector may mean patients must resort to higher priced private sector to access treatment.

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Wagner et al. (Wagner et al. 2011)	Access to care and medicines, burden of healthcare expenditures, and risk protection: Results from the World Health Survey	Multiple countries	To assess the contribution of health insurance and a functioning public sector to access care and medicines on household economic burden.	Quantitative	World health survey analysed on medicine expenditure in 70 countries. Analysed using logistic regression models.	Households in LMICs mostly purchased medicines from private sector. There was poor public perception and low availability and quality of medicines in the public sector.	A functioning public sector was related to better healthcare access and lower burden of expenditures. The perceived and actual availability and quality of medicines in the public sector were low, fees were high, and waiting caused additional opportunity costs.
Carapinha et al. (Carapinha et al. 2011)	Health insurance systems in five Sub-Saharan African countries: Medicine benefits and data for decision making	Multiple countries in Africa	To describe the structure of medicine benefits and data routinely available for decision making.	Quantitative	Survey to assess program structure, medicine benefits and data routinely available for decision making in 33 health insurance programs in Ghana, Kenya, Nigeria, Tanzania and Uganda.	Affordability and availability of medicines required data monitoring of key elements and resources.	Strategies used were common in high income countries (e.g.. formularies, generics policies, reimbursement limits, or price negotiations). Basic data to monitor performance in delivering medicine benefits were available in most programs; however, some key elements and resource data was missing. Identified need to investigate: 1) most effective medicines policy choices due to different organisation structures, 2) impacts of benefits design on quality and affordability of care on health outcomes, and 3) a way to facilitate use of routine data for monitoring.

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Robertson et al. (Robertson et al. 2009)	What essential medicines for children are on the shelf?	Multiple countries in Africa	To document the inclusion of key medicines for children in EMLs and STGs, and to assess the availability and cost of these medicines.	Quantitative	Audit Survey of availability and cost of medicines in 20 dosage forms for children in 14 African countries.	Appropriate use of EML was poor due to lack of inclusion on local STGs. Low availability and poor procurement of essential medicines.	Medicines in EMLs were not included in local STGs. Conversely, all medicines on STGs not included in EML. Although CMS stocked essential medicines, they were not always available. Half the medicines on EML/STG were available in surveyed facilities. Variation in availability of priority disease medicines. Existence of vertical programmes for these priority diseases may mean that the medicine supply is not coordinated with standard supply chains in these countries.
Jiang et al. (Jiang et al. 2013)	Measuring Access to Medicines: A Survey of Prices, Availability and Affordability in Shaanxi Province of China	China	To measure price and availability of selected medicines after health care reform in 2009.	Quantitative	WHO/HAI surveys. 47 medicines from 50 public and 36 private outlets. Measured price and availability.	Low availability in both public and private sectors. Unaffordable for those with low income.	Availability was low in both public and private sectors. High mark-up prices were associated with both generic and brand medicines. Wide range of prices. Medicines can still be unaffordable to those with low income.
Wang et al. (Wang et al. 2014)	Access to Paediatric Essential Medicines: A survey of prices, availability, affordability and	China	To evaluate prices and availability of paediatric essential medicines.	Quantitative	WHO/HAI surveys. 28 paediatric medicines from 30 outlets including hospitals. Measured price and availability.	Very low availability of EML medicines in both public and private sectors. Medicines were reasonably affordable.	Availability was found to be very low in public and private sectors. General affordability was found to be reasonable.

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
	price components in Shaanxi Province, China						
Yang et al. (Yang et al. 2010)	Prices, availability and affordability of essential medicines in rural areas of Hubei Province, China	China	To determine availability of essential medicines in Hubei province.	Quantitative	WHO/HAI surveys. 39 medicines from 18 public and 18 private outlets in rural mountainous China. Measured price and availability.	Low availability of EML listed medicines in public and private sector, not affordable for low income.	Low procurement prices and availability in public sector. Medicine prices were affordable to most of the population, but not for low income.
Zhu et al. (Zhu et al. 2008)	The influence of health insurance towards accessing essential medicines: The experience from Shenzhen labour health insurance	China	To evaluate the impact of the new Shenzhen labour health insurance on accessing essential medicines among migrant workers.	Quantitative	Data obtained from medicines data base, and revenue expenditure reports from community health service centres.	EML improved affordability and availability when applied to reimbursement lists for insurance schemes.	Essential medicines made up a majority of the reimbursement list for the health insurance scheme, and procurement for outpatients was increasing, yet still not high.
Babar et al. (Babar et al. 2007)	Evaluating Drug Prices, Availability, Affordability, and Price Components: Implications for Access to Drugs in Malaysia	Malaysia	To evaluate medicine prices, availability, affordability, and structure of price components.	Quantitative	WHO/HAI surveys for pricing, availability and affordability for 48 medicines in public and private sectors	Low availability of free essential medicines in public sector.	Availability of free essential medicines in the public sector was very low. Price mark-ups for generics were higher than brands.

