Surveillance approaches to detect the quality of medicines in low-middle income countries with a focus on artemisinin combination therapies for malaria.

MIRZA GHALIB LALANI

Thesis submitted in accordance with the guidelines for the degree of Doctor of Philosophy of the University of London.

August 2018

Clinical Research Department

Faculty of Infectious and Tropical Diseases

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE

Funding acknowledgement: The research was funded by the John Henry Memorial Fund and the Leverhulme Charities Trade Trust.

I, Mirza Ghalib Lalani, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:

6th August 2018

Abstract

Introduction

Recent years have seen an increase in reports of poor quality antimalarials with estimates that up to 30% have failed chemical analysis, even though robust empirical evidence for their prevalence remains scarce. Several internal (associated with national systems) and external (not under the direct control of national authorities) risk factors may contribute to the circulation of poor quality medicines. This thesis will explore these factors with an overall aim of providing evidence to strengthen medicines quality surveillance systems (MQSS) in low-middle income countries (LMICs).

Methods

Data collection was conducted in two phases in Senegal between March 2013 and April 2014. The first phase involved interviews with key stakeholders of the MQSS such as authority representatives as well as treatment providers and explored the system's vulnerability to risk factors for poor quality medicines and their perceptions of the quality of medicines available in Senegal. The second phase comprised a series of laboratory-based studies with technicians at the national medicine quality control laboratory (MQCL) including an assessment of the practical utility, usefulness and acceptability of a specific test, to check the quality of artemisinin based medicines, namely the artemisinin derivative test (ADT). Finally, a systematic literature review assessing the study design and reporting of antimalarial medicine quality studies and surveys was conducted with the included studies assessed for quality against our newly proposed list of criteria.

Findings

Overall, interviewees expressed confidence in the quality of medicines available in the public and regulated private sectors which was attributed to effective national medicines regulation and adequate technical capacity at the MQCL. In contrast, poor quality medicines were thought to be available in the unregulated (informal) sector as they were not subjected to national regulatory processes or stored appropriately, resulting in exposure to direct sunlight and high temperatures. Generic medicines were also perceived to be of inferior quality when compared to their brand versions as they were lower in cost and thought to be less effective in alleviating symptoms. The ADT demonstrated a promising level of accuracy to detect fake or grossly substandard artemisinin based medicines and laboratory technicians favoured its simplicity of use without the need for specific training. The literature review found that there

is much heterogeneity in study design and inconsistency in reporting which has impacted on the generalisability of findings for antimalarial medicine quality studies.

Conclusion

A major shift is required in the framing of medicine quality from a technical/legal to a clinical paradigm with evidence required to demonstrate the impact of poor quality medicines on public health. National governments need to invest in regulatory and technical capacity to strengthen MQSS to minimise the likelihood of poor quality medicines circulating in a country. Utilising simple, and portable (preferably handheld) tests like the ADT, in non-laboratory settings may enhance post-marketing surveillance, especially in resource constrained contexts. Nonetheless, comparative evaluation of all currently available screening technologies for their capability to distinguish poor quality antimalarials for confirmatory pharmacopeia testing and public health action is required. Suggestions that reduce the risk of bias and error have been proposed for conducting medicine quality studies to enable standardisation of study design and reporting, thereby increasing the reliability of findings and allowing comparison between studies.

Acknowledgements

The undertaking of this thesis would not have been possible without the financial support of the John Henry Memorial Fund and the Leverhulme Charities Trade Trust. I would like to express my sincerest thanks Professor Michael Miles for his instrumental role in assisting me to secure funding from the John Henry Memorial Fund. My supervisors Harparkash Kaur and Sian Clarke have provided excellent support and guidance. Aside from sharing their invaluable academic insights, they have tolerated reviewing long drafts and maintained their patience during the occasionally lengthy interval between revisions. Additionally, their pastoral care has provided great reassurance during some challenging personal circumstances experienced during the thesis. A further thanks to Harparkash for continually lobbying within the department, LSHTM and outside of the institution about the importance of assuring medicines quality, which contributed to the securing of funding for the PhD. I would also like to express my gratitude to my advisor Jayne Webster and the guidance and direction provided by Toby Leslie and Ron Behrens in the earlier stages of my PhD.

The support of several individuals in Senegal was essential to the successful undertaking of the data collection phase. Badara Cisse, Alioune Ly and Adama Diedhou were instrumental in organising and coordinating various aspects of the fieldwork. Thanks to Amina, Ilam and Ndongo who assisted with fieldwork and showed great patience in my attempts to speak broken French. I am very grateful to Maty, Gilles and Ibrahim who were wonderful hosts and their hospitality provided great comfort when being away from my own family for lengthy periods of time.

Finally, I would like to express my heartfelt gratitude to my family. My wife Sofeena and my daughters Mayah and Aylah have provided much love, happiness and laughter and the motivation to persist with the PhD even during the most challenging of times. A further final deserved mention for my mother and late father, who's passing very close to the submission of this thesis was painful to endure but I am grateful to them both for listening, advising and supporting me throughout.

List of publications

Publications from the thesis

- Lalani M, Kitutu FE, Clarke SE, Kaur H. Anti-malarial medicine quality field studies and surveys: a systematic review of screening technologies used and reporting of findings. *Malaria journal*. 2017 Dec;16(1):197.

Proposed publications from the thesis

- An absence of evidence breeds contempt: health system stakeholder perceptions of the quality of medicines available in Senegal.
- Evaluating the performance of screening tests to detect the quality of artemisinin based medicines; evaluation of the artemisinin derivate test and the GPHF MiniLab® with laboratory technicians in Senegal.
- Assessing the practical utility, usefulness and acceptability of the artemisinin derivate test (ADT); a new test for detecting the quality of artemisinin based medicines.

Additional relevant publications not included in the thesis

- Kaur H, Clarke S, **Lalani M**, Phanouvong S, Guerin P, McLoughlin A, et al. Fake anti-malarials: start with the facts. *Malaria journal*. 2016;15(1):86.
- **Lalani M**, Kaur H, Mohammed N, Mailk N, van Wyk A, Jan S, et al. Substandard antimalarials available in Afghanistan: a case for assessing the quality of drugs in resource poor settings. *The American journal of tropical medicine and hygiene*. 2015;92(6 Suppl):51-8.
- Fadeyi I, **Lalani M**, Mailk N, Van Wyk A, Kaur H. Quality of the antibiotics-amoxicillin and co-trimoxazole from ghana, Nigeria, and the United Kingdom. *The American journal of tropical medicine and hygiene*. 2015;92(6 Suppl):87-94.

Contents

List of tables

List of figures

List of Acronyms

ACT	Artemisinin combination treatment
AD	Artemisinin derivative
ADT	Artemisinin derivative test
AMFm	Affordable Medicines Facility for Malaria
APQ	Acceptable Pharmacopeial Quality
DPL	Direction des Pharmacies et des Laboratories
DNP	2,4 dinitrophenylhydrazine
FBS	Fast Blue Salt
FGD	Focus group discussion
GMP	Good manufacturing practice
GPHF	Global Pharma Health Fund
GSMS	Global surveillance and monitoring system
HPLC	High performance liquid chromatography
LMIC	Low-middle income country
LNCM	Laboratoire national de contrôle des medicaments
LQAS	Lot quality assurance sampling
MQAS	Medicines quality assurance system
MQCL	Medicines quality control laboratory
MQSS	Medicines quality surveillance system
NMRA	National Medicines Regulatory Authority
PDA	Photo diode array
PNA	Pharmacie Nationale d'Approvisionnement
PNLP	Programme National de Lutte Contre le Paludisme
RDT	Rapid diagnostic test
SAPI	Stated active pharmaceutical ingredient
SSFFC	Substandard/spurious/falsely-labelled/falsified/counterfeit
TLC	Thin layer chromatography
UCAD	Université Cheikh Anta Diop de Dakar
USAID	United States Agency of International Development
USP	United States Pharmacopeia
WHO	World Health Organization

Chapter 1: An introduction to monitoring the quality of antimalarial medicines and current strategies

1.1 Background

In 2015 the World Health Organization published 17 Sustainable Development Goals for 2030 comprising a range of issues including improving health and education. [1] Sustainable Development Goal 3; 'Ensure healthy lives and promote well-being for all at all ages' has several targets. Target 3.8 stipulates ''achieving universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all.'' [2] Hence, access to quality medicines is of great importance if this particular goal is to be achieved. However, studies of medicine quality conducted in low-middle income countries (LMICs) indicate that there are poor quality medicines in circulation. [3] WHO estimates from 2006 suggested that as many as 10-30% of medicines on sale in parts of Africa, Asia and Latin America were counterfeit. [4] More recent figures for counterfeit medicine in circulation are not available for these regions amid concerns of the lack of robust evidence to substantiate such estimates. [5]

The consequences of consuming medicines with the incorrect stated active pharmaceutical ingredient (SAPI) or occasionally, even toxic ingredients, can be debilitating or even fatal, as exemplified by around 500 cases of renal failure that led to the death of children in India, Bangladesh and Haiti after ingesting paracetamol and cough syrups containing a renal toxin.[6-8] The existence of poor quality medicines is of particular concern in LMICs, where the absence of robust medicines regulation and adequate technical capacity in the form of well-equipped laboratories and human resources to test the quality of medicines limits the ability of the health system to assure that the medicines available to the public are safe and effective.

1.1.1 What is a poor quality medicine?

Poor quality medicines result from a multitude of contributory factors. They may arise as a result of intentionally produced falsified medicines with fake packaging or the wrong active ingredient or low levels of the active ingredient. Inadequate manufacturing processes leading to non-compliance with international standards for a medicine set out in a drug monograph may render a medicine substandard, with not enough or too much of the active ingredient. Furthermore, inadequate storage of medicines during transport or storage may cause degradation of otherwise acceptable pharmacopeial quality medicines. These contributory or risk factors are discussed further in section 1.1.3 of this chapter.

Just as the reasons for poor quality medicines arising are varied and complex, there is also much variation of the description and definition of medicine quality which is dependent upon the field of study, the context, and the perceptions of individuals including policy-makers, health professionals, medicine sellers and consumers. In May 2017, the World Health Assembly agreed to use the term substandard and falsified medicinal products. The definition of both components of this new term is outlined in table 1.1 below, although there is no reference to degraded products. In addition, a new category, seldom used in the relevant academic and policy literature associated with medicines quality has also been agreed, 'unlicensed and unregistered medicines' defined as ''*Medical products that have not undergone evaluation and/or approval by the National Medicines Regulatory Authority (NMRA) for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.''* It is not clear in the latest working document if this group is a distinct category or encompassed by the term substandard and falsified products. [9] The consensus on the definitions for medicine quality were preceded by several years of debate and negotiation by WHO Member States during which time the WHO used a 'catch all' acronym namely, SSFFC (substandard, spurious, falsely-labelled, falsified and counterfeit). [5] This definition was criticised for its ambiguity as it encompassed all poor quality medicines suggesting their deficiencies are the same, whereas, they are in fact quite different, in terms of their causes and the solutions required to address them. [10, 11]

To some extent the new, simplified definitions for substandard and falsified medicines attempt to homogenise medicines quality. Yet, as mentioned above, the definitions for medicines quality vary greatly and have been the centre of much discourse with academics, lawyers, pharmaceutical manufacturers, health professionals, politicians and even the WHO using varying nomenclature. [12] The next section of this chapter provides a synthesis of the evidence for definitions for poor quality medicines with an overview of the most commonly ascribed terms (table 1.1) whilst identifying three paradigms within which medicines quality is perceived and defined; legal, technical and clinical.

Table 1.1: Commonly used definitions for medicines quality

Medicine quality	Definition(s) (or description where no official definition exists)	Defined by	Paradigm
Falsified	*'Medical products that deliberately/fraudulently misrepresent their identity, composition or source.'*	WHO, 2017 [9]	Legal
Substandard	*'Also called "out of specification", these are authorized medical products that fail to meet either their quality standards or specifications, or both.'*	WHO, 2017 [9]	Technical
Unregistered/ unlicensed	*'Medical products that have not undergone evaluation and/or approval by the National Medicines Regulatory Authority (NMRA) for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.'*	WHO, 2017 [9]	Legal
Acceptable pharmacopeial quality	*'…have the acceptable amount of active pharmaceutical ingredients as specified by the pharmacopeia's and meet other quality attributes (uniformity of dosage units, purity, bioavailability etc.).'*	Kaur *et al,* 2016 [13]	Technical
Counterfeit	*'…deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient (inadequate quantities of ingredient(s) or with fake packaging'* *'Medicines that do not comply with intellectual-property rights or that infringe trademark law'*	WHO, 1992 [5] European Medicines Agency, 2016 [14]	Legal/ technical Legal
Degraded	*'Degraded formulations may result from exposure of good-quality medicines to light, heat and humidity. It can be difficult to distinguish degraded medicines from those that left the factory as substandard.'*	Hall *et al, 2016* [15]	Technical

The most frequently used definitions for medicines quality presented in the table above are appropriate to either the legal or technical paradigm. The definitions do not encompass the potential clinical consequences of poor quality medicines which may comprise the perceptions of health professionals or the public. The three paradigms are discussed further below.

Legal paradigm

The discourse alluded to previously was largely centred on the legal status of poor quality medicines which is best illustrated by the debate on the precise definition of counterfeit medicines. Generic medicine manufacturers and those involved with intellectual property law were concerned that misuse of the term counterfeit may lead to misclassification of some legitimately manufactured generic medicines. [10] From a legal standpoint, any judicial process against a producer would be based on providing evidence that there was intent to produce a poor quality medicine. [10] Intent to produce poor quality medicines is often a specific

problem with falsified medicines that closely mimic authentic products with deliberately fake, but convincing packaging which may be fraudulently mislabelled with respect to their identity or source. They may often contain ingredients of low quality or in the wrong dose, the wrong ingredients, or low levels of the active ingredient. [14, 16] New definitions for poor quality medicines under which counterfeit medicines are classified as 'falsified' do not reference intellectual property rights, with counterfeits categorised as "trademark counterfeit goods" and ''pirated copyright'' as defined under the Agreement on Trade-Related Aspects of Intellectual Property Rights. [9]

Substandard medicines differ from falsified and counterfeit medicines in that they are genuine medicines that have been manufactured poorly and hence, do not meet quality specifications set for them by national standards. [5] They may contain low SAPI or too much SAPI and thus, do not comply with pharmacopeia tolerance limits for a medicine as stated in the authorised drug monograph. [17] In legal terms the difference in definitions is centred on intent, whereby falsified and counterfeit medicines are deliberately produced as opposed to a non-deliberate or accidental manufacturing error resulting in a substandard medicine. [10]

Technical Paradigm

The technical paradigm focusses on the chemical content and pharmaceutical properties of a medicine. From a technical perspective, an acceptable pharmacopeial quality medicine meets the specifications stated in its drug monograph detailed in an international pharmacopeia. [13, 18, 19] International pharmacopeia's such as the British, European or United States Pharmacopeia contain monographs for drugs which are written documents, or standards, that describe a drug, providing the name of a substance; its definition; packaging, storage, and labelling requirements; and information on tests needed to assess the drug for its strength, quality, purity and bioavailability. This thesis will predominantly refer to the United States Pharmacopeia (USP) which also refers to an agency that provides substantial financial, technical and logistical support to many LMICs in building capacity for medicines quality assurance.

Definitions are often centred on the results of content analysis to measure the amount of SAPI and calculating its percentage of the SAPI stated on the label or packaging of a medicine. Falsified medicines may contain zero SAPI, low SAPI or the wrong SAPI leading to treatment failure, severe disease and even death. [14, 16] Substandard medicines with some SAPI or too much SAPI or reduced bioavailability may result in treatment failure, recrudescence of infection (for anti-infectives such as antimicrobials and anti-parasitic medicines) and

potentially severe infection. [20, 21] In fact, the consequences of consuming substandard medicines are not only detrimental at the individual level but also at the population level through a theoretically posited association with drug resistance for antimalarials and antibiotics as sub-therapeutic doses are thought to be conducive to the selection and spread of drug-resistant pathogens. [22, 23] Finally, degraded medicines result from the exposure of acceptable pharmacopeial quality medicines to various environmental conditions such as high humidity and temperature, and direct sunlight. Distinguishing substandard medicines resulting from poor manufacturing practices from those that were degraded through improper storage is challenging. Currently, there is only one study which has described how degraded medicines should be classified, not just by their appearance but by measuring the products of degradation of one or both SAPIs in the formulation. [15]

The discourse on definitions detracts from the more serious issue of the public health consequences (treatment failure leading to severe disease, recrudescence, drug resistance or death) of the consumption of medicines that deviate from the chemical content or possesses pharmaceutical properties that do not meet the standards stated in the monograph for that drug. Moreover, poor quality medicines may increase the burden on already limited resources at the provider level as a result of treatment failure and/or recrudescence of infection which may result in patients requiring additional clinical consultation, repeat prescribing and additional purchase of medicines. In some cases, when treatment has failed and there has been progression to severe clinical disease, admission to health facilities maybe required with lengthy patient stay. The existence of poor quality medicines may also undermine confidence in health professionals, medicines quality assurance systems and the pharmaceutical industry.[24]

Clinical paradigm

The technical paradigm while including the specific public health consequences of poor quality medicines does not consider the perceptions of health professionals, medicine sellers and consumers. At the point of care, perceptions of medicine quality are more likely to be framed in a clinical paradigm, focussing on efficacy and safety of medicines. Treatment providers generally need information on the safety (side-effects) and effectiveness (how quickly and well the medicine works) of their medicine to enable them to make an informed decision on treatment selection. This information may also have an implication on patient adherence to the treatment regimen. [25] From the perspective of the treatment provider, medicine selection is sometimes a consideration of the benefits and risks of the treatment influenced by

numerous factors including, but not restricted to, local policy and clinical guidelines, cost and clinical knowledge (adverse effects) and experience (previous success with the treatment). [26]

However, there is a paucity of information on the consideration of medicine quality as a factor in clinical decision-making by health professionals or whether perceptions of the public about medicines quality, are considered by patients when purchasing or electing to consume a medicine. Studies in high income settings have found that a small proportion of doctors viewed generic medicines as being manufactured to a poorer quality, which they believed may have implications for patient safety. [27] Additionally, generic medicines were perceived as inferior in quality to their brand versions as they were lower in cost and manufactured by lesser known companies. [28] Similarly, studies of patient's perceptions of medicines quality in Lao and South Africa found that a medicine was considered to be of good quality, if it alleviated symptoms with minimal side effects (efficacy and safety), if it was a brand name medicine (made by a reputable company) and if it had a higher cost. [29, 30] The perceptions of health professionals and the public as consumers or patients demonstrate a divergent view of medicine quality to that presented as the technical paradigm above.

1.1.2 Implications of poor quality medicines for public health with a focus on malaria

Malaria remains a major public health concern in LMICs and is an affliction of the most vulnerable and impoverished in many countries in sub-Saharan Africa, Asia and Latin America. In 2016, globally there were around 216 million cases of malaria and an estimated 445,000 deaths, 91% of which were in Africa. [31] However, in recent years there has been an overall decline in both malaria incidence and prevalence due to application of improved strategies for prevention, control and treatment. [32] Successful control strategies have included the widespread distribution and use of insecticide treat nets (ITNs). In sub-Saharan Africa there was a 23% increase (to 53%) of the total population at risk of malaria sleeping under an ITN between 2010 and 2015. [33] Furthermore, the replacement of chloroquine, initially by sulphadoxine-pyrimethamine and then by artemisinin based treatment has significantly contributed to the reduction in transmission and burden of the disease, with 81 out of 88 malaria endemic countries having adopted Artemisinin Combination Treatment (ACTs) as the first line therapy for treatment of uncomplicated *P.falciparum* malaria by 2015. [34] Artemisinin based medicines are capable of rapidly reducing parasite levels, have minimal adverse effects, are less prone to the development of resistance and their gametocidal activity contributes to the reduction of transmission of malaria infection making them an effective treatment against *P.falciparum* malaria. [35] The advent of artemisinin based treatment was particularly important in the context of emerging drug resistance and subsequent

ineffectiveness of initially chloroquine and then sulphadoxine-pyrimethamine in malaria endemic countries. [36]

The primacy of ACTs for malaria treatment demonstrates the necessity for assuring their quality as well as that of the other antimalarials to ensure that the success of malaria control and treatment strategies is maintained. A recent WHO study used impact models to estimate the public health and socioeconomic impact of poor quality medicines including antimalarials.[24] The study reported that incremental deaths in sub-Saharan Africa due to substandard and falsified antimalarials comprised approximately 2.1% to 4.9% of total malaria deaths, or approximately 3.8% to 8.9% of malaria deaths relating to patients seeking treatment. The study authors suggested that given the limitations of the available data (aggregating data from just 10 studies in 17 countries between 2007-2016) it was likely that the results of the model underrepresented the full health and economic impact of substandard and falsified antimalarial medicines. Such findings illustrated that failing to assure the quality of antimalarials may have significant clinical and public health implications. Aside from potentially increasing the risk of mortality, clinical implications of the consumption of a falsified antimalarial medicine include treatment failure and progression to a severe manifestation of the disease as highlighted by the case of a patient who consumed purported artesunate monotherapy for uncomplicated malaria in Equatorial Guinea. The medicine, when tested did not contain the SAPI. [21] There are also public health implications from consuming substandard antimalarials. At the patient level, sub-therapeutic doses may lead to prolonged or severe illness and even death whilst also increasing the risk of recrudescence of malaria infection. [20] At the provider level this increases burden on already limited resources and may undermine confidence in health professionals. [37]

From a broader public health perspective sub-optimal medicine concentrations may select for drug resistant parasites. [20] The inability of a medicine to effectively kill all parasites may result in surviving parasite strains multiplying, a mechanism that is a precursor for recrudescence of infection. However, amongst these remaining parasites there may also exist drug resistant mutates that are less susceptible to a medicine and have hence survived, promulgating resistance. [38] Chloroquine resistance emerged in the 1950s initially in Southeast Asia, before eventually spreading to sub-Saharan Africa. Chloroquine became a victim of its own success, due to overuse and misuse (inappropriate prescription, administration and non-compliance) for decades and by the mid 1990's, studies in sub-Saharan Africa had shown a temporal association between chloroquine resistance and notable increases in malaria attributable mortality. [39] Whilst resistance to chloroquine developed

over many decades, pyrimethamine resistance emerged much faster and despite replacing chloroquine initially as the first line medicine for *P.falciparum*, within a decade, many malaria endemic countries had started to implement artemisinin based treatment as the first line therapy against uncomplicated *P.falciparum* malaria. [40] Sulphadoxine-pyrimethamine treatment in sub-Saharan Africa is now limited to seasonal chemoprevention in combination with amodiaquine in parts of West Africa [41] and as intermittent preventative treatment in pregnancy. [42]

As with its predecessors, drug resistance has been documented with artemisinin based antimalarials with multi-resistant parasites detected in Southeast Asia along the Cambodia-Thailand border. [43] Initial reports were of longer parasites clearance times, interpreted as an early indication of the emergence of drug resistance. [44, 45] An association between poor quality artemisinin based medicines and drug resistance has been postulated but not as yet proven. [23] This theoretical association is similar to that for other antimalarials that have conferred resistance. Drug pressure selects for resistant parasites especially when parasites are exposed to monotherapy or to sub-therapeutic concentrations. Therefore, substandard artemisinin based medicines theoretically increase the risk of the development of drug resistance as they may contain low SAPI or may have poor bioavailability. [46] The WHO recommended the use of combination treatments whilst mandating the removal from the market of artemisinin based monotherapy (artesunate, artemether and dihydroartemisinin) in tablet form, acknowledging that without a partner drug there was a greater likelihood for the development of drug resistance to artemisinin. [47]

1.1.3 Risk factors for poor quality medicines

Several factors may increase the risk of the circulation of poor quality medicines in LMICs. These factors can be categorised as internal (reflecting limitations in national health systems to control the medicines supply) and external (aspects over which countries may have less control). [48] Internal factors include inadequate medicine regulation, insufficient technical capacity for testing the quality of medicines and an inability to apprehend and prosecute manufacturers and distributors of poor quality medicines. [49] These factors are shaped by local systems for governance, law enforcement, and financing.

Additionally, external factors such as medicine shortages and high cost of a medicine to the consumer reduce access to affordable medicines and may lead patients to seek products from less regulated sources, increasing their potential risk of exposure to low-quality medicines. Moreover, medicine shortages create a gap in the market in which counterfeiters may operate.

Longstanding medicines shortages in parts of North America and Europe have been shown to provide an opportunity for illegal sellers to introduce potentially counterfeit medicines on to the market, a problem accentuated by the proliferation of internet pharmacies. [50, 51] Yet, the availability and cost of medicines is often determined by external agents, including pharmaceutical manufacturers and distributors, rather than by national governments.

Unfortunately, many of these internal and external factors are applicable to LMICs and maybe compounded by a lack of awareness amongst regulators, health professionals and the public and low political will to acknowledge and tackle the problem of poor quality medicines. [52] The factors that increase the risk of the presence of poor quality medicines in a country, and current strategies to control this risk, are discussed further in the introduction to Section 1 (Monitoring the quality of medicines in Senegal: a stakeholder perspective).

1.1.4 Scale of the problem of poor quality antimalarials

Since the beginning of this century, there have been several reports of the discovery of poor quality antimalarials, particularly artemisinin based medicines. [53, 54] A recent review (2014) found that 30% (2,813) of a total of 9,348 antimalarial medicine samples from parts of Asia, central and South America, and sub-Saharan Africa had failed chemical content/packaging analysis. [3] Furthermore, an earlier review from 2012 had claimed that around a third of 1649 antimalarials available in Southeast Asia and sub-Saharan Africa were falsified, although the authors did not provide separate estimates for substandard medicines. [55] ACTs are currently the first line medicines for uncomplicated *P .falciparum* malaria and in 2016 around 409 million ACTs courses were procured by malaria endemic countries. [31] The majority of studies assessing antimalarial medicine quality have focussed on the quality of artemisinin based medicines. Recently studies have employed larger sample sizes and robust sampling and analytical approaches, providing estimates of the prevalence of poor quality artemisinin based medicines and highlighting a greater problem of substandard as opposed to falsified versions.[56-58] There have also been several concerning reports of artemisinin resistance in parts of Southeast Asia. [59-61] Together these aspects may warrant the preference for assessment of ACT quality in antimalarial medicine quality studies in comparison to other antimalarials.

The first documented case of fake artemisinin based medicine was reported in 1999 in Cambodia where a nationwide survey found that 71% of 133 drug outlets stocked the artemisinin based monotherapy, artesunate, without the SAPI. [62] This initial discovery was the precursor for what has been subsequently described as a ‘’growing epidemic of fake

antimalarials'' in Southeast Asia. Indeed, of 1437 samples of antimalarial drugs collected and analysed in Southeast Asia from 2001-2011, 36% were found to be 'falsified'. [63] This is particularly worrying in the context of Southeast Asia which has been described as an 'epicentre of multi-drug resistant malaria.' [45]

The situation regarding the prevalence of poor quality antimalarials in sub-Saharan Africa is less clear, although, evidence suggests substandard medicines maybe of greatest concern. [56, 58] The 2009 and 2011 the 'Survey of the Quality of Selected Antimalarial Medicines in circulation in Sub-Saharan Africa' studies by the WHO and USP found that overall 30% (n=139) of 464 antimalarial drug samples did not meet USP compendia quality standards. According to the definitions used in the report, the failing drugs were substandard. [54, 64] Furthermore, a study in 2012 - 2013, from Enugu, Nigeria collected and analysed 3,024 ACTs and found that 6.6% were substandard, 1.3% were degraded and 1.2% were falsified. [56] The latter study also demonstrated that a representative sampling approach is essential to accurately quantify the scale of the problem of poor quality medicines. Several other studies suggest that West Africa in particular is prone to the problem of poor quality antimalarials, especially Nigeria and Ghana. [57, 65-69] Research focus appears to be directed toward Nigeria and Ghana in comparison to neighbouring countries which is reflected in the greater volume of studies and surveys published. The possible reasons for this include: a) medicines quality being higher on the political agenda in these two countries with national authorities making a concerted effort to tackle poor quality antimalarials; b) both countries producing medicines nationally and reportedly, manufacturing facilities not always complying with Good Manufacturing Practice requirements [54] which increases the possibility of substandard medicines entering the supply chain and may in turn heighten awareness, encouraging the NMRAs to conduct inspections of facilities, and undertake medicine quality surveys, c) the problem of antimalarial medicine quality is magnified, because less research is being conducted in other countries or d) it may simply reflect additional research effort in the two countries.

The exact scale of the global problem of poor quality antimalarials is not known, due to a relatively small number of studies, geographical disparities in research efforts and a lack of standardisation in study design and reporting. These geographical differences in medicines quality research efforts are shown in figure 1.1. Overall, research has focussed on two regions with highest global malaria burden, West Africa and Southeast Asia. However, there are relatively fewer studies from other high malaria transmission areas such as east and Central Africa and within West Africa the majority of studies are from Nigeria and Ghana.

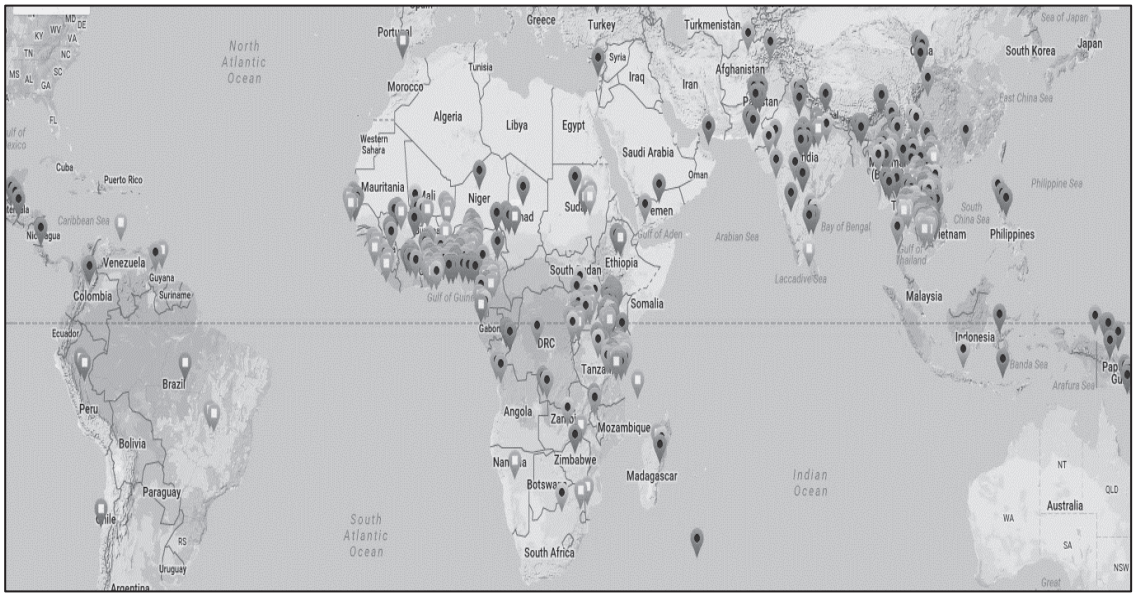


Figure 1.1: Geographical distribution of antimalarials medicine quality surveys and studies
Source: The Worldwide Antimalarial Resistance Network (WWARN) antimalarial drug quality surveyor is a database of antimalarial quality surveys and studies including academic publications, multi-country surveys conducted by international agencies, and where available, national surveys published by NMRAs. [70] The symbols show the locations in which antimalarial studies and surveys have been conducted between 1985 – 2018.

The lack of standardisation of antimalarial studies exemplified by the heterogeneity in the methods used and in the reporting of findings, also limits the assessment of the scale of the problem of poor quality antimalarials. There is variation in the strategies for sampling medicines, the analytical techniques employed to determine medicines quality, and definitions used to classify poor quality medicines. [13] Moreover, this heterogeneity may limit the reliability and generalisability of findings and the extent to which medicine quality studies and surveys can be compared and contrasted. The variation in how medicine quality studies and surveys are conducted and reported, and the need for greater standardisation, is discussed in more detail in chapter 4 of this thesis.

1.1.5 Global and national systems for preventing the circulation of poor quality medicines

The previous section presents the scale of the problem of antimalarial medicine quality, yet there are systems and mechanisms currently in place at the global and in some cases, national level to control medicines quality. In 2013, the WHO created a Surveillance and Rapid Alert System for SSFFC Medical Products which operates on a global scale. In 2017, this system became known as the Global Surveillance and Monitoring System for substandard and falsified medical products (GSMS) to reflect the recently agreed definitions for substandard and falsified medicines. The primary aim of the system is to improve the quantity, quality and analysis of data on the incidence of substandard and falsified products. The system provides

stakeholders with a basis to develop strategies for reducing the incidence of substandard and falsified products by identifying vulnerabilities in supply chains, measuring the harm caused and facilitating efficient exchange of information between countries to reduce the public health impact.

The WHO have trained NMRAs to report incidents involving substandard and falsified medicines to the system through the use of a WHO Rapid Alert Form. [71] When a report is received it is compared to existing reports on a database with any matches identified and details shared with the reporting Member State. If required the WHO will also provide technical support to the Member State such as facilitating urgent laboratory analysis or in complex cases, deploying experts to the country to provide assistance. The global alert system provides Member States with important information, allowing a country to tackle the problem swiftly, mitigating against the potential distribution and consumption of a poor quality medicine. In addition, technical support where required from the WHO provides reassurance to the Member State that the issue will be addressed by 'experts' as well as an opportunity for a national agency to learn and improve their post-marketing surveillance systems.

The effectiveness of this global alert system is dependent on the volume and accuracy of data collected by national medicines quality surveillance systems (MQSS), where they exist. Between 2013-2017 the GSMS received 1500 reports of substandard and falsified medicines of which 286 were for antimalarials from 26 Member States which account for just 29% of the 91 countries globally in which there is ongoing malaria transmission. [33, 72] Furthermore, there is no information currently on the number of countries with a MQSS. A 2010 report published by the WHO that assessed regulatory systems in 26 sub-Saharan African countries found that 17 had a national medicines quality control laboratory (MQCL) (of which just seven were part of the NMRA, with unknown status in terms of ownership of the remaining 10). Moreover, just five countries had all five of the main functions of a regulatory system (marketing authorisation, licensing, inspection, quality control and pharmacovigilance) and overall, regulatory systems were quite fragmented. [73]

At country level, the Unites States Agency of International Development (USAID) through their technical partner, USP have implemented the Promoting the Quality of Medicines programme which provides funding, training and logistical support for national medicines quality monitoring systems in LMICs including countries in central, south and Southeast Asia, Latin America and sub-Saharan Africa. [19] Since 1992, the Poor Quality of medicines programme has been active in 16 (30%) of a total of 54 countries in sub-Saharan Africa. The programme

aims to ''develop and implement systems-level interventions to combat poor quality medicines'' and enable country level partners to overcome system weaknesses, in particular, inadequate technical capacity for analysing medicine quality so as to strengthen monitoring systems, minimising their vulnerability to poor quality medicines. The programme builds technical capacity by providing guidance and training for the sampling and analysis of medicines as well as the provision of medicine quality screening techniques and training on their use. [74, 75]

The ability of a national MQSS to detect poor quality medicines is dependent upon the sampling strategies employed, the technical capacity to analyse these samples, the mechanism to share information between key agencies in a timely manner and the capability of regulatory systems to act based on findings. At the country level, an MQSS should be a component of a broader medicines quality assurance system which includes; effective regulatory mechanisms to control medicines quality at the point of entry; to authorise and register medicines and manufacturers and distributors; to monitor internal distribution and the appropriateness of medicines storage; advocate adherence to national medicines policies and to enact or support enforcement of action against regulatory contraventions.

Detecting poor quality medicines

Two of the key components of a MQSS are regular sampling of medicines and analysis of medicines quality. Where capacity exists, a MQSS should sample medicines at the point of entry into a country, (prior to distribution) on large batches of medicines received through official channels from manufacturers or international and/or regional wholesalers. However, due to limited resources, the majority of MQSS will sample medicines after they have been distributed, through post-marketing surveillance, at the point of care from health facilities, pharmacies and other medicine outlets. [76] Sampling through post-marketing surveillance may be instigated in response to a documented case of a poor quality medicine leading to an NMRA investigation, which may subsequently result in a batch recall. MQSS may also carry out periodic medicines quality surveys with more comprehensive sampling and analysis of medicines. Once sampled, medicines will be first tested using screening devices and where samples are suspected to be of poor quality they will be sent to a national MQCL (where they exist) for further testing using confirmatory analysis following pharmacopeia authorised methods.

1. Sampling strategies for collecting medicines

There are a few sampling strategies that have been employed in medicines quality surveys and studies. USP guidelines indicate that a convenience sampling method can be used to collect medicines. [75] The majority of antimalarial medicine quality studies have utilised convenience sampling which is a type of non-random sampling that involves medicine collection without specific guidance as to which outlets to sample. It is simple, inexpensive and does not require comprehensive lists of outlets in defined locations, which is difficult to acquire, especially for unregistered drug sellers. However, the technique is prone to selection bias as the results depend upon on the collector's choice of outlets. Even though convenience sampling can be useful to identify whether a problem of poor quality medicines exists in the selected location, indicating the need for further investigation [77], this sampling technique cannot be used to estimate the prevalence of poor quality medicines in a country. It may lead to an overestimation of poor quality medicines and results may be difficult to replicate.

In contrast, a randomised sampling approach with large sample sizes and a comprehensive sampling frame to provide representative data is the only technique that can accurately quantify the scale of the problem. Random sampling can provide a sound estimate of the prevalence of poor quality medicines in a defined geographical area, provided that the sampling frame of medicine sellers and suppliers in that area is accurate and up to date. [13] Additional resources may be required to update pre-existing sampling frames before sampling can begin. Selecting an appropriate sampling strategy thus requires consideration of the objectives of the survey, the context, resources and a time frame.

Another sampling technique utilised in health surveys to measure public health indicators such as immunisation coverage is Lot Quality Assurance Sampling (LQAS). [78] LQAS involves testing a sample of medicines from the same batch number to assess whether a batch of goods has met desired specifications, and is an approach which is particularly useful for assessing the quality of medicines at the point of entry into the supply chain (import or local manufacture).[77] If a poor quality batch is detected it can be withdrawn from the supply chain, without having to assess the whole lot, saving time and costs of sampling. LQAS is often employed to overcome issues associated with small sample sizes and convenience sampling.[79] LQAS does still require random sampling and its main drawback is that it does not estimate an exact prevalence. [77] LQAS cannot be used to determine the quality of medicines available to the patients from retail outlets i.e. it is more appropriate for point of entry sampling than point of care (post-marketing surveillance).

2. Analysis of medicine quality

A well-equipped MQCL is an integral component of a national MQSS with access to international pharmacopeia's that outline the methods to assess laboratory based procedures. Laboratories need essential equipment such as high performance liquid chromatography (HPLC) coupled with an appropriate detector i.e. photodiode array (PDA), as well as quality assured drug reference standards to measure the exact amount of SAPI, both of which have high capital and maintenance costs, limiting the number of medicines samples that can be analysed on a regular basis. Additionally, a MQCL requires staff with extensive technical expertise and experience in the use of analytical methods such as HPLC-PDA. [80] LMICs seldom have the requisite resource to operate a MQCL and hence rely on medicines quality screening techniques which are less expensive, simple to operate, portable (preferably handheld) and can be used for rapidly testing a larger volume of medicines. Screening technologies provide a cost-effective means to medicines quality testing, through bulk screening to identify medicines that may need further investigation and assessment using more expensive confirmatory tests such as HPLC. Advantages and disadvantages of confirmatory and screening medicine quality tests are listed in table 1.2.

Table 1.2: Comparisons of confirmatory and screening medicine quality tests

Analytical Method	**Advantages**	**Disadvantages**
Confirmatory tests e.g. HPLC	High specificity High sensitivity Quantification of SAPI Objective results with exact amounts measured	Expensive (capital and maintenance costs) Requires expertise for operation
Screening tests e.g. GPHF MiniLab®	Rapid Inexpensive Simple to operate Battery operated Portable (preferably handheld) Large number of samples analysed quickly Minimal training and skills required for operation	Poor accuracy Not quantitative Subjective interpretation of results

Screening technologies include a range of approaches and can be categorised based on whether they detect false labelling (product recognition and counterfeit identification), the presence or absence of an SAPI (detection of the SAPI) and an attempt to quantify the content of a medicine (determining composition). [81-83] The most widely used screening technology for detecting medicines quality is the Global Pharma Health Fund (GPHF) MiniLab®, which is reported to be available in over 95 countries worldwide, is capable of testing around 85 WHO essential medicines (including antimalarials) and is often used in LMICs as an integral

component of a MQSS. [84] Chapter 5 assesses the utility of a new screening test specifically developed for detecting the quality of artemisinin based formulations (the artemisinin derivative test, ADT) and compares its performance to the MiniLab® for detecting the quality of artemisinin based medicines. Screening technologies have an important role in monitoring medicines quality as they are the first step in the process of detecting the quality of medicines. Even so, as they only provide an indication of medicines quality in terms of the SAPI they detect, confirmatory testing methods such as HPLC must be used for accurate assessment through the quantification of the chemical content of a medicine (its SAPI). Screening tests cannot accurately quantify the amount of SAPI in a sample. HPLC is currently regarded as the 'gold standard' technique for medicine quality analysis. [80]

Monitoring medicine quality in LMICs

Using Senegal as a case study this thesis will explore the context of a MQSS in a LMIC in sub-Saharan Africa, assessing its strengths and weaknesses whilst exploring components of the medicines quality assurance system that if compromised, could increase the risk of the existence of poor quality medicines. This thesis will also specifically focus on a key element of a MQSS, the analytical techniques and methods used in evaluating the quality of medicines in field surveys at the point of care, highlighting the merits and drawbacks of screening technologies from the perspective of those that use them to undertake national medicines quality surveys in a LMIC. It will also evaluate the practical utility and perceptions of acceptability of a new screening test for assessing the quality of artemisinin based medicines, the ADT with a view to the feasibility of including this new screening test into a MQSS.

1.2 Aims and Objectives

1.2.1 Aim

The aim of this thesis is to generate evidence on strategies for strengthening medicines quality surveillance systems in low-middle income countries including an appraisal of screening tests used to detect the quality of medicines as well as providing suggestions for improving the quality of evidence generated by future studies and surveys of medicine quality.

1.2.2 Objectives

1. To generate evidence on strategies for strengthening medicines quality surveillance in Senegal by exploring stakeholder perceptions relating to the strengths and weaknesses of the system and its ability to control the quality of medicines nationally.

2. To explore the perceptions of a range of stakeholders involved in monitoring of medicine quality and provision of antimalarial treatment in Senegal regarding their understanding of the term 'medicine quality.'

3. To review the screening technologies and survey methods that have been used to assess medicine quality in low-middle income countries, as well as how findings have been reported and to provide a reporting template for future studies.

4. To evaluate the practical utility of the artemisinin derivative test (ADT) and perceptions of its usefulness and acceptability in a malaria endemic country context.

1.3 Research Justification

1.3.1 Surveillance of medicine quality

Empirical evidence has thus far not satisfied the gaps in knowledge relating specifically to MQSS at a national level. There is a scarcity of literature that relates specifically to medicines quality surveillance. However, useful insights can still be gained from the literature on disease surveillance systems used for public health, which frequently highlight the need for cooperation between a national healthcare system and its associated public health authorities to enable a rapid response to newly developing health threats. [85] Specifically, studies evaluating surveillance for infectious diseases have identified that more effective systems generally benefit from an adequate infrastructure and much willingness to participate in surveillance activities amongst stakeholders. Nonetheless, there are concerns about numerous challenges including; focus on reacting to disease outbreaks as opposed to prevention, a lack of appropriate technical capacity, obligations of national governments to contribute to financing the system (when funding is generally limited, especially in LMICs) and weak governance (poor administrative and managerial provisioning). [86, 87]

The issues described above are also relevant to MQSS which may affect their efficiency of operation and their effectiveness in controlling the quality of medicines nationally. Many MQSS are operated by several different authorities both national and external including Ministries of Health (MoH), National Malaria/HIV/Tuberculosis etc. Control Programmes, NMRAs and USP. With several stakeholders involved, there is undoubtedly the potential for inefficiency through duplication of work, confusion of roles and responsibilities and debate over funding allocation; all of which detracts from the main goal of operating a MQSS effectively. In addition to considerations of resourcing and the technical capacity of a MQSS to

conduct surveys and analyse medicines, there is a need to understand how a medicines quality assurance system operates, in particular, its capacity for the regulation of medicines. A focus on the perspectives of different stakeholders within a local context, including effects of policy, process and power is also required.

Furthermore, there are relatively few publications which focus on the awareness and perception of poor quality medicines amongst operators of a MQSS, treatment providers or drug shop operators in LMICs. Treatment providers and drug shop operators have a key role in a MQSS as they work at the end of the supply chain, at the point of care. Treatment providers, drug sellers and consumers in low, middle and high-income settings have associated quality with a medicine's cost, country of manufacture, perceived efficacy and whether it is an original brand version or a generic. [27, 29, 88] These perceptions maybe important in influencing the procurement, supply and consumption of medicines and provide challenges for a MQAS especially for policy makers and regulators in educating treatment providers and consumers about the realities of medicine quality. For example, consumers may choose to purchase medicines from unregulated sectors if a brand name medicine they are familiar with is not available or out of stock in the regulated sector. Indeed, in sub-Saharan Africa, those with fever often self-medicate with antimalarial drugs obtained from informal sector outlets or iterant drug sellers. [37] Medicines in these less regulated sectors are more likely to have bypassed regulatory processes and hence, their quality cannot be verified. [89] The perceptions of medicine quality of policy makers and senior (national agency) stakeholders of a MQSS may also be important in shaping the policy for medicines quality assurance and surveillance.

Using Senegal as a case study, the first section of this thesis explores the perceived strengths and weaknesses of the MQSS and perspectives of the understanding of medicine quality through qualitative interviews with the MQSS stakeholders. It is hoped that by establishing these perceptions and their impact on the operation of the MQSS this study can provide evidence that can be adopted to MQSS in other countries in sub-Saharan Africa as well as gaining a deeper understanding of the perceptions of medicines quality in LMICs.

1.3.2 Analytical methods for medicine quality surveys

Existing information on the scale of the problem of poor quality antimalarials in LMICs, is neither reliable nor robust. In part, this is because of the heterogeneity of study methodology for sampling antimalarials and assessing their quality. A recent systematic review found that there was a lack of standardisation in reporting from antimalarial quality surveys and studies

with data not being categorised by medicine or country. [3] Indeed, the review found that several studies employed screening technologies to assess antimalarial quality and in some cases, confirmatory analysis following pharmacopeia methods had not been conducted to verify the findings. Another review of counterfeit and substandard medicines also highlighted the lack of robust methodology to distinguish between these two categories as well as the use of convenience sampling and small sample sizes. [90] Guidance for conducting medicine quality studies includes just two sources including the aforementioned USP guidelines (for sampling and analysing medicines quality) and the Medicine Quality Assessment Reporting Guidelines (MEDQUARG) which is a proposed checklist ''to facilitate transparent, consistent, and accurate reporting.'' [77] However, since the publication of the MEDQUARG guidelines (2009), by 2014, only 15.4% of antimalarial medicine quality studies and surveys had mentioned using the checklist. [3]

Recent developments in the availability of data from antimalarial medicines quality studies and surveys include the aforementioned WWARN Antimalarial Quality Surveyor which has been created using data from more than 200 antimalarial medicine quality publications and reports.[70] In Chapter 4, I provide a systematic review that addresses some of the gaps in knowledge regarding appropriate guidelines for designing studies and surveys of antimalarial medicine quality, as well as the reporting of findings. The review in chapter 4 considers the extent of variation between study design and reporting as well an appraisal of the accuracy of the screening technologies used. It provides a new comprehensive checklist for reporting in antimalarial medicine quality surveys which we have developed from existing sources such as the MEDQUARG and USP sampling guidelines as well as following consideration of the GRADE guidelines (grading quality of evidence and strength of recommendations for diagnostic tests and strategies). [75, 77, 91]

The second section of this thesis focusses on screening technologies which are currently available for use in medicines quality surveys, and includes (i) an overview of the practical merits and drawbacks as well as the accuracy of the existing technologies used for screening antimalarial quality; (ii) a systematic review of the design and reporting of medicines quality studies (described above); and (iii) evaluation of a new screening test, the ADT which has been developed to detect artemisinin derivatives only, although, this colorimetric test comprising of two distinct assays has not been formatted into a kit and commercialised.

There are several medicine quality screening technologies at varying stages of development that can assess the quality of antimalarials. Research findings have suggested that these

devices need to be simple to operate, portable (preferably handheld), battery operated and low cost. [82, 83, 92, 93] Nevertheless, their accuracy for antimalarials in most cases, has thus far only been established in the laboratory and there is minimal literature on the sensitivity and specificity of these technologies under routine operational conditions in field surveys in the hands of laboratory technicians in LMICs. Just two studies have examined the sensitivity and specificity of the MiniLab® (the most widely used test) and both demonstrated that it had a propensity to overestimate the quality of a medicine, thereby potentially increasing the risk of antimalarials circulating in a country in which it is employed. [54, 82] One such screening test, the aforementioned ADT has previously shown a high level of specificity in the laboratory for artemisinin based derivatives. [93] Chapter 5 of this thesis aims to evaluate the practical utility of this test and perceptions of its usefulness and acceptability following 'field' evaluation in Senegal. Its performance in the hands of laboratory technicians was compared with that of the MiniLab®, and key considerations of employing screening tests outside the traditional laboratory setting were also explored.

1.4 Study Setting

Senegal is located at the western most point of the continent of Africa. The World Bank describes Senegal as one of West Africa's key political and economic hubs and considers it one of the most politically stable countries in Africa. [94] Senegal has a population of about 15.4 million (2016) with at least 23% concentrated around the coastal capital city of Dakar, and 40% in other urban areas. [94] Senegal has a GDP per capita of 958 USD and is ranked at 162 (out of 188) on the Human Development Index (2016). [95] Average life expectancy in Senegal is 67 years (2015) and in 2012 the three leading causes of death were lower respiratory infections (16.1%), malaria (8%) and diarrhoeal diseases (6.3%,). However, the rate of mortality of all three causes has gradually decreased in the last decade. [96]

Malaria has been a serious public health issue in Senegal for decades. In 2005 around 2 million cases of malaria were recorded and 2000 deaths attributable to malaria were reported and in 2008 malaria accounted for 32% [97] of all outpatient consultations and 19% of deaths in children under 5. [98] However, by 2009, there was a reduction in the overall malaria burden with cases falling by 41% within a year and there has been a continued downward trend in malaria associated mortality for all age groups to under 5% in 2015.[97] This decline can be credited to a number of intervention strategies implemented at the national level by the Programme National de Lutte Contre le Paludisme (the National Malaria Control Programme) through funding provided by the Global Fund, the President's Malaria Initiative and

UNICEF.[96] A key prevention intervention has been an increase in access and utilisation of insecticide treated nets (utilisation has increased from 10% of population in 2007 to around 50% in 2015). [96] In terms of diagnosis and treatment, the introduction of ACTs In line with WHO policy in 2006 as the first line treatment of uncomplicated *P.falciparum* malaria was seen as a significant intervention strategy. As of 2008, ACTs in the form of artemether-lumefantrine were available free of charge in public health facilities for treating malaria diagnosed by rapid diagnostic test (RDT). [99] Indeed, malaria cases being tested by an RDT gradually increased, since their introduction in the public sector in 2007 to a reported 100% in 2015. Likewise in the public sector, malaria cases treated with an ACT rose from around 50% in 2008 to 100% [96] in 2011, although this has somewhat decreased in recent years, perhaps reflecting the increase in utilisation of RDTs for accurate diagnosis as opposed to previous reliance upon presumptive treatment.

Senegal was selected as the country of study for this thesis as it has established its own national MQSS. It also has several laboratories and a network of sentinel sites for monitoring and checking the quality of certain classes of pharmaceuticals in use in the country. Available literature on the extent of the quality of antimalarials in Senegal is limited to a USP report from 2009 that published findings of a study that indicated the existence of poor quality antimalarials. [64] A total of 141 samples of sulphadoxine-pyrimethamine and ACTs from both wholesale and retail outlets in the regulated public and private sectors and from the unregulated informal market across seven regions were collected. Analysis of samples was carried out using a two-stage approach with initial screening using the GPHF MiniLab® and a smaller sample (n=62) sent for analysis following the medicines quality analysis methods listed in international pharmacopeia (confirmatory analysis). Overall 44% of the 62 samples sent for quality control failed (40% of ACTs failed the tests). Sample failure was most notable in the regulated private and unregulated informal sectors regardless of geographical location. Examination of the survey report revealed some important limitations. Firstly, the sample size of 62 for confirmatory testing is small; 35 were ACTs (n=14, failed) and 27 sulphadoxine-pyrimethamine (n=13, failed). Detailed scrutiny of the results showed that only five of the 35 ACT samples failed dissolution analysis and just one sample failed medicine content analysis with HPLC with the remainder having adequate SAPI but failing impurity testing. Medicine content analysis using HPLC is the most frequently used method of analysis in determining the quality of antimalarial medicines [100] and at the time of the study publication as well as currently, there are no authorised methods in international pharmacopeia to determine the bioavailability of ACTs using dissolution testing.

1.5 Thesis structure

This thesis comprises an overall introduction (chapter 1) followed by two sections containing section 1 (chapters 2 and 3) and section 2 (chapters 4 and 5), as well as a final concluding chapter (chapter 6). Section 1 is centred on medicine quality surveillance systems, using Senegal as a case study and includes two chapters which examine, firstly, perceptions of stakeholders of the operation and function of the MQSS (chapter 2) and secondly, perceptions of medicine quality available in Senegal (chapter 3). Section 2 focusses on medicine quality screening tests and includes two chapters. The first is a review of screening technologies and reporting of findings in antimalarial medicine quality studies and surveys (chapter 4) and the second presents an evaluation of the ADT (chapter 5).

A summary of content of each chapter is provided below.

Section 1*: Monitoring the quality of medicines in Senegal: a stakeholder perspective*

This section includes a short introduction to surveillance systems for medicines quality and provides a description of the current perceptions of medicines quality. A section outlining the methods and results which incorporates a description of participant characteristics and participation of MQSS stakeholders is also included. Section 1 is followed by chapters 2 and 3 which discusses the findings of qualitative interviews with stakeholders of the MQSS in Senegal.

Chapter 2: *Assuring the quality of medicines in low to middle Income countries; a health systems perspective from Senegal*

This chapter provides an overview of the operation and function of the MQSS in Senegal including its strengths and weaknesses. The data was obtained from qualitative interviews with various stakeholders of the MQSS including representatives of several national and external authorities, treatment providers (doctors and nurses) and pharmacists. The data was analysed and presented using a framework based on the WHO six building blocks of health systems. [101] Suggestions for improving the MQSS and the wider health system are made, both specific to Senegal and relevant to other LMICs.

Chapter 3: The quality of medicines available in Senegal; perspectives of health system stakeholders

This chapter uses the same data presented in chapter 2 but provides a different interpretation with a focus on the perceptions of stakeholders of the term ‘medicine quality’ and their confidence in the quality of medicines available in Senegal.

Section 2: *Screening Technologies for assessing antimalarial medicines quality: appraising the reliability of the information they provide.*

This section focusses on the specific technical aspects of the MQSS and includes a short introduction to screening tests outlining the current technologies available on the market and results from studies on their accuracy.

Chapter 4: Antimalarial medicine quality field studies and surveys: a systematic review of screening technologies used and reporting of findings

This chapter is a systematic review that assesses current screening technologies for detecting antimalarial quality and appraises the reporting of these studies. The chapter presents a proposed checklist as a template for future antimalarial medicine quality studies. This study was published in the Malaria Journal in May 2017. [102]

Chapter 5: The practical utility of medicine quality screening tests: an evaluation of a new test for assessing the quality of artemisinin based medicines

This chapter describes a laboratory study that evaluated the practical utility of the ADT test and perceptions of its usefulness and acceptability following 'field' testing in an LMIC. The study took place in Senegal at the Laboratoire Nationale de Controle de Medicaments and involved laboratory technicians undertaking a series of laboratory based exercises to evaluate the practical utility of the new test. The study also evaluated the performance of the ADT alongside the MiniLab®. The technicians participated in focus group discussions to provide opinions on the advantages and disadvantages of the new screening test as well as their experiences of using the MiniLab®.

Chapter 6: Reflections, implications and conclusions

This chapter provides a summary of the thesis and reflects on the findings from the various chapters. The chapter also considers the evidence gaps in medicines quality and provides suggestions on how medicines quality research could be focussed. It also outlines some priorities for LMICs with regard to monitoring and assuring the quality of medicines, providing broad considerations for countries with minimal resources who desire to create or develop an MQSS.

1.6 References

1. Griggs D, Stafford-Smith M, Gaffney O, Rockström J, Öhman MC, Shyamsundar P, et al. Policy: Sustainable development goals for people and planet. *Nature*. 2013;495(7441):305-7.
2. World Health Statistics 2016: Monitoring Health for the SDGs Sustainable Development Goals. Geneva, Switzerland: World Health Organization 2016. http://www.who.int/gho/publications/world_health_statistics/2016/en/.
3. Tabernero P, Fernandez FM, Green M, Guerin PJ, Newton PN. Mind the gaps--the epidemiology of poor-quality anti-malarials in the malarious world--analysis of the WorldWide Antimalarial Resistance Network database. *Malaria journal*. 2014;13:139.
4. IMPACT Counterfeit Medicines: an update on estimates. Geneva: World Health Organisation 2006. http://www.who.int/medicines/services/counterfeit/impact/TheNewEstimatesCounterfeit.pdf. [cited 16th December 2018]
5. Substandard/Spurious/falsely-labelled/falsified/counterfeit (SSFFC) medicines: Frequently asked questions. Geneva: World Health Organization 2016. http://www.who.int/medicines/services/counterfeit/faqs/SSFFC_FAQ_print.pdf. [cited 30th September 2016]
6. Singh J, Dutta AK, Khare S, Dubey NK, Harit AK, Jain NK, et al. Diethylene glycol poisoning in Gurgaon, India, 1998. *Bulletin of the World Health Organization*. 2001;79(2):88-95.
7. Kohler JC, Pavignani E, Michael M, Ovtcharenko N, Murru M, Hill PS. An examination of pharmaceutical systems in severely disrupted countries. *BMC Int Health Hum Rights*. 2012;12:34.
8. Hanif M, Mobarak MR, Ronan A, Rahman D, Donovan JJ, Jr., Bennish ML. Fatal renal failure caused by diethylene glycol in paracetamol elixir: The Bangladesh epidemic. *BMJ*. 1995;311(6997):88.
9. WHO member state mechanism on substandard/spurious/falselylabelled/falsified/counterfeit (SSFFC) medical products: Working definitions. Geneva: World Health Organisation 2017 http://www.who.int/medicines/regulation/ssffc/A70_23-en1.pdf?ua=1. [cited 21st July 2017]
10. Attaran A, Barry D, Basheer S, Bate R, Benton D, Chauvin J, et al. How to achieve international action on falsified and substandard medicines. *BMJ*. 2012;345:e7381.
11. Kelesidis T, Falagas ME. Substandard/Counterfeit Antimicrobial Drugs. *Clinical Microbiology Reviews*. 2015;28(2):443-64.
12. Clift C. Combating Counterfeit, Falsified and Substandard Medicines: Defining the Way Forward? Chatham House 2010. http://www.gphf.org/images/downloads/library/chathamhouseproject2010.pdf. [cited 26th February 2017]
13. Kaur H, Clarke S, Lalani M, Phanouvong S, Guerin P, McLoughlin A, et al. Fake anti-malarials: start with the facts. *Malaria journal*. 2016;15(1):86.
14. Measures to help protect patients from falsified medicines. London, United Kingdom: European Medicines Agency 2016. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/02/news_detail_002467.jsp&mid=WC0b01ac058004d5c1. [cited 7th March 2017]
15. Hall Z, Allan EL, van Schalkwyk DA, van Wyk A, Kaur H. Degradation of Artemisinin-Based Combination Therapies Under Tropical Conditions. *The American journal of tropical medicine and hygiene*. 2016;94(5):993-1001.
16. Newton PN, White NJ, Rozendaal JA, Green MD. Murder by fake medicines. *BMJ*. 2002;324.

17. Johnston A, Holt DW. Substandard drugs: a potential crisis for public health. *British journal of clinical pharmacology*. 2014;78(2):218-43.
18. USP Standards: Monographs (Written Standards). United States Pharmacopeia 2011. http://www.usp.org/sites/default/files/usp_pdf/EN/regulator/monograph_backgrounder_dec_2011.pdf. [cited 9th March 2017]
19. Promoting the Quality of Medicines in Developing Countries (PQM). United States Pharmacopeia https://www.usp-pqm.org/. [cited 18th March 2018]
20. Newton PN, Green MD, Fernandez FM. Impact of poor-quality medicines in the 'developing' world. *Trends in Pharmacological Sciences*. 2010;31(3):99--101.
21. Chaccour CJ, Kaur H, Mabey D, Del Pozo JL. Travel and fake artesunate: a risky business. *Lancet (London, England)*. 2012;380(9847):1120.
22. Buckley GJ, Gostin LO. Countering the problem of falsfied and substandard drugs. Washington: National Academies Press (US); 2013.
23. Newton PN, Caillet C, Guerin PJ. A link between poor quality antimalarials and malaria drug resistance? *Expert Rev Anti Infect Ther*. 2016;14(6):531-3.
24. A study on the public health and socioeconomic impact of substandard and falsified medical products. Geneva: World Health Organization 2017. http://www.who.int/medicines/regulation/ssffc/publications/Layout-SEstudy-WEB.pdf?ua=1. [cited 29th March 2018]
25. Nair K, Dolovich L, Cassels A, McCormack J, Levine M, Gray J, et al. What patients want to know about their medications. Focus group study of patient and clinician perspectives. *Canadian Family Physician*. 2002;48(1):104-10.
26. Prosser H, Almond S, Walley T. Influences on GPs' decision to prescribe new drugs—the importance of who says what. *Family Practice*. 2003;20(1):61-8.
27. Dunne SS, Shannon B, Cullen W, Dunne CP. Beliefs, perceptions and behaviours of GPs towards generic medicines. *Family Practice*. 2014;31(4):467-74.
28. King DR, Kanavos P. Encouraging the use of generic medicines: implications for transition economies. *Croat Med J*. 2002;43(4):462-9.
29. Syhakhang L, Freudenthal S, Tomson G, Wahlstrom R. Knowledge and perceptions of drug quality among drug sellers and consumers in Lao PDR. *Health Policy and Planning*. 2004;19(6):391-401.
30. Patel A, Gauld R, Norris P, Rades T. Quality of generic medicines in South Africa: perceptions versus reality - a qualitative study. *BMC health services research*. 2012;12:297.
31. World Malaria Report 2017. Geneva: World Health Organization 2017. http://apps.who.int/iris/bitstream/handle/10665/259492/9789241565523-eng.pdf;jsessionid=F25EB696ECA5E8FE0F88442C72A680B9?sequence=1. [cited 3rd April 2018]
32. Owens S. Malaria and the millennium development goals. *Arch Dis Child*. 2015;100 Suppl 1:S53-6.
33. World Malaria Report 2016. Geneva: World Health Organization 2016. http://apps.who.int/iris/bitstream/10665/252038/1/9789241511711-eng.pdf?ua=1. [cited 9th March 2017]
34. World Malaria Report 2015. Geneva: World Health Organization 2015. http://www.who.int/malaria/publications/world-malaria-report-2015/report/en/. [cited 3rd March 2017]
35. Nosten F, White NJ. Artemisinin-based combination treatment of falciparum malaria. *The American journal of tropical medicine and hygiene*. 2007;77(6 Suppl):181-92.
36. White NJ. Antimalarial drug resistance. *Journal of Clinical Investigation*. 2004;113(8):1084-92.

37. Lalani M, Kaur H, Mohammed N, Mailk N, van Wyk A, Jan S, et al. Substandard antimalarials available in Afghanistan: a case for assessing the quality of drugs in resource poor settings. *The American journal of tropical medicine and hygiene*. 2015;92(6 Suppl):51-8.
38. Bloland P. Drug Resistance in Malaria. Geneva: World Health Organisation 2001. http://www.who.int/csr/resources/publications/drugresist/malaria.pdf. [cited 16th June 2014]
39. Trape J-F, Pison G, Preziosi M-P, Enel C, du Loû AD, Delaunay V, et al. Impact of chloroquine resistance on malaria mortality. *Comptes Rendus de l'Académie des Sciences-Series III-Sciences de la Vie*. 1998;321(8):689-97.
40. Mutabingwa TK. Artemisinin-based combination therapies (ACTs): best hope for malaria treatment but inaccessible to the needy! *Acta Tropica*. 2005;95(3):305-15.
41. Cissé B, Sokhna C, NDiaye JL, Gomis JF, Dial Y, Pitt C, et al. Effectiveness of Seasonal Malaria Chemoprevention in Children under Ten Years of Age in Senegal: A Stepped-Wedge Cluster-Randomised Trial. *PLoS medicine*. 2016;13(11):e1002175.
42. Kayentao K, Garner P, van Eijk AM, Naidoo I, Roper C, Mulokozi A, et al. Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine-pyrimethamine and risk of low birth weight in Africa: systematic review and meta-analysis. *Jama*. 2013;309(6):594-604.
43. Paloque L, Ramadani AP, Mercereau-Puijalon O, Augereau J-M, Benoit-Vical F. Plasmodium falciparum: multifaceted resistance to artemisinins. *Malaria journal*. 2016;15(1):149.
44. Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, Tarning J. Artemisinin resistance in Plasmodium falciparum malaria. *N Engl J Med*. 2009;361.
45. Wongsrichanalai C, Meshnick SR. Declining artesunate-mefloquine efficacy against falciparum malaria on the Cambodia-Thailand border. *Emerging Infectious Diseases*. 2008;14(5):716-9.
46. Yeung S, Lawford HL, Tabernero P, Nguon C, Wyk A, Malik N. Quality of antimalarials at the epicenter of antimalarial drug resistance: results from an overt and mystery client survey in Cambodia. *The American journal of tropical medicine and hygiene*. 2015;92.
47. Rehwagen C. WHO ultimatum on artemisinin monotherapy is showing results. *BMJ*. 2006;332(7551):1176.
48. Gautam CS, Utreja A, Singal GL. Spurious and counterfeit drugs: a growing industry in the developing world. *Postgraduate Medical Journal*. 2009;85(1003):251-6.
49. Newton PN, Green MD, Fernández FM. Impact of poor-quality medicines in the 'developing' world. *Trends Pharmacol Sci*. 2010;31.
50. Kweder SL, Dill S. Drug shortages: the cycle of quantity and quality. *Clin Pharmacol Ther*. 2013;93(3):245-51.
51. Clark F. Rise in online pharmacies sees counterfeit drugs go global. *The Lancet*. 2015;386(10001):1327-8.
52. A Review of Drug Quality in Asia with Focus on Anti-Infectives. Review. United States Pharmacopeia 2004 February 2004. Report No. http://pdf.usaid.gov/pdf_docs/PNADH154.pdf. [cited 16th June 2014]
53. Kaur H. Analysing the quality and authenticity of ACT drugs. London: ACT consortium 2015. http://www.actconsortium.org/projects/9/analysing-the-quality-and-authenticity-of-act-drugs. [cited 5th May 2017]
54. Survey of the Quality of Selected Antimalarial Medicines Circulating in Six Countries of Sub-Saharan Africa. Geneva: World Health Organization 2011. http://www.who.int/medicines/publications/WHO_QAMSA_report.pdf. [cited 20th February 2017]

55. Nayyar GM, Breman JG, Newton PN, Herrington J. Poor-quality antimalarial drugs in Southeast Asia and sub-Saharan Africa. *The Lancet Infectious diseases*. 2012;12.
56. Kaur H, Allan EL, Mamadu I, Hall Z, Ibe O, El Sherbiny M, et al. Quality of artemisinin-based combination formulations for malaria treatment: prevalence and risk factors for poor quality medicines in public facilities and private sector drug outlets in Enugu, Nigeria. *PLoS One*. 2015;10(5):e0125577.
57. Tivura M, Asante I, van Wyk A, Gyaase S, Malik N, Mahama E, et al. Quality of Artemisinin-based Combination Therapy for malaria found in Ghanaian markets and public health implications of their use. *BMC Pharmacology & Toxicology*. 2016;17:48.
58. Kaur H, Allan EL, Mamadu I, Hall Z, Green MD, Swamidos I, et al. Prevalence of substandard and falsified artemisinin-based combination antimalarial medicines on Bioko Island, Equatorial Guinea. *BMJ Global Health*. 2017;2(4).
59. Nyunt MH, Hlaing T, Oo HW, Tin-Oo LL, Phway HP, Wang B, et al. Molecular assessment of artemisinin resistance markers, polymorphisms in the k13 propeller, and a multidrug-resistance gene in the eastern and western border areas of Myanmar. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2015;60(8):1208-15.
60. Leang R, Taylor WR, Bouth DM, Song L, Tarning J, Char MC. Evidence of Plasmodium falciparum malaria multidrug resistance to artemisinin and piperaquine in Western Cambodia: dihydroartemisinin-Piperaquine open-label multicenter clinical assessment. *Antimicrobial agents and chemotherapy*. 2015;59.
61. Takala-Harrison S, Jacob CG, Arze C, Cummings MP, Silva JC, Dondorp AM. Independent emergence of artemisinin resistance mutations among Plasmodium falciparum in Southeast Asia. *J Infect Dis*. 2015;211.
62. Rozendaal J. Fake antimalaria drugs in Cambodia. *Lancet (London, England)*. 2001;357(9259):890.
63. Nayyar GM, Breman JG, Newton PN, Herrington J. Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. *The Lancet Infectious diseases*. 2012;12(6):488-96.
64. Survey of the Quality of Selected Antimalarial Medicines Circulating in Madagascar, Senegal, and Uganda. United States Pharmacopeia United States Pharmacopeia U; 2009 November 2009. Report No. http://apps.who.int/medicinedocs/documents/s17069e/s17069e.pdf. [cited 26th February 2017]
65. Onwujekwe O, Kaur H, Dike N, Shu E, Uzochukwu B, Hanson K, et al. Quality of anti-malarial drugs provided by public and private healthcare providers in south-east Nigeria. *Malaria journal*. 2009;8:22.
66. Bate R, Coticelli P, Tren R, Attaran A. Antimalarial drug quality in the most severely malarious parts of Africa - a six country study. *PLoS One*. 2008;3(5):e2132.
67. Bate R, Hess K. Anti-malarial drug quality in Lagos and Accra - a comparison of various quality assessments. *Malaria journal*. 2010;9:157.
68. Shakoor O, Taylor RB, Behrens RH. Assessment of the incidence of substandard drugs in developing countries. *Trop Med Int Health*. 1997;2(9):839-45.
69. Osei-Safo D, Agbonon A, Konadu DY, Harrison JJEK, Edoh M, Gordon A, et al. Evaluation of the Quality of Artemisinin-Based Antimalarial Medicines Distributed in Ghana and Togo. *Malaria Research and Treatment*. 2014;2014:12.
70. Tabernero P, Newton PN. The WWARN Antimalarial Quality Surveyor. *Pathogens and Global Health*. 2012;106(2):77-8.
71. WHO Surveillance and Rapid Alert System for Substandard/Spurious/Falsely labelled/Falsified/Counterfeit (SSFFC) Medical Products. World Health Organization 2014. http://www.euro.who.int/en/health-topics/Health-

systems/medicines/news/news/2014/06/who-surveillance-and-rapid-alert-system-for-substandardspuriousfalsely-labelledfalsifiedcounterfeit-ssffc-medical-products. [cited 2nd April 2016]
72. Global Surveillance and Monitoring System for Substandard and Falsified Medical Products Geneva: World Health Organization 2017. http://www.who.int/medicines/regulation/ssffc/publications/GSMS_executive_Summary.pdf?ua=1. [cited 29th March 2018]
73. Assessing National Medicines Regulatory Systems. World Health Organisation 2010. http://www.who.int/medicines/areas/quality_safety/regulation_legislation/assesment/en/. [cited 11th March 2017]
74. Primo-Carpenter J, McGinnis M. Media Reports on Medicine Quality:Focusing on USAID-assisted Countries By the Promoting the Quality of Medicines program. United States Agency for International Development 2009. http://www.usp.org/pdf/EN/dqi/ghcDrugQualityMatrix.pdf. [cited 26th February 2017]
75. Guidelines for Drug Sampling, USP DQI Drug Quality Monitoring Program. Use of the Basic Tests at the Peripheral Level. Rockville: United States Pharmacopeia 2006. http://pdf.usaid.gov/pdf_docs/PNADH150.pdf. [cited 20th Feburary 2017]
76. Chikowe I, Osei-Safo D, Harrison JJ, Konadu DY, Addae-Mensah I. Post-marketing surveillance of anti-malarial medicines used in Malawi. *Malaria journal*. 2015;14(1):127.
77. Newton PN, Lee SJ, Goodman C, Fernandez FM, Yeung S, Phanouvong S, et al. Guidelines for field surveys of the quality of medicines: a proposal. *PLoS medicine*. 2009;6(3):e52.
78. Jutand M, Salamon R. [Lot quality assurance sampling: methods and applications in public health]. *Rev Epidemiol Sante Publique*. 2000;48(4):401-8.
79. Pezzoli L, Andrews N, Ronveaux O. Clustered lot quality assurance sampling to assess immunisation coverage: increasing rapidity and maintaining precision. *Trop Med Int Health*. 2010;15(5):540-6.
80. Kaur H, Green MD, Hostetler D, Fernandez FM, Newton PN. Antimalarial drug quality: methods to detect suspect drugs. *Therapy*. 2010;7(1):40--57.
81. Ricci C, Nyadong L, Yang F, Fernandez FM, Brown CD, Newton PN, et al. Assessment of hand-held Raman instrumentation for in situ screening for potentially counterfeit artesunate antimalarial tablets by FT-Raman spectroscopy and direct ionization mass spectrometry. *Anal Chim Acta*. 2008;623(2):178-86.
82. Batson JS, Bempong DK, Lukulay PH, Ranieri N, Satzger RD, Verbois L. Assessment of the effectiveness of the CD3+ tool to detect counterfeit and substandard anti-malarials. *Malaria journal*. 2016;15:119.
83. Wilson BK, Kaur H, Allan EL, Lozama A, Bell D. A New Handheld Device for the Detection of Falsified Medicines: Demonstration on Falsified Artemisinin-Based Therapies from the Field. *The American journal of tropical medicine and hygiene*. 2017;96(5):1117-23.
84. GPHF Minilab. Frankfurt, Germany: Global Pharma Health Fund 2012. www.gphf.org. [cited 25th April 2017]
85. Beatty ME, Stone A, Fitzsimons DW, Hanna JN, Lam SK, Vong S, et al. Best Practices in Dengue Surveillance: A Report from the Asia-Pacific and Americas Dengue Prevention Boards. *PLOS Neglected Tropical Diseases*. 2010;4(11):e890.
86. Baker MG, Fidler DP. Global public health surveillance under new international health regulations. *Emerg Infect Dis*. 2006;12(7):1058-65.
87. Butler D. Disease surveillance needs a revolution. *Nature*. 2006;440(7080):6-7.

88. Patel A, Norris P, Gauld R, Rades T. Drug quality in South Africa: perceptions of key players involved in medicines distribution. *Int J Health Care Qual Assur*. 2009;22(5):547-60.
89. Gaudiano MC, Di Maggio A, Cocchieri E, Antoniella E, Bertocchi P, Alimonti S, et al. Medicines informal market in Congo, Burundi and Angola: counterfeit and sub-standard antimalarials. *Malaria journal*. 2007;6:22.
90. Almuzaini T, Choonara I, Sammons H. Substandard and counterfeit medicines: a systematic review of the literature. *BMJ Open*. 2013;3(8):e002923.
91. Holger J. GRADE: grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ*. 2008;336:1107.
92. Weaver AA, Lieberman M. Paper test cards for presumptive testing of very low quality antimalarial medications. *The American journal of tropical medicine and hygiene*. 2015;92(6 Suppl):17-23.
93. Ioset JR, Kaur H. Simple field assays to check quality of current artemisinin-based antimalarial combination formulations. *PLoS One*. 2009;4(9):e7270.
94. The World Bank in Senegal - an overview. World Bank 2016. http://www.worldbank.org/en/country/senegal/overview. [cited 17th March 2018]
95. Human Development Report Senegal United Nations 2016. http://hdr.undp.org/sites/all/themes/hdr_theme/country-notes/SEN.pdf. [cited 17th March 2018]
96. Senegal country profile: World Health Organisation; 2015 [21st July 2017]. Available from: http://www.who.int/malaria/publications/country-profiles/profile_sen_en.pdf.
97. Mouzin E. Focus on Senegal. WHO/Roll Back Malaria Partnership 2010 November 2010. Report No. http://rbm.who.int/ProgressImpactSeries/docs/report4-en.pdf. [cited 18th October 2011]
98. Senegal: health profile: World Health Organisation; 2008/2009 [31st October 2011]. Available from: http://www.who.int/gho/countries/sen.pdf.
99. World Malaria Report, Summary. World Health Organisation 2010. http://www.who.int/malaria/world_malaria_report_2010/worldmalariareport2010.pdf. [cited 16th June 2014]
100. Amin NCC, Fabre H, Blanchin M-D, Montels J, Aké M. Determination of artemether and lumefantrine in anti-malarial fixed-dose combination tablets by microemulsion electrokinetic chromatography with short-end injection procedure. *Malaria journal*. 2013;12:202-.
101. Everybody's Business: Strengthening Health Systems to Improve Health Outcomes: WHO's Framework for Action. . Geneva: World Health Organisation 2007. http://www.who.int/healthsystems/strategy/everybodys_business.pdf. [cited 7th March 2013]
102. Lalani M, Kitutu FE, Clarke SE, Kaur H. Anti-malarial medicine quality field studies and surveys: a systematic review of screening technologies used and reporting of findings. *Malaria journal*. 2017;16(1):197.

Section 1: Monitoring the quality of medicines in Senegal: a stakeholder perspective

A1. Introduction

This section examines the national medicines quality assurance system (MQAS) in Senegal presenting two chapters which explore the functioning of the MQAS, its perceived strengths, and points of weakness from the perspective of stakeholders. Perspectives include those of treatment providers and pharmacists responsible for patient care, as well as the representatives from authorities responsible for the regulation, monitoring and supply of medicines.