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Saleh & Ibrahim (Saleh and Ibrahim 2005)	Are essential medicines in Malaysia accessible, affordable and available?	Malaysia	To assess whether people in Malaysia had access to essential medicines.	Quantitative	WHO/HAI surveys for pricing, availability and affordability for 13 medicines in public and private sectors. Measured availability, prices and prevalence of stock-outs of dispensed medicines.	High affordability and availability of medicines through public sector, but not affordable in private sector. Rural areas had less availability.	The majority of the population in Malaysia have access to essential medicines through public sector. Private sector medicines are not affordable. Access in rural areas was still a problem.
Akaleephan et al. (Akaleephan et al. 2009)	Extension of market exclusivity and its impact on the accessibility to essential medicines, and drug expense in Thailand: Analysis of the effect of TRIPs-Plus proposal	Thailand	To quantify the impact of market exclusivity and its impact on medicine expense and accessibility.	Quantitative	Data obtained between 2000-2003 from the Thai FDA and drug and medical supply information centre. Generic and brand medicine prices and quantities were compared.	The TRIPs agreement would make medicines unaffordable.	TRIPs-Plus proposal would result in significant increase in medicine expenditure and delay access to generics.
Burapadaja et al. (Burapadaja et al. 2007)	Effects of essential medicines on cardiovascular products available for the market in Thailand	Thailand	To examine if the EML concept affects the patterns and values of cardiovascular products available on the market in Thailand.	Quantitative	Cross-sectional study of generic cardiovascular medicines available from national Thai EML. Comparison with Thai FDA and Thailand Index of Medical Specialties. Analysed with descriptive statistics and simple regression.	EML improved availability of generic cardiovascular essential medicines.	There was a greater proportion of essential medicines products with more generics available than non-essential medicines. Domestic production was greater than foreign producers. Demonstrated advantages to using EML to promote generics and guide procurement.

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Burapadaja & Chinawong (Burapadaja and Chinawong 2010)	Response of a government hospital to prescription cost savings through its hospital formulary in Thailand	Thailand	To determine a measure reflecting the response of a government hospital to prescription cost savings by looking at hospital formularies and additions to it.	Quantitative	Thai EML was compared to a hospital formulary.	EML improved appropriate use, availability and lowered cost of medicines.	There were more essential medicines on the formulary than non-EMs which influenced prescribing with generics to lower costs. Broad price range was evident for single availability of generic or brand drugs, while dual availability (have both generic & brand) narrowed the price. Prescription cost savings were demonstrated by high proportion of essential medicines prescribed off the formulary.
Gitanjali & Manikandan (Gitanjali and Manikandan 2011)	Availability of five essential medicines for children in public health facilities in India: A snapshot survey	India	To describe availability of 5 paediatric essential medicines in public health facilities in India.	Quantitative	Snapshot survey for 5 paediatric medicines in 129 health facilities.	Average availability of paediatric medicines in private sector and very low in public sector.	There was a reasonable availability of most paediatric medicines, except zinc sulphate which still had very low availability in the public sector (36%).
Kotwani et al. (Kotwani et al. 2007)	Prices and Availability of common medicines at six sites in India using a standard methodology	India	To measure price and availability of medicine in public and private sectors.	Quantitative	WHO/HAI surveys. 27 medicines at 6 sites	Low availability and affordability in public sector.	Public sector had low procurement prices and poor availability of medicines.

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Kotwani A (Kotwani 2013)	Where are we now: Assessing the price, availability and affordability of essential medicines in Delhi as India Plans free medicine for all	India	To determine price, availability and affordability of essential medicines in public and private sectors in Delhi, India.	Quantitative	WHO/HAI surveys. 50 medicines in public and private sectors in Delhi.	Low availability or medicines despite cost sharing policies.	Cost sharing was not seen to have improved the quality of care or availability of medicines. The medicine supply chain was seen as unreliable; thus, the high fees seemed unfair.
Cheraghali et al. (Cheraghali et al. 2004a)	Evaluation of availability, accessibility and prescribing pattern of medicines in the Islamic Republic of Iran	Iran	To evaluate prescribing, dispensing, availability and affordability of essential medicines, and the availability of health information.	Quantitative	WHO/HAI surveys. 12 medicines, in 100 primary health care centres in 5 provinces.	Average to high affordability and availability in public sector. Inappropriate use of EML shown through poor adherence to STGs and high use of antibiotics.	Essential medicines are generally available (60-95%) and affordable (85% subsidised) in public sector. But long periods of stock outs (e.g. average 29 days). Very low adherence to STGs.
Dabare et al. (Dabare et al. 2014)	A national survey on availability, price and affordability of selected essential medicines for non communicable diseases in Sri Lanka	Sri Lanka	To determine availability, price and affordability of non communicable diseases.	Quantitative	WHO/HAI surveys. 50 medicines at 9 sites. Total 109 surveys. Measured price and availability.	High availability and affordability of essential medicines in both public and private sectors.	Most medicines were available in both public and private sectors. Generic medicines were affordable to lowest income earners.

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Ganga Senarathna et al. (Ganga Senarathna et al. 2011)	Medicine prices, availability and affordability in Sri Lanka	Sri Lanka	To determine the prices, availability, and affordability of medicines in the Sri Lankan private sector without price controls.	Quantitative	WHO/HAI surveys. 28 medicines at 15 sites.	High availability and affordability of generic medicines in private sector.	Low cost generics of essential medicines were highly available (more than 80%) in private sector.
Cheraghali & Idries (Cheraghali and Idries 2009)	Availability, affordability, and prescribing pattern of medicines in Sudan	Sudan	To address gaps arising from multi-tier medicine assessment processes and how these issues are dealt with.	Quantitative	WHO/HAI surveys. 15 medicines in 36 health facilities, in 6 geographic regions.	Generally high affordability and availability in public sector. Inappropriate use of EML shown through poor adherence to STGs for diarrhoea and malaria, and high use of antibiotics.	Essential medicines are generally available in the public sector. Low adherence to STGs for diarrhoea and malaria.
Mouala et al. (Mouala et al. 2009)	Essential medicines and access to primary health care in the medical district of Mambere-Kadei	Central African Republic	To assess if people had access to medicines in primary healthcare settings.	Quantitative	WHO/HAI surveys. 14 generic medicines in 14 public health care centres, in central African republic.	Average availability and affordable of generic medicines. Low affordability for those with low income.	Reasonable availability and affordability of generic essential medicines in this district. Still unaffordable to the very poor.

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Maiga & Williams-Jones (Maiga and Williams-Jones 2010)	Assessment of the impact of market regulation in Mali on the price of essential medicines provided through the private sector	Mali	To assess the impact of the 2006 government decree on the evolution of market prices, availability and access to essential medicines in Mali.	Quantitative	Cross-sectional descriptive study of 49 medicines in 16 wholesalers and 30 private drugstores. Assess availability and prices of medicines to evaluate fixed maximum pricing policy in the private sector.	Lowering prices was not shown to increase availability of essential medicines.	No change to availability of medicines before and after maximum medicine pricing policy. Prices of medicines were decreased. Unable to show that market regulation had a negative impact on availability.
Mikkelsen-Lopez et al. (Mikkelsen-Lopez et al. 2014)	Essential medicines in Tanzania: Does the new delivery system improve supply and accountability?	Tanzania	To assess if reform of the Tanzanian delivery system from a central "push" kit system to a decentralized 'pull' integrated logistics system has improved medicines accountability.	Quantitative	Inventory data was collected using the push kit system and applied inventory ordering program. Compared 11 medicines in 6 health facilities in Rufiji district in coastal south east Tanzania.	Could not determine if inventory program was able to improve availability of medicines or accountability by suppliers.	No uniform improvements in availability, no increased accountability due to uncertainty, incompleteness and inaccuracies of available information. Needed to reconcile demand of medicines with supply to improve accountability of resources.
Bertoldi et al. (Bertoldi et al. 2008)	Medicine access and utilization in a population covered by primary health care in Brazil	Brazil	To describe medicine utilisation and access in the population.	Quantitative	Cross sectional, survey structured interviews with 2988 subjects living in one Brazilian city on their medicine use in the previous 15-day period. Described medicine utilisation patterns, evaluated access to medicines, and assessed proportion of medicines obtained at no charge.	High availability of medicines, but many paid out of pocket. 68% with low income received medicines for free but 26% paid out of pocket. Poor local use of EML.	Generally, there was good access to medicines. Small proportion of people unable to obtain their medicines, and half were able to get it for free. 80% of essential medicines were not included on the municipal basic medicines list. Poor local use of EML.

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Bertoldi et al. (Bertoldi et al. 2012)	Is the Brazilian pharmaceutical policy ensuring population access to essential medicines?	Brazil	To evaluate medicine availability, price, and affordability in Brazil across 3 types of medicines: originator brands, generics, or similar medicines (brand generics).	Quantitative	WHO/HAI surveys. 50 medicines in 56 pharmacies across 6 cities in southern Brazil.	Moderate availability but low for poorer regions. Affordability was high for generics in public sector and lower in private sector.	Moderate access to medicines in all cities (69% in public, 74% in private), but poorer access than other regions of Brazil. Only generics found in public sector facilities. Generics were approximately half the price of originator brands, but there were still cases of unavailable essential medicines, and out of pocket purchases at private vendors.
Santos Pinto et al. (Santos Pinto et al. 2010)	Medicine prices and availability in the Brazilian Popular Pharmacy Program	Brazil	To analyse the performance of the Brazilian Popular Pharmacy Program in the public and private sectors via availability and cost of medicines treating hypertension and diabetes.	Quantitative	WHO/HAI surveys. 4 medicines in 30 cities.	Reimbursement program with "co-payments" had higher availability of essential medicines than both public and private sectors and shown to be affordable. People turn to alternative programs due to Low availability of public sector and high prices of private sector.	Reimbursement program with "co-payments" had higher availability than both public and private sectors and shown to be affordable. People turn to alternative programs due to Low availability of public sector and high prices of private sector.
Anson et al. (Anson et al. 2012)	Availability, prices and affordability of the WHO's essential medicines for children in Guatemala	Guatemala	To measure availability, price and affordability of children's medicines in Guatemala.	Quantitative	WHO/HAI surveys. 27 medicines and 1 device, in urban and rural areas, in 50 outlets	Lower availability of children's formulations in public than private sector. Lower medicine availability for chronic than acute conditions.	Generally, unaffordable, low availability of children's formulations, lower availability of essential medicines in public than private sector, and lower for chronic conditions than acute conditions.

Table B2: Availability and Affordability of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Madden et al. (Madden et al. 2010)	Measuring Medicine Prices in Peru: Validation of key aspects of WHO/HAI survey methodology	Peru	To assess possible bias due to the limited target list and geographic sampling of the WHO/HAI Medicines Prices and Availability survey used in >70 countries since 2001.	Quantitative	Validate WHO/HAI surveys. Addressed bias due to small sample of purposely selected facilities (excluded remote areas), specific case types of therapeutic classes, and restriction of data collection of originator brand and lowest priced generic products. Study included 38 medicines, rural/remote centres -52 public, 96 private. Medicine prices included in 3 expanded therapeutic classes with all product versions. Availability measured by physical presence in an outlet at time of survey. Price per unit recorded in local currency in recommended pack size. Affordability measured by comparing lowest paid government worker wage with treatment cost/month/episode.	EML products had similar low availability, better affordability in public sector due to lower public prices due to generic use, and higher retail prices. There were no statistically significant differences in rural and urban regions in this study due to sufficient distribution systems.	Use of comprehensive global data across WHO member countries for select therapeutic classes to assess country versus WHO EML price, relative affordability and availability. Compared median retail prices with wholesale prices from IMS data. Validation study showed no statistically significant difference in bias. The WHO/HAI Prices and Availability survey can play an important role for advocacy for pharmaceutical policy in LMICs.

ACT-Artemisinin-based Combination Therapy; ARV-Antiretroviral Therapy; CMS-Central Medical Stores; EML-Essential Medicines List; FDA-Food and Drug Administration; HCTZ-Hydrchlorothiazide; LMIC-low to middle income country; MDG-Millennium Development Goals; NGO-Non-governmental Organisation; R&D-Research and Development; STG-Standard Treatment Guideline; TRIPS-Trade Related Aspects of International Property Rights; WHO-World Health Organization; WHO/HAI-World Health Organization Health Action International; WHO EML- World Health Organization Model List of Essential Medicines.