The findings presented in this section are based upon the data generated from qualitative interviews with the various stakeholders of the MQAS which focussed on the processes involved in assuring the quality of medicines, the roles and responsibilities of different stakeholders relevant to the MQAS and the relationship between agencies, and functionality of the system. Scrutiny of the data also revealed a prominent emerging theme of confidence, in the quality of medicines available in Senegal and in the national system to monitor medicines quality. These data were then subjected to further analysis to explore potential emerging sub themes which form the basis of chapter 3, which focuses on perceptions of medicine quality. Thus, chapter 2 includes; 1) an examination of the national system which has been established to monitor medicine quality, by investigating stakeholder perceptions relating to the strengths and weaknesses of the MQAS and its components and associated parts, 2) an assessment of the system's capability to control the quality of medicines in Senegal and 3) consideration of the risk factors for poor quality medicines nationally. Chapter 3 explores the perceptions of the same stakeholders but with a focus on their understanding of the term 'medicine quality' and perceptions of the quality of medicines in circulation in Senegal.

A2. Evidence summary

A2.1 Risk factors for poor quality medicines

A multitude of factors can contribute to the circulation of poor quality medicines in a country.[1] They can be compartmentalised into internal and external factors. Internal factors relate to systems in place nationally (e.g. health, judicial, political etc.) whereas external factors consider systems not under the direct control or influence of national authorities (e.g. medicine manufacturers and distributors) (see figure A1 below).

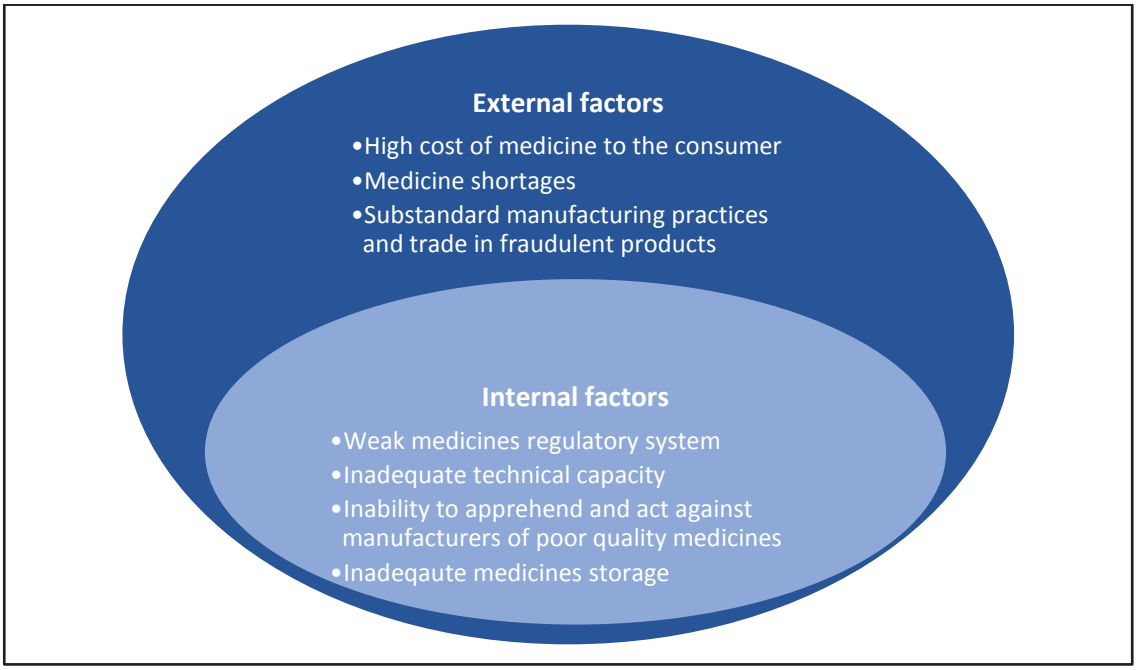


Figure A1: Risk factors for poor quality medicines

A2.1.1 External factors

a) Sub-standard manufacturing practices and trade in fraudulent products

As discussed in chapter 1 the distinction between substandard and falsified medicines is centred on intent, whereby the former arises as a result of non-deliberate poor manufacturing practices (such as a lack of quality control), whereas the latter are deliberately produced to be fraudulent. International regulatory mechanisms that encompass scientific, technical and legal aspects into their frameworks are designed to reduce the risk of poor manufacturing practice and the trade in fraudulent products. Scientific standards for medicines listed in drug monographs in international pharmacopeia such as the United States Pharmacopeia (USP) recommend procedures for assessing quality and specifications for the determination of pharmaceutical substances and dosage forms. [2]

Technical aspects include manufacturer compliance with Good Manufacturing Practice (GMP), a system for ensuring that pharmaceutical products are produced according to quality standards on a consistent basis. [3] The World Health Organization (WHO) have established guidelines for GMP that some countries have adapted. Furthermore, they have created a prequalification programme for medicines, medicines quality control laboratories (MQCLs) and active pharmaceutical ingredients that aims to increase the availability of quality assured medicines. [4] The prequalification programme assesses the quality, efficacy and safety of medicines through the inspection of the relevant manufacturing sites to ensure compliance with WHO guidelines for GMP. MQCLs that comply with WHO GMP guidelines can apply to

become a WHO prequalified laboratory. This accreditation should provide confidence to users of the services the laboratory provides. [5] WHO prequalification status of medicines and MQCLs should reduce the likelihood of the circulation of poor quality medicines.

Furthermore, from a law enforcement and legal perspective INTERPOL have been working alongside the WHO to investigate and apprehend manufacturers of counterfeit medicines. Well known initiatives such as Operation Mamba (East Africa 2008-11) and Storm (south-east Asia 2008-15) have seized millions of counterfeit and illicit medicines. These initiatives may act as a deterrent, discouraging the production and illicit trade of counterfeit medicines. [6]

b) High cost of the medicine to consumer

Medicines with a high market price or high-volume sales may be a particularly attractive prospect to the producers and distributors of counterfeit medicines. Artemisinin based medicines for the treatment of malaria, which, until quite recently, were deemed relatively expensive (up to 20 times more than conventional antimalarials) to the local population in malaria endemic countries, [7-11] satisfy both these criteria, with over 409 million courses of artemisinin combination treatments (ACTs) being procured by malaria endemic countries in 2016. [12] Indeed, within the last two decades, several reports have emerged of counterfeit antimalarials available on the market in parts of Southeast Asia, where artemisinin based treatments were first introduced. [9, 10, 13-15] Additionally, the high cost of medicines may dissuade a consumer from purchasing medicines from authorised treatment providers and instead access medicines from less regulated sectors such as market stalls and other informal retailers (unauthorised treatment providers such as itinerant sellers or mobile vendors) where their quality is not assured. [16]

Between 2010 and 2011, the high cost of ACTs was addressed in part by the Affordable Medicines Facility-malaria (AMFm) which was established by the Global Fund and aimed to improve access to affordable and quality assured antimalarial medicines in malaria endemic countries. [17] AMFm was initially piloted in nine sites (one in Southeast Asia and eight in sub-Saharan Africa) and overall, was deemed to be successful especially in terms of: reducing the cost of ACTs to a price comparable to that of other antimalarials; increasing the availability of ACTs in public and private outlets and increasing the market share of ACTs among antimalarials so as to 'crowd' out medicines like chloroquine which were no longer effective at treating falciparum malaria in sub-Saharan Africa. [18] Furthermore, AMFm logos on medicines packaging raised treatment provider, health professional and consumer awareness, providing reassurance that such medicines had been subject to appropriate quality assurance

procedures. [17] Following this large scale pilot, AMFm was subsumed into the private sector co-payment mechanism which provided continuation of private sector subsidies for quality-assured ACTs, especially in countries where the private retail sector was a major provider of health provision for malaria. [19]

c) Medicines shortages

There have been several recent reports of shortages of essential medicines in low, middle and high income countries. [20-23] Shortages can arise from inefficiencies in the procurement and distribution of medicines in the public supply chain and/or budgetary constraints, resulting in stock outs at the point-of-care. Periodic medicine stock outs in government-funded public health facilities are a well-recognised problem in many low-middle income countries (LMICs). Medicine supply problems can also result from disagreement over pricing of medicines between manufacturers and governments, shortages of raw material and the failure of medicines batches undergoing quality control processes at a national level. [20] In the United States, there have been widely publicised [24] concerns that illicit sellers may fill gaps in the market exposed by medicines shortages. Low availability of medicines may encourage health facilities and providers to access alternative sources for medicines such as internet pharmacies, which may be more difficult to regulate and thus provide an opportunity for exploitation by counterfeiters. [25] Shortages may also increase the cost of a medicine providing further opportunities to illegal traders who sell counterfeited medicines at lower prices than the authentic version.

A2.1.2 Internal factors

d) Weak medicine regulatory system

The World Health Organization (WHO) has previously estimated that 30% of countries had either 'no medicine regulation or a capacity that hardly functions' mentioning lack of sustainable funding and a shortage of qualified staff as prominent challenges. [26] Studies have suggested that weak medicine regulation may lead to the public not being adequately protected from access to poor quality antimalarials citing the need for wholesalers and medicines to be registered and authorised for use in a country. [27, 28] Furthermore, in most countries a NMRA has a key role in post marketing surveillance activities and is required to recall batches of poor quality medicines, but the WHO estimate that only 12% of NMRAs are able to enact an effective pharmaceutical recall. [29] National investment in medicines regulation, through the provision of better qualified staff such as drug inspectors and improved administrative processes to scrutinise wholesalers and manufacturers, and the

medicines they supply and distribute, would contribute to minimising the possibility of poor quality medicines circulating.

e) Inadequate technical capacity

The capacity of a country to test medicines is crucial in ensuring that poor quality medicines are detected. This requires the use of both screening technologies and confirmatory testing to work in tandem to reduce the risk of poor quality medicines. A fully equipped and accredited MQCL is integral to a medicine quality surveillance system (MQSS), although these seldom exist in LMICs due to resource constraints (particularly financial) as well as a lack of expertise to operate specialist equipment. [30, 31] As of July 2017, there were only eight WHO prequalified MQCLs in five countries ((Zimbabwe, Kenya, Tanzania, Uganda and South Africa) in sub-Saharan Africa and none in West Africa. [32] Enhanced technical capacity would increase the capability of pre and post-marketing surveillance mechanisms, thereby increasing the sensitivity of the MQSS to detect poor quality medicines.

f) Inability to apprehend and act against manufacturers of poor quality medicines

Without adequate traceability in a MQAS, counterfeiters may fail to be apprehended. Additionally, individuals who unknowingly consume counterfeit medicines may reside in a different country to the site of production and in the absence of an appropriate international legal framework, counterfeiters are able to evade authorities. [33] If caught, the punishment for counterfeiting varies and is greatly dependent on the judicial process in the country with India having previously considered introducing the death penalty for counterfeiters. [34] Nigeria has introduced a 5-15 year sentence for the distributors of counterfeit medicines, recognising that that the manufacturers themselves cannot always be identified and caught.[35] In China, the national government have exacted the most severe possible sentence, executing its former head of the food and drug regulator after it was found that he was taking bribes to approve untested medicines. [36] A recognised international treaty against counterfeiters may provide the basis for countries to enact legislative powers. Cross boarder agreements for extradition and greater penal sanctions for counterfeiters and distributors may act as a deterrent.

g) Inadequate medicines storage

Medicines storage (in the tropics and hence, malaria endemic countries) is also a challenging risk factor to address in LMICs. Environmental factors such as temperature and humidity which often exceed those recommended by manufacturers of many essential medicines may contribute or even accelerate degradation processes [37, 38], although to date there is no

information on the prevalence of degraded medicines from any global region. Maintaining adequate storage conditions would reduce the risk of poor quality medicines. However, it is acknowledged that controlling humidity and temperature is extremely challenging in malaria endemic countries due to lack of refrigeration and air conditioning equipment. The financial investment in cooling technologies may be affordable to some national medicines distributors but are too costly for individual health facilities and smaller businesses such as pharmacies, and drug stores. With many locations in the Sahel region of Africa often reaching in excess of 40°C, even cooling technologies may struggle to adequately control temperature.

Many malaria endemic countries are predisposed to most, if not all of the risk factors described above. Resource constraints such as a lack of sustainable funding and minimal numbers of staff with requisite expertise, exacerbate several of the internal risk factors. Nevertheless, establishing a functional and effective MQSS designed to detect poor quality medicines and a robust wider quality assurance system with stringent medicines regulation and supply chains supported by judicial powers for illegal drug manufacturing and distribution, will minimise the vulnerability of a country to the circulation of poor quality medicines. The external factors require much broader consideration and are dictated by global market forces over which national authorities have limited control.

A2.2 Medicine quality assurance systems at national level

This section outlines the importance of monitoring the quality of medicines, and the value of a national MQSS. Chapter 1 described two key components of a MQSS, namely the sampling and laboratory analysis of medicines. However, two further components can be identified that are integral to a wider MQAS in order for national authorities to have effective control of the quality of medicines available within a country: medicine regulation and medicine supply chains (see figure A2). These four components are described in detail below with a focus on minimising the risk of poor quality medicines in a country.

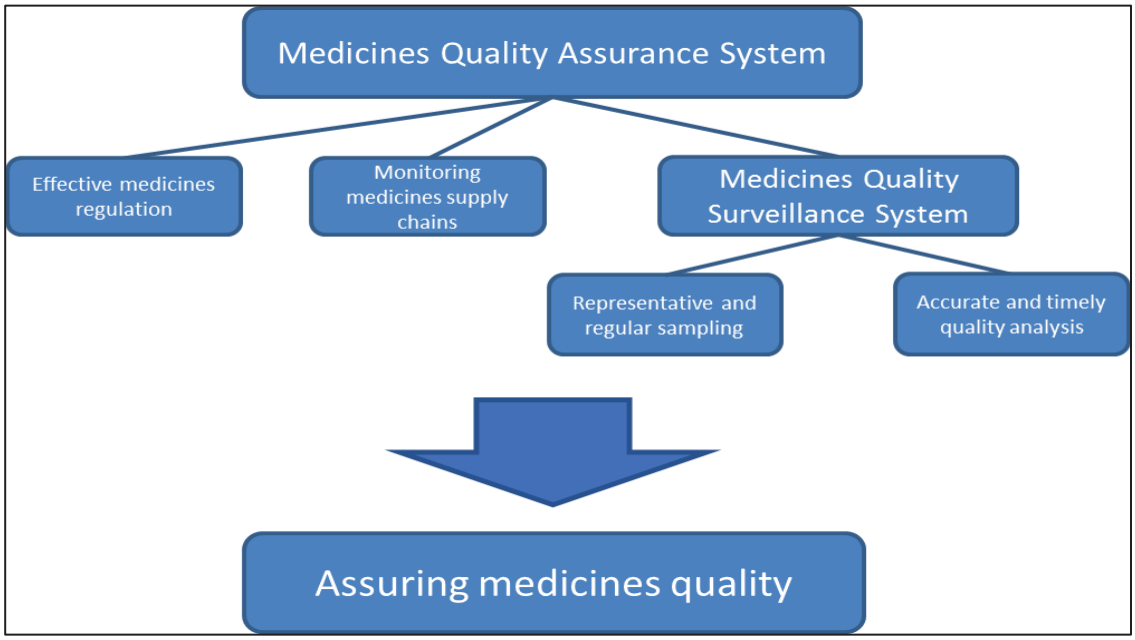


Figure A2: Essential components of a medicines quality assurance system

1. Medicines Regulation

The regulation of health sector goods and services should be a core government function and requires good governance to contribute to the effective performance of the wider health sector. [39, 40] The WHO believes that effective medicines regulation is important to protecting public health and suggests that national regulatory systems are primarily responsible for assuring medicines quality, safety and efficacy as well as ensuring that medicines are appropriately manufactured, stored and distributed and that illegal manufacturing and trade are detected and sanctioned within their borders. [41] Between 2002 and 2008 the WHO carried out an assessment of regulatory systems in 26 countries in sub-Saharan Africa. [29] In this report, the WHO identified five key functions of medicines regulation; marketing authorisation, licensing, inspection, quality control and pharmacovigilance. Overall, of the 26 countries that were assessed, only five had all these functions in place. The report concluded that whilst the structures for medicines regulation existed and the main functions were considered in these structures, in practice the measures were often inadequate, with several important gaps that resulted in a fragmented system in many cases. Major weaknesses that were identified included; poor governance structures and management processes, a dearth of personnel and financial resources, with concerns that overall, most countries lacked the capacity to control the quality, safety and efficacy of medicines available on the market nationally. The report also concluded that additional support for Member States in the form of training, information and guidelines was required.

An effective NMRA can play a key role in assuring the quality of medicines that both enter the national supply chain and that are circulating in a country. Relevant to medicines quality, NMRAs are responsible nationally for marketing authorisation and registration of medicines, monitoring of medicines safety and quality before authorisation, and licensing of manufacturers and wholesalers. [42] This role should also include regulation at point of care, through licensing of retail premises and acting on evidence provided by the MQSS of suspected poor quality medicines detected through post-marketing surveillance and recalling batches of medicines, where appropriate. According to WHO recommendations, NMRAs should also share relevant information about medicines with health professionals and the public, including information on poor quality medicines. [29] Finally, NRMAs should also be involved in establishing a relevant national legal framework that permits the apprehension and prosecution of producers and distributors of poor quality medicines.

One of the greatest challenges for medicines regulation and public health more generally in sub-Saharan Africa, is the presence of an unregulated (informal) health sector. People with malaria fever often self-medicate with antimalarial medicines obtained from both the regulated and unregulated private sector, in particular, informal sector outlets or iterant drug sellers. [43] However, it is the large-scale presence of the latter that poses the greatest challenge for NMRAs. A study of treatment seeking behaviour for malaria of primary caregivers for children under 5 in Accra, Ghana found that 47% preferred to visit drug shops or market vendors as opposed to government owned health facilities. [44] A survey of 11,505 adults in three districts in Kenya found that 47% would in the first instance seek over the counter treatment from private sector outlets for fever symptoms. [45] A further study in Northern Nigeria of primary caregivers (n=814) showed that there was a preference to access the informal sector (54%) (primarily loosely regulated proprietary and patent medicine vendors) as opposed to formal health facilities (46%). [46] A systematic review of the role of informal health care providers in developing countries found great variation in utilisation from as high as 60-77% of study participants in Bangladesh first seeking treatment for any illness from the less regulated providers, compared to just 9 % from a study in Kenya. [47] This extensive reliance of large swathes of the population upon the informal sector for the treatment of malaria poses a risk to public health as antimalarials in this sector may have bypassed the normal regulatory processes and hence, their quality cannot be assured. [16, 48]

2. Medicines supply chains

Medicines supply chains are channels by which medicines enter the country and are distributed by wholesalers which in turn provide medicines to health facilities such as

hospitals, health centres, pharmacies and drug shops. Broadly speaking, in many LMICs there are two types of medicines distributors. The first, national medical stores, supply public (government owned) facilities such as hospitals and health clinics via smaller regional and district distribution warehouses. Donations from external agencies may be an additional source of medicines that are supplied to the public sector through the national medical stores.[49] The second type of distributor is private wholesalers, which acquire medicines directly from manufacturers and supply the private regulated sector such as individual pharmacies or private health clinics. In some LMICs an additional distribution channel is operated by not for profit agencies such as charities, non-governmental organisations and social enterprises. These agencies may supply medicines to public or non-governmental organisation run health facilities on a long term basis, for short term public health programmes or during humanitarian crises. [50] Medicines may also infiltrate supply chains by illegal means or be diverted from the official distribution channels, from the public to the regulated private sector as well as to the informal (less regulated) sector. [43]

A secure supply chain is essential for reducing the likelihood of poor quality medicines circulating in a country. Supply chains are intrinsically linked to medicines regulation and the oversight of their governance is often the responsibility of the NMRA. Where regulation is effective, medicines entering the supply chain should have been authorised, registered, safe and quality assured. To ensure a robust supply chain, medicines quality needs to be assessed (through sampling) at the point of entry into a country as well as at the level of distribution to health facilities (national and regional medical stores and wholesalers) and at the point of care (hospitals, health centres, pharmacies etc.). Where unofficial supply chains exist, as is the case with the informal sector, the risk of poor quality medicines reaching the public is higher due to a lack of regulatory oversight and hence, no assessment of medicine quality at the point of entry and distribution or minimal sampling and analysis at the point of care. [51]

As discussed in the previous section, medicine quality in the supply chain maybe compromised by the environmental conditions during the storage of medicines in warehouses, during transit and in health facilities. A study investigating the impact of light, moisture and temperature on antibiotics and anti-fungal medicines demonstrated that degradation was accelerated by high temperature and humidity. [52] In LMICs storage conditions are most likely to be compromised at the point of care as most health facilities and retail outlets are unlikely to contain air conditioning units or cold rooms due to the financial investment required and potential intermittent electrical supply, which is especially pertinent in more remote areas.

3. Medicines sampling to check the quality of medicines

Regulation alone is not sufficient to assure the quality of medicines, and often in LMICs it is also the responsibility of the NMRA to check the quality of medicines entering the supply chain through the sampling of medicines and analysis of their chemical content. Medicine sampling in the context of a MQSS involves the collection of medicines from wholesalers and a range of drug outlets through post-marketing surveillance. Sampling through post-marketing surveillance, usually at the point of care enables a MQSS to assess the quality of medicines available to the public in a given geographical area. Robust sampling strategies and a large sample size will provide a prevalence estimate for the area from which the medicines were sampled. [31] In LMICs in which the USP is present, its Promoting the Quality of Medicines programme recommends the sampling of antimalarials, antiretrovirals (ARVs), tuberculosis and oral contraceptive drugs on an annual or bi-annual basis using convenience sampling. [53]

There is a dearth of information available on the extent of point of entry medicines quality sampling and analysis in LMICs. However, as mentioned previously, this is a key responsibility of a NMRA. Post-marketing surveillance in LMICs faces additional challenges in terms of the cost of sample collection from more remote geographical areas, as well as limited laboratory capacity to analyse medicines at the peripheral level (away from the national MQCL). The use of lower cost screening technologies in field surveys and post-marketing surveillance in LMICs is thus key and constitutes the focus of the second section of this thesis.

4. Medicine quality analysis

USP guidelines suggest that in a national program, collected samples can be initially screened in peripheral laboratories for quality using the Global Pharma Health Fund MiniLab®, to facilitate wide geographical coverage and timely results. Samples providing unsatisfactory or dubious results should then be subject to repeat testing by the MiniLab® and further analysis using USP compendia methods, primarily High Performance Liquid Chromatography (HPLC), at the national reference laboratory, for more confirmatory results. [54] Medicine quality analysis in LMICs supported by USP thus typically involves a two stage process; 1) medicine quality screening by the MiniLab® followed by 2) confirmatory testing using USP compendia methods.[55]

To operate effectively, a medicines quality assurance system needs (i) effective regulations and guidelines, (ii) knowledge of the supply chain(s) and means to sample at different points along the supply chain, (iii) the technical means to sample in a comprehensive and representative manner and to analyse drugs with a high degree of accuracy, and (iv) a clear action plan on the

steps to take when poor quality medicines are detected. Enactment of these processes requires the financial means and political will, as well as the organisational capacity, to do so in an effective and timely manner.

To further exemplify the roles of a MQAS in assuring and controlling medicine quality, figure A3 summarises the process through which a medicine progresses through a national MQAS. Stringent national medicines regulation has been proposed as an integral part of an effective MQAS and contributes to reducing the likelihood of poor quality medicines entering the country. [30] The figure illustrates the importance of medicines regulation as an overarching and integral component encompassing; authorisation and marketing of a medicine, implementing strategies for sampling for medicines quality assessment, acting upon findings from medicine quality surveys and where possible, enforcing laws set out in national medicines regulatory and statutory frameworks.

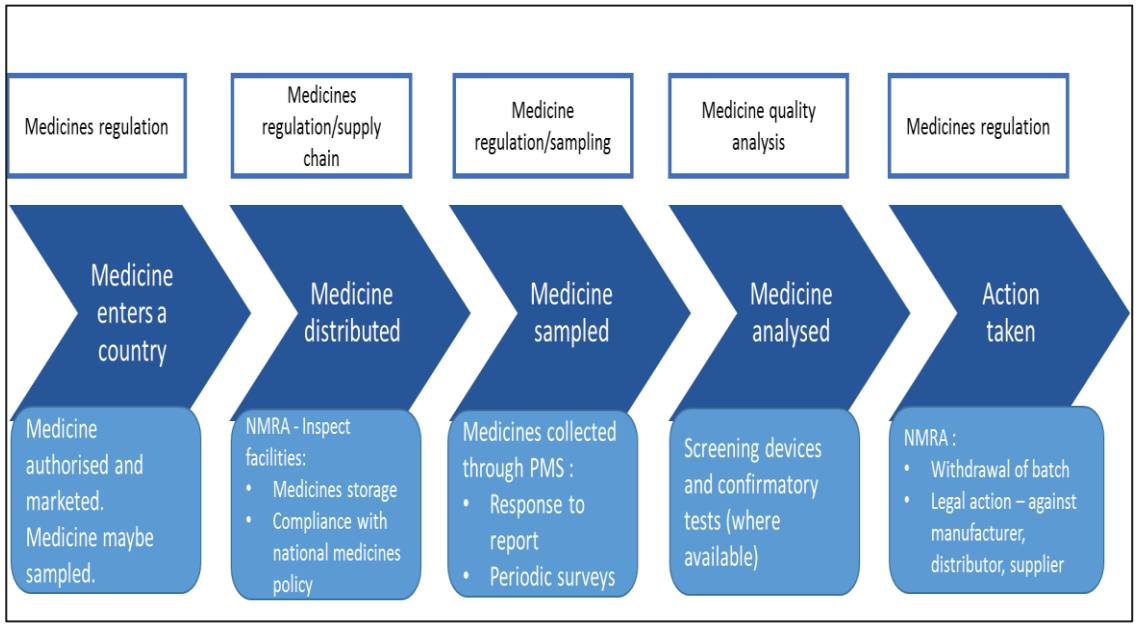


Figure A3: Typical process of a medicine as it passes through a medicines quality assurance system. Each stage of this process has been assigned a component of the MQAS. PMS refers to post-marketing surveillance.

There is limited publicly accessible documentation on MQSS or how well they function especially in sub-Saharan Africa. The country case study of Rwanda's medicines regulatory system which includes medicine quality monitoring and pharmacovigilance is a rare exception.[56] Strengths of the Rwandan system include, the systematic testing of medicines shipments prior to distribution, the sampling and analysing of ACTs as part of post-marketing surveillance on a quarterly basis, and training of over 2000 health care workers on national guidelines for medicine quality monitoring and pharmacovigilance. In addition, the Rwandan

government's interest in medicines quality has harmonised a successful working relationship with the Bureau of Standards, Customs Services and the MoH ensuring the assurance of medicines quality is a collaborative effort. The authors of the study that evaluated this system did not identify any areas of improvement but suggested a need for better collaboration with neighbouring countries to reduce the possibility of poor quality medicines entering Rwanda whilst also working toward a regional medicines quality assurance and surveillance strategy.[56] Nevertheless, this is an example of a relatively sophisticated system in a small country with a limited and highly-controlled private sector, which may not be generalisable to other settings.

The lack of academic or policy literature and documentation on MQSS demonstrates the need to explore such systems where they do exist, although it remains unclear how many LMICs have a system for monitoring medicines quality or whether sampling and analysis activities alone are conducted on an ad hoc basis within a fragmented MQAS. Where a MQSS exists, there is minimal information on how they operate, their infrastructure for regulation, governance arrangements, roles and responsibilities of agencies, and resource capacity. Hence, there is a need to explore how MQAS operate in LMICs with a specific focus on the surveillance of medicines quality.

A2.3 Describing and defining medicines quality

As discussed in chapter 1, medicine quality is typically defined in terms of one or more of the legal, technical and clinical paradigms.

At the national level, the legal paradigm is particularly important for regulatory action and the recent World Health Assembly standardised definitions [57] may provide NMRAs and law enforcement agencies with the basis to develop their national medicines regulatory framework to include a judicial process for dealing with falsified and substandard medicines producers and distributors. However, to quantify the extent of the problem of poor quality medicines for health systems to act to mitigate the risk to public health, evidence on the chemical content and pharmaceutical properties of a medicine (technical paradigm) is also required. Internationally accepted definitions for poor quality medicines may also enable comparisons between regions, between countries at a regional level and within a country at a national level. Nonetheless, these recent definitions are overarching and appear more pertinent at a global level and aim to address some of the previous discourse centred on definitions of poor quality medicines between different actors such as legal professionals, policy makers, academics and

the pharmaceutical industry. They are less relevant to the national level context in which legal frameworks (especially in LMICs) for addressing poor quality medicines are lacking or not consistently applied. Furthermore, as mentioned previously, many LMICs have inadequate technical and regulatory capacity and hence may struggle to provide reliable results upon which legal action can be taken against producers and distributors of poor quality medicines.

Therefore, to effectively determine the vulnerabilities in the MQAS and the actions that need to be taken to counter this threat, there is a need not only to detect poor-quality medicines, but also to correctly classify how a medicine fails to meet quality standards, in order to determine the likely cause and thus to enforce the preventive measures which will be of most benefit. To do this, requires the following: a) robust MQAS with stringent medicine regulation, a robust sampling strategy and sufficient technical capacity for testing medicines quality underpinned by good governance; b) a legislative framework for action against producers and distributors of poor quality medicines; c) sustainable financing and d) adequate human resource.

Chapter 3 of this thesis discusses how medicines quality is defined and described by examining the perceptions of medicine quality and the degree of confidence of MQSS organisation representatives, treatment providers and pharmacists in Senegal have in the quality of medicines in circulation. There is little evidence on the perceptions of medicines quality amongst individuals responsible for quality assurance at a national level. Their perceptions are important as they may influence the enactment of policy with regard to medicine quality, as well as the routine operation of the MQSS.

A3. Monitoring of medicines quality within the context of health systems – a theoretical framework

A MQSS operates within a wider medicine quality assurance system which is part of a much broader health system. Many of the challenges presented earlier in this section that constrain the effective functioning of a MQSS include those of finance, governance and human resource. These factors are also fundamental to the functioning of the health system as a whole. Therefore, to evaluate the function and operation of the MQSS and its perceived effectiveness in reducing the risk of poor quality medicines in Senegal, this section of the thesis will make use of a theoretical framework that is commonly used to evaluate the structure and performance of health systems. [58-60] This framework identifies six building blocks of health systems; governance, financing, service delivery, products and technologies, health

information and human resources. [61] The WHO have described the six building blocks as serving three purposes; 1) to define the attributes of a health system, 2) to define health systems priorities and 3) to identify gaps that require support within a health system. [61] Within health systems there is a degree of interaction and/or interdependence between these building blocks that impacts upon the performance and effectiveness of the system.

In this thesis, these building blocks were examined for their prominence, their level of priority and those which require addressing within the context of the MQAS and MQSS in Senegal (see figure A4).

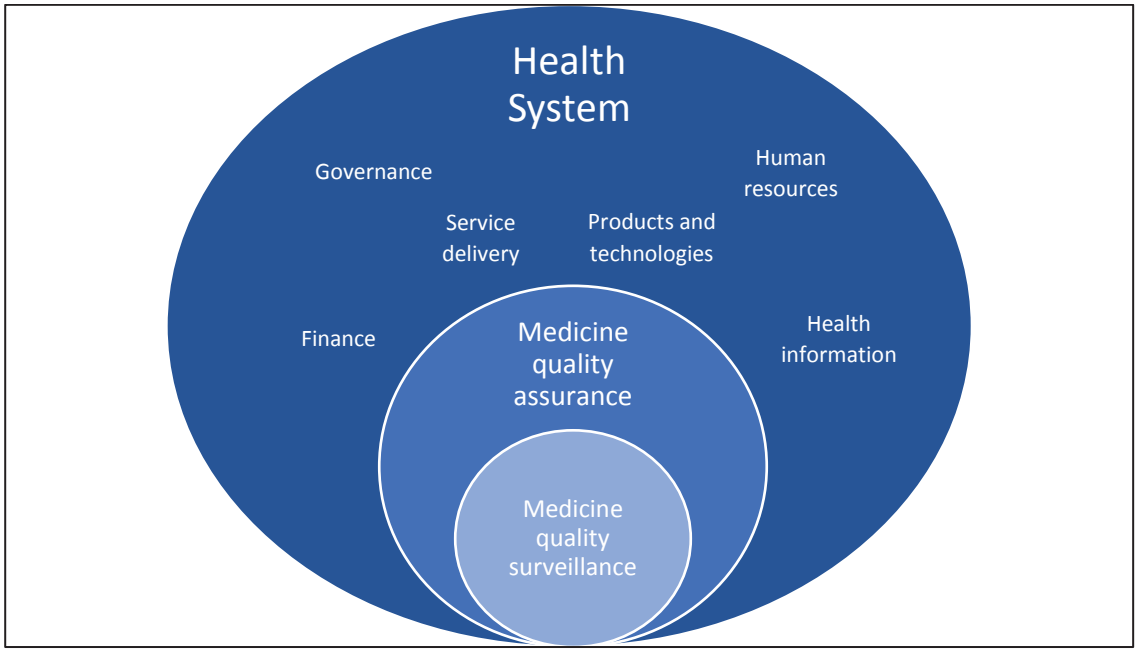


Figure A4: Medicine quality surveillance as a component of medicine quality assurance and the wider health system.
The six building blocks of health systems impact on the operation and the function of the overall health system but are also applicable to its components including the MQAS and MQSS.

Processes around the quality assurance of medicines will shape, and be shaped by, the perceptions that all stakeholders have of the quality of medicines and the factors which they believe affect medicine quality. For example, this perception may impact upon the priority that is placed on the formation and enactment of policy for medicine quality at the authority level. At the point of care, health professionals and drug outlet owners may procure, sell and supply medicines based on their own perceptions of quality. Furthermore, individual perceptions of quality may influence the purchase and use of medicines by the public. These decisions at all levels of the health system are thus influenced by the extent of confidence that policy-makers, treatment providers, drug sellers and consumers have in the quality of medicines available

within their country, and the confidence they have in the medicines quality assurance system to control medicines quality.

A4. Aims and Objectives

The aim of the qualitative study in this section is to generate evidence for strengthening medicine quality surveillance systems in LMICs, through a focus on the processes involved in assurance of the quality of the medicine supply in Senegal, the roles and responsibilities of and relationships between different stakeholders, and their perceptions of the functionality of the system and the quality of medicines nationally.

A4.1 Objectives

1. To explore stakeholder perceptions relating to the strengths and weaknesses of the medicines quality surveillance system and its ability to control the quality of medicines in Senegal.

2. To explore the perceptions of a range of stakeholders involved in monitoring of medicine quality and provision of antimalarial treatment in Senegal regarding their understanding of the term 'medicine quality.'

A5. Methods

This section is the preceding methodology for chapters 2 and 3 for which the same qualitative data set was used but analysed from a different thematic viewpoint in each of the chapters. In chapter 2 a thematic framework approach was used to arrange and analyse the data. In chapter 3 an open coding approach (thematic analysis without a framework) was used. These approaches are described further in each of chapter 2 and 3 under the respective methods sections.

A5.1 Study setting and participants

Medicine quality surveillance in Senegal

In response to the findings of the existence of poor quality antimalarials from an antimalarial quality survey conducted by USP in 2009, the Ministry of Health (MoH) established a medicines quality surveillance coordinating committee, in 2011, in order to strengthen medicines quality surveillance in Senegal. [62] This committee included the Pharmacie Nationale d'Approvisionnement (PNA), Direction des Pharmacies et des Laboratoires (DPL) and

Laboratoire National de Contrôle des Médicaments (LNCM), as well as the national agencies tasked with overseeing control and treatment of tuberculosis, HIV and malaria. [63]

The authorities involved in the operation of the MQSS also have other roles in the health system. The DPL authorises wholesalers for importing medicines into Senegal and medicines for marketing, regulates outlets (public health facilities and private regulated pharmacies) that sell or supply medicines and oversees pharmacovigilance activities. The LNCM and DPL are also collaboratively responsible for national medicines quality control. At the national level the PNA is responsible for the procurement and distribution of medicines, medical devices and other commodities. As the primary focus of this thesis was on the quality of antimalarial medicines, the agency responsible for malaria control and treatment, namely the Programme National de Lutte contre le Paludisme (PNLP) was also included in the study. [64] Funding, logistical and technical support for the MQSS has been provided by the United States Agency for International Development (USAID) through its implementing partner USP. [53] Senegal has been using the GPHF MiniLab® to screen the quality of medicines including antimalarials since 2004 in sentinel site laboratories, with confirmatory analysis using methods such as HPLC, taking place at the LNCM in Dakar. As of 2011 there were nine sentinel sites across the country where staff have been trained to operate the MiniLab®.

The structure of the health system in Senegal

The health system in Senegal can be compartmentalised into 3 sectors; public, private and informal. The public sector includes hospitals, centre de santé (large health clinics), poste de santé (small health clinics) and community health workers who provide preventative and curative services including health promotion and education, treatment of malaria, acute respiratory infections and diarrhoeal diseases. [65] At the time of the study there were around 88 health clinics (centre de santé and poste de santé) in Senegal. [66] A further 1,703 health huts staffed by community health workers represented the primary point of care, especially in rural areas. [67] Since 2008, a new type of village based health worker provides testing with rapid diagnostic tests (RDTs) and treatment with artemisinin based combination therapies (ACTs) through the home-based management of fever program, Prise en Charge à Domicile (known as PECADOM). [64] The private sector includes pharmacies that are licensed and regulated by the DPL and operated by a pharmacist registered with the National Pharmacy Board as well as private health clinics. In 2009, there were approximately 870 private pharmacies (ten times as many as public health facilities) in Senegal. [68] Little is known about the unregulated sector (referred to as informal sector throughout this chapter) in Senegal but

evidence suggests that medicines are available in market stalls in many of the major urban centres in Senegal. [69]

The study was undertaken in Senegal from April-May 2013 in the capital city Dakar and two nearby towns, Thies and Mbour, both of which are representative of urban centres outside of the capital (see map below, figure A5). Stakeholders of several organisations involved in medicine quality monitoring as well treatment providers and pharmacists were recruited. The former group comprised representatives of the PNA, DPL, PNLP, LNCM, University of Cheikh Anta Diop (UCAD), USAID and USP. Treatment providers including doctors and nurses from public health facilities only, and pharmacists from public health facilities and private providers were recruited.

Figure A5: Map of study sites in Senegal. The red stars indicate locations where interviews were conducted.

A5.2 Study procedure and sampling

All the aforementioned organisations were identified through consultation with research partners in Senegal as the key stakeholder authorities of the MQSS. Individuals from each of these authorities as well as former employees were purposively selected for the study to represent the views of those primarily responsible for the strategic and operational function of the MQSS. Undertaking interviews with both current and former employees of the MQSS authorities provided a broad spectrum of perceptions as the participant sample included individuals with intimate knowledge and experience (both current and historical) of medicines quality surveillance in Senegal. Former employees were selected to participate as it was thought they would provide views that represented their personal experiences which may

contrast with those of current employees. Such an approach is encouraged in qualitative research studies to increase the validity or trustworthiness of the data obtained. [70] In qualitative studies, researchers aim to obtain a maximum variation sample but, the findings are not intended to be numerically representative. A purposive sampling approach is intended to demonstrate the diversity in responses, including those that are divergent. [71]

For the MQSS authorities, a senior representative of each organisation was contacted by the local research coordinator who explained the nature of the study. This representative then designated themselves or another individual(s) they deemed appropriate for the interview. Despite lodging a request, the MoH were not able to provide a representative for interview. Interviews conducted with treatment providers included district health officers, poste de santé officers (public sector) and private pharmacy owners (pharmacists) in Dakar, Thies (40km east of Dakar) and Mbour (60km south east of Dakar). A list of all public providers (centre de santé and poste de santé) was provided by the DPL but at the time of the study it was outdated and incomplete. Hence, outlets were selected based on logistical convenience in the selected districts. A list of regulated private pharmacies in the three locations was obtained from the DPL and verified by the National Pharmacy Board. Private pharmacies were randomly selected for participation from the list using a random number generator.

Semi-structured interviews were conducted in English and French by the researcher (Mirza Lalani) and a local research assistant respectively. My relevant experience to this study was knowledge of the subject matter (medicine quality) and previous experience of working in Senegal and therefore, some familiarity of the health system. I also had practical experience of conducting interviews gained during my MSc project, interviewing drug shop operators in Uganda. The research assistant was a Senegalese national, who spoke fluent English with an undergraduate degree in Medical Anthropology and experience of using qualitative methods on research projects in Senegal. Interviews lasted between 45-90 minutes and were usually conducted at the interviewee's place of work, in a private office (when available) with only the participant and researchers present (n=26); two were conducted over Skype™ and one at the home of the interviewee. Written informed consent was obtained from each interview participant.

Interview guides were designed to be iterative allowing exploration of emergent issues from the interviews. An inductive approach was taken throughout the study, field notes were discussed and reviewed by the principal researcher and the research assistant at the end of

each interview, and emergent themes from one interview incorporated into the guide for further exploration in subsequent interviews. [70]

All audio recorded interviews were transcribed verbatim in the language they were recorded in. Interviews conducted in French were transcribed and then translated into English. Interview data was entered into NVivo version 10* for management and analysis. An individual external to the research team was employed to undertake translation. The quality of translation of 3-4 transcripts was verified by the research assistant.

Ethical approval for the undertaking of this study was granted by the London School of Hygiene and Tropical Medicines Research Ethics Committee (see annex 1) and the National Council for Health Research, Senegal (annex 2).

A6. Results

This section presents the characteristics of the study participants and participation of the MQSS authority representatives and treatment providers in the study which is the same for chapters 2 and 3. The results section included in each of chapters 2 and 3 describes the qualitative data itself, presenting the emerging themes.

A6.1 Characteristics of participants

A total of 29 semi-structured interviews were held with a range of stakeholders from various levels of the health system in Senegal. This included current and previous employee representatives of the key MQSS authorities (Table A1), other stakeholders (e.g. UCAD) and treatment providers (Table A2). The treatment providers interviewed were doctors, nurses and pharmacists from the regulated public (n=6) and private (n=10) health sectors in Senegal.

Table A1: Representatives of the MQSS authorities

Authority	Number of interviewees	
	Current employees	Former employees
Direction des Pharmacies et des Laboratoires (DPL)	2	
Laboratoire National de Contrôle des Médicaments (LNCM)	2	1
Programme National de Lutte contre le Paludisme PNLP	1	1
Pharmacie Nationale d'Approvisionnement (PNA)	1	
University of Cheikh Anta Diop (UCAD)	2	
United States Pharmacopeia (USP)	1	
United States Agency of International Development (USAID)	1	1
Total	**10**	**3**

* NVivo qualitative data analysis Software; QSR International Pty Ltd. Version 10, 2012.

Table A2: Treatment provider by location and sector

Treatment Provider	City/District	Number of treatment providers (n=16)	Sector	Outlet/Facility
Medical doctor/District Health Official	Dakar	2	Public	Centre de santé
	Thies	1	Public	Centre de santé
Nurse	Dakar	2	Public	Poste de santé
Pharmacist	Dakar	1	Public	Hospital
	Dakar	5	Private	Pharmacy
	Thies	3	Private	Pharmacy
	Mbour	2	Private	Pharmacy

A6.2 Participation

None of the MQSS authority representatives or public sector treatment providers refused to be interviewed. For the private pharmacies, of the 27 that were initially selected for interview, 16 interviews were successfully arranged. Reasons for failure to arrange an interview included; incorrect contact details (n=4), pharmacist absent (n=4), unable to arrange a day convenient for the pharmacist (n=2) and refusal to participate (n=1). If the pharmacist was absent at time of first contact, the research team made one further attempt to contact them but if told that the pharmacist was still absent, then no further attempts were made. For those pharmacists with which it was not possible to organise an interview at their convenience, several alternative days were offered but none were deemed suitable.

Despite reaching a degree of response saturation after around 10/13 interviews with the MQSS authority representatives, all interviews were completed. After just 12 interviews with treatment providers, responses had started to converge, and no new themes were emerging, thus, the research assistant and I deemed that response saturation was reached. Despite reaching response saturation, four additional interviews were conducted with treatment providers based on specific outlet characteristics to further sample diversity. Two of these additional interviews were conducted in Mbour (town outside Dakar) and the other two in more socio-economically deprived districts of Dakar. This purposive approach was designed to capture any differing views from treatment providers with slightly different characteristics to those already sampled (geography and socio-economic status of local population), yet, no new themes emerged.

Of the treatment providers interviewed, 5 were male and 11 female aged between 35 and 53 years, and all but one had university level education. The selected outlets were primarily in urban or peri-urban areas.

A7. Section summary

Senegal was selected as a country case study as antimalarial medicine quality has been well documented there over the last 20 years [72] subsequent to which it established a MQSS which is currently operated by the NMRA and a MQCL both of which are government agencies under the auspice of the Ministry of Health. USP's Promoting the Quality of Medicines programme has been active in Senegal since the beginning of the century with continued investment over many years resulting in an existing infrastructure for medicines quality assurance. Therefore, the focus on Senegal in this thesis provided an opportunity to explore what an MQSS in a LMIC can achieve. By examining how the MQSS functions, the roles and responsibilities of its stakeholders and characterising the challenges the system faces in minimising the risk of poor quality medicines circulating in the country, this thesis provides evidence for other countries in sub-Saharan Africa who seek to establish and sustain an effective MQAS.

A8. References

1. Gautam CS, Utreja A, Singal GL. Spurious and counterfeit drugs: a growing industry in the developing world. *Postgraduate Medical Journal*. 2009;85(1003):251-6.
2. The International Pharmacopeia, 6th Edition 2016. World Health Organization 2016. http://apps.who.int/phint/en/p/about/. [cited 17th June 2017]
3. GMP questions and answers. World Health Organization 2017. http://www.who.int/medicines/areas/quality_safety/quality_assurance/gmp/en/. [cited 6th June 2017]
4. World Health Organization Prequalification programme. A United Nations programme managed by WHO. Geneva: World Health Organization 2016. http://www.apps.who.int/prequal/. [cited 12th May 2016]
5. Prequalification of quality control laboratories. Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies (Technical report series, no. 961). Geneva: World Health Organization; 2011.
6. Mackey TK. Global health diplomacy and the governance of counterfeit medicines: a mapping exercise of institutional approaches. *J Health Diplomacy*. 2013;1(1).
7. Dondorp AM, Newton PN, Mayxay M, Van Damme W, Smithuis FM, Yeung S, et al. Fake antimalarials in Southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials. *Trop Med Int Health*. 2004;9(12):1241-6.
8. Newton PN, McGready R, Fernandez F, Green MD, Sunjio M, Bruneton C, et al. Manslaughter by fake artesunate in Asia - Will Africa be next? *PLoS medicine*. 2006;3(6):752-5.
9. Rozendaal J. Fake antimalaria drugs in Cambodia. *Lancet (London, England)*. 2001;357(9259):890.
10. Sengaloundeth S, Green MD, Fernandez FM, Manolin O, Phommavong K, Insixiengmay V, et al. A stratified random survey of the proportion of poor quality oral artesunate sold at medicine outlets in the Lao PDR - implications for therapeutic failure and drug resistance. *Malaria journal*. 2009;8:172.
11. Bosman A, Mendis KN. A major transition in malaria treatment: the adoption and deployment of artemisinin-based combination therapies. *The American journal of tropical medicine and hygiene*. 2007;77(6 Suppl):193-7.
12. World Malaria Report 2017. Geneva: World Health Organization 2017. http://apps.who.int/iris/bitstream/handle/10665/259492/9789241565523-eng.pdf;jsessionid=F25EB696ECA5E8FE0F88442C72A680B9?sequence=1. [cited 3rd April 2018]
13. Newton PN, Fernandez FM, Plancon A, Mildenhall DC, Green MD, Ziyong L, et al. A collaborative epidemiological investigation into the criminal fake artesunate trade in South East Asia. *PLoS medicine*. 2008;5(2):209--19.
14. Fernandez FM, Hall KA, Newton PN, Green MD, De Veij M, Vandenabeele P, et al. Characterization of counterfeit artesunate antimalarial tablets from southeast Asia. *American Journal of Tropical Medicine and Hygiene*. 2006;75(5):804-11.
15. Newton P, Proux S, Green M, Smithuis F, Rozendaal J, Prakongpan S, et al. Fake artesunate in southeast Asia. *Lancet (London, England)*. 2001;357(9272):1948-50.
16. Gaudiano MC, Di Maggio A, Cocchieri E, Antoniella E, Bertocchi P, Alimonti S, et al. Medicines informal market in Congo, Burundi and Angola: counterfeit and sub-standard antimalarials. *Malaria journal*. 2007;6:22.
17. Tougher S, Ye Y, Amuasi JH, Kourgueni IA, Thomson R, Goodman C, et al. Effect of the Affordable Medicines Facility—malaria (AMFm) on the availability, price, and market share of quality-assured artemisinin-based combination therapies in seven countries: a before-and-after analysis of outlet survey data. *The Lancet*. 2012;380(9857):1916-26.

18. Talisuna AO, Adibaku S, Amojah CN, Amofah GK, Aubyn V, Dodoo A, et al. The affordable medicines facility-malaria—A success in peril. *Malaria journal*. 2012;11(1):370.
19. Tougher S, Hanson K, Goodman C. What happened to anti-malarial markets after the Affordable Medicines Facility-malaria pilot? Trends in ACT availability, price and market share from five African countries under continuation of the private sector co-payment mechanism. *Malaria journal*. 2017;16(1):173.
20. Dragic J. Analysis of drug shortages in a hospital pharmacy. *European Journal of Hospital Pharmacy: Science and Practice*. 2012;19(2):130-1.
21. Kweder SL, Dill S. Drug shortages: the cycle of quantity and quality. *Clin Pharmacol Ther*. 2013;93(3):245-51.
22. Mujinja PG, Mackintosh M, Justin-Temu M, Wuyts M. Local production of pharmaceuticals in Africa and access to essential medicines: 'urban bias' in access to imported medicines in Tanzania and its policy implications. *Global Health*. 2014;10:12.
23. Mutabingwa TK. Artemisinin-based combination therapies (ACTs): best hope for malaria treatment but inaccessible to the needy! *Acta Tropica*. 2005;95(3):305-15.
24. Ventola CL. The drug shortage crisis in the United States: causes, impact, and management strategies. *Pharmacy and Therapeutics*. 2011;36(11):740.
25. Blackstone EA, Fuhr JP, Pociask S. The Health and Economic Effects of Counterfeit Drugs. *American Health & Drug Benefits*. 2014;7(4):216-24.
26. Effective medicines regulation: ensuring safety, efficacy and quality. Geneva: World Health Organization 2003. http://apps.who.int/medicinedocs/pdf/s4921e/s4921e.pdf. [cited 18th March 2018]
27. Amin AA, Snow RW, Kokwaro GO. The quality of sulphadoxine-pyrimethamine and amodiaquine products in the Kenyan retail sector. *Journal of clinical pharmacy and therapeutics*. 2005;30(6):559-65.
28. Almuzaini T, Choonara I, Sammons H. Substandard and counterfeit medicines: a systematic review of the literature. *BMJ Open*. 2013;3(8):e002923.
29. Assessment of medicines regulatory systems in sub-Saharan African countries: an overview of findings from 26 assessment reports Geneva, Switzerland: World Health Organization 2010. http://apps.who.int/medicinedocs/documents/s17577en/s17577en.pdf. [cited 12th May 2016]
30. Newton PN, Green MD, Fernandez FM. Impact of poor-quality medicines in the 'developing' world. *Trends in Pharmacological Sciences*. 2010;31(3):99--101.
31. Kaur H, Clarke S, Lalani M, Phanouvong S, Guerin P, McLoughlin A, et al. Fake anti-malarials: start with the facts. *Malaria journal*. 2016;15(1):86.
32. WHO list of prequalified quality control laboratories (43rd edition). 2017. https://extranet.who.int/prequal/sites/default/files/documents/PQ_QCLabsList_23.pdf. [cited 14th December 2017]
33. Attaran A, Bate R, Kendall M. Why and how to make an international crime of medicine counterfeiting. *Journal of International Criminal Justice*. 2011:mqr005.
34. Mudur G. India to introduce death penalty for peddling fake drugs. *BMJ*. 2003;327(7412):414.
35. Akunyili D. Fake and counterfeit drugs in the health sector: The role of medical doctors. *Annals of Ibadan Postgraduate Medicine*. 2004;2(2):19-23.
36. China Quick to Execute Drug Official. New York: The New York Times 2007. http://www.nytimes.com/2007/07/11/business/worldbusiness/11execute.html. [cited 18th March 2018]

37. Hall Z, Allan EL, van Schalkwyk DA, van Wyk A, Kaur H. Degradation of Artemisinin-Based Combination Therapies Under Tropical Conditions. *The American journal of tropical medicine and hygiene*. 2016;94(5):993-1001.
38. Nogueira FH, Moreira-Campos LM, Santos RL, Pianetti GA. Quality of essential drugs in tropical countries: evaluation of antimalarial drugs in the Brazilian Health System. *Revista da Sociedade Brasileira de Medicina Tropical*. 2011;44(5):582-6.
39. Kohler JC. Fighting corruption in the health sector: methods, tools and good practices. New York: United Nations Development Programme 2011. http://www.u4.no/recommended-reading/fighting-corruption-in-the-health-sector-methods-tools-and-good-practices/downloadasset/3086. [cited 9th January 2015]
40. Kohler JC, Pavignani E, Michael M, Ovtcharenko N, Murru M, Hill PS. An examination of pharmaceutical systems in severely disrupted countries. *BMC Int Health Hum Rights*. 2012;12:34.
41. WHO Essential Medicines and Health Products - Annual Report 2015. Geneva: World Health Organisation 2015. http://www.who.int/medicines/publications/emp_annual-report2015/en/. [cited 25th February 2017]
42. Boxtell C, Santoso B, Edwards I. Drug Benefits and Risks: International Textbook of Clinical Pharmacology 2nd Revised edition edition ed: IOS Press; 2008 (15 Aug. 2008).
43. Goodman C, Brieger W, Unwin A, Mills A, Meek S, Greer G. Medicine sellers and malaria treatment in sub-Saharan Africa: what do they do and how can their practice be improved? *The American journal of tropical medicine and hygiene*. 2007;77(6 Suppl):203-18.
44. Klein EY, Lewis IA, Jung C, Llinas M, Levin SA. Relationship between treatment-seeking behaviour and artemisinin drug quality in Ghana. *Malaria journal*. 2012;11(1):110.
45. Abuya TO, Mutemi W, Karisa B, Ochola SA, Fegan G, Marsh V. Use of over-the-counter malaria medicines in children and adults in three districts in Kenya: implications for private medicine retailer interventions. *Malaria journal*. 2007;6:57-.
46. Millar KR, McCutcheon J, Coakley EH, Brieger W, Ibrahim MA, Mohammed Z, et al. Patterns and predictors of malaria care-seeking, diagnostic testing, and artemisinin-based combination therapy for children under five with fever in Northern Nigeria: a cross-sectional study. *Malaria journal*. 2014;13(1):447.
47. Sudhinaraset M, Ingram M, Lofthouse HK, Montagu D. What is the role of informal healthcare providers in developing countries? A systematic review. *PLoS One*. 2013;8(2):e54978.
48. Klein EY, Lewis IA, Jung C, Llinas M, Levin SA. Relationship between treatment-seeking behaviour and artemisinin drug quality in Ghana. *Malaria journal*. 2012;11:110.
49. Bloland PB, Kazembe PN, Watkins WM, Doumbo OK, Nwanyanwu OC, Ruebush TK, 2nd. Malarone-donation programme in Africa. *Lancet (London, England)*. 1997;350(9091):1624-5.
50. Mackintosh M, Chaudhuri S, Mujinja PG. Can NGOs regulate medicines markets? Social enterprise in wholesaling, and access to essential medicines. *Globalization and Health*. 2011;7(1):4.
51. Evans L, 3rd, Coignez V, Barojas A, Bempong D, Bradby S, Dijiba Y, et al. Quality of anti-malarials collected in the private and informal sectors in Guyana and Suriname. *Malaria journal*. 2012;11:203.
52. Langner MD, Maibach HI. Many common drugs in dermatology are light, temperature, or moisture-sensitive. *Skin Therapy Lett*. 2009;14(1):3-5.
53. Promoting the Quality of Medicines in Developing Countries (PQM). United States Pharmacopeia https://www.usp-pqm.org/. [cited 18th March 2018]

54. Guidelines for Drug Sampling, USP DQI Drug Quality Monitoring Program. Use of the Basic Tests at the Peripheral Level. Rockville: United States Pharmacopeia 2006. http://pdf.usaid.gov/pdf_docs/PNADH150.pdf. [cited 20th Feburary 2017]
55. GPHF Minilab. Frankfurt, Germany: Global Pharma Health Fund 2012. www.gphf.org. [cited 25th April 2017]
56. Binagwaho A, Bate R, Gasana M, Karema C, Mucyo Y, Mwesigye JP, et al. Combatting substandard and falsified medicines: a view from Rwanda. *PLoS medicine*. 2013;10(7):e1001476.
57. WHO member state mechanism on substandard/spurious/falselylabelled/falsified/counterfeit (SSFFC) medical products: Working definitions. Geneva: World Health Organisation 2017 http://www.who.int/medicines/regulation/ssffc/A70_23-en1.pdf?ua=1. [cited 21st July 2017]
58. Sayinzoga F, Bijlmakers L. Drivers of improved health sector performance in Rwanda: a qualitative view from within. *BMC health services research*. 2016;16:123.
59. Rutta E, Liana J, Embrey M. Accrediting retail drug shops to strengthen Tanzania's public health system: an ADDO case study. 2015;8:23.
60. Jones A, Howard N. Feasibility of health systems strengthening in South Sudan: a qualitative study of international practitioner perspectives. 2015;5(12):e009296.
61. Everybody's Business: Strengthening Health Systems to Improve Health Outcomes: WHO's Framework for Action. . Geneva: World Health Organisation 2007. http://www.who.int/healthsystems/strategy/everybodys_business.pdf. [cited 7th March 2013]
62. Survey of the Quality of Selected Antimalarial Medicines Circulating in Madagascar, Senegal, and Uganda. United States Pharmacopeia United States Pharmacopeia U; 2009 November 2009. Report No. http://apps.who.int/medicinedocs/documents/s17069e/s17069e.pdf. [cited 26th February 2017]
63. PNLP / PLAN STRATEGIQUE NATIONAL 2011-2015. Senegal: Programme National de Lutte Contre le Paludisme 2011 August 2011. Report No. http://www.africanchildinfo.net/clr/policy%20per%20country/senegal/senegal_malaria_2011-2015_fr.pdf.
64. Malaria Operational Plan, Year Six – Fiscal Year 2012; Senegal. President's Malaria Initiative 2012. https://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy12/senegal_mop_fy12.pdf?sfvrsn=6. [cited 7th Septmeber 2012]
65. Sarli L, Enongene E, Bulgarelli K, Sarli A, Renda A, Sansebastiano G, et al. Training program for community health workers in remote areas in Senegal. First experience. *Acta bio-medica : Atenei Parmensis*. 2010;81(1):54-62.
66. Malaria Operational Plan 2014, Senegal. United States: United States Agency for International Development 2014. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy14/senegal_mop_fy14.pdf?sfvrsn=10. [cited 25th April 2017]
67. Tine RC, Ndiaye P, Ndour CT, Faye B, Ndiaye JL, Sylla K, et al. Acceptability by community health workers in Senegal of combining community case management of malaria and seasonal malaria chemoprevention. *Malaria journal*. 2013;12(1):467.
68. Tousignant N. Pharmacy, money and public health in Dakar. *Africa*. 2013;83(4):561.
69. Senegal Health Authorities Organize Campaign against “Street Drugs” with Participation of USP, USAID, and other International Groups. The Standard. 2009:11.
70. Green J, Thorogood N. Qualitative methods for health research. 2nd ed. Los Angeles: SAGE; 2009. xv, 304 p. p.

71. Marshall MN. Sampling for qualitative research. *Fam Pract*. 1996;13(6):522-5.
72. Trape J-F, Pison G, Preziosi M-P, Enel C, du Loû AD, Delaunay V, et al. Impact of chloroquine resistance on malaria mortality. *Comptes Rendus de l'Académie des Sciences-Series III-Sciences de la Vie*. 1998;321(8):689-97.

Chapter 2: Assuring the quality of medicines in low to middle income countries; a health systems perspective from Senegal

2.1 Background

Poor quality medicines are a challenging issue for public health globally and at a national level, especially in low to middle income countries (LMICs). The World Health Organization (WHO) and United States Pharmacopeia (USP) have provided recommendations on how countries can assure the quality of medicines through guidance on (i) establishing regulatory mechanisms, (ii) building technical capacity (through the WHO prequalification of medicines quality control laboratories) and (iii) specific suggestions on how to sample and analyse the quality of medicines. [1-3] However, these overarching recommendations do not account for the complexity of individual health systems and the nuances of the country context.

At the national level in many LMICs, there are several risk factors for the existence of poor quality medicines as described in the introduction to section 1. These risks can be minimised through the establishment and effective operation of a medicines quality surveillance system (MQSS) within a broader medicines quality assurance system (MQAS). A review of the literature on medicine quality identifies four major components of a MQAS that need to perform effectively to assure the quality of medicines used for treatment, namely; comprehensive and robust medicines regulation, authorised and secure medicines supply chain(s), regular and representative medicines sampling, and accurate and timely medicines quality analysis (figure A2, section 1).

Forming a MQAS is challenging in LMICs as it requires significant sustainable financial and human resource as well as political will. [4] Effective regulatory mechanisms for medicines quality control and building technical capacity in the form of a national medicines quality control laboratory (MQCL) fully equipped with sophisticated analytical equipment and well-trained staff are essential for ensuring the quality of medicines available to the public are safe and effective. This chapter discusses the MQSS in Senegal, West Africa through exploring stakeholder perceptions relating to its strengths, weaknesses and its ability to control the quality of medicines in the country.

As mentioned in Chapter 1, the gap in knowledge and understanding of how a MQSS functions in a LMIC against the backdrop of constrained resources requires further investigation. Whilst most countries in sub-Saharan Africa will have some regulatory mechanism for marketing and authorisation of medicines, registration and accreditation for wholesalers and manufacturers

and oversight of the safeguarding of medicines supply chains, few have a system to monitor medicines quality through post-marketing surveillance and fewer still have the capacity to control medicines quality at the point of entry. [5, 6] The case study of Senegal provides an opportunity to explore what can be achieved and the challenges faced in terms of monitoring medicines quality in a LMIC. This study set out to generate evidence on strategies for strengthening the MQSS in Senegal by establishing stakeholder perceptions relating to the strengths and weaknesses of the MQSS and its ability to control the quality of medicines in the country.

2.2 Theoretical Framework

A realist epistemological approach was undertaken using qualitative interviews to produce knowledge relating to various aspects of the MQSS. In philosophical terms the realist paradigm acknowledges an external reality which is independent of the researcher. [7] Therefore using a realist approach provided a 'window' into the world of the interviewee in terms of their perceptions (external reality) and revealed important facts (reality) relating to various components of the MQSS. [8] Realist researchers often have preconceptions that guide them in selecting interviewees and topic areas for discussion. In this study, the main MQSS authorities in Senegal were selected for inclusion in the study and predetermined interviews themes were created based on the limited pre-existing literature about medicines quality monitoring and regulation in LMICs as well as through discussion with research partners in Senegal.

For the interview guide for interviews with the MQSS authority representatives (see annex 3), *a priori* codes were centred on context and purpose of the MQSS (roles and responsibilities, background, strengths and challenges) and the four major components of a MQAS (medicines regulation, supply chain monitoring, medicine sampling, and medicines quality analysis). This study aimed to explore the perceptions of stakeholders in Senegal in relation to the MQSS, ascertaining which components of the system needed improvement, as well as those that were performing well. The MQSS is part of a wider MQAS operating as component of a broader health system. To evaluate the functioning and operation of the MQSS and its perceived effectiveness in reducing the risk of poor quality medicines in Senegal in the context of a health system, a coding framework based upon the six building blocks of health systems; governance, financing, service delivery, products/technologies, health information and human resources, was applied. [9] Using a health systems lens, the study identified the key roles and responsibilities of the MQSS, examined the strengths and weaknesses of the four components

of the MQAS and identified gaps that may require additional support. A modified interview guide (annex 4) was used for interviews with treatment providers with a focus on specific aspects of medicines including national policy for treatment of malaria, procurement approaches, perceptions of medicines quality and their knowledge and interaction with the system for monitoring medicines quality.

2.3 Methods

See section 1, A5 for the methods for this chapter. The approach to coding and analysis is described below.

2.3.1 Coding and analysis

A thematic framework approach was undertaken for analysis at two levels (see figure 2.1). The first level included the *a priori* codes. The second level of the framework included the six building blocks of health systems; governance, finance, human resources, products and technology, health information and service delivery [9]; a framework that can be particularly useful in understanding the structure and performance of a health system of which a MQAS and hence, a MQSS are components. The responses from each interviewee in relation to the primary themes of context, function, strengths etc. were coded for the six building blocks.

2.4 Results

The characteristics of the study participants and participation of the MQSS authority representatives and treatment providers in the study are described in section 1, A6.

2.4.1 Emerging themes

After the process of familiarisation of the data [10] thematic analysis was used to identify emerging sub-themes within the six building blocks of health systems. Throughout the process of coding the first and second levels of the framework were largely applicable. However, for some of the first level *a priori* themes, codes for health systems building blocks were less relevant. Furthermore, a few themes emerged from the data as a result of the inductive approach taken, such as confidence in the MQSS and its capacity to assure medicine quality in Senegal. The research assistant also undertook coding of a few transcripts using the original coding framework and a second iteration of the framework was produced. The framework was reviewed by an LSHTM staff member who formed part of the PhD advisory panel subsequent to which a final version was produced for analysis (figure 2.1).

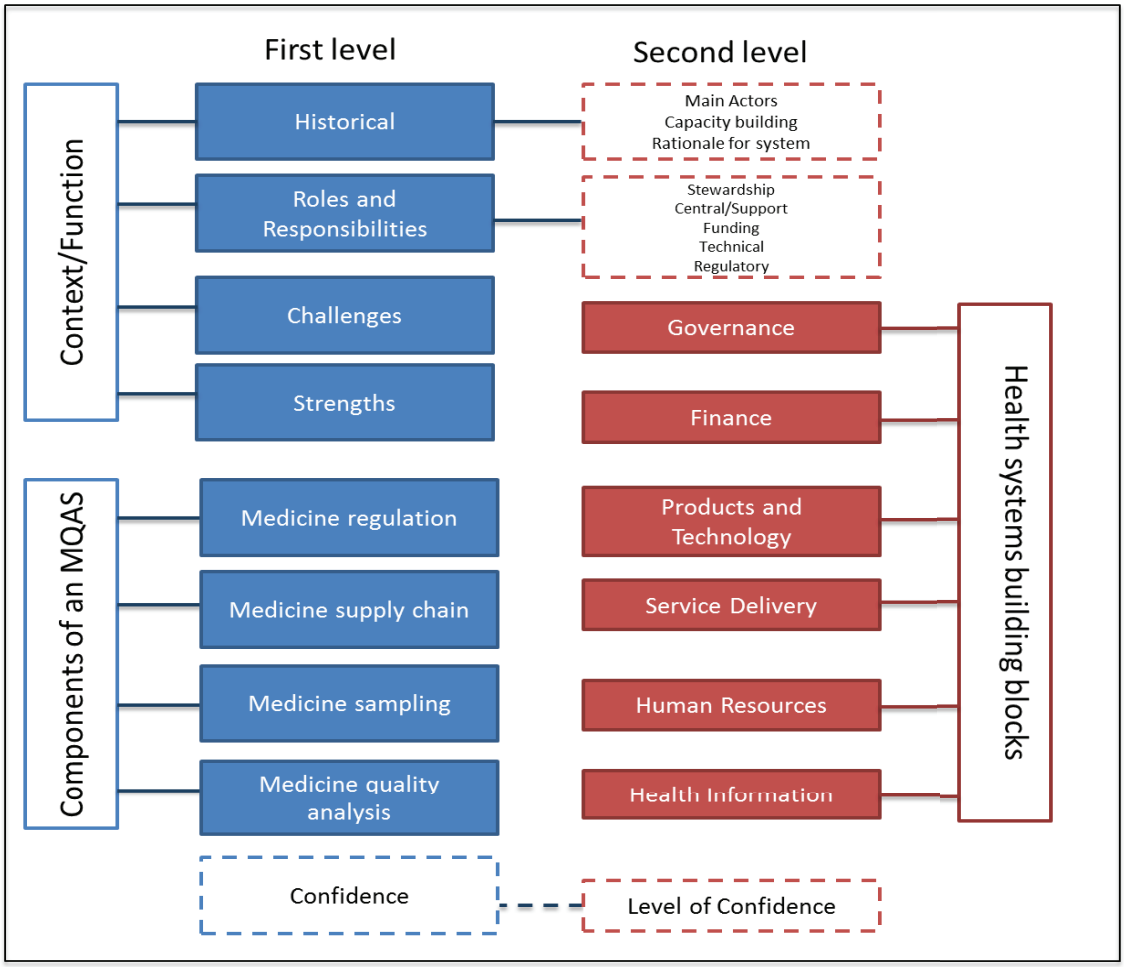


Figure 2.1: Final version of coding framework with first and second levels
The solid blue and red boxes are a priori themes. Themes in boxes with dashed outline are those emerging during the course of data collection and analysis.

2.4.2 Context and function of the medicine quality surveillance system

The context of the MQSS and its function impact upon its capacity to work effectively at minimising the risk of poor quality medicines appearing in Senegal. The main aspects of the system that were explored were its history and background, institutional roles and responsibilities, and its strengths and challenges. As strengths and challenges specifically address the functioning of the system, it was appropriate to apply the framework of the six building blocks of the health system as codes. However, during the coding process it was found not to be a useful framework for the analysis of the data relating to context (historical and roles and responsibilities) and an open coding approach of emerging sub-themes was undertaken. The various sub-themes emerging from the data are presented below under each primary theme, together with quotes from interviewees in inverted commas.

Historical

Three main sub-themes emerged from the data: rationale for the system, capacity building, and main actors in the inception and development of the MQSS.

Rationale for system: Three main reasons for the conception and development of the MQSS were suggested. Firstly, toward the end of the 1990s a handful of *ad hoc* research surveys of antimalarials conducted by UCAD found the presence of poor quality medicines (primarily chloroquine). Secondly, it was proposed that the growing problem of chloroquine resistance, identified by instances of treatment failure was perhaps attributable to the availability of poor quality formulations of the medicine. Thirdly, the USP/WHO survey of 2009 which suggested a problem of poor quality antimalarials in Senegal, resulted in heightened awareness of the issue especially within the MoH. The MoH requested immediate clarification from the existing authorities responsible for surveillance of medicines quality on the survey findings as well as how the problem would be addressed.

Capacity Building: The USAID through its implementing partner USP assisted in the establishment of sentinel sites across Senegal, equipped with the MiniLab® for medicine quality screening. They were involved in the strengthening of technical capacity at the LNCM. Further, those initially involved in *ad hoc* medicine quality surveys undertaken by the analytical chemistry department at UCAD were now employed in prominent positions in the DPL and LNCM.

Main Actors: MQSS authority stakeholders acknowledged that the role of the PNLP and USAID was paramount to the inception and development of the MQSS in its early stages. The former acted as a conduit for the latter's technical and financial support which may explain the continued focus on antimalarial medicine quality and malaria more generally.

> *'The malaria program earlier benefited from the support of some partners especially USAID and USP. They really boosted the national control laboratory and DPL, which has enabled them to carry out a lot of quality control activities in Senegal.*' MQSS authority representative

Roles and Responsibilities

Despite the historical involvement of other authorities, the general consensus amongst MQSS authority representatives was that the LNCM and DPL were most central to its function and operation. As the national MQCL, the LNCM was seen to provide the technical evidence upon which the DPL (national medicine regulator) could act. The role of the PNA was to supply medicines to the public sector, and the PNLP and USAID/USP continued to provide financial

and technical support. At the time of this study UCAD's role was seen as historical and centred on involvement in establishing the system, from around 2001 onwards. All stakeholders acknowledged the MoH as the overarching steward of the MQSS. However, it was suggested that USP/USAID's role remains as significant currently as it was historically and without their funding the MQSS would be weaker.

> *'We are not decision makers, we just produce technical results and the authority, which in this case is the Minister, makes the decisions.'* MQSS authority representative

> *'If USP withdrew from Senegal tomorrow the MQSS would still operate but not at a level that is required, it needs USP's support.'* MQSS authority representative

Figures 2.2 and 2.3 contrast the structure described in the PNLP strategic plan 2011-2015 (figure 2.2) with the perceived structure of the MQSS and the roles and influences of the key organisations (figure 2.3). This plan stated that USP/USAID had a supporting role in the MQSS and that the other four national authorities were collaborative and equal partners in its operation. In contrast, figure 2.3 shows that the role of the PNA in the MQSS is perceived to be quite minimal and the DPL and LNCM are thought to be integral to the function of the MQSS. Additionally, it illustrates that whilst the PNLP are not seen to be as influential as they were historically, the role of external partners, particularly USP/USAID, was regarded as essential to the ability of the MQSS to maintain its current standard and function

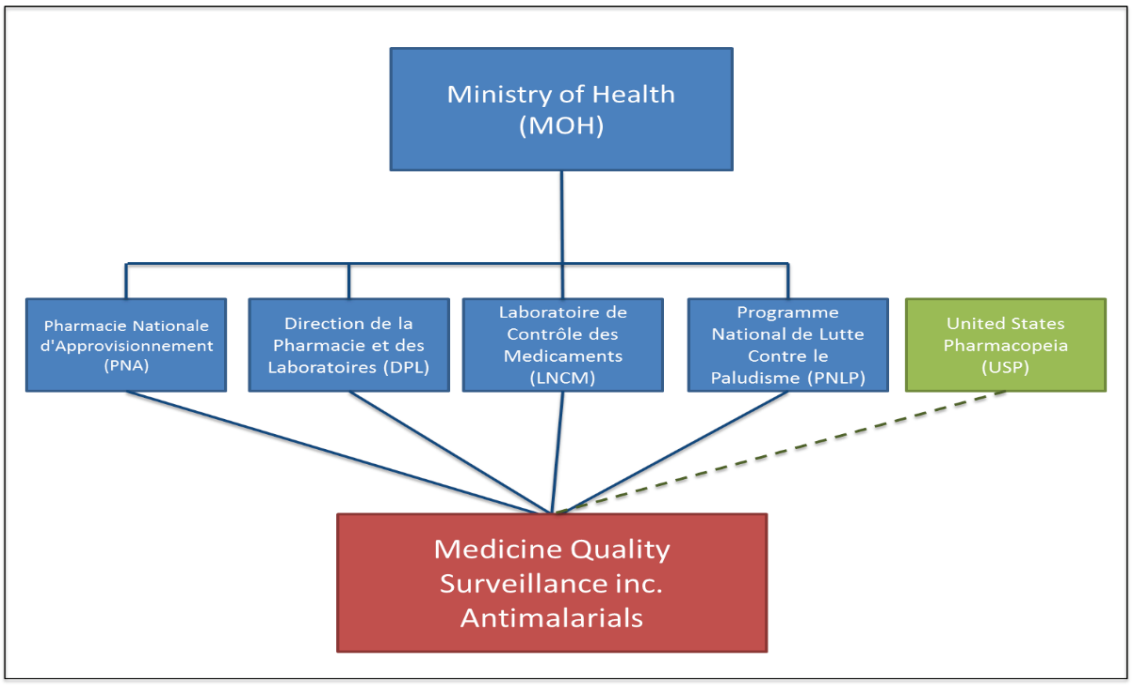


Figure 2.2: Structure of MQSS as stated in the PNLP strategic document (2011-2015)
Connecting solid lines represent the integral role of some of the organisations in the MQSS. The connecting dash line indicates lesser involvement of the organisation in the MQSS.

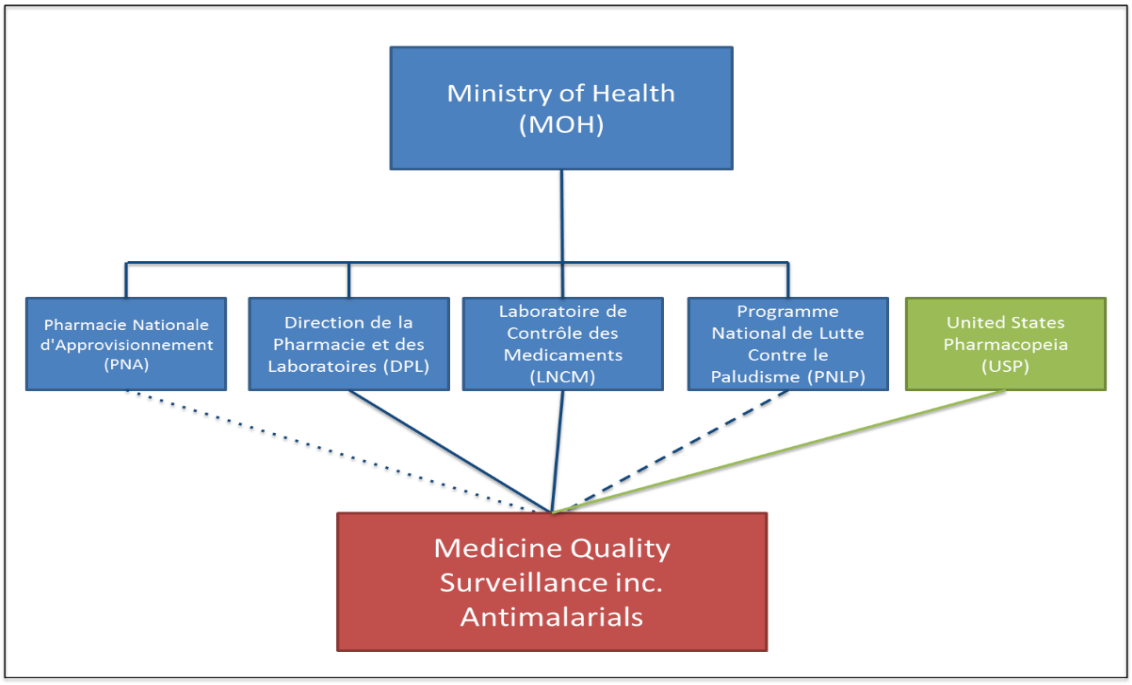


Figure 2.3: Perceived organisational structure of the MQSS in Senegal as summarised from interviews with authority representatives.
Connecting solid lines represent the integral role of some the organisations in the MQSS. The connecting dash line indicates lesser involvement of the organisation in the MQSS. The lightly connecting dashed line shows minimal involvement in the MQSS.

Strengths and challenges

Strengths and challenges of the MQSS have been compartmentalised into the building blocks of health systems.

Governance: From the interview data there was a common notion that Senegal had a sound health infrastructure with good collaboration, particularly between the DPL and LNCM. Medical regulation as a component of the MQAS was viewed as a strength by all interviewees. MQSS authorities also believed that the existence of a formal MQSS acted as a deterrent to manufacturers of poor quality medicines.