Table B3: Quality of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Caudron et al. (Caudron et al. 2008)	Substandard medicines in resource-poor settings: a problem that can no longer be ignored	Multiple countries	To describe key concerns to assure quality of medicines in relief programmes in LMICs.	Literature Review	Pubmed plus bibliographic literature search.	Quality of essential medicines has been susceptible to substandard and counterfeit products due to lack of standardisation in regulation and resources to address the problem.	LMICs are vulnerable to substandard medicines due to lack of standardised regulation and lack of resources by regulatory agencies in these countries to address the problem.
Wilson et al. (Wilson et al. 2012)	The make or buy debate: Considering the limitations of domestic production in Tanzania	Tanzania	To examine the "make or buy" dilemma and critical limitations of domestic manufacturing through Tanzania case study of ARVs.	Qualitative	Qualitative semi structured interviews with key informants, observation and review of documents.	Quality and availability of essential medicines can be improved by building local manufacturing capacity.	There is a lack of coherent policy strategy to develop the pharmaceutical industry and manufacturing. Required improved capacity building and incentives.
Khan et al. (Khan et al. 2011)	Perceptions and practices of pharmaceutical wholesalers surrounding counterfeit medicines in a developing country: a baseline survey	Cambodia	To investigate the risk of counterfeit medicines in the Cambodian medicine supply chain.	Mixed Methods	Quantitative cross sectional surveys. Qualitative semi-structured interviews with 62 wholesalers around counterfeit issues, observational data of warehouses.	Quality of essential medicines was not reinforced at the wholesaler level.	Most wholesalers were not properly informed on counterfeit medicines issues and how to handle these situations.

Table B3: Quality of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Patel et al. (Patel et al. 2012)	Quality of generic medicines in South Africa: Perceptions versus Reality - A qualitative study	Tanzania	To describe the process of updating STGs and EMLs with consideration of criteria and underlying evidence used in decision making.	Mixed Methods	Qualitative semi-structured interviews with 15 healthcare providers and 12 consumer focus groups. 135 products from public and private sector tested in vitro for quality.	Poor understanding of what warrants quality medicines can impact appropriate use and availability of affordable generics.	All formulations passed the in vitro test. Poor and variable understanding/misconception of what quality was (confused with efficacy, side effects, recognisable, reputation, brand image, trust). Need for improved education and consumer and healthcare provider engagement to address needs and information on medicines.
Nakyanzi et al. (Nakyanzi et al. 2010)	Expiry of medicines in supply outlets in Uganda	Uganda	To determine main contributing factors to expiry of medicines in medicine supply outlets in Uganda.	Mixed Methods	Quantitative cross sectional surveys. Qualitative semi structured questionnaires with 13 closed questions on expiry. One participant from each of the 38 sites was interviewed.	Poor quality medicines take up shelf space but cannot be given to consumers. Therefore, the availability of medicines was lowered due to waste of expired medicines.	Medicines were prone to expiry if used for vertical programs, donated, or had slow turnovers. While bulk purchasing can improve negotiated prices for medicines, it can lead to overstocking and exacerbate expiry and waste. Need for improved coordination and implications or logistics feasibility of lean supply and stock rotation.
Lauffenburger et al. (Lauffenburger et al. 2011)	A public-health approach to site specific formulary management: addressing deficient drug supplies in Malawi	Malawi	To assess and address deficiencies in a clinic's medicine supply using formularies.	Quantitative	Conducted in NPOs supporting orphans and community. Inventory compared to clinic logbooks and WHO EML. Prices compared in local medicine stores and wholesalers.	Inappropriate use of EML and expiry contributing to lowered availability of essential medicines.	High proportion (over half) of expired stock, many medicines not generally prescribed. Need to use a formulary for targeted international donations when resources are limited.

Table B3: Quality of Medicines Study Comparison

Author	Title	Country	Objective	Type of Study	Study Design	How does it relate to EML	Comments
Bevilacqua et al. (Bevilacqua et al. 2011)	Procurement of generic medicines in a medium size municipality	Brazil	To analyse the financial impact of medicine procurement with the required bioavailability and or bioequivalence tests for the basic pharmaceutical services component.	Quantitative	Retrospective study. Looked at competitive procurement bids that occurred with (2007) and without (2008) the requirement of bioequivalence and/or bioavailability tests were analysed.	To keep medicine prices affordable and available, quality of medicines have been compromised and allowed to stay in the system. Therefore, there are poor quality medicines offered at cheap prices.	In 2007 and 2008 respectively, 2.6% and 56.9% of items failed to pass tests. Medicine purchases increased 60% for some and decreased 29.3% for others. Procurement costs doubled. Bio-equivalency/availability tests increased costs by more than 100%. Due to the high percentage of failed items, a third bidding process was necessary for which the bioavailability and/or bioequivalence tests were not required due to the risk of catastrophic stock-outs in the health system.

ARV-Antiretroviral Therapy; EML-Essential Medicines List; LMIC-low to middle income country; NPO-Non-Profit Organisation; STG-Standard Treatment Guideline; WHO EML- World Health Organization Model List of Essential Medicines

Appendix C - Ethics Approval (chapter 2,3)

THE UNIVERSITY OF SYDNEY

RESEARCH INTEGRITY
Human Research Ethics Committee
Web: http://sydney.edu.au/ethics/
Email: ro.humanethics@sydney.edu.au

Address for all correspondence:
Level 6, Jane Foss Russell Building - G02
The University of Sydney
NSW 2006 AUSTRALIA

Ref: [SA/KFG]

8 October 2012

A/Prof Timothy Chen
Faculty of Pharmacy
The University of Sydney
Email: timothy.chen@sydney.edu.au

Dear A/Prof Chen

I am pleased to inform you that the Human Research Ethics Committee (HREC) approved your protocol entitled "**The Management and Supply of Essential Medicines: A Global Perspective**" at its meeting held on 2 October 2012.