> *'But now at least the system is a barrier that discourages those who are tempted to make bad medicines, because we can control any type of producer or any manufacturer and any type of product.'* MQSS authority representative

Additionally, all MQSS authority interviewees referred to the LNCM as competent and efficient, often exceeding expectations in its performance especially in light of its limited resources. This was attributed to strong leadership, relevant expertise and support from USP. Moreover, it was suggested that the health system in Senegal was underpinned by a robust national governance structure allied to political and economic stability.

> *'One of the main messages is good governance and this means everything at all levels is done the right way. I think it's an important message. In all different parts people are confident of good governance in Senegal.'* MQSS authority representative

Despite good collaboration and a sense of shared ownership, a lack of coordination and communication were frequently cited as challenges associated with governance. Communication in Senegal was perceived by all interviewees to be limited, at all levels and in many institutions (not just the health sector). Coordination and communication problems can be categorised into two groups; i) communication among the MQSS authorities and ii) communication between MQSS authorities and treatment providers. Despite reported improvements in coordination and communication in recent years, inter-authority medicine quality meetings were infrequent, and primarily held in response to major issues such as concerns relating to the detection of a batch of poor quality medicines. Coordination and communication bilaterally between two-three authorities was quite common but was infrequent multilaterally (cross-authority). Interviewees also suggested the working relationship between the DPL and LNCM required improvement. At the time of the study, MQSS authority representatives suggested a closer working partnership between the LNCM

and USP had been formed and was focussed on achieving accreditation for the LNCM to become a WHO prequalified laboratory for which USP were providing support and expertise.

> *'There's a connection between the lab (LNCM) and USP. The LNCM coordinates with DPL and with PNA but this is not necessarily a cross coordination, the bodies do not meet all the time, except in the context of malaria but even for this it is bilateral. It is not multilateral, which would be ideal to discuss these issues.'* MQSS authority representative

Most treatment providers from both the public and private sector suggested that the coordination and communication between authorities and themselves was inadequate. Some treatment providers (particularly private sector pharmacists) felt isolated and on the periphery of the health system. Treatment providers also suggested communication between health authorities and the public was limited. Furthermore, they claimed that there was no official feedback mechanism for medicines that they suspected to be of poor quality. This was a specific concern for private sector pharmacists who were professionally regulated by the National Pharmacy Board and obtained their medicines from private wholesalers. Private sector pharmacists had little interaction with the DPL other than occasional visits by medicine inspectors.

> *'There is a communication problem between the operational level and the central level because the pharmacy, laboratories or the DPL, which manages these products do not give us the feedback on the information they receive on these products from the districts.'* Treatment provider (private sector)

Interestingly, only half of the treatment providers (from both sectors) interviewed knew that a MQSS existed, although all had heard of the DPL and LNCM. Even some of those treatment providers (from both sectors) who were aware of the LNCM, were unclear as to its role and purpose as evidenced by the following exchanges:

> *'Do you know a system for monitoring medicine quality exists in Senegal?'* Interviewer
>
> *'No, I did not know this.'* Treatment provider (public sector)
>
> *'Have you heard of the DPL or LNCM? What do you think they do with regard to medicine quality?'* Interviewer
>
> *'I have heard of them. The DPL is the medicine regulator and gives licenses for the pharmacy. The LNCM tests the quality of the medicines. But I don't know of a working system. I have never heard of this.'* Treatment provider (public sector)

In terms of governance and leadership arrangements, some of the MQSS authority representatives wished for the MQSS to become an independent system, not directly

governed by the MoH, believing the system would function more effectively if it operated autonomously. MQSS authority interviewees claimed to have a better grasp of aspects of medicines quality and its monitoring and were concerned that they were implementing irrelevant or outdated MoH policies, in some cases. This was compounded by the perceived lack of interest from the MoH in medicine quality activities, and inadequate financing.

Finance: MQSS authority representatives mentioned inadequate funding for the MQSS as a major challenge and part of a widespread issue of limited financial resources for medicines regulation. Limited funding was suggested as a reason for minimal medicines quality control at the point of entry, for only bi-annual post-marketing sampling and for not collecting and testing medicines from the informal (unregulated) sector. Limited funding was also cited as reason for a shortage of functional equipment at the LNCM (e.g. HPLC machines) and an insufficient number of medicine inspectors at the DPL (numbering just 2-3 nationally). The MoH was held almost entirely responsible for the perceived funding shortfall. In contrast, a few of the MQSS authority representatives were encouraged by the MoH's decision to increase funding for medicine quality activities in 2011 and by the continued financial commitment of USP/USAID which was viewed as vindication for a well performing MQSS.

Products and technologies: Two prominent challenges were stated, an inadequate number of medicine reference standards and limited medicine quality control analytical equipment. Both these challenges are crucial to enable a MQCL to operate efficiently and to produce results that are reliable and accurate. Medicine reference standards are expensive but essential for verifying the quality of sampled medicines. [11] Furthermore, insufficient functional technical equipment would also limit the capacity of the laboratory.

Human Resources: Individuals working at senior levels within the MQSS were seen as a strength for their knowledge and expertise. Several individuals in key positions within the MQSS, had previous experience of medicine quality research from UCAD, when the system was in its infancy. This had enabled the MQSS to build capacity in personnel, providing the system with specialists from academic backgrounds who had knowledge and experience in the field of medicine quality with expertise in analytical chemistry, pharmacy and public health. Nonetheless, at lower levels in the system, a shortage of skilled workers was reported as an important challenge for the MQSS. For example, whilst a sound level of expertise and knowledge existed amongst the current staff at the LNCM, their numbers remained insufficient to ensure optimal operation of the laboratory. USP have invested in staff training at the LNCM over many years to build capacity and enable the LNCM to provide 'in house' training for

medicine quality work. Since 2010, LNCM staff have been delivering training and development for new employees.

Service delivery: Treatment providers mentioned that providing health related information to their patients was a key aspect of their role and a potential strength to the MQAS if the system appropriately cascaded information to them to disseminate to the public. Treatment providers suggested they were highly regarded by the public for their health knowledge especially as Senegalese culture encourages the respect of individuals in positions of authority, particularly health professionals. However, some treatment providers suggested that the MQSS did not sufficiently utilise their position at the point of care in the health system and their experience in disseminating information to the public and felt that this was a missed opportunity for the MQSS and the health system as a whole.

Health Information: There was some discussion of the validity of the findings of poor quality antimalarials from the USP report of 2009 which were widely disputed by the MQSS authority interviewees. This scepticism was as a result of a perceived small sample size (n=141) of antimalarials collected and tested which was seen as not representative of the true picture of antimalarial quality in Senegal. Nonetheless, the study was thought to have facilitated several positive outcomes including: 1) increased awareness of the issue of medicine quality amongst the MoH, 2) a public health information campaign in 2009 (coordinated with the National Board of Pharmacists) warning about the dangers of purchasing medicines from the informal sector, 3) the retention of funding from USAID and 4) initiation of the process of WHO accreditation for the LNCM laboratory in Dakar.

> *'The main issue was the way in which the findings were shared. The media publicised the interesting results – the 40% failure, but this was not the real picture of medicine quality in Senegal. It complicated matters with the Ministry. But maybe there is something positive that has come from this. It has opened the eyes of the authorities to a problem, and so sampling activities have increased and there is an intention to improve the technical capacity of the laboratory.'* MQSS authority representative

Interviewees cited challenges of information flow within the MQSS centred on the lack of information shared with the public on matters associated with medicine quality, admitting dissemination was infrequent. Indeed, most treatment providers could only recall a single public health information campaign in 2009 called 'Street medicines kill' which focussed on dissuading the public from purchasing medicines from the informal sector. [12] Prior to this, pharmacists alone were largely responsible for raising awareness about the dangers of purchasing medicines from informal sellers through personal communication and small-scale

dissemination activity. However, a spate of violent robberies targeting pharmacies in 2009 in which stolen medicines were then allegedly discovered for sale in the informal sector, led to this larger scale public engagement exercise. [13] Perspectives of all treatment providers and the MQSS authorities on public understanding of health issues differed. MQSS authority representatives claimed that sharing health information with the public may be ineffectual as the majority were not educated enough to appreciate its significance. Conversely, treatment providers believed that the public were becoming increasingly aware about health issues due to greater access to health associated information on the internet.

Overall, MQSS authority interviews perceived strengths as measures of success of the MQSS against a backdrop of challenges typically faced by LMICs; limited funding and resources. Many of the mentioned challenges were outside of the interviewee's sphere of influence e.g. funding issues (table 2.1).

Table 2.1: Perceived strengths and challenges of the MQSS arranged by theme

Health system building blocks	**Strengths**	**Challenges**
Governance	Sound health infrastructure Good national governance structure	Limited coordination and communication at all levels and between levels. MQSS not independently operated – governed by MoH
Finance	External agency support	Lack of national funding for medicine quality activities
Products/technologies	Improving technical capacity – working toward WHO accreditation	Few medicine reference standards and technical equipment at LNCM
Health information		Paucity of information sharing
Service delivery	Relationship between treatment providers and public	
Human Resources	Strong leadership in key positions	Inadequate human resources (need for more technical expertise)

2.4.3 Components of a medicine quality surveillance system

Medicine regulation, medicine supply chains, medicine quality sampling and medicine quality analysis have been identified as key components of the MQAS which if compromised, may lead to the circulation of poor quality medicines in a country. Medicine regulation and the management of the medicine supply chain are also key components of the wider health system. Within each component, themes were arranged by the health system's building blocks with several sub-themes emerged incorporating varying degrees of prominence.

Medicines regulation

Governance: Within the MQAS, the DPL was responsible for authorising and registering medical products for use in Senegal, as well as providing licenses for manufacturers and wholesalers. Regulatory policies and procedures were only applicable to the public and regulated private sectors with limited influence on medicines and medicinal products in the unregulated informal sector. Medicine regulation was generally regarded as a major strength. Three main sub themes that emerged relating to governance were authorisation, post-marketing surveillance and the informal sector. All interviewees deemed the process of marketing authorisation and registration of medicines as being undertaken diligently by the DPL such that if a medicine was not registered by the DPL it should not be available in the regulated sectors.

> *'…we have a health system that works on laws and regulations, and a regulatory authority, a Directorate of Pharmacy and medicine that allows the flow of medicines through licensing and granting of marketing authorisations.'* Treatment provider (private sector)

Nonetheless, some treatment providers (from both sectors) raised concerns that despite post-marketing surveillance, unregistered products were available in Senegal and that the 'upstream monitoring (at the point of distribution) of medicines for their registration status was better than downstream (at the point of care).'

The theme of the informal sector (primarily referred to by the interviewees as informal medicine sellers) was further compartmentalised as follows; risks posed by the sector, legitimacy, ignorance, illegal trade and socio-cultural elements. All interviewees mentioned the informal sector as the foremost risk factor for poor quality medicines in Senegal. Interviewees believed that the informal sector trade of selling medicinal products was illegal. It was thought that medicines available in this sector had not been registered by the DPL and may have been brought into Senegal through illicit means. Interviewees perceived all people transacting in this sector (suppliers of medicines, business owners and workers) to be committing a criminal act. All interviewees suggested that MoH action against the informal medicine sector was challenging in isolation and that a collaborative effort with customs and the police was needed with coordinated action by central government through engagement with the Ministry of Justice, the Interior Ministry and the MoH. At the time of this study, government action against the informal sector was viewed as ineffectual and inadequate, particularly by treatment providers. Pharmacists especially derided the informal sector and perceived it as both a threat to public health and to their own livelihood.

> *'They (informal sellers) just have to pay a small fine, of around 100,000 CFA (approx. €150), it's not enough to dissuade people. The act of selling illegal medicines should be heavily penalized with a ten-year prison sentence plus many millions to pay. Pharmacists are advocating for the decree to be signed. For over ten years we are fighting for that, but it has not yet been adopted… The commitment to this policy is lacking.'* Treatment provider (private sector)

Despite widespread concerns about the informal sector it transpired that the MQSS did not monitor the quality of medicines in this sector and sampling activities ceased in around 2010, soon after the USP report was published. [6] The main reason provided for ceasing sampling was fear of legitimising informal sector trade.

> *'Let's suppose we controlled the quality of the medicine in the informal sector and we found that there are good quality medicines….what would we do? Would we tell everyone that the medicine at the illegal market is of good quality? This would be a way to promote the sector; in fact, if people find that there are good quality medicines in this market, they will rush there, and we would have legitimised the market.'* MQSS authority representative

An additional reason for not sampling was related to the socio-political and cultural context within which the informal sector operated. Senegal is a predominantly Islamic country in which religious brotherhoods have a key role in society and politics. These brotherhoods were thought to be the main proponents of the informal sector, operating a large proportion of street markets and employing many people from the lowest socio-economic groups in Senegalese society. A few interviewees suggested that apprehending operators and halting informal sector trade may have grave political ramifications for government officials who relied on support from religious brotherhoods. Additionally, targeting the informal sector may be regarded as discriminatory as the sector employed people from and catered to, the lowest socio-economic group in society.

> *'The politics involved in the informal sector were also a bit of a risk and that made it very tricky, for the ministry to regulate the informal sector. It was clear that this sector had the ability to scare off ministry people through their connections. Also, if you think about it, if you are riding hard on the informal market you were seen as kind of an elitist.'* MQSS authority representative

Despite these issues a few of interviewees expressed the view that medicine quality in the informal sector had to be monitored, as it posed a potential risk to public health.

> *'The informal sector, they are not sampling? Why? That is not good.* MQSS authority representative
>
> *'They said that by sampling there it's legitimatising their work.'* Interviewer
>
> *'The problem is that some people are continuing to buy their medicines from this sector….sampling their medicines, showing there is an issue…the official can say ''look these medicines you are buying in these sectors are not good. We have made a scientific evaluation.'' I don't agree with decision to stop sampling. It's not legitimisation, it's a process to verify and be comfortable in the message you deliver to the population'* MQSS authority representative

Additional risks relating to the informal sector that were mentioned included; sellers lacking appropriate knowledge, improper medicines storage conditions, origin of medicines and registration status of medicines (not having passed through the appropriate channels and not being registered with the DPL). These are discussed in further detail in chapter 3.

Finance: Insufficient funding was seen as another significant reason for not monitoring informal sector medicine quality, although there was no suggestion that if additional funding were available, that medicines would be collected and tested from this sector. Some interviewees considered the informal sector economy as quite lucrative. Sellers were thought to prioritise financial gain over the potential negative public health consequences of selling unregistered medicines. Some private pharmacists suggested that a small proportion of their peers may be selling their own stock to informal providers for profit, describing such individuals as a scourge on the profession who should face harsh penalties for such actions.

Service delivery: Stakeholders reported that a large proportion of the population from lower socio-economic groups frequently purchased medicines from the informal sector due to their lower cost in comparison to regulated private sector pharmacies.

Human Resources: Concerns among stakeholders about the robustness of post-marketing surveillance activities in Senegal arose from the supposed low number of drug inspectors nationally. The role of a drug inspector is in part to visit public and regulated private sector pharmacies checking on registration status of the outlet and health worker as well as monitoring compliance with national medicine policy.

Medicine supply chain

Governance: The official medicine supply chain in Senegal has two distinct channels; public sector and the regulated private sector. Public sector outlets obtained medicines from the PNA. Larger hospitals ordered direct from the PNA, whereas *centre de santés* and *post de santés* would obtain medicines from district wholesalers supplied exclusively by the PNA.

Private sector pharmacies and clinics were supplied by 4 or 5 private independent wholesalers who were licensed and registered with the DPL. In addition to these channels, there were medicines donated by external organisations e.g. antimalarials donated by the Chinese Cooperation. [14]

Most interviewees felt that the supply chain was secure for the sectors regulated by the DPL (public and regulated private sector) (see 'confidence' section below). Nonetheless, it was thought that despite stringent medicine regulation and robust supply chains, the porosity of Senegal's borders for goods and commodities (including medicines) may still compromise medicine quality. Furthermore, stakeholders believed that preventing illegal medicines entering the country needed to be addressed through inter-agency collaboration (between health, justice and customs) as the MQAS authorities were not powerful enough alone to prevent (or act) against this trade.

> *'The borders are porous to an extent and so a joint effort is needed between law enforcement agencies and the health authorities to monitor and act, the DPL cannot do this alone, they need the law behind them.'* MQSS authority representative

Products/Technologies: Emerging sub themes relating to the quality of medicines in the supply chain were: origin (country of manufacture), storage, procurement, generic medicines and shortages. With the exception of medicine procurement, the other sub themes are described in detail in chapter 3. According to treatment providers, customer demand for specific medicine brands, low cost medicines and sometimes 'better quality medicines' dictated their procurement strategy. Treatment providers stocked certain brands of a medicine even if it was more expensive than a generic alternative to meet the demands of their customers who preferred well-known medicines made by familiar manufacturers. Moreover, most interviewees believed that medicines available in the regulated private and public sectors were of good quality in contrast to poor quality or unknown quality in the informal sector (see chapter 3).

Health information: A supposed lack of awareness amongst the public of the risks of buying medicines from the informal sector was also a key issue. Interviewees stated that promoting the 'good' quality of medicines available in the public and regulated private sectors was required, aligned with messaging that warned of the risk of purchasing medicines from the informal sector.

Medicine sampling

Governance: Medicine quality sampling activities were undertaken by the LNCM. In general, medicines in Senegal were sampled through post-marketing surveillance as part of periodic national medicine quality surveys. Additional sampling was also undertaken to further investigate any batches of a medicine of poor quality that were detected through the testing of samples collected as part of the routine field surveys. Sampling for the national surveys was from public sector facilities or regulated private pharmacies in a variety of locations. [15] There was also *ad hoc* sampling, and quality control at the point of entry into Senegal at the PNA for medicines procured for the public sector. Sampling of medicines for the regulated private sector at the point of entry was unknown. A few MQSS authority interviewees mentioned that point of entry sampling took place. Those that did, suggested that it was performed when medicines were acquired from a new manufacturer or supplier. An accredited WHO prequalification laboratory would have the legislative and technical authority to conduct such inspections of medicines, [16] although at the time of the study, the LNCM held no such accreditation.

Among MQSS authority representatives, there was little consensus on the sampling strategies employed for collecting medicines. Random sampling was mentioned and was perceived to produce fairly representative and reliable data, but none of the interviewees could provide details on the precise process. Moreover, no documentation on sampling strategies was available or supplied when requested. Treatment providers (from both sectors) suggested that sampling approaches were vague and hence, they were sceptical about the representativeness of findings from medicine quality surveys. They accepted that testing every medicine in circulation was not possible but emphasised that sampling activities needed to be enhanced at the point of entry and for post-marketing surveillance by collecting a larger sample of medicines, randomly and from the informal sector in addition to the regulated sectors.

Finance: According to the MQSS authority representatives, an increase in funding for medicine quality activities would result in a more systematic sampling strategy with a greater number of sites and medicines collected, with the possibility of sampling additional medicine classes.

> *'But I'm sure that if they had a little more money, they would make a much more representative sample of the overall situation. I think the weakness is that they do not have enough resources to go to a maximum number of sites that are representative, and also to ensure maximum output at the sites to collect samples and bring them to the laboratories to determine the dosage.'* MQSS authority representative

Products and technologies: The four main medicine classes collected through post-marketing surveillance were antiretrovirals, antituberculosis, antimalarial and oral contraceptive medicines. With the exception of antimalarials, which were collected annually, medicines from these other classes were collected biannually. An interesting emerging theme was a concern that the sampling strategy was restricted to just these four medicine classes. Some interviewees mentioned that other commonly supplied or purchased classes such as antibiotics and analgesics should also be routinely sampled and tested. This is discussed further in chapter 3.

Medicine quality analysis

Governance: All MQSS authority interviewees believed that technical capacity at the LNCM was a key strength of the MQSS, although most treatment providers did not agree with this view. MQSS authority representatives also repeatedly mentioned the work being conducted by USP and the LCNM to acquire WHO ISO 17025 accreditation for the laboratory in Dakar. Only a handful of such accredited laboratories exist in sub-Saharan Africa (Zimbabwe, Kenya, Tanzania, Uganda and South Africa), none of which are in Francophone West Africa. [17] Working toward accreditation appeared to be a shared purpose and goal for key individuals in the MQSS. It was thought that accreditation would enhance the reputation of the LNCM regionally and provide an opportunity to diversify its role; extending quality control to include vaccines and foodstuffs. One individual remarked that a key outcome of achieving accreditation; would be generating additional income from this diversification of quality control.

> *'The support of USP that may result in the accreditation of the lab, which is highly supported by USAID. This will be a step forward…. there will be further opportunities, notably in terms of revenue that may also permit the laboratory improve its functioning. Indeed, this is going to strengthen the health system.'* MQSS authority representative

Products/technologies: The most recent medicine quality assessment procedures provided by the LNCM stated that collected medicines were screened by the MiniLab® at one of nine sentinel sites or the main LNCM laboratory in Dakar. [18] Suspect samples detected at this stage were re-analysed using HPLC, undertaken entirely at the LNCM in Dakar. The LNCM thus adhered to USP guidelines for medicine quality analysis. [2] The MiniLab® was perceived to be a quick, simple and fairly accurate screening technology that performs its primary function in indicating the quality of a medicine. It was viewed as a useful tool to employ at sentinel site laboratories where more sophisticated facilities were not available. Nevertheless, it was

recognised that only analysis conducted at the LCNM in Dakar using HPLC was the most accurate and reliable approach for determining medicine quality.

> *'It is a very good tool for that. It is functional, it is quick and you can work with this MiniLab® in different areas to do the medicine quality control. But it is only a small picture; the work needs to be done at the LNCM.'* MQSS authority representative

Stakeholders also acknowledged that whilst the validity of findings from medicine quality assessments was highly dependent on technological capacity of the LNCM, the source of the samples being representative of the medicines used for treatment was also significant.

Finance: A key challenge mentioned was a lack of funding for the LNCM hindering medicine quality analysis within the MQSS, although the high cost of operating a national MQCL was acknowledged. The LNCM owned three HPLC machines but only one was fully operational. A HPLC machine costs in excess of $20,000, hence their reliance upon the GPHF MiniLab® which costs significantly less at around $10,000. [19]

2.4.4 Confidence

Confidence emerged as a major theme throughout the course of the interviews. Varying degrees of confidence were described by interviewees in relation to different components of the MQSS and medicine quality. Interviewees also identified a level of confidence in other aspects of the MQAS and the wider health system. In general, interviewees had a higher level of confidence if they had a direct involvement in a specific component of the MQSS e.g. the MQSS authority representatives were quite confident in the LNCM's capacity to monitor the quality of medicines in Senegal. In contrast treatment providers, who mentioned they had little interaction with the MQSS, were less confident in its capacity. Data relating to confidence has been organised into levels of confidence.

Level of confidence- very good

MQSS authority representatives and some older and more experienced treatment providers from both sectors, were very confident in medicine regulation. MQSS authority representatives expressed confidence in the DPL citing the experience of key individuals in the organisation and the capacity they had built thus far. Relating this to supply chains, MQSS authority interviewees were very confident in the work of the DPL who as part of their regulatory activities, conducted due diligence on both producers and suppliers and authorised (licensed) them accordingly. This is contrary to the concern expressed by all interviewees of the presence of the informal sector, which whilst unlikely to infiltrate the supply chains of the

regulated sectors, was not monitored and was perceived to be selling unregistered and potentially poor quality medicines.

> *'The supply system is much more secured. Medicines come from the factory to the distributing company to the PNA or other private wholesalers. They then go to hospitals and health posts and from the private wholesaler to the pharmacy. Not anyone can have access to these medicines. It is much more secured in this way.'* MQSS authority representative

Moreover, the high level of confidence in certain aspects of the MQSS and the quality of medicines nationally was best illustrated by the common assertion that Senegal was the standard bearer for medicine quality monitoring among countries in West Africa. Specifically, Senegal's desire to act against the threat of poor quality medicines and more broadly its perceived superior political and economic stability played a significant role in the reported success of the MQSS. Most interviewees purported that in contrast, many of Senegal's neighbours had neither the volition nor the capacity to monitor the quality of medicines, and Senegal was therefore quite fortunate.

> *'In fact, all the structures are there, and it is a strength, so much so that we have always been envied by all neighbouring countries because they know that it exists here and not elsewhere. If we compare what is going on in some places in Asia and in the region in places like Nigeria, we can say that in Senegal the system is doing well and its improving and mainly the medicine quality is good.'* MQSS authority representative

Level of confidence - moderate

MQSS authority representatives were also quite confident in governance within the MQSS and the wider health structure, trusting in policies and procedures employed by the various MQSS authorities, the national health system and the government. Both MQSS authorities and treatment providers were moderately confident in the supply chains of medicines and trusted their suppliers to provide good quality medicines.

> *'I think we have a good system, a good organisation, with laws and the medicines are licenced and so the quality of medicines in Senegal is good, in general. For example, the ACTs, the PNLP help to get them, they are produced by prequalified manufacturers, so it is of good quality.'* MQSS authority representative

Despite a lack of funding, MQSS authority representatives were quite confident in the technical capacity of the LNCM, especially its capability to operate within tight parameters whilst maintaining good standards and in its ability to produce reliable results on medicines quality as well as in the currently employed sampling strategy.

Level of confidence – less confidence

All stakeholders indicated less confidence in the quality of generics and medicines made in Africa and Asia. Treatment providers also had less confidence in the quality of medicines from classes that were not routinely monitored by the MQSS. Pharmacists specifically queried the quality of medicines donated to the public sector by various external agencies. These aspects are discussed further in the next chapter.

All treatment providers had less confidence in the MQSS as a whole and its capacity to control the quality of medicines in Senegal. They questioned the technical capacity of the LNCM and some of the younger treatment providers also questioned the regulatory capability of the DPL. They specifically cited the lack of medicine quality monitoring at point of entry into the country as well as the low number of medicine inspectors as concerns.

> *'Are they equipped well enough to do the job required? They need to do many inspections at the control laboratory before a medicine can be verified. Unfortunately, they do not have enough staff required to do the work properly, so I think the work is not well done.'* Treatment provider (private sector)

This is contrary to the MQSS authority representatives view as they reported a greater confidence in medicines quality assurance as whole and its specific components. MQSS authority representatives generally only referred to the quality of medicines classes that are routinely sampled (e.g. antimalarials) as being of good quality.

Level of confidence – lacking confidence

There was distinct lack of confidence among all interviewees in the quality of medicines available in the informal sector for a multitude of reasons including i) the source of medicines - it was not clear where informal medicine sellers obtained products from, ii) the storage of medicines, especially exposure to sunlight and high temperatures and iii) the lack of monitoring of medicine quality and insufficient or absent regulation of medicines (sale of unregistered medicines) and sellers. This is also covered in greater detail in the next chapter. A brief overview of the level of confidence in aspects of the MQSS amongst the interviewees is provided in table 2.2.

Table 2.2: Level of confidence in MQSS and its associated processes

Level of confidence	MQAS component/process or related aspect	Stakeholder group
Lacking confidence	Informal sector	All
Less confident	Generic medicines MQSS as a whole Regulatory capacity of DPL and technical capacity of LNCM Quality of medicine classes not monitored by MQSS	All Treatment providers Treatment providers Treatment providers
Moderately confident	Technical capacity of LNCM Sampling strategies Governance Medicine supply chains (public and regulated private)	MQSS authorities MQSS authorities MQSS authorities All
Very confident	Medicine regulation Quality of medicines in public and regulated private sector	MQSS authorities and some treatment providers All

2.5 Discussion

This study has provided insights into the health systems context of a MQSS and how medicine quality is monitored within this context in a LMIC. The findings have revealed key factors that affect the function and operation of a MQSS as perceived by its stakeholders, highlighting the challenges to be addressed and identifying strengths that can be harnessed to assure medicines quality.

The study also points to some of the main internal and external risk factors for poor quality medicines that may be present in low-resource settings; medicine shortages, a vibrant informal sector, a lack of political will and financing, and powerlessness to apprehend and take action against falsified and substandard medicine producers and distributors. Nevertheless, based on the perceptions of those interviewed, Senegal was thought to have a sound medicine regulatory system and adequate medicine quality testing facilities which can reduce the risk of poor quality medicines circulating nationally. Particular points of weakness that emerged from the findings included the lack of surveillance of medicine quality in the informal sector and inadequate communication and information flow within the MQSS. The reminder of this section will summarise findings from the study that may provide important lessons and learning for MQSS in other LMICs.

2.5.1 The role of external agencies

The financial and technical support provided by USP's Poor Quality Medicines programme in LMICs is intended to enable the improvement of technical capacity nationally with an ultimate

goal of ensuring the availability of acceptable pharmacopeial quality medicines for the public.[20] In Senegal, USP have built technical capacity at the LNCM, and have demonstrated an ongoing a commitment through support for WHO ISO/IEC 17025 accreditation, which may be of great benefit to the health system in terms of efficiency (reducing the need to outsource quality control work), productivity and income generation. [21] The findings indicate that USP's influence is embedded in the MQSS and the system is highly reliant upon their financial and technical support. This is exemplified by the amount of funding provided for medicine quality activities by USAID. In the period 2011-2015 USAID provided around $825,000 for medicine quality monitoring, advocacy and pharmacovigilance. In the same time period the PNLP (on behalf of the MoH) allocated around $300,000 for medicine quality monitoring and pharmacovigilance for antimalarials, which was twice the amount from the previous period (2006-2011). [22-24] Whilst this demonstrates a degree of commitment to medicines quality, one interviewee mentioned that it may be due to USAID persistently advocating to the MoH to increase funding for medicines quality activities.

Nevertheless, there was some ambivalence of the significance of the role of USP in the MQSS. Some believed in the ability of the MQSS to operate without 'external' assistance expressing confidence in current technical and regulatory capacity at the LNCM and DPL. However, such perceptions overlook some of the challenges for the MQSS that have been presented in this study, such as limited financing from the MoH for medicine quality activities and the broader implications of divestment from USP. In contrast, there was also support for the role of USP in maintaining the current good standard of the system and concerns that disassociation of the MQSS would be unwise, as the system was not yet sustainable without USP's support.

2.5.2 Political will

The study findings suggest the MoH views medicine quality as a lesser public health priority. Whilst this is concerning it is offset by the continued financial commitment of USP. Annual sampling surveys have shown a decreasing proportion of poor quality medicines available in the public and regulated private sectors, from 21% in 2011 to 6.2% in 2013, perhaps suggesting the measures taken by USP and the MQSS are proving effective. Whether this perceived success would lead to an eventual decrease in financial support both internally and externally (especially if the LNCM can become more self-sufficient through accreditation) was a concern for some. As the principal authority of the MQSS the MoH ought to be both engaged and involved in medicine quality, especially as a lack of political will has been mooted as a risk factor for poor quality medicines. [25] Even though interviewees perceived MoH disengagement as disinterest it is quite possible that external support may undermine

continued commitment from the national government. Indeed, external donor funding is perceived as not being without risk; undermining national agencies, increasing bureaucracy through additional reporting requirements and influence on programme strategy, content and outcomes to meet their own priorities. [26, 27]

Some MQSS authorities expressed a desire for greater autonomy for the system with more responsibility for governance, management of funding allocation for the various medicine quality workstreams and the design and implementation of relevant medicine quality policies. Nonetheless, any departure from the status quo may require USAID to negotiate funding directly with the MQSS authorities, which may result in even less funding and commitment from the MoH. None of the authorities demonstrated a particular interest in assuming leadership of the MQSS, indeed each perceived their role as a quite specific component of the system whether it be regulatory, technical or logistical.

2.5.3 Governance and information flow

The study has demonstrated major challenges relating to governance and health information both of which are complex to address. Ineffective coordination among stakeholders may undermine the overall performance of the MQSS. [28] Coordination and communication between different agencies are frequently cited issues for public health surveillance systems.[29] In the context of medicine quality and assurance, inter-agency collaboration enabled by better communication and coordination would ensure that the appropriate regulatory and technical mechanisms are in place and operating effectively, to control medicine quality at a national level.

In Senegal, the problem of ineffective communication and coordination is less apparent across agencies, but evident between the strategic and operational levels of the MQSS and the service delivery level (treatment providers). Treatment providers reported a disconnect between themselves and the MQSS authorities with a top down flow of information which was often inconsistent, infrequent or absent. However, treatment providers were more frustrated and concerned by the lack of acknowledgment for information they had fed back into the system e.g. the treatment provider reporting mechanism for pharmacovigilance. Senegal has established a pharmacovigilance system [30] with a reporting mechanism that can be used to feedback on potential adverse drug reactions or safety incidents, a component that was viewed positively by treatment providers. However, treatment providers suggested that there was little acknowledgment or further discussion of the safety incidents they had reported. This

in part may explain the apparent low levels of confidence of treatment providers in several aspects of the MQSS.

Feedback mechanisms, and in particular, the closing of feedback loops and the involvement and engagement of treatment providers is perhaps of greater significance to medicines quality assurance and control. In comparison to other surveillance systems for public health, surveillance for medicines quality, even where it is rigorous and robust, cannot possibly contain all incidents of poor quality medicines and in LMICs heavily relies on less than comprehensive post-marketing activities. Hence, actively involving treatment providers in a MQAS through regular information sharing of data from medicine quality surveys and holding regular stakeholder meetings as well as acknowledgment of reporting, may act as a basis for provider-led post-marketing surveillance in LMICs, strengthening the MQAS as a whole. [31] This may address the issue of treatment providers inferred sense of detachment from the health system, especially among private sector pharmacists. If the MQSS and the health system in general are to operate effectively there must be good working relationships between health authorities and treatment providers.

Moreover, in many African countries, pharmacies are at the forefront of healthcare and treatment seeking by the public (reflected by their larger representation in this participant sample compared to other providers). In Senegal, the public perceive pharmacies as accessible and convenient with no user (consultation) fees providing care for minor injuries and illnesses.[32] Health systems in LMICs can capitalise on the wide availability of pharmacists given their extensive clinical, pharmacological and healthcare knowledge and location, both geographically and conceptually in communities. The provider level is effectively the first line in detecting poor quality medicines. Treatment failure, unexpected adverse events, suspect medicine packaging and visibly diminished medicine formulations could all be identified at the provider level. There is a need for provision of adequate training for treatment providers to recognise and report such instances. The MQSS would benefit greatly from poor quality medicines being identified at the provider level as part of post-marketing surveillance.

2.5.4 Informal (unregulated) sector

The informal sector was viewed as a considerable threat to public health in Senegal. There were also several references to insufficient governmental action against the informal sector. There was contempt for informal medicine sellers who were frequently referred to as ‘illegal traders.’ Indeed, informal medicine sellers were perceived to be contravening national medicine regulatory policy (and law), yet there was no concerted effort by law enforcement

agencies to apprehend them. Such action can only be authorised by the national government and their apparent reluctance in light of potential socio-cultural and political consequences for doing so, means that ultimately the DPL are powerless to act. Inept legislative procedures and an inability to apprehend manufacturers and distributors of poor quality medicines have been suggested as risk factors for poor quality medicines in LMICs. [33]

Addressing issues with the informal sector in LMICs is challenging. Approaches to improving the treatment provided in the private retail sector (both regulated and unregulated) include programmes such as the Management Sciences for Health Sustainable Medicine Seller Initiative which focusses on improving access to acceptable pharmacopeial quality medicines and services in parts of Uganda and Tanzania in which few pharmacies or health facilities exist, through accreditation of medicine shops that are not part of the formal health system. [34] In Tanzania, these medicines shops have become known as ADDOs (Accredited Medicine Dispensing Outlets) and operators have been provided with training and business incentives and have been subject to regulatory enforcement. Evidence suggests that ADDOs have had a positive impact on health outcomes for the local population. [35] The appropriateness of such an initiative in Senegal is questionable as most informal sellers operate in large urban markets that sell a range of contraband goods including medicines, [36] hence these itinerant sellers have no fixed location (unlike medicine shops) making monitoring and regulation difficult.

To address the perceived problem of the informal sector, MQSS' must provide empirical evidence of the quality of medicines, good or poor, especially as the study findings suggest that the sector was perceived to be accessed by a large proportion of the population. A lack of funding and fears of legitimising informal sector trade are barriers to sampling medicines to assess their quality from this sector. A convenience and covert sampling approach (where the seller is unaware of the purchaser's reason for buying medicines, assuming them to be a customer/patient) from known informal providers (such as those operating from large markets in major urban centres) on a periodic basis may suffice and would be affordable. Such surveys as a minimum would indicate the quality of medicines available in the informal sector. [37] Moreover, fears of legitimacy can be addressed by carrying out formal assessments on the knowledge and practices of informal providers such as the reported practice of storing medicines improperly. [38] If the MQSS authorities were able to prove that there were gaps in the general health and medicines knowledge and practices of informal medicine sellers (as suggested by interviewees) this would demonstrate to the public that regardless of the quality of medicines available in this sector, inappropriate medicines storage practices (which may affect their quality), non-adherence to national clinical and medicines guidelines and a lower

standard of healthcare expertise compared to that of treatment providers in the regulated sector all pose a risk to public health. [38]

There was overwhelming confidence in several elements of the system. Firstly, medicine regulation was perceived to be approached in a systematic manner through a robust process of marketing and registering all medicines entering the country, at least for the regulated sectors. [3] Secondly, the procurement of medicines from WHO prequalified manufacturers ought to validate the belief of a robust supply chain, for the public sector. Thirdly, the national MQCL (LNCM) was thought to employ a geographically representative sampling strategy and test medicines using recommended screening and analytical technologies, in a relatively well equipped laboratory. [39] Fourthly, with the help of USP, Senegal has built capacity in terms of monitoring medicine quality with significant evidence based input through academic research in the early stages of the development of the MQSS. Finally, all stakeholders illustrated a commitment to assuring medicine quality in Senegal and a desire to develop and improve the system, regardless of political will.

2.5.5 Strengths and limitations

A limitation of the study was that representatives from the MoH were not available for interview even though a request was made for their specific participation in the study. However, the views of each of the main MQSS authorities were captured by conducting interviews with senior individuals in each organisation The MQSS authorities implement MoH policies on medicine quality and are responsible for the system's day to day function, thus they are best placed to identify strengths and weaknesses of the system and of the overarching policies. Yet, an interview with a MoH representative would have provided an opportunity to explore some of the emerging salient themes such as political will and commitment to addressing medicine quality nationally.

Additionally, due to restrictions in study funding and resources, only treatment providers in urban and peri-urban areas close to the capital were interviewed. Therefore, the sample may not be representative of the views of treatment providers in more distant cities, provincial towns and rural locations. Nonetheless, despite geographical proximity of this sample to the capital, weaknesses in communicating information to providers from MQSS authorities still emerged as a major concern. Unfortunately, the researchers were not permitted by the national ethics committee from interviewing informal medicine providers. The views of actors from this sector would have provided some useful and comparative insight into their trade, knowledge and awareness of poor quality medicines.

Overall there was a 41% (11/27) non-response rate amongst treatment providers. However, just one private pharmacist refused to participate. Non-response was largely as a result of private pharmacists being unavailable for an interview. Nevertheless, a range of treatment providers in terms of profession and sector (public and regulated private) were recruited. Of further interest, most interviewees who consented were from 'downtown' Dakar which generally has a higher socio-economic status than peripheral districts of the city. However, it is unlikely that perceptions would have differed amongst pharmacists given the homogeneity of the regulatory system for medicines and the profession as a whole.