Details of the approval are as follows:

Protocol No.:   15291

Approval Date: **2 October 2012**

First Annual Report Due: **31 October 2013**

Authorised Personnel: **A/Prof Timothy Chen**
                                Dr Rebekah Moles
                                Ms Mai Duong

Documents Approved:

Document	Version Number	Date
Participant Information Statement	Version 1	September 4, 2012
Participant Consent Form	Version 1	September 4, 2012
Interview Guide	Version 1	
Safety Protocol	n/a	September 27, 2012

HREC approval is valid for four (4) years from the approval date stated in this letter and is granted pending the following conditions being met:

Condition/s of Approval

- Continuing compliance with the National Statement on Ethical Conduct in Research Involving Humans.

- Provision of an annual report on this research to the Human Research Ethics Committee from the approval date and at the completion of the study. Failure to submit reports will result in withdrawal of ethics approval for the project.

- All serious and unexpected adverse events should be reported to the HREC within 72 hours.

Manager Human Ethics
Dr Margaret Faedo
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Human Ethics Secretariat:
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ABN 15 211 513 464
CRICOS 00026A

- All unforeseen events that might affect continued ethical acceptability of the project should be reported to the HREC as soon as possible.

- Any changes to the protocol including changes to research personnel must be approved by the HREC by submitting a Modification Form before the research project can proceed.

Chief Investigator / Supervisor's responsibilities:

1. You must retain copies of all signed Consent Forms (if applicable) and provide these to the HREC on request.

2. It is your responsibility to provide a copy of this letter to any internal/external granting agencies if requested.

Please do not hesitate to contact Research Integrity (Human Ethics) should you require further information or clarification.

Yours sincerely

Dr Stephen Assinder
Chair
Human Research Ethics Committee

cc: Mai Duong
        mduo8406@uni.sydney.edu.au

Appendix D - Participant Information statement for research (chapter 2,3)

THE UNIVERSITY OF SYDNEY

Faculty of Pharmacy

ABN 15 211 513 464

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Dr. Rebekah Moles
PhD, Grad Cert Ed Stud (Higher Ed), BPharm,
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Essential Medicines: A Global Perspective

PARTICIPANT INFORMATION STATEMENT

(1) **What is the study about?**

The Essential Medicines List is a global concept that was established in 1977 by the World Health Organization (WHO) to establish international pharmaceutical standards and guidelines that offer therapeutic and economic benefits, which has been implemented in nearly 160 countries. Access to essential medicines hugely impacts the health of people in developing and low to middle income countries. You are invited to participate in a study aimed at gathering perspectives of international stakeholders on the role and application of the Essential Medicines List. An understanding of the factors that facilitate and/or create barriers to the effective use of the Essential Medicines List in different practice settings will help inform future policies and procedures to consider these identified issues.

(2) **Who is carrying out the study?**

The study is being conducted by Mai Duong, BScPharm, and will form the basis for the degree of Masters of Philosophy in Pharmacy at The University of Sydney under the supervision of Dr. Timothy Chen (Faculty of Pharmacy, University of Sydney) and Dr. Rebekah Moles (Faculty of Pharmacy, University of Sydney).

(3) **What does the study involve?**

This study involves an interview discussing your thoughts on the essential medicines list in your practice setting. This interview will be audio taped to ensure accuracy of the interview.

(4) **How much time will the study take?**

This Interview will take between 20 to 30 minutes

(5) **Can I withdraw from the study?**

Being in this study is completely voluntary - you are not under any obligation to consent and - if you do consent - you can withdraw at any time without affecting your relationship with The University of Sydney.

You may stop the interview at any time if you do not wish to continue, the audio recording will be erased and the information provided will not be included in the study.

(6)   Will anyone else know the results?

All aspects of the study, including results, will be strictly confidential and only the researchers will have access to information on participants. A report of the study may be submitted for publication, but individual participants will not be identifiable in such a report.

(7)   Will the study benefit me?

We cannot and do not guarantee or promise that you will receive any benefits from the study

(8)   Can I tell other people about the study?

Yes, this is entirely up to you

(9)   What if I require further information about the study or my involvement in it?

When you have read this information, Mai Duong will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact Mai Duong, at +61 4 1020 3783 or mduo8408@uni.sydney.edu.au.

(10)   What if I have a complaint or any concerns?

Any person with concerns or complaints about the conduct of a research study can contact The Manager, Human Ethics Administration, University of Sydney on +61 2 8627 8176 (Telephone); +61 2 8627 8177 (Facsimile) or ro.humanethics@sydney.edu.au (Email).

This information sheet is for you to keep

Appendix E - Participant Consent form for participation in research,(chapter 2,3)

Faculty of Pharmacy

ABN 15 211 513 464

Dr. Timothy Chen
PhD, DipHPharm BPharm, MPS MSHP

Dr. Rebekah Moles
PhD, Grad Cert Ed Stud (Higher Ed), BPharm, Dip.Hosp.Pharm

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PARTICIPANT CONSENT FORM

I, ...[PRINT NAME], give consent to my participation in the research project

TITLE: *Essential Medicines: A Global Perspective*

In giving my consent I acknowledge that:

1. The procedures required for the project and the time involved have been explained to me, and any questions I have about the project have been answered to my satisfaction.

2. I have read the Participant Information Statement and have been given the opportunity to discuss the information and my involvement in the project with the researcher/s.

3. I understand that being in this study is completely voluntary – I am not under any obligation to consent.

4. I understand that my involvement is strictly confidential. I understand that any research data gathered from the results of the study may be published however no information about me will be used in any way that is identifiable.

5. I understand that I can withdraw from the study at any time, without affecting my relationship with the researcher(s) or the University of Sydney now or in the future.

6. I understand that I can stop the interview at any time if I do not wish to continue, the audio recording will be erased and the information provided will not be included in the study.