It is acknowledged that although the interviews were with key informants (representatives of the MQSS authorities with the benefit of insider knowledge), a few seemingly provided elite accounts and tended to speak on behalf of their organisation providing aligned views, overall. [8] Such public accounts are often unavoidable and in the context of this study their inclusion was deemed absolutely necessary. Senior stakeholders are sometimes less willing to be candid in their responses due to a strong organisational identity or simply a lack of familiarity with the researcher. [40] However, the five interviewees (three former MQSS employees and two individuals employed by UCAD) without a current involvement in medicine quality or the MQSS in Senegal nationally, provided ostensibly private accounts and these are often represented in the study as the contrasting or even deviant views. It is plausible that in this study, such elite accounts presented a few of the MQSS authority stakeholders as advocates and proponents of the system, whereas treatment provider accounts and those of the stakeholders less involved with the MQSS, were a comparative reflection of their true beliefs and perceptions. Overall, the treatment providers (especially private pharmacists) were more at ease once it had been established that the interviewers were independent (not authority affiliated) researchers and that the main interviewer was also a pharmacist by training.

It is also important to highlight that as a pharmacist in the United Kingdom, my experiences of medicine regulation and medicine quality control are based on a more robust, well financed and resourced system in a high income country. This is in contrast to the approaches to regulation and quality control in LMICs. This was considered when interpreting the data. In addition, as some interviewees mentioned, I was an 'outsider' and Senegal's health systems (and medicine quality) issues can only be solved internally. This may have affected the openness and honesty of some interviewees as well as their willingness to engage. The findings were interpreted in the context of my knowledge of health systems in LMICs and their associated challenges and through drawing upon my previous work in Senegal and other low income settings.

Finally, the analysis of the study was largely conducted by the main researcher. However, to maximise reliability several steps were taken. Transcription and translation of a sample of transcripts was verified by the research assistant. The coding framework was shared, discussed and agreed amongst myself and two other colleagues. Finally, in the process of data collection, myself and the research assistant discussed the content of all interviews (with the exception of the two conducted over skype) and compared field notes.

2.6 Policy implications for medicine quality surveillance systems

The study findings provide the basis for a series of suggestions for the MQSS but are not necessarily specific to Senegal. Whilst, findings from qualitative studies are seldom generalisable, the learning from this in-depth country case study provides useful insights and may offer some transferable recommendations for MQSS in LMICs more generally. [8] This is enhanced by the inclusion of a range of interviewees at all levels of the health system, extending to a few individuals working for external agencies who had an overview of MQSS' in several other African countries. Furthermore, the MQSS 'model' in Senegal has been supported in its development by USP who are implementing similar approaches to building technical, logistical and resource capacity for medicines quality in other African countries where their Poor Quality Medicines programme operates.

The recommendations are based on approaches to strengthening health systems in LMICs taking into account potential constraints in both financial and human resource:

1. Improving communication and coordination amongst authorities.

Despite the MoH acting as steward of the MQSS, the system maybe be better coordinated if one of the authorities (e.g. DPL, LNCM) assumed a leadership role in which they could act as an interface between the MoH and the rest of the MQSS and have oversight of the whole system. Alternatively, a transformation in the governance structure of the MQAS could be undertaken, whereby representatives from each authority would form a partnership board (as opposed to a coordinating committee). This board could be responsible for funding allocation to relevant MQSS activities and have collective accountability for medicines quality in Senegal. This type of governance structure is employed in several high-income settings to enable accountable care in health and social care systems through the bringing together of several different organisations to form a collaboration. [41] This type of structure would provide the MQAS with more power to lobby to the MoH, as a partnership and a collective voice in national public health agendas and strategies.

2. Improving communication between the authorities and treatment providers (especially pharmacists).

For the MQSS to operate effectively the authorities must actively engage with treatment providers, including private pharmacists. Establishing regular communication through information sharing with the regulated private sector would benefit the health system as a whole. The appointment of a representative of the National Board of Pharmacists to the MQSS coordinating committee may facilitate this engagement. Furthermore, a reporting mechanism for suspected events relating to medicine quality needs to be implemented. Utilising the existing pharmacovigilance system may be a viable option. [30]

3. Addressing the perceived problem of the informal sector

The MoH through the MQSS needs to take a two-pronged approach to address the problem of the informal sector. Firstly, the precise status of medicine quality should be established by adapting the current sampling strategy to included collections from informal sellers. If medicines are found to be of poor quality, there should be a resolute effort by government agencies to apprehend illegal traders and seize unregistered medicines. However, evidence suggests that punitive actions are not always successful. [34] Therefore, the second approach should be a focus on raising awareness and facilitating engagement to inform and educate the public about the potential risk posed to their health of purchasing medicines from the informal sector. Even if good quality medicines are detected, the MQSS authorities must make the public aware that informal medicine providers may lack sufficient health care knowledge and that the origin or status of medicines from the sector cannot be verified. This approach assumes that informal medicine sellers are not concerned about the quality of the products they sell. The opposite maybe true and further research is required to establish the quality of medicines available in the less regulated health sectors in LMICs as is the need to explore the perceptions of medicines quality amongst informal medicines sellers and their understanding of the impact of poor quality medicines on their clients.

2.7 Conclusion

This study has illustrated how an LMIC can address medicine quality issues through the collaboration of different national authorities and a shared purpose in controlling the quality of medicines. According to the interviewees in this study, Senegal has made substantial progress in assuring medicine quality through the establishment of a functioning MQSS and can be regarded as ‘standard bearer’ for other countries in the region. However, the MQSS and

the engagement of stakeholders in controlling medicine quality are undermined by the challenges highlighted in this chapter.

Strengthening health systems in sub-Saharan Africa is a complex task for multiple reasons. Challenges for health systems in LMICs often evolve from a lack of finance and resources and both of these issues are prominent for the MQSS in Senegal. This study has demonstrated the significance of the role of external agencies, such as USP, and USAID, in medicine quality monitoring in Senegal, yet their support alone is insufficient. Poor quality medicines must be viewed as a public health priority on a global scale to enable international donor funding to be directed to address the problem. A concerted international effort to tackle poor quality medicines manufacture and distribution as well as a commitment to the ongoing surveillance of medicines quality through the establishment of statutory legal frameworks and robust evidenced based research of the prevalence of poor quality medicines, may encourage individual governments to address the problem at a national level.

Moreover, pharmaceutical companies could invest more resources, especially in LMICs, to tackle medicine quality issues including sharing of expertise and building of technical and regulatory capacity. Medicines quality should be viewed as a shared responsibility to maintain provider and public confidence in the quality and efficacy of the medicines most commonly used for medical treatment. Efforts need to embrace all sources of treatment, whether located in the public, private or informal sector. Though surveillance and control of medicines in the informal sector raises particular challenges, the sheer volume of medicines purchased here mean that, in many LMICs, medicine quality in the informal sector cannot be overlooked.

2.8 References

1. Prequalification of quality control laboratories. Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies (Technical report series, no. 961). Geneva: World Health Organization; 2011.
2. Guidelines for Drug Sampling, USP DQI Drug Quality Monitoring Program. Use of the Basic Tests at the Peripheral Level. Rockville: United States Pharmacopeia 2006. http://pdf.usaid.gov/pdf_docs/PNADH150.pdf. [cited 20th Feburary 2017]
3. Assessment of medicines regulatory systems in sub-Saharan African countries: an overview of findings from 26 assessment reports Geneva, Switzerland: World Health Organization 2010. http://apps.who.int/medicinedocs/documents/s17577en/s17577en.pdf. [cited 12th May 2016]
4. Risha PG, Msuya Z, Clark M, Johnson K, Ndomondo-Sigonda M, Layloff T. The use of Minilabs to improve the testing capacity of regulatory authorities in resource limited settings: Tanzanian experience. *Health Policy*. 2008;87(2):217-22.
5. Lalani M, Kitutu FE, Clarke SE, Kaur H. Anti-malarial medicine quality field studies and surveys: a systematic review of screening technologies used and reporting of findings. *Malaria journal*. 2017;16(1):197.
6. Survey of the Quality of Selected Antimalarial Medicines Circulating in Madagascar, Senegal, and Uganda. United States Pharmacopeia United States Pharmacopeia U; 2009 November 2009. Report No. http://apps.who.int/medicinedocs/documents/s17069e/s17069e.pdf. [cited 26th February 2017]
7. Sabh R, Perry C. Research design and data analysis in realism research. *European Journal of Marketing*. 2005;40(11/12):1194-209.
8. Green J, Thorogood N. Qualitative methods for health research. 2nd ed. Los Angeles: SAGE; 2009. xv, 304 p. p.
9. Everybody's Business: Strengthening Health Systems to Improve Health Outcomes: WHO's Framework for Action. . Geneva: World Health Organisation 2007. http://www.who.int/healthsystems/strategy/everybodys_business.pdf. [cited 7th March 2013]
10. Ritchie J, Lewis J, Nicholls CM, Ormston R. Qualitative research practice: A guide for social science students and researchers: Sage; 2013.
11. Reference Standards. Rockville United States Pharmacopeia 2016. (http://www.usp.org/reference-standards. [cited 11th February 2016]
12. Senegal Health Authorities Organize Campaign against “Street Drugs” with Participation of USP, USAID, and other International Groups. The Standard. 2009:11.
13. Guèye A. Haro Aur les Faux Médicaments. Courrier International. 2009.
14. Teaming Up Against Malaria: The Story of Senegal’s Successful Partnership. Speak Up Africa 2013. http://www.makingmalariahistory.org/wp-content/uploads/2013/12/SENEGAL-PARTNERSHIP-STORY-ENGLISH.pdf. [cited 20th March 2018]
15. Diedhou A. Programme de Suivi et Controle de la Qualite des Medicaments Antipaludiques au Senegal 2012-2013. Dakar, Senegal: Laboratoire National de Controle des Medicaments 2012.
16. t’Hoen EF, Hogerzeil HV, Quick JD, Sillo HB. A quiet revolution in global public health: the World Health Organization’s Prequalification Of Medicines Programme. *J Public Health Policy*. 2014;35.
17. WHO list of prequalified quality control laboratories (43rd edition). 2017. https://extranet.who.int/prequal/sites/default/files/documents/PQ_QCLabsList_23.pdf. [cited 14th December 2017]

18. Coordination des Activites de Suivi de la Qualite des Medicaments Antiretroviraux, Antituberculeux, Antipaludiques et Contraceptifs. Ministere de la Sante et de la Prevention 2010.
19. Kovacs S, Hawes SE, Maley SN, Mosites E, Wong L, Stergachis A. Technologies for detecting falsified and substandard drugs in low and middle-income countries. *PLoS One*. 2014;9(3):e90601.
20. Promoting the Quality of Medicines in Developing Countries (PQM). United States Pharmacopeia https://www.usp-pqm.org/. [cited 18th March 2018]
21. World Health Organization Prequalification programme. A United Nations programme managed by WHO. Geneva: World Health Organization 2016. http://www.apps.who.int/prequal/. [cited 12th May 2016]
22. Malaria Operational Plan, Year Six – Fiscal Year 2012; Senegal. President's Malaria Initiative 2012. https://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy12/senegal_mop_fy12.pdf?sfvrsn=6. [cited 7th Septmeber 2012]
23. Malaria Operational Plan 2014, Senegal. United States: United States Agency for International Development 2014. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy14/senegal_mop_fy14.pdf?sfvrsn=10. [cited 25th April 2017]
24. Malaria Operational Plan - Fiscal Year 2013; Senegal. United States: President's Malaria Initiative 2013. https://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy13/senegal_mop_fy13.pdf?sfvrsn=8. [cited 20th March 2018]
25. Gostin LO, Buckley GJ, Kelley PW. Stemming the global trade in falsified and substandard medicines. *JAMA*. 2013;309(16):1693-4.
26. Moucheraud C, Schwitters A, Boudreaux C, Giles D, Kilmarx PH, Ntolo N, et al. Sustainability of health information systems: a three-country qualitative study in southern Africa. *BMC health services research*. 2017;17(1):23.
27. Pfeiffer J, Johnson W, Fort M, Shakow A, Hagopian A, Gloyd S, et al. Strengthening Health Systems in Poor Countries: A Code of Conduct for Nongovernmental Organizations. *American Journal of Public Health*. 2008;98(12):2134-40.
28. Nayyar GM, Breman JG, Newton PN, Herrington J. Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. *The Lancet Infectious diseases*. 2012;12(6):488-96.
29. Butler D. Disease surveillance needs a revolution. *Nature*. 2006;440(7080):6-7.
30. Thiam S, Ndiaye JL, Diallo I, Gatonga P, Fall FB, Diallo NE, et al. Safety monitoring of artemisinin combination therapy through a national pharmacovigilance system in an endemic malaria setting. *Malaria journal*. 2013;12:54.
31. Mutale W, Chintu N, Amoroso C, Awoonor-Williams K, Phillips J, Baynes C, et al. Improving health information systems for decision making across five sub-Saharan African countries: Implementation strategies from the African Health Initiative. *BMC health services research*. 2013;13 Suppl 2:S9.
32. Patterson D. Pharmacy in Senegal: Gender, Healing, and Entrepreneurship: Indiana University Press; 2015.
33. Newton PN, Green MD, Fernandez FM. Impact of poor-quality medicines in the 'developing' world. *Trends in Pharmacological Sciences*. 2010;31(3):99--101.
34. MDS-3: Managing Access to Medicines and Health Technologies. Arlington, VA: Management Sciences for Health 2012. http://apps.who.int/medicinedocs/documents/s19577en/s19577en.pdf. [cited 20th March 2018]

35. Rutta E, Liana J, Embrey M, Johnson K, Kimatta S, Valimba R, et al. Accrediting retail drug shops to strengthen Tanzania's public health system: an ADDO case study. *Journal of pharmaceutical policy and practice*. 2015;8(1):1-15.
36. Granström SC. The informal sector and formal competitiveness in Senegal. Sweden: University of Lund 2009. https://liveatlund.lu.se/intranets/LUSEM/NEK/mfs/MFS/194.pdf. [cited 20th March 2018]
37. Newton PN, Lee SJ, Goodman C, Fernandez FM, Yeung S, Phanouvong S, et al. Guidelines for field surveys of the quality of medicines: a proposal. *PLoS medicine*. 2009;6(3):e52.
38. Sudhinaraset M, Ingram M, Lofthouse HK, Montagu D. What is the role of informal healthcare providers in developing countries? A systematic review. *PLoS One*. 2013;8(2):e54978.
39. Kaur H, Green MD, Hostetler D, Fernandez FM, Newton PN. Antimalarial drug quality: methods to detect suspect drugs. *Therapy*. 2010;7(1):40--57.
40. Kirkevold M, Bergland Å. The quality of qualitative data: Issues to consider when interviewing participants who have difficulties providing detailed accounts of their experiences. *International journal of qualitative studies on health and well-being*. 2007;2(2):68-75.
41. Shortell S, Addicott R, Walsh N, Ham C. Accountable care organisations in the United States and England. 2014.

Chapter 3: The quality of medicines available in Senegal; perspectives of health system stakeholders

3.1 Background

Defining medicines quality has been the subject of much debate over the last decade with an inability to reach consensus amongst policy makers, academic researchers, lawyers, medicine manufacturers etc. [1, 2] Until very recently there was no universally agreed definition of medicines quality. However, in May 2017 the World Health Assembly (WHA) Member State mechanism agreed on definitions that categorise medicines quality as falsified, substandard and unlicensed/unregistered. [3] The individual definitions for each of these have already been discussed in previous chapters. These recent definitions possibly fit the legal and technical paradigms of medicines quality.

However, other studies from low-middle income countries (LMICs) [4-6] have highlighted an important clinical paradigm that is of greater relevance to the perceptions of treatment providers and the public and considers medicine quality in terms of the impact on the health of the population. [7] These, studies have explored perceptions of medicines quality among treatment providers and consumers and have found that respondents tended to characterise a medicine as good quality, if it alleviated symptoms with minimal side effects (efficacy and safety), if it was a brand name medicine (made by a reputable company) and if it was high in cost. Furthermore, treatment providers have expressed greater confidence in the quality of medicines made in Europe in comparison to those manufactured in countries in Asia and Africa. [5, 8, 9] In high income countries studies have shown mixed opinions about the quality of generics with most health professionals perceiving generic medicines to be comparable in quality and efficacy to the original brand version. [10] Nonetheless, a minority have expressed concerns that generics are manufactured to a poorer quality with potential implications for patient safety. [11]

At the strategic and operational levels of medicine regulatory and quality assurance systems in LMICs there is limited information on views about medicine quality. The perceptions of individuals working at these levels is important as it may shape their approach to medicines quality assurance. This may include their motivation to address pertinent issues, their specific focus on certain components of the system, their overall confidence in the medicine quality surveillance system (MQSS) and subsequently, the quality of medicines controlled by the system. We have discussed in chapter two that MQSS authority representatives had greater

confidence in the surveillance system, this chapter will explore the perceptions of the understanding of medicines quality of a range of health system stakeholders including representatives of the MQSS authorities and treatment providers.

3.2 Methods

See section 1, A5 for the methods for this chapter. The approach to coding and analysis is described below.

3.2.1 Coding and analysis

Thematic analysis of the data was undertaken and three overarching themes relating to the perceptions of medicine quality emerged; 1) the source of drugs 2) the type of medicine, and 3) the perceived impact of health systems on medicine quality. Within each of these several further sub-themes also emerged as illustrated in figure 3.1 below.

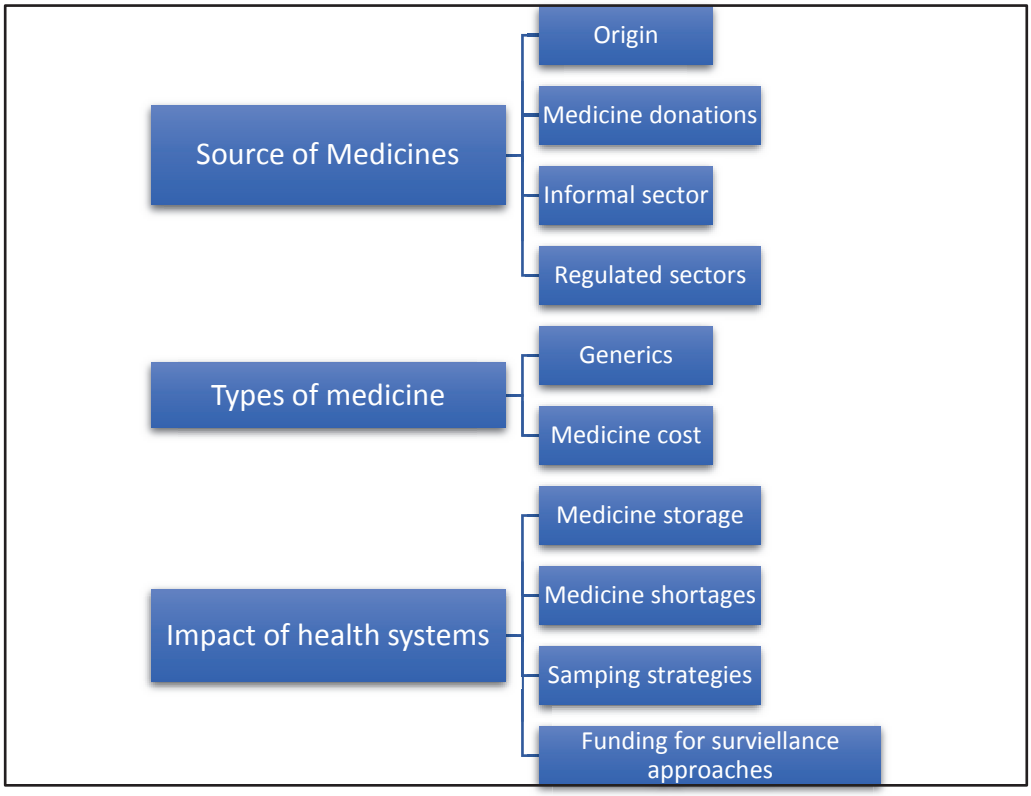


Figure 3.1: Coding framework of emerging themes related to medicines quality

3.3 Results

The characteristics of the study participants and participation of the MQSS authority representatives and treatment providers in the study are described in section 1, A6.

3.3.1 Source of medicines

Perceptions relating to the source of medicines and their quality included: country of manufacture or origin, donated medicines, the informal (unregulated) and regulated (public and private) sectors.

Country of manufacture/origin

All interviewees mentioned a preference for medicines manufactured by European and North American companies as these were judged to be of reliable quality. This perception was founded on three main premises; 1) these medicines were produced by reputable manufacturers, 2) these were thought to undergo strict regulatory controls in the country of manufacture before export and 3) these must have been of a high standard since these medicines were the same as those that were consumed by European and American citizens. In contrast, treatment providers expressed negative views of medicines made in India, China and Nigeria citing that these posed a risk to medicines quality.

> *'I was in the rural area; Vélingara where you can see many products entering Senegal…There were a lot of fake products coming from Nigeria……. I do not know if all of them are not of good quality because as they say, drugs come from Asian countries like India and China, but why not from France, Belgium, which are countries that have the means to control these products.'* Treatment provider (private sector)

Medicine donations

The Chinese Cooperation, an international aid organisation donates antimalarials to Senegal periodically. [12] However, the quality of these donated medicines was queried by one treatment provider, who suggested that these were not sampled and analysed by the LNCM in the same manner as other medicine imports.

> *'Public health facilities receive donations; but do those medicines have marketing authorisation? Now I'm not saying donations are bad, otherwise it would be returned immediately. But among the donations, we do not know what happens, the expiry date, storage conditions, and the person who has given these products.'* Treatment provider (public sector)

In fact, one MQSS authority stakeholder provided an example of the difficulties faced when quality issues are detected with donated medicines and the results of medicine quality assessments at the LNCM are scrutinised by external experts. In this instance, the results were

disputed by the manufacturer, who claimed the medicines were of good quality when they left the factory and that their quality was compromised due to improper storage in Senegal or that the LNCM's findings were questionable as, in their opinion, the technical capacity of the LNCM laboratory was inadequate. Indeed, the interviewee admitted that a higher standard of technical capacity at the LNCM such as accreditation for WHO prequalification (which the laboratory was working toward), would have meant less scrutiny of their findings.

> *'Once we were granted drugs by the Chinese. We took these drugs to the laboratory [LNCM] and after testing, found a problem. Then the Chinese came in with their quality experts. The laboratory could not continue this debate because of many problems with the procedure, and the Chinese went off saying that we were mistaken.'* MQSS authority representative

Informal sector

Senegal has a large informal sector in the guise of vast open markets such as Keur Serigne Bi in Dakar and similar structures in other principal cities, such as Touba. There was a general consensus that medicines available in this sector were more likely to be of poor quality for two main reasons. Firstly, the conditions under which medicines are stored here were deemed inadequate as they were available as loose tablets in transparent plastic bags and exposed to direct sunlight and high temperatures for prolonged periods. Secondly, the origin and status of the medicines available in this sector was questionable as medicines may have been brought into the country illegally and thus not subject to national regulatory measures.

> *'Drugs sold in this market are of poor quality. When you go to Keur Serigne Bi you see drugs exposed to the sun, lying on the ground which may damage them…They are not registered, we know nothing about the origin, who manufactured them and when they made them.'* MQSS authority representative

Public and private sectors

The perception of medicines quality available in the regulated sectors was in stark contrast to the informal sector. As mentioned in chapter 2, all stakeholders were quite confident in medicines quality in the public and regulated private sector mentioning that medicines regulation was stringent and supply chains robust. In particular, the source of medicines in these sectors (manufacturers and wholesalers) were deemed trustworthy. A LNCM report from medicine quality surveys in Senegal from 2012 found that 93.8% of 481 antimalarial samples collected from the public and regulated private sectors passed the MiniLab® screening test for medicines quality. [13]

> *'You know the tenders were done, there was better traceability, you know who was making the drug and providing it and so the public sector I felt really comfortable, the private sector – quite comfortable, the illicit sector – not very comfortable.'* MQSS authority representative

3.3.2 Type of medicine

Perceptions about medicine quality were also expressed in relation to the type of medicine i.e. generic or brand as well as its cost. Generic medicines were widely available in both public and regulated private sectors and were generally cheaper than their brand versions. Most interviewees doubted the quality of generics. In addition, treatment providers suggested that patients were less trusting of generics, perceiving them as less efficacious than the brand version. The lack of familiarity with the 'name' of a generic and its manufacturer raised doubts with all interviewees and reportedly with patients and consumers as well. Treatment providers also mentioned that patients associated quality with cost, perceiving more expensive drugs to be more effective at treating their symptoms and hence of better quality.

> *'Sometimes because when the drug is not expensive they think it is not good. This is Senegalese mentality…They think that drugs sold here are cheaper in price and quality… As we are here in town, there are some wealthy people who prefer to buy in pharmacies.'* Treatment provider (public sector)

Several interviewees provided anecdotes of supposedly ineffective generic medicines which compromised patient safety. The most frequently cited example was that of diazepam (a benzodiapine with anxiolytic and sedative properties).

> *'If I take diazepam for example which is a drug that is prescribed against convulsions in children, it has since been said that it does not work in generic form properly. When you put it on a convulsing child, he would still convulse; whereas if you give him Valium®, convulsion would stop.'* MQSS authority representative

3.3.3 The perceived impact of health systems on medicines quality

Three main sub-themes relating to medicine quality as an outcome of the health system emerged, including medicines storage, medicine shortages and sampling strategies. The MQSS itself was thought to have partly been established upon the perception of the suspected quality of the antimalarial medicine, chloroquine. MQSS authority representatives suggested that the emergence of chloroquine resistance indicated by a decline in its efficacy was linked with poor quality samples collected in the same geographical locations as the resistant foci. A similar hypothetical link between poor quality chloroquine and treatment failure attributed as an indication of drug resistance has been reported in Cameroon. [14]

Medicine storage

All interviewees mentioned that medicine quality was directly affected by conditions of storage (especially at the outlet level). This is a well-known issue in the tropics given high temperatures and humidity, especially in rural areas where power supplies may be intermittent. [15] Quality was thought to be acceptable when medicines arrived at a facility but improper storage conditions contributed to their degradation. Despite this being a major concern, interviewees appeared resigned to accepting improper medicine storage, suggesting the most obvious approach to overcoming this challenge was to install cooling systems to regulate temperature and humidity whilst acknowledging that such systems were unaffordable to individual facilities in most cases.

> *'We realised that the quality of the drugs stored at the PNA was better than the quality of drugs stored in health facilities. This means that the environment, the temperature etc. at the facility has an impact on the quality*.' *But individual facilities cannot pay for equipment to make the temperature acceptable.'* MQSS authority representative

Medicine shortages

Interviewees reported that medicine stock outs may affect the availability of good quality medicines. If medicines were in short supply in the public sector then patients would have to seek alternative sources, such as the informal sector. One MQSS authority representative believed that prolonged stock outs had forced some nurses working in rural facilities to obtain medicines from the informal sector to address the shortfall, thereby exposing patients to medicines that have not been through national regulatory processes and hence, their quality cannot be verified. Public sector treatment providers mentioned that in instances where medicines or medical appliances were not available from the PNA, they would contact authorised private wholesalers. Regulated private sector pharmacists suggested that medicines shortages were a rarity in the private sector due to the larger number of private medicines wholesalers (4-5) and deemed it to be an entirely public sector problem.

Medicine sampling strategies

Many stakeholders expressed concerns that the LNCM only collected samples from the regulated sectors as part of post-marketing surveillance, and not the illicit informal sector. The four main classes routinely collected were antimalarials, antiretrovirals, anti-tuberculosis drugs, and oral contraceptives. With the exception of antimalarials, which were collected annually, the other medicines were collected twice a year, as the MQSS authorities were more reassured by antimalarial quality since preceding surveys had indicated very low proportions of poor quality samples. [16] The sampling of these four medicine classes alone was a concern for

some interviewees who felt that they were not entirely representative of the national medicines market. Treatment providers in particular expressed concern about the lack of quality control of other medicines they sold in high volumes such as antibiotics and analgesics. They acknowledged that the MQSS had restricted financial resources but felt that a sampling strategy also encompassing these other medicine classes was required.

> *'I know they (LNCM) control some drugs, like for malaria. But what about the others? I sell many drugs for pain and antibiotics. They do not check these drugs. We need to know about their quality as well.'* Treatment provider (private sector)

3.4 Discussion

The findings from this study illustrate that medicine quality was an important consideration among all those interviewed, revealing a wide variety of perceptions relating to the quality of medicines available in Senegal. The findings presented here are mainly pertinent to the clinical paradigm, framing medicine quality in terms of its efficacy (the ability of the medicine to alleviate physical symptoms). Furthermore, the findings contrast how generic medicines are believed to be inferior in quality than their brand versions and that medicines from the 'east' (China/India) are perceived less favourably (in terms of their quality) than those from Europe and North America. The study findings also reveal perceptions of how certain aspects of the health system such as storage conditions, medicine shortages and sampling strategies may affect the quality of medicines available in a country.

The source of the medicine, type of medicine (generic or brand), its cost, its perceived efficacy and safety are factors which may be considered by treatment providers and consumers when supplying or purchasing a medicine. [17] In this study, the country of manufacture of a medicine was often viewed as a proxy for quality, with suspicion of medicines originating from or made in India, China and Nigeria. Distrust in the quality of generic medicines and those originating from the 'east' mirror similar findings from other countries [4, 8, 18, 19] and there is some objective evidence to support this view with some reports of the discovery of poor quality medicines, including antimalarials made in India and China. [20-22] Other studies have also found poor quality artemisinin based medicines (both substandard and falsified) and other antimalarials (substandard) in Nigeria. [23, 24] Of interest, in one of these studies, the source of the medicine as a risk factor for poor quality artemisinin based medicines was found to be higher where the medicines were stated on the packaging to be manufactured in North America, compared to Africa or Asia. [23] Regional media reports about Nigeria's problems with poor quality medicines and a prominent incident reported in the international press of

'fake' antimalarials found in Angola that arrived from China, may further fuel the suspicion of the quality of medicines from these countries. [25-27] Conversely, medicines from Europe or North America were typically thought to be of good quality, echoing similar findings amongst consumers in urban Tanzania. [28] The superior quality of medicines manufactured in Europe was a perception predicated on assumptions of a more robust approach to quality and regulatory control within European countries, as well as the international reputation of 'western' pharmaceutical companies.

Generic medicines were often seen as inferior in quality to their brand versions, a view that has also been reported in other studies. [29, 30] Brand name medicines are usually marketed by reputable pharmaceutical firms based in Europe and North America and are more expensive, and it may be difficult to disentangle perceptions of quality of generics, from concerns about place of origin, manufacturing standards and cost. Nonetheless, brand versions have usually been on the market longer than generics due to the length of patent, establishing a good record of efficacy and safety. Conversely generics are less well known and recognised, they cost less and most of those available in at the time of the study in Senegal were reported to have been made in India and China. Treatment providers reported that patients equated cost with quality and therefore preferred brand name medicines. The efficacy of generic medicines was also associated with quality. Brand versions were thought to be more efficacious and hence of superior quality which confers with perceptions of treatment providers in studies conducted in other LMICs. [4, 6]

However, there is little evidence to evaluate whether these perceptions are warranted. If treatment providers were to convey these views to consumers this would only substantiate pre-existing negative preconceptions of generics. The view that generics are of doubtful quality or less efficacious because they cost less could act as a barrier to their use; and effectively undermine international efforts to increase access to affordable medicines for the world's poor. This is contrary to the premise of the WHO essential medicines list that was established to promote the use of those medicines that were more essential than others, highlighting that many medicines in LMICs were not useful and those that were useful were not always accessible, where they were needed most. [31] Nevertheless, findings from a recent study conducted in Nigeria found samples of one generic dihydroartemisinin combination product to be 2.4 times more likely to not have the recommended stated active pharmaceutical ingredient than other brand versions of the same drug. [23] Such a finding may provide some credence for the belief in the superior quality of brand versions.

Although the cumulative 'negative' beliefs of generic medicine quality may ultimately make them less desirable to the consumer, treatment provider and regulator [4, 18], the demand for generics globally is huge, with some Organisation for Economic Co-operation and Development (OECD) countries reporting a 75% market share nationally in 2011. [32] Market dominance can be partly attributed to the lower cost of generics. Indian pharmaceutical companies accounted for 17.7% of medicine imports (mainly generics) in 2011 in sub-Saharan Africa (up from 2.2% in 2002) [33] and if this increase in market share continues along the same trajectory, there will be an even greater number of generic medicines available in health facilities and pharmacies. Indeed, a notable proportion of medicines (especially generics) in Senegal are made in India and China. [13] Generic medicines are not a homogenous entity, although in terms of perceptions of their quality, they may be viewed as such. Suspicions about generic medicine quality and country of manufacture need to be grounded in objective empirical evidence. Detailed medicine quality studies using epidemiologically sound sampling methods to investigate the quality of generics in use at the point of care and studies that quantify the scale of the problem, can provide the much-needed evidence to either substantiate or allay these widely-held concerns. The market share of generics is already substantial and may continue to grow over the next few years, hence their quality should be investigated scientifically to reassure regulators, health professionals and consumers.

The doubts expressed regarding the quality of donated medicines highlights another important issue faced by LMICs. The supposed altruistic nature of medicine donations means that often the recipient has limited control over the product received and is in a weak position to express doubts or dissatisfaction. Donated medicines can sometimes be industry surpluses with packaging and medicine information in a language not appropriate to the local population or be medicines which are close to their expiry date or may have even expired [34, 35], raising additional concerns for the recipients.

The informal health sector in sub-Saharan Africa provides a convenient alternative for consumers, especially in locations where regulated health facilities (public or private) are difficult to access. [36] Medicines sold through this sector are thought to be both available and affordable in comparison to the regulated sectors, where medicines can be more expensive (regulated private sector) and stock outs are common (public sector). [37] In this study, there was considerable disdain toward the informal sector which was viewed as a significant threat to medicine quality in Senegal primarily as a result of improper medicine storage practices and a lack of authentication of source or origin of the medicines available. Data on medicine quality in the informal sector in Senegal is scarce. A study conducted by the USP in Senegal in 2010

found that 68% (13/19) of samples of antimalarials in the informal sector failed quality control testing (stated as confirmatory analysis as listed in the drug monograph) in comparison to 25% (3/12) and 35% (11/31) in the public and regulated private sectors. [38] The MQSS ceased sampling from the informal sector in 2010, therefore there were no reliable estimates of medicine quality from this sector at the time of this study in 2013. As outlined in chapter 2, sampling from the informal sector was ceased for three main reasons; 1) a fear of endorsing their existence, 2) concerns relating to the cultural and political influence of the religious brotherhoods that were involved in the operation of the sector and 3) a lack of funds to extend medicine quality monitoring activities to the informal sector. Contempt for this sector is not uncommon and is thought to be driven by concerns that informal medicine sellers are motivated by financial gain which threatens both the business income of formal sector providers and the health of the population. [39] Similar perceptions among regulated private sector pharmacists were also apparent in this study, as discussed in chapter 2.

In contrast, both public and regulated private sector interviewees were quite confident in national medicines regulation and in medicines supply chains. A degree of this confidence was attributed to the WHO prequalification programme which assures the 'quality, safety and efficacy' of medicines prior to their distribution to recipient countries. [40] However, a recent medicine quality review paper found that 8.2% of 2813 antimalarial samples that failed chemical/packaging analysis tests were labelled as being from a WHO prequalified manufacturer. [41] Trust in the quality assurance of prequalified medicines, relies upon the quality control work of external agencies such as the WHO, manufacturers and wholesalers. The quality of medicines arriving in Senegal cannot be officially verified as the LNCM was not a WHO prequalified quality control laboratory at the time of the study but was working toward the accreditation. However, as mentioned in chapter 2, MQSS authority representatives and treatment providers had confidence in the ability of the national medicines regulator to regulate and authorise manufacturers and wholesalers and the products they supply as well as a degree of confidence (mainly MQSS authority interviewees) in the MQSS as a whole to assure the quality of medicines in Senegal.

Confidence in external agencies such as medicine manufacturers and wholesalers may result from manufacturing facilities meeting Good Manufacturing Practice (GMP) standards as well as the medicines they produce and distribute meeting WHO prequalification programme criteria.[42, 43] In addition, at a national level WHO accreditation for a medicines quality control laboratory coupled with the capacity to implement point of entry medicines quality

screening as well as robust post marketing surveillance would provide confidence in the capability of a national MQSS to minimise the risk of poor quality medicines.

The perceived association between medicine stock outs and medicine quality is based on the notion that if a prescribed medicine is not available in the public sector, the patient may purchase it from elsewhere. [44] Using artemisinin based medicines as an example (which are free in the public sector in Senegal), if medicines were not available in the public sector, patients were advised to visit a private sector pharmacy but some reportedly chose to visit an informal seller instead (as antimalarials are reportedly cheaper than in private pharmacies). Given that the quality of informal sector medicines in Senegal cannot be verified, stock outs pose a potential risk to public health.

Another notable concern for all stakeholders was the effect of storage conditions on medicine quality. Medicine degradation and loss of activity may be accelerated by storage conditions such as exposure to sunlight, high temperatures (greater than 30°C) and high humidity. Indeed the antibiotics, clarithromycin and erythromycin and antifungals, ketoconazole and itraconazole have been demonstrated to be sensitive to these extreme conditions. [45] In this study, inadequate storage was perceived as a reality of the climatic situation in the tropics and therefore there was an ambivalence about what could be done to address the issue. Potential solutions such as air conditioning units for cooling were deemed impractical as they are seldom affordable for most outlet owners to operate regularly. Yet, a recent study assessing the stability of half tablets of dihydroartemisinin-piperaquine over a three month period when exposed to 30°C and 70% humidity found that the stated active pharmaceutical ingredients remained at around 95% and hence quality was maintained. [46] Nevertheless, there is currently not enough empirical evidence to substantiate or disprove climatic effects on medicine degradation. Hence, more research exploring the degradation of medicines, especially of generic medicines needs to be conducted to establish the effect of tropical environmental conditions on medicine quality. This ought to be conducted by manufacturers, who should endeavour to test the quality of each new product following exposure to environmental conditions similar to those in the tropics. Manufacturers should state relevant information (such as the temperature at which sustained exposure would increase the risk of degradation) on the medicine's packaging so as to enable medicine providers and sellers to store medicines appropriately.

The MQSS in Senegal has been sampling and testing the quality of antimalarials, antiretrovirals, anti-tuberculosis medicines and oral contraceptives for several years and these

are generally perceived to be of acceptable pharmacopeial quality which is validated by results from recent medicine quality surveys. [13, 16] However, the quality of medicine classes not sampled by the MQSS is unknown. The USP Poor Quality Medicines Programme promotes the integration of the monitoring of medicine quality into national malaria, HIV and tuberculosis programmes. [47] An expansion of the sampling strategy to encompass other medicine classes would require additional funding, but MQSS stakeholders believed that the MoH did not perceive medicine quality as a public health priority. Hence, MoH funding for medicine quality surveillance activities was limited and sampling strategies restricted, to those recommended by the USP programme.

Nonetheless, the appropriateness of the current sampling approach must be considered against the context of more pressing public health priorities in Senegal. The estimated HIV prevalence rate in 2013 for adults aged 15-49 in Senegal was just 0.5% with deaths due to HIV/AIDS recorded as 14 per 100,000. [48] Antiretrovirals are sampled twice a year. In contrast, in 2012 an estimated 34% of all-cause mortality in Senegal was attributable to non-communicable diseases. [49] There is no known sampling for medicines used to treat non-communicable disease such as anti-hypertensives or anti-diabetics. Verification of the quality of other medicine classes would alleviate stakeholder concern. The case of inefficacious generic diazepam purportedly associated with its quality mentioned by some interviewees, illustrates how readily such instances can undermine confidence in a particular medicine.

3.4.1 Strengths and limitations

The data for analysis in this study was drawn from a representative sample of stakeholders of the MQSS including representatives in strategic and operational roles within the authorities responsible for operating the system and treatment providers from the public (doctors, nurses and pharmacists) and private sector (pharmacists only). Previous studies examining perceptions of medicines quality have primarily sought views from health providers and consumers and have seldom explored the beliefs of representatives at senior levels in the health system. These views may also be transferable to health systems in other LMICs especially as Senegal shares some similar features with other sub-Saharan African countries. Firstly, Senegal is one of several countries in sub-Saharan Africa that is supported by the USP's Promoting the Quality of Medicines Programme. Secondly, Senegal imports the majority of its medicines (including generics) from India, China and Nigeria. Finally, Senegal also has a reportedly burgeoning informal sector for medicines.

This study was limited by the findings being extracted from a data set obtained using questions not directly linked to the perceptions of medicines quality and overall, this study has mostly considered views of those responsible for supplying medicines. Any perceptions of consumers or patients referred to in this study are effectively one step removed as they are relayed by treatment providers. The views of patients and consumers are important as they provide insights into how demand for medicines is shaped by views on their quality. A better understanding of these views may inform relevant public health campaigns to educate the public on how there is scarce evidence to prove factors such as origin/source, cost and type (generic/brand) affect medicine quality and that the vast majority of generics are safe and effective as they are approved by the WHO prequalification programme or similar initiatives.[43] Furthermore, as with chapter 2, this study does not include perceptions of informal medicine sellers which are also significant, especially as interviewees perceived the inadequate storage and non-verifiable source of medicines in this sector as prominent risk factors for medicines quality in Senegal.

3.5 Conclusions

Perceptions of medicine quality are likely to be informed by personal experience, knowledge of empirical evidence (known facts), physical appearance of the medicine and hearsay, especially from peers or colleagues. Medicine quality studies are generally conducted in the technical paradigm, yet the perceptions of medicine quality do not fit this model but align better to the clinical paradigm which involves the impact of medicine quality on population health and the effectiveness of medicines in treating symptoms of illness.

This study has also illustrated the complexity of the perceptions of medicine quality and presents some contradictory views. For example, generics were thought to be of inferior quality to their brand versions, yet, treatment providers had confidence in the quality of medicines they sold and supplied to the public and many of these were generic products. Also, patients were thought to view cost as an indicator of quality, yet it was reported that patients bought medicines from the informal sector because they were cheaper which perhaps gives credence to the perception that medicine cost is thought to be a risk factor for poor quality medicines. The heterogeneity of these views provides challenges for policy makers, pharmaceutical companies and regulators in educating treatment providers and consumers about the realities of medicine quality.

Public information campaigns by pharmaceutical companies and national regulators supported by research-based evidence of generic medicine quality may change these perceptions. Furthermore, the publicising of epidemiologically sound data for medicines quality that is in format suitable for the lay reader is needed. This will clarify the status of generic medicines and the quality of medicines manufactured in newly-emerging economies, such as China, India and Nigeria, as recent reports only act to undermine confidence in generics which are vital to improving access and affordability of modern medicine for the world's poorest.

3.6 References

1. Attaran A, Barry D, Basheer S, Bate R, Benton D, Chauvin J, et al. How to achieve international action on falsified and substandard medicines. *BMJ*. 2012;345:e7381.
2. Clift C. Combating Counterfeit, Falsified and Substandard Medicines: Defining the Way Forward? Chatham House 2010. http://www.gphf.org/images/downloads/library/chathamhouseproject2010.pdf. [cited 26th February 2017]
3. WHO member state mechanism on substandard/spurious/falselylabelled/falsified/counterfeit (SSFFC) medical products: Working definitions. Geneva: World Health Organisation 2017 http://www.who.int/medicines/regulation/ssffc/A70_23-en1.pdf?ua=1. [cited 21st July 2017]
4. Patel A, Gauld R, Norris P, Rades T. Quality of generic medicines in South Africa: perceptions versus reality - a qualitative study. *BMC health services research*. 2012;12:297.
5. Patel A, Norris P, Gauld R, Rades T. Drug quality in South Africa: perceptions of key players involved in medicines distribution. *Int J Health Care Qual Assur*. 2009;22(5):547-60.
6. Syhakhang L, Freudenthal S, Tomson G, Wahlstrom R. Knowledge and perceptions of drug quality among drug sellers and consumers in Lao PDR. *Health Policy and Planning*. 2004;19(6):391-401.
7. Newton PN, Amin AA, Bird C, Passmore P, Dukes G, Tomson G, et al. The primacy of public health considerations in defining poor quality medicines. *PLoS medicine*. 2011;8(12):e1001139.
8. Chemwolo AK, Ngondi J, Clark B. Perceptions and views of regulatory pharmacists on the registration system for generic drugs for human use in Kenya. *East Afr Med J*. 2010;87(3):120-6.
9. Jamshed SQ, Hassali MA, Ibrahim MI, Babar ZU. Knowledge attitude and perception of dispensing doctors regarding generic medicines in Karachi, Pakistan: a qualitative study. *J Pak Med Assoc*. 2011;61(1):80-3.
10. Dunne SS, Shannon B, Cullen W, Dunne CP. Beliefs, perceptions and behaviours of GPs towards generic medicines. *Family Practice*. 2014;31(4):467-74.
11. King DR, Kanavos P. Encouraging the use of generic medicines: implications for transition economies. *Croat Med J*. 2002;43(4):462-9.
12. Malaria Operational Plan 2014, Senegal. United States: United States Agency for International Development 2014. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy14/senegal_mop_fy14.pdf?sfvrsn=10. [cited 25th April 2017]
13. Diedhou A. Programme de Suivi et Controle de la Qualite des Medicaments Antipaludiques au Senegal 2012-2013. Dakar, Senegal: Laboratoire National de Controle des Medicaments 2012.
14. Basco LK, Ringwald P, Manéné AB, Chandenier J. False chloroquine resistance in Africa. *The Lancet*. 1997;350(9072):224.
15. Kupper TE, Schraut B, Rieke B, Hemmerling AV, Schoffl V, Steffgen J. Drugs and drug administration in extreme environments. *J Travel Med*. 2006;13(1):35-47.
16. Cordination des activites de suivi de la qualite des medicaments antiretroviraux, antituberculeux , antipaludiques et contraceptives. Dakar, Senegal: Ministry of Health 2010.
17. Waber RL, Shiv B, Carmon Z, Ariely D. Commercial features of placebo and therapeutic efficacy. *JAMA*. 2008;299(9):1016-7.

18. Wong ZY, Hassali MA, Alrasheedy AA, Saleem F, Yahaya AH, Aljadhey H. Patients' beliefs about generic medicines in Malaysia. *Pharm Pract (Granada)*. 2014;12(4):474.
19. Dunne S, Shannon B, Dunne C, Cullen W. Patient perceptions of generic medicines: a mixed-methods study. *The Patient-Patient-Centered Outcomes Research*. 2014;7(2):177-85.
20. Dyer O. Drugs exported from India to Africa are poorer quality than those sent elsewhere. *BMJ*. 2014;349:g6017.
21. Newton PN, Fernandez FM, Plancon A, Mildenhall DC, Green MD, Ziyong L, et al. A collaborative epidemiological investigation into the criminal fake artesunate trade in South East Asia. *PLoS medicine*. 2008;5(2):209--19.
22. Survey of the Quality of Selected Antimalarial Medicines Circulating in Six Countries of Sub-Saharan Africa. Geneva: World Health Organization 2011. http://www.who.int/medicines/publications/WHO_QAMSA_report.pdf. [cited 20th February 2017]
23. Kaur H, Allan EL, Mamadu I, Hall Z, Ibe O, El Sherbiny M, et al. Quality of artemisinin-based combination formulations for malaria treatment: prevalence and risk factors for poor quality medicines in public facilities and private sector drug outlets in Enugu, Nigeria. *PLoS One*. 2015;10(5):e0125577.
24. Onwujekwe O, Kaur H, Dike N, Shu E, Uzochukwu B, Hanson K, et al. Quality of anti-malarial drugs provided by public and private healthcare providers in south-east Nigeria. *Malaria journal*. 2009;8:22.
25. Ebeleke E. NAFDAC destroys N320m fake products. Vanguard. 2010 January 28th 2010.
26. Nigeria: Nafdac Seizes N32 Million Fake Anti-Malarial Drugs. News Release. All Africa 2009. https://www.vanguardngr.com/2010/01/nafdac-destroys-n320m-fake-products/. [cited 22nd March 2018]
27. Faucon B, Murphy C, Whalen J. Africa's Malaria Battle: Fake Drug Pipeline Undercuts Progress. Wall Street Journal. 2013.
28. Mujinja PG, Mackintosh M, Justin-Temu M, Wuyts M. Local production of pharmaceuticals in Africa and access to essential medicines: 'urban bias' in access to imported medicines in Tanzania and its policy implications. *Global Health*. 2014;10:12.
29. Kaplan WA, Ritz LS, Vitello M, Wirtz VJ. Policies to promote use of generic medicines in low and middle income countries: a review of published literature, 2000-2010. *Health Policy*. 2012;106(3):211-24.
30. Shrank WH, Liberman JN, Fischer MA, Girdish C, Brennan TA, Choudhry NK. Physician perceptions about generic drugs. *Ann Pharmacother*. 2011;45(1):31-8.
31. Laing R, Waning B, Gray A, Ford N, t Hoen E. 25 years of the WHO essential medicines lists: progress and challenges. *The Lancet*. 2003;361(9370):1723-9.
32. Pharmaceutical generic market share. Health at a Glance 2013: OECD Indicators. Paris: OECD 2013. [cited 22nd March 2018]
33. Understanding the pharmaceutical market opportunity and developing sustainable business models in Africa. IMS 2011. https://www.canback.com/files/2014_IMS_Africa_Opportunity_Whitepaper.pdf. [cited 22nd March 2018]
34. Snell B. Inappropriate drug donations: the need for reforms. *Lancet (London, England)*. 2001;358(9281):578-80.
35. Lalani M, Kaur H, Mohammed N, Mailk N, van Wyk A, Jan S, et al. Substandard antimalarials available in Afghanistan: a case for assessing the quality of drugs in resource poor settings. *The American journal of tropical medicine and hygiene*. 2015;92(6 Suppl):51-8.
36. Goodman C, Brieger W, Unwin A, Mills A, Meek S, Greer G. Medicine sellers and malaria treatment in sub-Saharan Africa: what do they do and how can their practice

be improved? *The American journal of tropical medicine and hygiene*. 2007;77(6 Suppl):203-18.
37. Williams HA, Jones CO. A critical review of behavioral issues related to malaria control in sub-Saharan Africa: what contributions have social scientists made? *Soc Sci Med*. 2004;59(3):501-23.
38. Survey of the Quality of Selected Antimalarial Medicines Circulating in Madagascar, Senegal, and Uganda. United States Pharmacopeia United States Pharmacopeia U; 2009 November 2009. Report No. http://apps.who.int/medicinedocs/documents/s17069e/s17069e.pdf. [cited 26th February 2017]
39. Hughes R, Chandler CR, Mangham-Jefferies LJ, Mbacham W. Medicine sellers' perspectives on their role in providing health care in North-West Cameroon: a qualitative study. *Health Policy Plan*. 2013;28(6):636-46.
40. WHO Prequalification of Drugs Factsheet. Geneva: World Health Organisation 2013 January 2013. Report No. http://www.who.int/mediacentre/factsheets/fs278/en/. [cited 7th March 2017]
41. Tabernero P, Fernandez FM, Green M, Guerin PJ, Newton PN. Mind the gaps--the epidemiology of poor-quality anti-malarials in the malarious world--analysis of the WorldWide Antimalarial Resistance Network database. *Malaria journal*. 2014;13:139.
42. GMP questions and answers. World Health Organization 2017. http://www.who.int/medicines/areas/quality_safety/quality_assurance/gmp/en/. [cited 6th June 2017]
43. t'Hoen EF, Hogerzeil HV, Quick JD, Sillo HB. A quiet revolution in global public health: the World Health Organization's Prequalification Of Medicines Programme. *J Public Health Policy*. 2014;35.
44. Hill J, Hoyt J, van Eijk AM, D'Mello-Guyett L, Ter Kuile FO, Steketee R, et al. Factors affecting the delivery, access, and use of interventions to prevent malaria in pregnancy in sub-Saharan Africa: a systematic review and meta-analysis. *PLoS medicine*. 2013;10(7):e1001488.
45. Langner MD, Maibach HI. Many common drugs in dermatology are light, temperature, or moisture-sensitive. *Skin Therapy Lett*. 2009;14(1):3-5.
46. Hodel EM, Kaur H, Terlouw DJ. Stability of Dihydroartemisinin–Piperaquine Tablet Halves during Prolonged Storage under Tropical Conditions. *The American journal of tropical medicine and hygiene*. 2017;96(2):338-40.
47. Promoting the Quality of Medicines in Developing Countries (PQM). United States Pharmacopeia https://www.usp-pqm.org/. [cited 18th March 2018]
48. Epidemiological Fact Sheet on HIV and AIDS, Senegal. United States: UNAIDS 2013. http://www.unaids.org/en/regionscountries/countries/senegal. [cited 22nd March 2018]
49. Non-Communicable Diseases Country Profiles, Senegal. Geneva, Switzerland: World Health Organisation 2014. http://www.who.int/nmh/countries/sen_en.pdf. [cited 22nd March 2018]

Section 2: Screening technologies and surveys for assessing the quality of antimalarial medicines

B1. Introduction

Having considered the international context for medicines quality as well as providing, an assessment of a national medicines quality assurance system (MQAS), this section focuses on the technical parameters of how medicine quality is monitored. It describes in particular, a fundamental aspect of a medicines quality surveillance system (MQSS), the laboratory analysis of medicines quality, with emphasis on an appraisal of the currently available screening technologies for assessing the quality of antimalarial medicines. The negative impact of poor quality medicines on public health warrants the need for their swift detection ideally before they enter a national supply chain (at the point of entry) or as part of a post-marketing surveillance system (often at the point of care). [1] Unfortunately, most LMICs lack the capacity to implement point of entry screening and some have a limited system of post-marketing surveillance to enable detection of poor quality medicines circulating within their country. This exemplifies the need for screening tests that can be used as part of routine post-marketing surveillance in remote locations, in field surveys and at the point of care.

As a background to this section, the role of screening technologies is discussed in relation to how the technical component of a MQSS functions to detect poor quality medicines, set against the backdrop of the key technical challenges faced by health systems in low-middle income countries (LMICs). An overview of the current screening technologies that can assess antimalarial medicine quality (with a focus on artemisinin combination therapies (ACTs) as the first line medicines in treating uncomplicated *P.falciparum* malaria) is also provided in this section, together with an assessment of these devices, their cost, practical utility, accuracy compared to the gold standard technique and potential for integration into a MQSS. Chapter 4 comprises our published systematic review [2] which provides an overview of the types of screening technologies used to assess antimalarial medicine quality, the survey methods that have been used to assess antimalarial quality in field surveys and the standard of reporting. We also devised a template for reporting future studies. Chapter 5 presents the results of a pilot study carried out in Senegal to evaluate the practical utility of a new screening test, comprising two assays, both of which specifically detect the artemisinin derivative in mono and combination therapies (the artemisinin derivative test, ADT). The chapter assesses the ADT in operational use in a LMIC, including perceptions of its usefulness and acceptability by

laboratory staff working at the national medicine quality control laboratory (MQCL) who were routinely involved in analysing the quality of antimalarials collected from field surveys nationally. The performance of this new test was also evaluated in comparison to the Global Pharma Health Fund MiniLab® (discussed in detail later in this section), the screening test currently used in Senegal to assess the quality of artemisinin based medicines (and other medicine classes). The approach to the evaluation of the ADT was designed to establish its requirements in terms of utility and acceptability to enable its use in malaria endemic countries as a component of a MQSS.

B2. The technical component of medicines quality monitoring

The previous chapters have outlined the importance of technical capacity within a national health system in identifying poor quality medicines and providing reliable findings upon which a National Medicines Regulatory Authority (NMRA) can act to minimise the likelihood of such medicines circulating in a country. An efficient, effective and functional MQAS should have a fully equipped MQCL consisting of: 1) confirmatory testing equipment (high performance liquid chromatography (HPLC) systems; also referred to as the gold standard test), so that international pharmacopeia methods can be used to assess the quality of medicines; 2) quality-assured drug reference standards and 3) staff with the expertise and experience of operating specialist technology. [3, 4]

However, MQCLs have high capital and maintenance costs that may deter national governments in LMICs from initial or continued investment. This was mentioned in the interviews with MQSS representatives in Senegal (presented in chapter 2) where the national MQCL (the Laboratoire National de Contrôle des Médicaments (LNCM)) had three HPLC machines, but only one was fully operational. The other two machines were not operating having developed faults to components that were not repaired as result of insufficient funds allocation in the annual budget. Yet, the findings presented in chapter 2 from interviews with MQSS stakeholders (representatives of the key authorities of the system and treatment providers) also revealed a common perception; that the health system in Senegal benefitted from a sound medicines regulatory system (which provides the foundation for an effective MQAS) and that the MQSS was an asset to the health system. This was because of the undertaking of periodic medicines quality sampling of certain medicine classes and testing at the LNCM which was further strengthened by gradual improvements in technical capacity supported by United States Pharmacopeia (USP).

To improve technical capacity whilst trying to overcome the challenge of a lack of funding for medicines quality control, the LNCM in Senegal (with support from USP) was working towards WHO prequalification accreditation at the time of data collection in 2013/2014. The World Health Organization (WHO) operates a prequalification programme for MQCLs in LMICs providing accreditation for prequalification through ISO (ISO/IEC17025) certification. [5] To achieve accreditation a MQCL must pass an assessment that satisfies requirements for 'good practice for pharmaceutical quality control laboratories.' [6] Prequalification accreditation has a two-fold benefit for an MQCL; 1) it enables participation in WHO prequalification monitoring projects that assess the quality of medicines procured by UN agencies and 2) it reassures potential users of the service that the laboratory meets international standards. From interviews with the MQSS authority representatives, it was suggested that attaining prequalification status could enable the LNCM in Senegal to generate additional income from undertaking quality control of medicines, medical devices, vaccines and foodstuffs for NMRAs from neighbouring countries, non-governmental organisations and other external agencies. As of July 2017 there were only eight WHO accredited laboratories in just five countries in sub-Saharan Africa with three in South Africa, two in Kenya and one each in Zimbabwe, Uganda, Tanzania. [7] This suggests a need for greater investment in prequalification processes with cooperation between the WHO, USP and individual countries to enable the establishment of local prequalified laboratories. [8]

The limited technical capacity in LMICs presents a challenge for medicines quality assurance and surveillance nationally, regionally and internationally. In part, this challenge can be addressed by using medicines quality screening technologies, not as a replacement for confirmatory methods but for both to work in tandem. In some LMICs, screening tests are a key component of a MQSS. USP through its Promoting the Quality of Medicines programme encourage the use of screening technologies for rapid assessment in the field. Countries in which USP are active, employ the MiniLab® as the first stage in the screening of medicines quality. [9] The USP testing guidelines suggest that any failing or doubtful samples along with 5-10% of 'passed samples' ought to be sent for confirmatory testing. [10] Such an approach reduces the need for analysis of all samples collected through periodic medicine quality surveys by confirmatory testing which would be time consuming and expensive. In countries where confirmatory testing is not available screening technologies may play a crucial role in assessing medicines quality. Screening tests indicate that a problem exists with a medicine (or batch of medicines) which can then be further investigated at MQCLs. [2] Screening technologies can also be used in non-laboratory settings such as health facilities or border

posts (at the point of care and point of entry). However, their use in these settings has not been widely implemented and evaluated yet.

Screening tests that are employed as part of a MQSS or for assessing the quality of medicines as a component of post marketing surveillance need to have certain key attributes. In the screening and diagnosis of diseases and infections the accuracy of the test is important and should ideally be highly sensitive (able to correctly identify those patients with a disease) and highly specific (able to correctly identify those patients without the disease). However, it is accepted that in the context of medical screening there is often a trade-off between sensitivity and specificity. [11] In terms of medicines quality, a key attribute of a screening test is its capacity to detect a poor quality medicine. Poor quality medicines have negative clinical implications at the individual and population level. [12, 13] Hence, an ideal medicine quality screening test needs to be highly sensitive and give accurate results i.e. produce minimal 'false passes' hence, allowing the lowest proportion of poor quality medicines to go undetected as is possible. Additionally, given the large number of samples requiring testing, a screening test, needs to be inexpensive to purchase and maintain, easy to use and portable (preferably handheld).

B3. Medicine quality screening technologies for antimalarials

There are several screening technologies currently available for assessing the quality of antimalarial medicines, at varying stages of development from initial product testing to pilot feasibility studies on the ground in LMICs with a view to evaluating their potential for wider use as part of a MQSS either through post-marketing surveillance such as through routine medicines quality surveys or for assessment at border posts, at the point of entry into a country. Basic tests for medicine quality are primarily based on, but not restricted to, chromatographic and spectrometric techniques with the addition of visual inspection. Product recognition by comparing the packaging with that of the accredited product, counterfeit identification, detection of the stated active pharmaceutical ingredient (SAPI) and determining composition are just some of the approaches adopted by current screening technologies. [14] These technologies are summarised in Table B1 below, which compares the method of detection for medicine quality used by each test, approximate cost and practical features such as portability, simplicity of operation etc.

The WHO medicine testing guidelines recommend combining qualitative and quantitative approaches to analysis, to establish the identity, content and disintegration of a medicine. [15]

Qualitative tests that rely on a subjective interpretation by the operator include visual inspection, colorimetric tests and tablet or capsule disintegration. Visual inspection involves assessment of the medicine packaging, patient information leaflet and the medicine itself. Misspellings, absence of an expiry date or batch number and obvious signs of deterioration of the product itself may indicate a poor quality medicine. [16] Colorimetric tests involve a simple colour reaction to verify presence of the SAPI. The disintegration test requires the tablet/capsule to disintegrate in water heated to 37°C, within 30 minutes. If this does not occur, it could indicate a poor quality product. Thin layer chromatography (TLC) is an example of semi-quantitative testing and is described further in the MiniLab® section below. [17] Used in combination, these basic tests provide an indication of the quality of a medicine. Visual inspection alone may suggest a medicine is falsified or counterfeit. Disintegration testing provides an indication of deficiencies related to medicine solubility and bioavailability. The next step of carrying out a colour reaction indicates if the SAPI is present before carrying out a TLC run for verification of whether the quantities of medicine claimed on the label are in the sample.

Table B1: Comparison of key features of screening devices used to assess the quality of antimalarials

Device	Method of detection for medicines quality	Approximate Cost	Portability	Training required	Other medicine classes	Other Comments
MiniLab®	Visual inspection; disintegration; TLC	$10,000 (capital investment) Commercially available	Not handheld (laboratory only)	Yes - several days	Yes	Toxic reagents Previous laboratory experience essential
TruScan® (Raman spectroscopy device)	Identification of a unique spectral 'fingerprint'	$17000-50000 Commercially available	Handheld, no additional reagents	Some - one day	Yes	
SCiO (Near Infrared device)	Identification of a unique spectral 'fingerprint'	$250 Commercially available, but not for antimalarials as yet	Handheld, no additional reagents	Some - one day	Yes	
Counterfeit detection device	Optical wavelength testing	$1000 Commercially available	Handheld, no additional reagents	Minimal – a few hours	Yes	
Paper Test Cards	Paper-based chromatography	$0.50 per card. Not commercially available	Handheld	None	Yes	Water required - immersion of bottom part of card Mobile phone with camera to capture results
ADT	TLC chromatography and colorimetry	To be decided when kit is formatted Not commercially available	Handheld, minute amounts of two reagents needed	Minimal – a few hours	No (artemisinin derivatives only)	

GPHF MiniLab®

Visual inspection, tablet/capsule disintegration and thin layer chromatography (TLC) are incorporated into the GPHF MiniLab®. A key component of the MiniLab® is the TLC test which requires a spot of the test solution of a sample to be compared to two reference spots representing the concentration range of an SAPI (80% and 100%). For the sample to pass the TLC test, the spot must travel as far as the reference spot representing the lower working limit (80%) and be of the same shape, size and intensity (see figure B1).

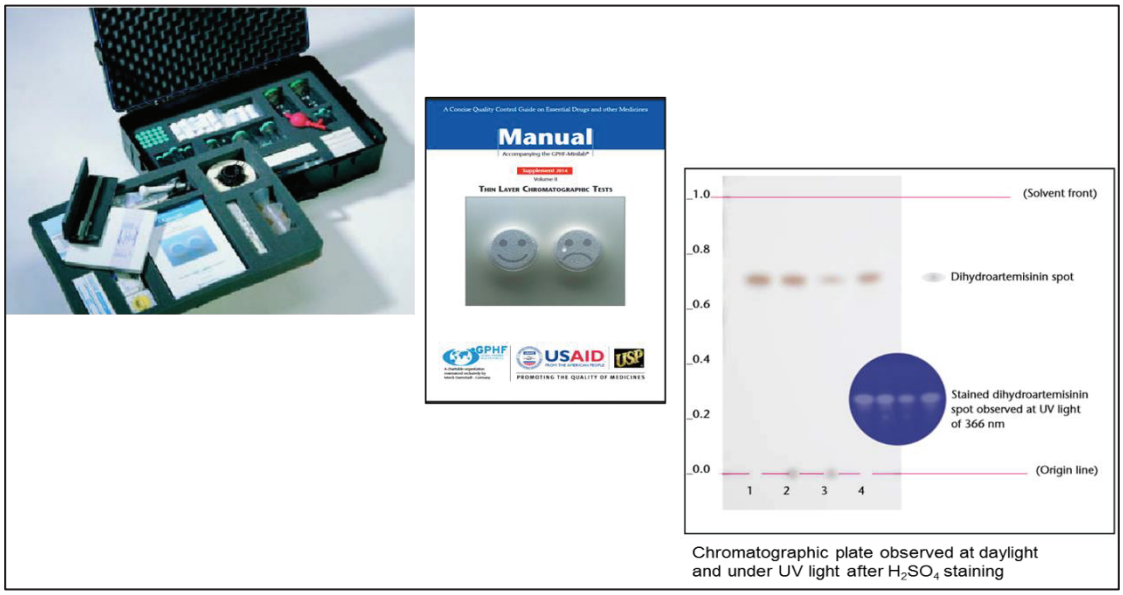


Figure B1: The GPHF MiniLab® with results of screening of dihydroartemisinin using the TLC test

The MiniLab® is capable of screening the quality of 85 WHO essential medicines and is reported to be used in around 95 countries globally. [18] Initial feasibility studies were carried out in four countries in Africa and Asia in 1997 [19] and by 2009 USP had identified the MiniLab® as a key component of its Promoting the Quality of Medicines programme in a number of LMICs. [9] The MiniLab® is reported to be currently available in 27 countries in sub-Saharan Africa but information on its utilisation is unknown. The manufacturers of the MiniLab® state that it can be used in laboratory and non-laboratory settings as part of a MQSS, in particular for post-marketing surveillance activities including the testing of medicines collected through routine medicines quality surveys. The manufacturers regard it as a simple and inexpensive testing kit requiring minimal training and no electricity to operate, which is contrary to some of the attributes of the test presented in table 1. Indeed, week long training sessions on its procedures and use are suggested for health professionals and treatment providers. Those with some knowledge of analytical chemistry may require less training. [20] In addition, in terms of its routine utilisation, the MiniLab® uses several hazardous reagents for testing medicines quality including sulphuric acid solution, glacial acetic acid and toluene. The cost per test for the MiniLab® is around $1.50 (cost of undertaking the test on one sample, using visual inspection, disintegration and TLC). [21] However, the initial capital investment in a MiniLab® could be as much as 10,000$. [19]

Furthermore, there is limited evidence for the accuracy of its TLC component with just two studies having conducted sensitivity and specificity calculations and no relevant data published to date by the manufacturer. One of these studies, a WHO multi-country survey in sub-Saharan

Africa reported the TLC component MiniLab® as having low sensitivity, passing medicines that had actually failed the gold standard technique (HPLC) for chemical content analysis of the SAPIs. [22] The second study compared the performance of another screening device, the Counterfeit Detection Device (CD3+) with the MiniLab® (and is described in the CD3+ section below). [23] In terms of identifying poor quality medicines the MiniLab® has been described as only being able to detect falsified or grossly substandard medicines (those with zero SAPI or very little SAPI). [24] For assessing the quality of ACTs, the MiniLab® has TLC procedures for detecting all artemisinin derivatives in mono and combination therapy formulations.

The MiniLab® was the first screening kit developed and remains the only method in widespread use at the current time. In some LMIC countries it plays an important role in medicines quality surveillance acting as the first stage of medicines quality testing providing an indication of the quality of sample. However, compared to other screening devices currently available, it is quite bulky, weighing 40kg and despite it being promoted for use outside of the laboratory by the manufacturer, the need to use toxic reagents and degree of training (around one week) for its optimal use, renders it a technology that can only be safely used in a laboratory setting.

Handheld spectroscopy – Raman and Infrared devices

Figure B2: Image of the Raman Truscan® device
Source: Thermofischer website

Raman and infra-red devices such as the TruScan® (figure B2) and SCiO (figure B3) scan medicine samples through the blister pack to identify a unique spectral 'fingerprint' for a medicine. [23, 25] These devices require a comprehensive database of spectra of each medicine (including every brand), from every manufacturer, which is not available at present and thus effectively limits their actual utility. Although, the TruScan® was shown to be capable of detecting 'counterfeit' antimalarial medicines, authors in one study cautioned against its use for certain fixed dose combinations of antimalarials such as ACTs citing that its capability depends on the nature and strength of the dosage form tested. [26] This was as a result of the device producing spectra for samples that matched the signature of a comparator of a different brand resulting in a false pass result which can occur if the intensity of the Raman signal is overwhelming. Hence, testing of medicines containing SAPI that produce either very strong or very weak Raman scatter may

be challenging. This is particularly important in the case of fixed-dose combinations where one SAPI may have a strong Raman scatter that can mask the Raman signal of the other SAPI(s). Thus the authors suggested that the Truscan® cannot be used to detect substandard medicines that have some SAPI content thus giving a weak spectra which may not be detected by the device. [26] Hence, based on the evidence available it is not clear on whether the Truscan® could be used to assess the quality of ACTs.

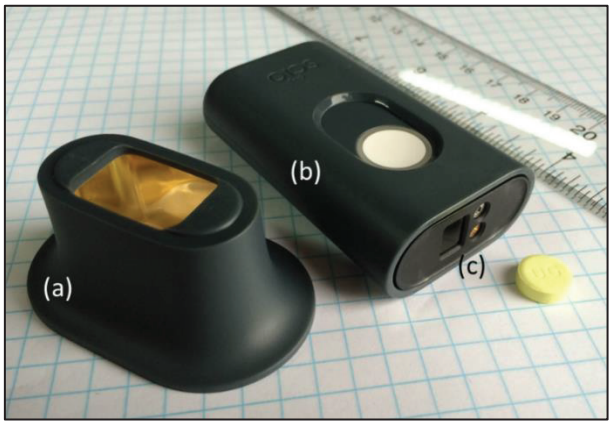


Figure B3: The Consumer Physics NIRS research model SCiO. This image shows the integrating attachment (a), the NIRS spectrometer (b) and (c) which indicates the location of the light source and sensor on the NIRS. A dose of Lumartem® is shown for scale.

In contrast, the SCiO screening device was found to be capable of detecting all of the varying brands of falsified ACTs as well as identifying substandard amounts of artesunate but not amodiaquine in the ACT, artesunate-amodiaquine. This was due to the spectra of the reference standard amodiaquine not being distinguishable in the spectral signature of combination therapies containing amodiaquine.[25] The SCiO device is much less expensive than Raman handheld devices, with an approximate cost of $250 compared to between $17000 - $50000; but information on the sensitivity and specificity is not available yet for the SCiO device with regard to antimalarials as minimal product testing with this group of medicines has been undertaken. There is minimal data available on the sensitivity and specificity of the Truscan® for antimalarials apart from one study which compares the device to the MiniLab® and the CD3 and is discussed in detail in the section below. Both the Truscan® and SCiO devices do require some training (up to one day) to operate them effectively but this is not as extensive as the training needed for the MiniLab® which may be up to a week long. Both devices are handheld and can be used in non-laboratory settings. Indeed, the Truscan® has been employed in the testing of medicines in Nigeria at the point of entry where it was previously reported to have detected a shipment of fake antimalarial tablets. [27] The extent of its use in LMICs as part of routine medicines quality testing is not known.

Counterfeit Detection Device

The United States Food and Drug Administration (FDA) have developed a counterfeit detection device known as CD3+ (figure B4) which was awarded a patent in 2017. It works by illuminating a sample with a range of wavelengths of light to provide a visual comparison of an unverified product with an authentic product. [28] The device has an inbuilt LED and digital camera. The light from the LED interacts with the inks and tablet colours on sample packaging and dosage form surfaces. The operator's eye observes differences between the suspect dosage form and packaging and an authentic medicine which may take the form of changes in colours, shading, contrast, fluorescence, or a combination of all of these. The differences observed in the suspect sample may be attributed to chemical differences between the products such as variation in the SAPI and excipients, colours used in coatings, or packaging materials. Differences between suspect and authentic dosage forms can also be observed through the blister package which allows for rapid screening of samples. The greater the number of visual differences observed between suspect and authentic samples, the more likely the medicine sample is counterfeit. [28]

Figure B4: The Counterfeit Detection Device (CD3+) Source: from United States Food and Drug Authority website.

The manufacturers suggest it is designed for use in non-laboratory settings and it has already been field tested in Ghana by the NMRA in the screening of two ACTs, artemether-lumefantrine and artesunate-amodiaquine [29] but there is no information available on whether the device can detect dihydroartemisinin-piperaquine, another commonly used ACT in sub-Saharan Africa. Indeed, its capability to test a sample in a few minutes and its cheaper cost compared to similar devices that screen the chemical compositions of medicines such as the Truscan®, make it a viable option for resource limited NMRAs in LMICs. During product testing it was found to exhibit a high level of inter-observer agreement of 100%. [28] There is currently limited information on the inter-operator variability of other medicine quality screening devices. Also, in field testing, it was shown to be effective at detecting counterfeit antimalarials. [30] The CD3 is handheld, battery or mains operated and requires minimal training (a few hours) for effective operation. The cost of materials to produce a CD3+ are thought to be around $1000. [31]

In one study, comparison of the CD3+ device with the MiniLab® and Raman Truscan® suggested that the CD3+ (1.00) had a superior sensitivity in detecting counterfeit/substandard antimalarial products compared to the other two screening technologies (both 0.79) but a much lower specificity for quality assured medicines, 0.59 vs 0.99 (MiniLab®) and 1.00 (TruScan®).[30, 32] The CD3+ is more likely to correctly classify counterfeit antimalarials than either the MiniLab® or Truscan®, although separate specific data indicating results for substandard products was not provided in the study. However, due to a lower specificity for quality assured medicines the CD3+ is more likely than the other two tests to classify medicines of acceptable pharmacopeial quality as poor quality. Information on the parameters of screening tests, (which is presently limited) is needed to enable policy makers and medicines regulators to determine which tests are most appropriate for use within their country. However, data on such parameters may vary depending on the operators of the test, participating in feasibility studies. Sensitivity and specificity of screening tests has been shown to be affected by the experience of an operator in terms of their ability to adhere to test procedures and particularly in their interpretation of results. [33] According to the United States FDA the specificity of the CD3+ for quality assured antimalarials may increase (or improve) the more experienced an operator becomes at using the device [30], although this would be the case with any screening test.

Paper test cards

A relatively new screening tool are paper test cards (figure B5) that use separation techniques employing paper-based chromatography which allows the testing of multiple SAPIs on a single piece of card (known as multiplexing). [34] In field testing they have demonstrated the ability to detect and distinguish between 'authentic' and very poor quality (very low SAPI) non-artemisinin based antimalarials. [35] Nevertheless, they have a low accuracy in terms of their sensitivity and specificity in comparison to the gold standard and it is not possible to quantify the amount of SAPI in a sample. These test cards are useful for testing some antimalarials (chloroquine, doxycycline, quinine, sulphadoxine, pyrimethamine, and primaquine) but they cannot currently detect ACTs.

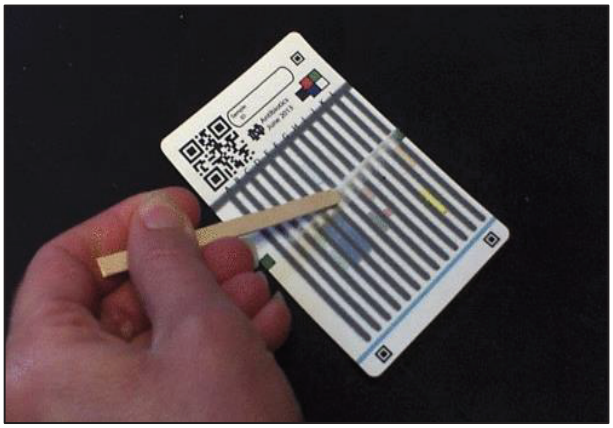


Figure B5: Image of an operator using a paper test cards
Source: Weaver et al (2015).

Advantages of the tool include its ease of use, minimal training (a few hours or less) rapid results (within 10 minutes) and potential for use outside of a laboratory setting such as border posts and health facilities. They also have very low manufacturing costs at just $0.50 per test card. [35] A further advantage is the ability of the tool to test multiple samples at the same time which is cost effective and may facilitate rapid processing of medicine samples collected as part of medicine quality surveys.

Artemisinin derivative test

The artemisinin derivative test (ADT) is chromatographic and colorimetric utilising TLC silica gel sheets and minute volumes of either 2,4 dinitrophenylhydrazine (DNP) or 4-Benzoylamino-2, 5-dimethoxybenzenediazoniumchloride hemi (zinc chloride) salt (Fast Blue Salt – FBS) as reagents to detect artemisinin based medicines (artemether, artesunate and dihydroartemisinin only) producing specific pink (DNP) and blue (FBS) colours, only if the artemisinin derivative is present. In addition, the tests have been proven to be able to detect as low as 10% of the SAPI. A patent for the test was filed by London School of Hygiene & Tropical Medicine and awarded in 2013.[†]

This test has not yet been evaluated in the field which is one of the aims of this research. The findings from the evaluation of the test relating to its practical utility and perceptions of its usefulness and acceptability to staff working in a MQSS in a malaria endemic country are presented in chapter 5. Chapter 5 also presents data on the sensitivity and specificity of the ADT. Initial product testing at LSHTM confirmed that the test is simple to operate and requires minimal training (a few hours). The equipment required is shown in figure B6. The test could be used in laboratory and non-laboratory settings. These and other key attributes of the ADT are discussed further in chapter 5.