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7. I consent to:

- Audio-recording   YES ☐   NO ☐
- Receiving Feedback   YES ☐   NO ☐

If you answered YES to the "Receiving Feedback" question, please provide your details i.e. mailing address, email address.

Feedback Option

Address: _____

_____

Email: _____

....
Signature

....
Please PRINT name

....
Date

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

Developed from:
Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

No. Item	Guide questions/description	Reported on Page #
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Interviewer/facilitator	Which author/s conducted the interview or focus group?	Mai Duong
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	Mai Duong, BSc.Pharm,BHSc(Hons), RPh, M.Phil Candidate Rebekah J. Moles, PhD,DipHPharm,BPharm, Senior Lecturer Betty Chaar, PhD,MHL,BPharm, Senior Lecturer Timothy F. Chen, PhD,DipHPharm,Pharm, MPS,MSHP,Associate Professor
3. Occupation	What was their occupation at the time of the study?	Pharmacist, M.Phil student, Teaching Assistant
4. Gender	Was the researcher male or female?	Female
5. Experience and training	What experience or training did the researcher have?	Methods - The researcher gathered data from hospital interviews in Costa Rica in a study at the University of Toronto in 2006. She participated in ACSPRI qualitative

		research methods training courses in Australia in 2013.
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	No
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	Participant information sheet and Consent Form
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	Methods
Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	Methods
Participant selection		
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	Methods
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	Methods
12. Sample size	How many participants were in the study?	Methods
13. Non-participation	How many people refused to participate or dropped out? Reasons?	Methods
Setting		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	Methods
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	No
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	Methods
Data collection		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Methods
18. Repeat interviews	Were repeat inter views carried out? If yes, how many?	No

19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	Methods
20. Field notes	Were field notes made during and/or after the inter view or focus group?	Methods
21. Duration	What was the duration of the inter views or focus group?	Methods
22. Data saturation	Was data saturation discussed?	Methods
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	Methods
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	Methods
25. Description of the coding tree	Did authors provide a description of the coding tree?	Methods
26. Derivation of themes	Were themes identified in advance or derived from the data?	Methods
27. Software	What software, if applicable, was used to manage the data?	Methods
28. Participant checking	Did participants provide feedback on the findings?	Methods
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	Results
30. Data and findings consistent	Was there consistency between the data presented and the findings?	Discussion
31. Clarity of major themes	Were major themes clearly presented in the findings?	Results
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Results

Appendix G- Interview protocol (chapter 2,3)

Interview Guide

Title: The Management and Supply of Essential Medicines

Country: _____

Occupational Setting: _____

Profession: _____

Number of Years Practiced: _____

Gender: M / F

Age: _____

PBI Code: _____

Date: _____

Time Started:_____ Time Completed: _____

Location: _____

Interaction Type: Face-to-Face   Teleconference Skype

The Role and Application of the Essential Medicines List:

1. Are you familiar with the Essential Medicines List in your country?

2. What does the concept of having an Essential Medicines List mean to you?

3. What makes a drug essential?

4. How is the concept of the Essential Medicines List applied in your practice setting?

5. Please describe examples of effective use of the Essential Medicines List in your practice setting.

6. Please discuss some barriers to the effective use of the Essential Medicines List in your practice setting.

The Appropriate use of the Essential Medicines List:

7. What factors influence how essential and non-essential medicines are used in your practice setting?

8. How does the essential medicines list affect your practice?

The Availability of the Essential Medicines List:

9. Have you encountered any difficulties obtaining any medicines from the Essential Medicines List?
   Please describe your experience.

10. Please describe the availability of medicines from the Essential Medicines List in your practice setting.

The Affordability of the Essential Medicines List:

11. How does the Essential Medicines list effect costs for individuals, health care professionals, health facilities/institutions, governments, and pharmaceutical manufacturers?

The Quality of Medicines from the Essential Medicines List:

12. Please describe the quality of essential medicines available in your country.

Other:

13. How does the essential medicine list effect patients and their health care experience?

14. In your opinion, what are the key issues surrounding the Essential Medicines List?

Additional Comments:

The Supply and Management of Essential Medicines

Does Australia Prioritise Essential Medicines?

Mai Duong, Rebekah Moles, Betty Chaar, Timothy Chen
Faculty of Pharmacy, The University of Sydney

Background

Determining the value of medicines in the current global health framework is a high priority for industrialised countries. The Essential Medicines List (EML) is a global concept that was established in 1977 by the World Health Organization (WHO) to establish international pharmaceutical standards and guidelines to improve access to medicines within national medicines programs. The need to prioritise medicines in Australia is reflected by increased drug shortages, the absence of national co-ordination of procurement processes, and rising consumption of high cost drugs. The objective is to explore stakeholders' perspectives on the application of EML policy to the Australian context in comparison with international views.

WHO Definition of Essential Medicines

Essential Medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative cost effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times, in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility.

Aim

To explore the perspectives of key opinion leaders and decision makers surrounding the concept of an EML and whether prioritising medicines facilitate access to the population in Australia.

Methods

Interview Guide	Participants	Interviews	Analysis
Framework of questions based on Essential Medicines Access to Medicines principles of: 1) Available 2) Affordable 3) Appropriate 4) Quality/Safety	Purposive and Snowball Sample. 28 Key opinion leaders and senior management in settings of: • Government • Industry • Hospital • Academia • Wholesale and Distribution • Medicines Non-Profit Organizations	Semi-structured interviews. Mean Interview Time: 60 Mins. Interviews recorded and transcribed. Validation offered to participants	Qualitative thematic content analysis. Constant comparative approach. NVivo data management. 10% double coded

Results

The quotes below reflect the variation in stakeholder views when considering the WHO model list of essential medicines in an Australian context.

Does Australia Prioritise Essential Medicines?

The Pharmaceutical Benefits Scheme provides reimbursed medicines to the Australian population as part of the National Medicines Policy

"Australia has an essential medicines list through its PBS in many ways. We identify those medicines Australians needs, and make sure we have access to them at a price the individual, or the government, or the country, community can afford, which is important."-Non profit

"having a list of essential medicines acknowledged can help direct our society to develop infrastructure and supply chains to protect the most important medications. Today the essential medicines list is a PBS kind of by default. It's far from essential." - Hospital

Who decides what are essential medicines in Australia?

The Pharmaceutical Benefits Advisory Committee (PBAC), consisting of multi-stakeholders, makes recommendations to parliament to reimburse medicines as part of the PBS.

"It's got too many alternatives... You have to look at the make-up of the PBAC, I believe the current PBAC membership has the necessary expertise and looks appropriately comprehensive [but] Drug companies can exert influence- directly - or through consumers who then pressure MPs. I believe they could be under a lot of pressure to put new things on the list which probably should not be on the PBS. It is important that there are mechanisms to deal with that pressure." –Government

Does an EML have a role in prioritising the supply chain?

Priorities vary across sectors and stakeholders. This is reflected in the lack of national coordination in the drug supply chain.

"we've been trying to develop our own essential medicines list to make sure that we can provide hospitals without running out as much as possible." – Wholesale/Distribution

"we live in a globalized industry or economy, and shortages, essential medicine, need to be looked upon on a global level rather than just an Australian level because there's very few of these drugs manufactured here in Australia. There is not a one size fits all approach, not for 'Big Pharma'. Putting in the money into an essential medicine, particularly if that's the only version that's available, is like putting all your eggs in one basket." – Industry

How does Australia's medicines policy compare to the WHO EML?

The Australian National Medicines Policy has adapted the EML principles to the Australian context; however an EML is not explicitly defined within the PBS national reimbursement program.

"the PBS is regarded as an essential list? But it comes from a different context of WHO's essential list. Although both of course, require cost effectiveness and there's some similarity. But the WHO list is not a defined list within Australia, although [almost] all drugs on that list are available on the PBS." -Government

"So the PBS is different, because they're not essential by definition. They are things that have been proven to be cost effective and the government is willing to pay to give their citizens access to these medications. I think the structure in a country like Australia is different because it's how much you're willing to pay for an extra innovation, for an extra something. So the concept is different from an essential medicines list." -Academia

Conclusion

Convergence of views in favour of having a national medicines reimbursement program

There was a diversity of views amongst Australian stakeholders in defining the term "essential" due to differences in applied contexts and points of view; which in turn may be a reflection of the absence of a national procurement process.

There is fragmented understanding between stakeholders in the application and relevance of an EML in Australia

Shared views on the prioritisation of medicines can provide a platform for increased communication, national coordination of procurement processes and drug shortage contingency plans

Acknowledgements

This study was conducted in affiliation with the World Hospital Pharmacy Research Consortium (WHoPReC)

References: Available upon request

Appendix K- Global Home – Access to Essential Medicines Newsletter (chapter2,3)

what is ACCESS TO ESSENTIAL MEDICINES?
...and what it's like in Australia

"**Essential medicines** are those that satisfy the priority health care needs of the population.

They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost effectiveness.

Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford."
- *World Health Organization*

From public health perspective, essential medicines save lives and improve health, when they are available, affordable, of assured quality, and rationally used.

In 1977, the WHO developed the first essential medicines model list. Since then, the list has been revised every two years. To date, there are more than 350 medicines included on the model list. Countries can use the model list to develop their own national essential medicines list, which is used as the basis for procurement and supply of medicines, development of reimbursement schemes, medicine donations and guidance for local medicine production.

Access to essential medicines is underpinned by four factors:

rational selection and use of medicines – the selection and appropriate use by governments and other health service providers of medicines that respond to the priority needs of their populations, and that represent the best balance of safety, efficacy, quality and cost.

affordable prices – to ensure that drug expenditure is cost effective and provides the best value for money.

sustainable financing – through the establishment of equitable financing mechanisms, such as social health insurance, and through appropriate models of drug development assistance.

reliable supply systems – medicines are supplied through both public and private sector means. Good health care depends on a regular supply of essential drugs of assured quality, and research and development of new drugs to address the priority needs for the population.

Clearly, equitable access to medicines is a complex, multi-faceted issue.

The high cost of drug development means that private pharmaceutical companies continue to dominate the development and manufacturing space. Without other incentives, they tend to focus on medicines that will generate greater financial return for them, meaning some diseases become neglected.

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These companies would also want to price their products at levels that justify their investments. More often than not, it means without adequate government reimbursement, these drugs are unaffordable to ordinary patients.

Globalisation and the drive for efficiency and profit maximisation have resulted in the manufacturing of medicines being centralised to one or two global sites. Should the production be interrupted or malfunction at these sites, it would result in wide-spread shortage of those medicines globally.

Nationally, governments are responsible for developing their essential medicines list and relevant standard treatment guidelines, in order to guide the safe use of treatments that are most effective for a particular disease, and coordinate the funding and procurement of medicines for those treatments. This is important because guidelines are developed based on scientific evidence. Off-guideline treatments may result in sub-optimal efficacy and adverse side effects. In addition, limited resources should not be wasted on funding substandard or inappropriate treatment options. Adequate forward

procurement planning also ensures the timely supply of essential medicines.

Competition drives down price. Appropriate government policies that encourage generic competition helps keep medicines prices at affordable level. Such policies include incentives for pharmacists and consumers to choose generics over branded products, or the removal of patent exclusivity.

Individuals also have roles to play to ensure equitable access to medicines. Healthcare professionals are responsible for the rational use of quality medicines by adhering to evidence-based medicine and standard treatment guidelines, as well as educating patients on compliance, most notably

the use of antibiotics.

Before considering access issues in underprivileged areas in the world, let us look at our own issues here in Australia.

We can consider ourselves luckier than many others here in Australia. We have established standard treatment guidelines for most diseases, which underpin the rational use of medicines; our health professionals are well trained, therefore carry out evidence-based medicine most of the time; reasonable policies are in place to encourage generics competition to drive down price; most of the common medicines are funded through the PBS scheme; the supply system is generally reliable and supported by infrastructure.

Even so, access issues continue to plague our system. In 2011, 82% of cancer medicines seeking reimbursement on cost-effectiveness grounds were rejected by the PBS. It means that patients requiring these medicines will have to bear the full costs on their own, which can be as much as $200,000 a year.

The process of listing with PBS is also complex and time-consuming, impeding the timely access to subsidised medicines.

With limited manufacturing capacity locally, we rely heavily on importing medicines from overseas. With globally centralised manufacturing, any issues in the supply chain could result in wide-spread shortage. A recent example include the shortage of Diabex in 2012, a diabetes medicine, due to problems in manufacturing its active ingredient. Pharmacists were forced to swap formulations to account for the shortage, which posed added risks for patients. The active ingredient is now manufactured in Queensland to ensure supply. Other shortage examples include injectable morphine due to overseas packaging delay, and

benzylpenicillin due to increased demand from flood and disaster affected regions of the world.

Generics competition helps drive down price, it also can help ensure supply, because multiple companies are able to manufacture the same medicine. However, patent exclusivity means that newer medicines are manufactured and marketed exclusively by one company. Until patent expires, generics companies are barred from producing the drug.

As individuals, you may feel powerless to make a difference, or think that it is the government's

responsibility. However, there are simple things you can do as health professionals. For example, adhere to standard treatment guidelines and evidence-based medicine; educate yourself and your patients in the rational use of medicines; keep up to date about any shortage and know the contingent plans should that happen; lend your voice to credible organisations that advocate for equitable access. As active players in the healthcare system, your actions will have a direct impact in promoting the equitable access to essential medicines. ■

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Further reading

1. WHO essential medicines, policies and fact sheets
http://goo.gl/c0Ltba

2. WHO essential medicines definition and access framework
http://goo.gl/zEcFPF

3. Report on access to cancer medicines in Australia by Deloitte
http://goo.gl/fM1CTT

4. Read about how the lack of platelets affected a junior doctor, see attachment – *'Nightmare in Gippsland'*

5. Factors affecting supply, see attachment – *'Securing the supply chain'*, De Somer, E 2011

6. News article on shortage of essential medicines in Australia, see attachment – *'A case for our own medicine'*, The Australian, March 2012

Relevant organisations

1. Doctors Without Borders (MSF) Access Campaign
http://msfaccess.org/

2. Health Action International
http://haiweb.org/

3. HAI Asia Pacific
http://haiasiapacific.org/

Case study:
Nightmare in Gippsland

Platelets are essential blood products that are used to treat a variety of diseases, and they are in chronic short supply globally, partly due to their short shelve life (5 days).

The shortage is exacerbated in regional and remote locations, due to barriers in acquisition, transportation and storage.

In this case study, we will look at how the shortage of platelets in a regional hospital affected a junior doctor, and put a patient's life in danger.

Location

A major regional hospital in Gippsland, Victoria, 200km from Melbourne

Hospital annual patient admissions

~12,000

Hospital staff number

~1,200

Time

5 a.m.

Junior doctor Sarah* was called into the hospital by a concerned nursing staff.

Third year out of university, she was on her three-month registrar rotation at the regional hospital. It also meant that most of the time, she was the most senior medical staff on site.

The medical emergency that brought in Sarah involved a patient with late stage sigmoid colon cancer, which had eroded the nearby artery and resulted in

massive bleeding from the rectum. The amount of blood loss from the patient was like nothing the junior doctor had ever seen, and the patient's blood pressure was dangerously low.

Immediately, Sarah started the patient on blood transfusion. However, over a period of two hours, the patient continued to lose large amount of blood. After receiving four bags of blood, the patient still could not achieve stable blood pressure and was drifting in and out of consciousness.

At this point, Sarah decided to implement the massive transfusion protocol, which indicated the transfusion of red cells, cryoprecipitate, platelets and plasma.

However, upon requesting the blood products from the regional blood bank, Sarah was told that there was only limited cryoprecipitate available, and no platelets at all in the whole of Gippsland region. The only way to get platelets in was by train from Melbourne.

The patient was not going to wait for the train.

Sarah had no choice but to go ahead and administer the protocol. By now, the patient had three cannulas in his veins, and the nurses were squeezing blood products in with their hands, because even the highest setting on the mechanical pump was not enough to compensate for the rate at which the patient was losing blood.

*Fictional name

Sarah soon ran out of cryoprecipitate, and without the platelets, it was extremely difficult to restore the balance of blood contents and stabilise blood pressure, which were required before the patient could be operated on.

'I'm going to die, I'm going to die.', the patient moaned, and Sarah was getting more and more worried.

Thankfully, Sarah and the nurses eventually managed to control the patient's blood pressure, and the patient was rushed to the theatre.

While taking stock, Sarah realised that the amount of blood loss was equivalent to the patient's total blood volume, and three times of that was administered from all the fluids given to the patient by Sarah.

While the patient survived the ordeal in the end, their life was placed at great, unnecessary danger.

The crisis was primarily due to issues in reliable supply, and it could have been caused by a number of reasons. For example, a failure in forward planning and coordination to ensure stock level adequacy; a sudden increase in demand in the region; disruption in initial plan to deliver the products with no contingent plan in place.

We are likely to encounter similar situations at some point in our career as health professionals. It highlights how access issues can acutely affect us and our patients. As a result, it is every health professional's responsibility to recognise, understand and address these issues, in order to promote and achieve equitable access to essential medicines for all. ■