[†]Bulletin 2013/21 (22.05.2013). Kaur H; Ioset JR. ASSAY, KIT AND APPARATUS FOR DETECTION OF ARTEMISININ DERIVATIVES UK Intellectual Property Office, 2007; WO2007077444(A1)

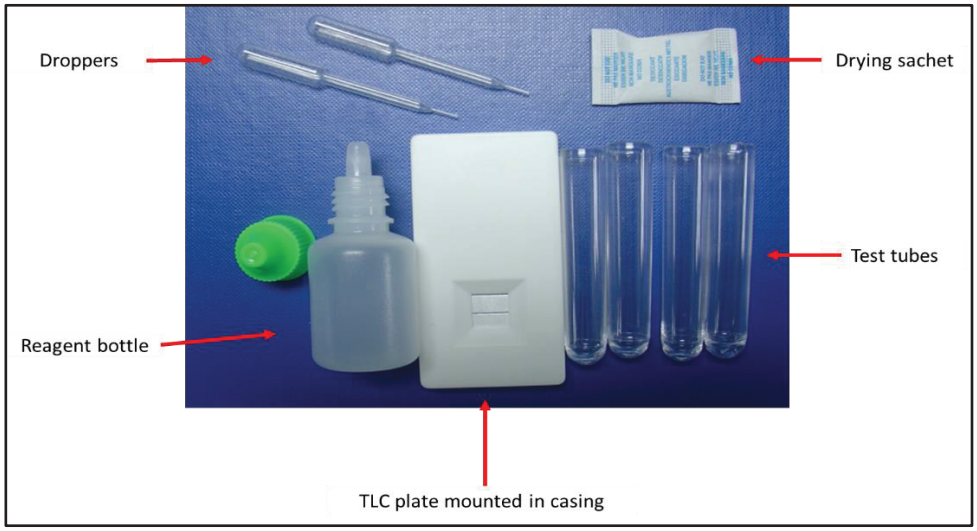


Figure B6: Potential components of an ADT kit

The ADT test has not yet to be formatted into a 'kit'. A potential 'kit' will consist of test tubes (to solubilise the tablet), droppers to transfer the solutions to the TLC plates and a reagent bottle. Analysis of one tablet will require one test tube, one dropper and one TLC plate. The white box in figure B6 above contains a TLC plate with a window in which the test solution and reagents can be applied to develop the sample. Each TLC plate is for one test only.

Currently, aside from the MiniLab® none of the devices described above are in routine use as part of an MQSS in LMICs or even for post-marketing surveillance activities. Moreover, despite their merits for use as part of a MQSS, findings from the various studies cited above demonstrate a gap in evidence of the accuracy of screening technologies in detecting poor quality antimalarials. [22, 30] A specific concern is their limited capability to detect substandard antimalarials, although screening tests have been demonstrated to be capable of detecting counterfeit antimalarials. Additionally, little is known about the parameters of screening tests in terms of their sensitivity and specificity in identifying/distinguishing between poor quality and acceptable pharmacopeial quality antimalarials. This exemplifies how confirmatory testing using methods listed in pharmacopeia are fundamental to detecting poor quality medicines and should, where possible, form the basis of the medicines quality analysis component of a MQSS. Moreover, apart from the two studies [30, 36] utilising the CD3+ device there is no published literature on the potential for inter-operator variability in terms of adherence to test procedures and in the interpretation of results for the other screening tests described in this section. Both these aspects are thought to affect the performance of screening tests and will be explored further in chapter 5 using the MiniLab® and ADT as examples. [37]

B4. Aims and Objectives

The aim of this section is to appraise the current screening technologies available to assess the quality of ACTs and to provide suggestions for improving the quality of future evidence in medicines quality studies and surveys.

B4.1 Objectives

1. To review the screening technologies and survey methods that have been used in LMICs to assess the quality of antimalarial medicines (ACTs in particular) in common use, as well as how findings have been reported.

2. To evaluate the practical utility of the ADT and perceptions of its usefulness and acceptability to local laboratory technicians engaged in national medicines quality surveillance in a malaria endemic country context.

B5. References

1. Chaccour CJ, Kaur H, Mabey D, Del Pozo JL. Travel and fake artesunate: a risky business. *Lancet (London, England)*. 2012;380(9847):1120.
2. Lalani M, Kitutu FE, Clarke SE, Kaur H. Anti-malarial medicine quality field studies and surveys: a systematic review of screening technologies used and reporting of findings. *Malaria journal*. 2017;16(1):197.
3. Kaur H, Green MD, Hostetler DM, Fernández FM, Newton PN. Antimalarial drug quality: methods to detect suspect drugs. *Therapy*. 2009;7(1):49-57.
4. Kaur H, Clarke S, Lalani M, Phanouvong S, Guerin P, McLoughlin A, et al. Fake anti-malarials: start with the facts. *Malaria journal*. 2016;15(1):86.
5. t'Hoen EF, Hogerzeil HV, Quick JD, Sillo HB. A quiet revolution in global public health: the World Health Organization's Prequalification Of Medicines Programme. *J Public Health Policy*. 2014;35.
6. Quality Control Laboratories. Geneva: World Health Organisation 2016. http://extranet.who.int/prequal/information/quality-control-laboratories. [cited 25th April 2017]
7. WHO list of prequalified quality control laboratories (43rd edition). 2017. https://extranet.who.int/prequal/sites/default/files/documents/PQ_QCLabsList_23.pdf. [cited 14th December 2017]
8. Bassat Q, Tanner M, Guerin PJ, Stricker K, Hamed K. Combating poor-quality anti-malarial medicines: a call to action. *Malaria journal*. 2016;15(1):302.
9. Promoting the Quality of Medicines in Developing Countries (PQM). United States Pharmacopeia https://www.usp-pqm.org/. [cited 18th March 2018]
10. Guidelines for Drug Sampling, USP DQI Drug Quality Monitoring Program. Use of the Basic Tests at the Peripheral Level. Rockville: United States Pharmacopeia 2006. http://pdf.usaid.gov/pdf_docs/PNADH150.pdf. [cited 20th Feburary 2017]
11. Maxim LD, Niebo R, Utell MJ. Screening tests: a review with examples. *Inhalation toxicology*. 2014;26(13):811-28.
12. Newton PN, Green MD, Fernandez FM. Impact of poor-quality medicines in the 'developing' world. *Trends in Pharmacological Sciences*. 2010;31(3):99--101.
13. Newton PN, Caillet C, Guerin PJ. A link between poor quality antimalarials and malaria drug resistance? *Expert Rev Anti Infect Ther*. 2016;14(6):531-3.
14. Kovacs S, Hawes SE, Maley SN, Mosites E, Wong L, Stergachis A. Technologies for detecting falsified and substandard drugs in low and middle-income countries. *PLoS One*. 2014;9(3):e90601.
15. Basic Tests for Drugs. Geneva: World Health Organisation 1998. http://whqlibdoc.who.int/publications/1998/9241545135.pdf. [cited 7th March 2017]
16. Guidance for inspection when pharmaceutical products are suspected to be counterfeit, spurious or substandard. Geneva: World Health Organisation 1999. http://apps.who.int/medicinedocs/en/d/Jh1792e/21.10.html#Jh1792e.21.10. [cited 7th March 2017]
17. Guidelines to develop measures to combat "counterfeit" drugs. Geneva: World Health Organisation Medicines DoEDaO; 1999. http://whqlibdoc.who.int/hq/1999/WHO_EDM_QSM_99.1.pdf. [cited 20th February 2017]
18. GPHF Minilab. Frankfurt, Germany: Global Pharma Health Fund 2012. www.gphf.org. [cited 25th April 2017]
19. Jahnke RWO. The GPHF-Minilab: boosting medicines testing capacity for counterfeit medicines detection and post-marketing drug quality monitoring in developing countries. The Global Fund 2013.

https://www.theglobalfund.org/media/5802/p4i_2013-07-09-globalfundsupplychainthreatsconference_presentation_en.pdf?u=636476635700000000. [cited 23rd March 2018]
20. Jahnke R. A Concise Quality Control Guide on Essential Drugs and other Medicines: Volume II on Thin Layer Chromatographic Tests. Frankfurt: Global Pharma Health Fund 2008 Contract No.: Volumes I-III. http://www.gphf.org/web/en/minilab/manuals.htm. [cited 7th March 2017]
21. Jähnke RW, Küsters G, Fleischer K. Low-cost quality assurance of medicines using the GPHF-Minilab®. *Drug information journal*. 2001;35(3):941-5.
22. Survey of the Quality of Selected Antimalarial Medicines Circulating in Six Countries of Sub-Saharan Africa. Geneva: World Health Organization 2011. http://www.who.int/medicines/publications/WHO_QAMSA_report.pdf. [cited 20th February 2017]
23. Ricci C, Nyadong L, Yang F, Fernandez FM, Brown CD, Newton PN, et al. Assessment of hand-held Raman instrumentation for in situ screening for potentially counterfeit artesunate antimalarial tablets by FT-Raman spectroscopy and direct ionization mass spectrometry. *Anal Chim Acta*. 2008;623(2):178-86.
24. Risha PG, Msuya Z, Clark M, Johnson K, Ndomondo-Sigonda M, Layloff T. The use of Minilabs to improve the testing capacity of regulatory authorities in resource limited settings: Tanzanian experience. *Health Policy*. 2008;87(2):217-22.
25. Wilson BK, Kaur H, Allan EL, Lozama A, Bell D. A New Handheld Device for the Detection of Falsified Medicines: Demonstration on Falsified Artemisinin-Based Therapies from the Field. *The American journal of tropical medicine and hygiene*. 2017;96(5):1117-23.
26. Hajjou M, Qin Y, Bradby S, Bempong D, Lukulay P. Assessment of the performance of a handheld Raman device for potential use as a screening tool in evaluating medicines quality. *J Pharm Biomed Anal*. 2013;74:47-55.
27. NAFDAC praises TruScan role in Nigerian counterfeit fight. Securing Industry 2010. https://www.securingindustry.com/pharmaceuticals/nafdac-praises-truscan-role-in-nigerian-counterfeit-fight/s40/a443/#.WjKqelVl_IU. [cited 23rd March 2017]
28. Ranieri N, Tabernero P, Green MD, Verbois L, Herrington J, Sampson E, et al. Evaluation of a new handheld instrument for the detection of counterfeit artesunate by visual fluorescence comparison. *The American journal of tropical medicine and hygiene*. 2014;91(5):920-4.
29. USP starts field trials of FDA fake drug screening device. Securing Industry 2014. https://www.securingindustry.com/pharmaceuticals/usp-starts-field-trials-of-fda-fake-drug-screening-device/s40/a2056/. [cited 12th April 2016]
30. Batson JS, Bempong DK, Lukulay PH, Ranieri N, Satzger RD, Verbois L. Assessment of the effectiveness of the CD3+ tool to detect counterfeit and substandard anti-malarials. *Malaria journal*. 2016;15:119.
31. Taylor P. FDA may offer counterfeit detection device to other bodies. Securing Industry 2012. https://www.securingindustry.com/pharmaceuticals/fda-may-offer-counterfeit-detection-device-to-other-bodies/s40/a1417/#.WLiONm_yjIU. [cited 2nd March 2017]
32. Kaur H. Counterfeit Pharmaceuticals and Methods to Test Them. In: Walport, Mark, (ed) Annual Report of the Government Chief Scientific Adviser 2015: Forensic Science and Beyond: Authenticity, Provenance and Assurance Evidence and Case Studies. London: Government Office for Science; 2015. p. 132-7.
33. Lalkhen AG, McCluskey A. Clinical tests: sensitivity and specificity. *Continuing Education in Anaesthesia Critical Care & Pain*. 2008;8(6):221-3.

34. Weaver AA, Reiser H, Barstis T, Benvenuti M, Ghosh D, Hunckler M, et al. Paper analytical devices for fast field screening of beta lactam antibiotics and antituberculosis pharmaceuticals. *Anal Chem*. 2013;85(13):6453-60.
35. Weaver AA, Lieberman M. Paper test cards for presumptive testing of very low quality antimalarial medications. *The American journal of tropical medicine and hygiene*. 2015;92(6 Suppl):17-23.
36. Tabernero P, Mayxay M, Culzoni MJ, Dwivedi P, Swamidoss I, Allan EL. A repeat random survey of the prevalence of falsified and substandard antimalarials in the Lao PDR: a change for the better. *The American journal of tropical medicine and hygiene*. 2015;92.
37. Rennie W, Phetsouvanh R, Lupisan S, Vanisaveth V, Hongvanthong B, Phompida S, et al. Minimising human error in malaria rapid diagnosis: clarity of written instructions and health worker performance. *Trans R Soc Trop Med Hyg*. 2007;101(1):9-18.

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Mirza Lalani
Principal Supervisor	Harparkash Kaur
Thesis Title	Surveillance approaches to detect the quality of medicines in low-middle income countries with a focus on artemisinin combination therapies for malaria

If the Research Paper has previously been published please complete Section B, If not please complete Section C

SECTION B

Where was the work published?	Malaria Journal		
When was the work published?	May 2017		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**
If yes, please attach evidence of copyright retention. If not please provide evidence of permission from copyright holder.	Malaria Journal states that '*Copyright on any open access article in a journal published by BioMed Central is retained by the author(s).'* See: https://malariajournal.biomedcentral.com/submission-guidelines/copyright		

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from copyright holder (publisher or other author) to include work*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed the review. Myself and a colleague undertook the systematic review. Myself and three other colleagues (including both PhD supervisors) developed, reviewed and approved the criteria for reporting findings. I wrote the first draft of the manuscript. All authors revised the manuscript. All authors read and approved the final manuscript

Student Signature: [redacted] **Date: 4th April 2018**

Supervisor Signature: [redacted] **Date: 4th April 2018**

Chapter 4: Anti-malarial medicine quality field studies and surveys: a systematic review of screening technologies used and reporting of findings

Lalani *et al. Malar J (2017) 16:197*
DOI 10.1186/s12936-017-1852-6

Malaria Journal

REVIEW Open Access

Anti-malarial medicine quality field studies and surveys: a systematic review of screening technologies used and reporting of findings

Mirza Lalani[1*], Freddy Eric Kitutu[2,3], Siân E. Clarke[1] and Harparkash Kaur[1]

Abstract

Background: Assessing the quality of medicines in low-middle income countries (LMICs) relies primarily on human inspection and screening technologies, where available. Field studies and surveys have frequently utilized screening tests to analyse medicines sampled at the point of care, such as health care facilities and medicine outlets, to provide a snap shot of medicine quality in a specific geographical area. This review presents an overview of the screening tests typically employed in surveys to assess anti-malarial medicine quality, summarizes the analytical methods used, how findings have been reported and proposes a reporting template for future studies.

Methods: A systematic search of the peer-reviewed and grey literature available in the public domain (including national and multi-national medicine quality surveys) covering the period 1990–2016 was undertaken. Studies were included if they had used screening techniques to assess the quality of anti-malarial medicines. As no standardized set of guidelines for the methodology and reporting of medicine quality surveys exist, the included studies were assessed for their standard against a newly proposed list of criteria.

Results: The titles and abstracts of 4621 records were screened and only 39 were found to meet the eligibility criteria. These 39 studies utilized visual inspection, disintegration, colorimetry and Thin Layer Chromatography (TLC) either as components of the Global Pharma Health Fund (GPHF) MiniLab® or as individual tests. Overall, 30/39 studies reported employing confirmatory testing described in international pharmacopeia to verify the quality of anti-malarials post assessment by a screening test. The authors assigned scores for the 23 criteria for the standard of reporting of each study.

Conclusions: There is considerable heterogeneity in study design and inconsistency in reporting of field surveys of medicine quality. A lack of standardization in the design and reporting of studies of medicine quality increases the risk of bias and error, impacting on the generalizability and reliability of study results. The criteria proposed for reporting on the standard of studies in this review can be used in conjunction with existing medicine quality survey guidelines as a checklist for designing and reporting findings of studies. The review protocol has been registered with PROSPERO (CRD42015026782).

Keywords: Antimalarial medicines, Medicine quality, Screening technologies, Medicine quality field surveys

Background

Malaria remains a major public health concern in low and middle income countries (LMICs), although, in recent years, there has been an overall decline in malaria incidence due to application of improved strategies for prevention, control and treatment [1]. The advent of artemisinin-based treatment has contributed to the reduction in disease transmission, with 79 out of 88 malaria-endemic countries having adopted artemisinin-based combination therapy (ACT) as first-line treatment

*Correspondence: mirza.lalani@lshtm.ac.uk
[1] London School of Hygiene and Tropical Medicine, London, UK
Full list of author information is available at the end of the article

for uncomplicated *Plasmodium falciparum* malaria by 2015 [2]. Assuring the quality of ACTs and other anti-malarials used to counter malaria is paramount in ensuring that the success of malaria prevention and control strategies is maintained. Yet, the reported finding that a third of anti-malarial medicines from malaria endemic countries failed chemical content analysis is a source of substantial concern, potentially threatening progress in control [3]. At the patient level, poor quality anti-malarials may result in treatment failure, leading to prolonged or severe illness and even death, as sub-therapeutic medicine concentrations increase the risk of recrudescence of malaria infection [4]. At the provider level this increases burden on already limited resources and undermines confidence in health providers [5]. From a public health perspective medicines with low stated active pharmaceutical ingredients (SAPI) or low bioavailability may select for drug resistant parasites [6]. An association between the quality of artemisinin-based medicines and drug resistance has been postulated but not as yet proven [7].

In-country, medicine quality can most readily be assessed at two stages in the supply chain; at point of entry and point of care. Firstly, anti-malarials permitted to enter the official supply chain in LMICs should, ideally be restricted to those produced by World Health Organization (WHO) prequalified manufacturers that have attained accreditation for good manufacturing practice (GMP) [8]. However, this is seldom the case, and often National Medicines Regulatory Authorities (NMRAs) will permit non-WHO prequalified medicines, assuming they have met GMP standards. Some countries may also have anti-malarials on the market that may not have been registered with the NMRA. Secondly, wholesalers have to obtain authorization from the NMRA before they can distribute medicines [9], and the products they import should satisfy the national regulatory requirements for obtaining pre-marketing authorization. Finally, subsequent medicine batches may undergo routine lot-quality sampling [10] and testing by a NMRA at the point of entry in some countries. However, the source of anti-malarials often varies, ranging from international wholesalers to direct donations from external organizations or medicine manufacturers [11]. Donated medicines can sometimes bypass these initial checks, making verification of their quality more challenging. Indeed, studies have shown that some donated medicines are more likely to be close to their manufacturer expiry date or have exceeded their shelf-life [12].

Point of entry sampling and analysis requires substantial initial and recurrent investment in resources, expertise and equipment, all of which are rarely affordable or available to LMICs on a routine basis. Thus, NMRAs most frequently rely on post marketing surveillance through periodic medicine quality sampling surveys at the point of care, using screening technologies [13]. Even so, the proportion of NMRAs in LMICs with regular access to screening technologies is not known. To this end, several new screening technologies have been developed in recent years. This review aims to present an overview of the screening tests used to assess medicine quality at point of care. It will also focus on the screening technologies and survey methods that have been used to assess medicine quality in field surveys, and the standard of reporting. A template for future reporting of studies is also proposed and is used to score the anti-malarial medicine quality studies included in this review.

Principles of assessing medicine quality

Tests for medicine quality are based on assessment of identity, chemical assay, disintegration and dissolution (bioavailability). These four core 'principles' provide the basis for medicine quality analytical technologies, which can also be further categorized as screening and confirmatory functions in a medicine quality surveillance system (MQSS) [14]. Fundamentally, an ideal test should be capable of detecting both counterfeit (or falsified) and substandard medicines (see Fig. 1 for definitions) through verification of the chemical content in terms of the stated active pharmaceutical ingredients (SAPIs) [15–17].

Surveillance systems for medicine quality in LMICs employ screening techniques and devices as the first stage for medicine quality analysis. Some of these technologies (listed in Table 1 together with their description, cost (where available) and role in the MQSS) are portable, simple to use and relatively inexpensive, making

> Counterfeit (falsified) medicines: "Deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging"' *World Health Organisation 1992*
>
> Substandard medicines: 'Genuine medicines produced by manufacturers authorized by the national medicines regulatory authority (NMRA) which do not meet quality specifications set for them by national standards.' *World Health Organisation 2009*

Fig. 1 Definitions of poor quality medicines. *As of January 2017, the WHO member state mechanism has recommended that the use of "substandard/spurious/falsely-labelled/falsified/counterfeit medical products" should be replaced with "substandard and falsified medical products"

Table 1 Tests for assessing the quality of a medicine

Test dimensions	Description	Medicine analytical technology	Role in a MQSS	Cost[a]
Identity	Verifies identity of SAPI	Visual examination of packaging	Screening	n/a
		Counterfeit detection device (CD3)	Screening	*
		RAMAN spectroscopy (hand-held device)	Screening	**
		Specialized mass spectrometry (MS) techniques Direct analysis in real time (DART) Desorption electrospray ionization—(DESI)	Confirmatory	***
Assay	Detection and quantitation of SAPI	Semi-quantitative thin layer chromatography (TLC) (GPHF MiniLab®)	Screening	*
			Confirmatory	**
		High performance liquid chromatography (HPLC) and coupled to mass spectrometer (LC–MS) Mass spectroscopy (MS)	Confirmatory	***
Disintegration	Determines that a tablet or capsule will disintegrate	GPHF MiniLab®	Screening	*
Dissolution	Proxy measure of the bioavailability of a medicine (extent to which medicine will dissolve in the body)	Dissolution apparatus	Confirmatory	**

[a] Denotes relative cost of the technology; inexpensive—less than $10,000 (*), moderate—$10,000–$100,000 (**), very expensive—greater than $100,000 (***) [24]

them suitable for screening large volumes of medicines. Nevertheless, they may only provide an indication of medicine quality, necessitating subsequent confirmation and quantification of the SAPI with more specific quantitative techniques found in medicine quality control laboratories, following methods described in international pharmacopeia.

Laboratory methods such as high performance liquid chromatography (HPLC) and mass spectrometry (MS) are needed to confirm the chemical content of a medicine in terms of its SAPI and are regarded as the 'gold standard' technique for medicine quality analysis. HPLC detects the SAPI and its amount is determined from the calibration curve measuring the peaks achieved using increasing known amounts of the reference standard. Thereafter, an analyst will assess if a medicine falls within tolerance limits for content in accordance with international pharmacopeia. Dissolution tests to determine the bioavailability of the medicine require specialist apparatus and can only be carried out when authorized pharmacopeia monographs exist. These techniques incur a high capital and maintenance cost and require specific laboratory infrastructure including highly skilled individuals for effective operation. Not all LMICs have the human and capital resources to thus maintain a fully functional MQSS. To enable medicines quality control laboratories to conform to international standards, the WHO operates a prequalification programme providing accreditation through ISO (ISO/IEC17025) certification. To achieve accreditation a medicines quality control laboratory must satisfy requirements for 'Good practices for pharmaceutical quality control laboratories', which will provide confidence in the services they provide [18].

In LMICs medicine quality screening technologies (Table 2) thus play a pivotal role in the surveillance of the quality of anti-malarials due to limited technical capacity. Analytical equipment such as HPLC and dissolution testing apparatus may be absent or only available at the national reference laboratory and even then, all pharmacopeia methods may not be possible to set up due to interrupted power supply, prohibitive costs involved (HPLC columns, reference standards etc.) and the requirement for highly skilled chemists to carry out the analysis. In contrast, portable screening techniques, require no electricity or advanced expertise to perform, can be used for testing large numbers of medicines in field surveys, and identifying suspect samples which are then subjected to comprehensive content analysis using confirmatory tests. Screening tests can thus be used as part of a national MQSS, most suitable for use in peripheral laboratories, border posts and other points of entry into a country.

Guidelines for conducting medicine quality studies and surveys

Currently, there are no universally agreed guidelines on the study design and reporting of medicine quality

Table 2 Descriptions for screening and confirmatory tests

Type of test	Description	Examples of tests
Screening	Basic tests for quality based on, but not restricted to, chromatographic and spectrometric techniques with the addition of visual inspection	GPHF MiniLab®; Raman handheld spectroscopy; counterfeit detection device (CD3)
Confirmatory	Methods listed in pharmacopeia, that can only be conducted in a laboratory by trained personnel and the results from which are quantifiable	HPLC; Dissolution; MS; LC–MS

studies or surveys, although there are at least three primary sources of information and guidance available. The United States Pharmacopeia (USP) operates a Promoting the Quality of Medicines Program providing technical and logistical support to LMICs. In 2006, USP published guidelines for sampling and analysing medicines for their quality [19]. In the same year Global Health Pharma Fund (GPHF) also produced a manual of testing procedures for the quality of medicines, to accompany the MiniLab®. The manual is updated on an annual basis to include testing guidelines for new medicines and modified procedures for existing medicines [20]. Lastly, in 2009, a proposal for a checklist for the sampling of medicines for medicine quality studies and surveys called MEDQUARG, was published [21].

Methods

A systematic review of the published literature between 1990 and 2016 was undertaken in January 2016 and updated in October 2016. PubMed, Web of Science and Google Scholar were searched using predefined search terms as described in the protocol in Table 3. This review was carried out in accordance with PRISMA guidelines [22] and the protocol has been registered with PROSPERO, (ref: CRD42015026782). Articles were imported into Endnote and duplicates removed. Further searches were conducted using ancestral and forward citation of two prominent anti-malarial medicine quality reviews as well as searches of the grey literature using the Worldwide Antimalarial Resistance Network (WWARN) medicine quality surveyor [3, 23]. Where accessible, published national medicine quality surveys and reports were also obtained.

Titles, abstracts and executive summaries were assessed by the first author (ML) of this manuscript for their relevance (summarized in Table 3). Studies that reported utilizing screening tests for anti-malarials were included for full text review. Studies and reports published in English and French were included.

An assessment of the quality of reporting of the eligible reports and studies was undertaken to examine the rigour of study design and sources of potential bias in findings. The authors applied criteria adapted from a previously published review [25], published procedures of individual tests, USP Medicine Quality and Information Program Guidelines [19], MEDQUARG guidelines [21], and the GRADE guidelines (quality of evidence and strength of recommendations for diagnostic tests or strategies) [26, 27]. The process gave rise to a final list of 23 criteria of reporting quality (listed in Fig. 2); these items assessed how studies report aspects of field collection of medicine samples, storage, method of medicine

Table 3 Summary of review search criteria

Databases	1. PubMed 2. Web of Science 3. Google Scholar
Other sources	1. Nayyar et al. [23] 2. Tabanero et al. [3] 3. USP DQI country reports [85] 4. WWARN anti-malarial medicine quality surveyor [86]
Key search terms	Medicine OR drug quality AND survey OR screening Screening: AND poor quality OR counterfeit OR substandard (medicine OR drug) Detection: AND poor quality OR counterfeit OR substandard (medicine OR drug)
Eligibility criteria	
Dates	1990–2016
Language	English, French
Location	Central, South and South East Asia, Sub-Saharan Africa, Central and South America, Pacific Islands
Article type	Scientific publications in international peer-reviewed journals and grey literature (reports and surveys)
Types of studies	Field surveys in which anti-malarial medicines were assessed for quality, using a screening technique
Screening technique and outcome	1. Screening techniques: tests based on but not restricted to chromatographic and spectrometric techniques with the addition of visual inspection or visual inspection alone 2. Outcome measure (medicine quality)
Exclusion criteria	1. Reviews/Commentaries/Conference Papers/Letters 2. High specification, non-portable technologies (as defined by Kovacs et al. [24] with LMIC score <4[b]) 3. Feasibility studies 4. Non-anti-malarial medicine assessed for quality alone 5. Only results of either screening or confirmatory tests presented when both undertaken
Search dates	January 2016, updated October 2016

[b] Kovacs et al. [24] have reviewed all medicine quality screening technologies in use and categorized them by cost and portability. Their scoring matrix has been used as an exclusion criterion with an LMIC score of less than 4 representing those technologies that are less feasible for use in LMICs due to their lack of portability and high cost

quality assessment categorized as level I (visual inspection), level II (screening tests) and level III (confirmatory tests), medicine quality analysis and interpretation, dissemination, study limitations and bias. Data extracted from eligible studies were organized under the following headings; study details (year of collection and location), medicine sampling and storage, screening tests, confirmatory tests, classification of quality, statistical tests, limitations, bias and dissemination. Studies included at this stage were full text versions and were independently assessed by two of the authors (ML and FEK). Discrepancies were clarified and a final list of reconciled studies was produced for inclusion. Two separate tables were compiled, one listing studies that used a screening test only and studies using both screening plus confirmatory tests (see Additional files 1, 2). The scoring criteria was applied to both sets of studies (screening alone and screening plus confirmatory).

Results

The titles and abstracts of 4621 records were screened (after duplicates were removed) and 146 were identified based on the eligibility criteria (Fig. 3). Studies excluded at this stage were predominantly not related to medicine quality and included pharmacovigilance (drug safety) studies, diagnostic testing for illicit or banned substances and several clinical trials of new drug targets. The remaining 146 records were subjected to full text review against the exclusion criteria. This resulted in 39 articles that assessed the quality of anti-malarial medicines using a screening test which were subsequently reviewed and summarized.

Types of studies

Of the 39 included studies and surveys in this review, the vast majority (36/39) were peer-reviewed articles published in international journals and three were non-peer-reviewed publications, which comprised two multi-country surveys (one conducted by the WHO [28] and the other by USP [29]) and a national medicine quality survey undertaken by the Malaria Control and Pharmacy and Poisons Board for Kenya [30]. The latter was the only national Ministry of Health agency survey report that met the eligibility criteria to be included in this review. Of the 39 included studies, 33 were conducted in South East Asia and Sub-Saharan Africa, with the remainder undertaken in Afghanistan [5], India [31, 32] Guyana and Suriname [33], the Amazon Basin [34] and Papua New Guinea [35]. Of the 25 studies from Africa, 15 were conducted in Nigeria and Ghana [28, 36–48]. The remainder comprized the aforementioned national medicine quality survey conducted by a Ministry of Health agency in Kenya [30] and two multi-country surveys, conducted by USP in Madagascar, Senegal and Uganda [29] and the WHO in Kenya, Nigeria, Ghana, Ethiopia, Tanzania and Cameroon [28]. Multi-country studies accounted for 12/39 (30.8%) [28, 29, 33, 34, 42–46, 49–51] that met the inclusion criteria.

A variety of outlets from all levels of the distribution chain were represented among the studies. Most of the studies sampled at point-of-care; public health facilities (government funded hospitals and clinics), private sector pharmacies and the informal sector (markets stalls, itinerant sellers and grocery shops). Three studies sampled from the highest level of the distribution chain such as wholesalers and central medical stores (in addition to hospitals, pharmacies etc.) [30, 52, 53]. In the included studies, a broad range of anti-malarial medicines were sampled and analysed for quality.

Tests used for screening medicine quality

The WHO medicine testing guidelines recommends combining qualitative and quantitative approaches to analysis, to establish the identity, content and disintegration of a medicine [54]. Qualitative tests include visual inspection, colorimetric tests and tablet or capsule disintegration. Visual inspection involves assessment of the medicine packaging, patient information leaflet and the medicine itself. Misspellings, absence of an expiry date or batch number and obvious signs of deterioration of the product indicate a poor quality medicine [55]. However, for a full appraisal, prior knowledge of the authentic manufacturers packaging is required, which would not be routinely available to a patient or a medicine outlet proprietor. Colorimetric tests are identity tests that involve a simple colour reaction to verify presence of the SAPI. The disintegration test requires the tablet/capsule to disintegrate in water heated to 37 °C, within 30 min. If this does not occur, it could indicate a poor quality product. Thin layer chromatography (TLC) is an example of semi-quantitative testing [56]. The combination of the steps of visual inspection followed by disintegration testing give an assessment of deficiencies related to medicine solubility and availability. The third step of carrying out a colour reaction indicates if the SAPI is present before employing a TLC run for verification of whether the quantities of medicine claimed on the label are in the sample.

All of these tests are incorporated in the GPHF MiniLab® which is capable of testing around 80 WHO essential medicines (including anti-malarials) and is reportedly available in over 90 countries worldwide, and often used in LMICs as an integral component of a MQSS [57]. TLC is an identity/content test that provides a semi-quantitative analysis in which a spot of the medicine under investigation is solubilized in an appropriate solvent and applied to a TLC plate and should migrate at

Standard of Reporting Assessment Criteria

Drug collection and storage

1. Does the study report the storage conditions during transportation?
2. In the assessor's view, were drugs appropriately stored in accordance with desirable environmental conditions in the laboratory, prior to analysis?
3. Was the analysis of drug quality screening performed on a sample size > 30 (units of a drug)?

Drug quality analysis

Visual/packaging analysis

4. Was visual and physical inspection analysis of the drug packaging and the drug dosage form performed?
5. Does the study report the basis (guidelines) upon which visual inspection was carried out?
6. In the case of packaging analysis, does study report the source of reference package?

Screening tests employed

7. Does the study report source/origin of reference standards for screening methods?
8. Does the study report the version and source of the screening equipment used?
9. Were screening tests (TLC, colorimetry) performed blinded to visual and physical inspection findings and vice versa?
10. Does the study state that samples providing dubious results or indicating failure were retested by the screening technology or were duplicate tests run simultaneously?
11. Were screening test results verified by a second operator? (This would be expected as minimum for those samples providing dubious results or that indicate failure).
12. Do the authors provide a description of how the samples for screening tests were selected from among the sampled products?

Confirmatory tests

13. Were confirmatory tests performed? Does the study report the methods used and provide information on the detailed methods used?
14. Does the study report the source/origin of reference standards for confirmatory methods?
15. Does the study report the pharmacopeia compendium (e.g. USP) used to provide the basis of the tests?
16. Does the study report the version and source of the analytical equipment used?

Categorising test results

17. Does the study assign the sampled and analysed products into internationally-agreed/WHO classifications (quality assured, falsified, substandard, degraded) based on the test results?
18. Is evidential basis provided for the classification by describing the results in comparison to tolerance limits in international pharmacopeia?

Evaluation of study findings (Statistical treatment of results)

19. Is a statistical analysis of the results performed (p-values and confidence intervals as a minimum)?
20. Is there a discussion of any disparity between the screening results and those from analysis by using the gold standard pharmacopeia methods and a potential justification for this difference?
21. If a disparity exists, do the authors report the results of any sensitivity and specificity calculations for the screening technology?

Limitations and bias

22. Do the authors discuss study limitations? Including specific reference to limitations of the laboratory (analytical) stage of the study. Is their discussion of potential bias in its extent and or direction?

Dissemination

23. Did the author report the findings to a national drug regulatory authority or equivalent?

Fig. 2 Criteria for assessing the standard of reporting of medicine quality surveys. Adapted from a previously published review, published procedures of individual tests, MEDQUARG guidelines, USP Medicine Quality and Information Program Guidelines and consideration of the GRADE guidelines (quality of evidence and strength of recommendations for diagnostic tests or strategies)

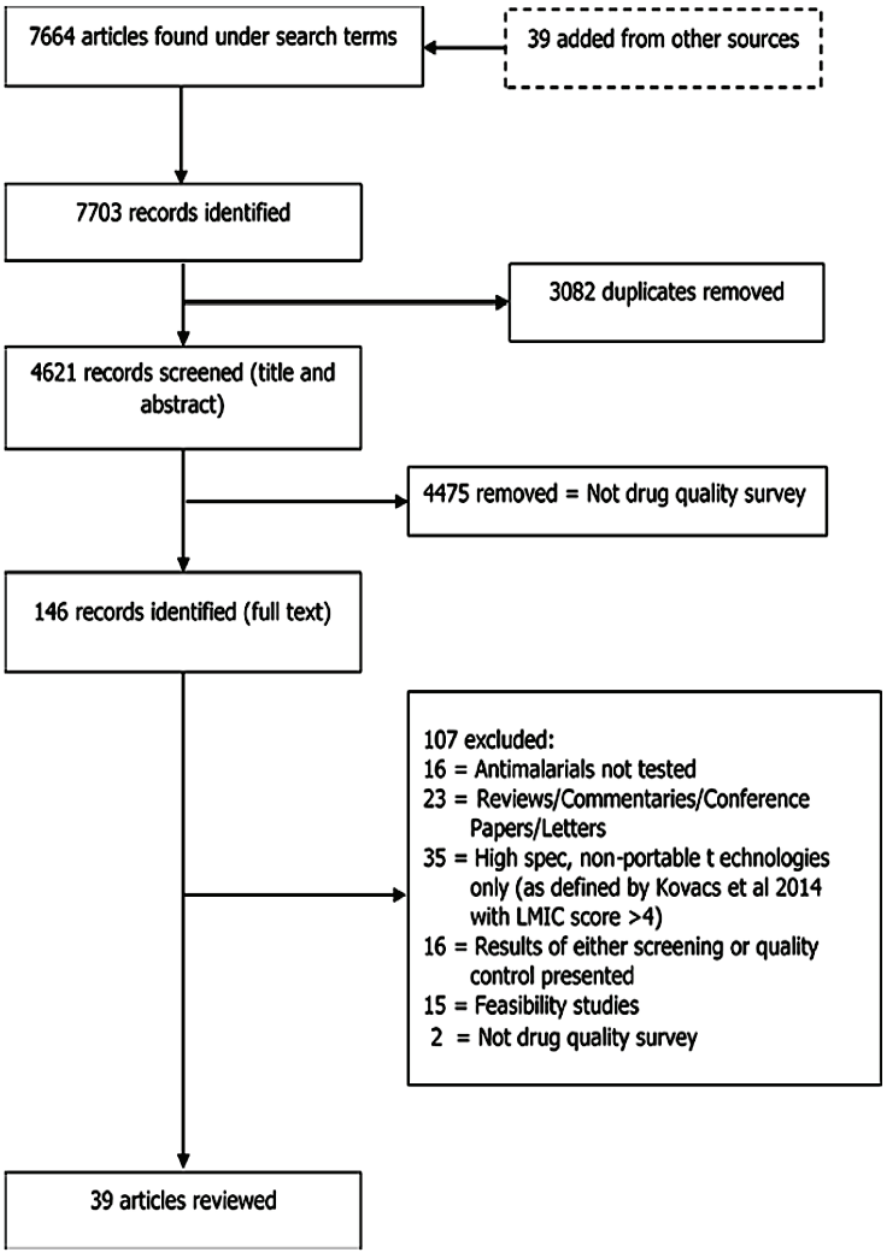


Fig. 3 Literature review search strategy

the same rate as that for the similarly solubilized reference standard (equivalent to 80 and 100% of the SAPI). If the spot formed by the medicine is obviously different to the reference spots in colour and size this may indicate a poor quality sample. Indeed the sample spot must be at least similar to the lower working reference spot representing '80%' to be considered as a 'pass' according to MiniLab® guidelines [20]. Thus colorimetric tests and TLC constitute a subjective evaluation of medicine quality, dependent on the visual acuity of the technician conducting the test.

Other tests intended for use in field surveys for detecting poor quality medicines include paper test cards, the Raman handheld device and near-infrared spectrometers (NIR), all of which are in various stages of development [58, 59]. These tests employ spectroscopy or separation techniques and are based on the principle of identity, verifying the SAPI in a medicine sample. The Raman

and NIR spectrometer devices scan medicine samples through the blister pack. They identify a unique spectral 'fingerprint' allowing comparison of a suspect sample with a genuine medicine which requires access to a library of spectra for each individual brand of medicine on the market. Thus far, only the TruScan® handheld Raman device has demonstrated the ability to detected counterfeits the field [60]. In contrast to the Raman device, NIR can distinguish whether the excipients in a medicine sample are in the correct proportions, suggesting that the medicine is falsified, but it cannot detect substandard medicines [61]. Separation techniques employing paper-based chromatography allow testing of multiple SAPIs on a single piece of card (known as multiplexing) [62]. They are inexpensive and simple to use but have a low accuracy in terms of quantification of the SAPI. Field experience of the Raman, NIR and paper tests cards to date is restricted to a limited number of studies [46, 60, 63]. The cost of the Raman device remains a limiting factor to more widespread use. Nevertheless, a new, comparatively low cost and portable prototype version of NIR has recently demonstrated a promising capability in detecting falsified samples of ACTs and artemisinin monotherapies [64].

Amongst the 39 eligible field surveys of medicine quality published between 1990 and 2016, there was limited variation in the screening techniques that had been employed. All studies had utilized visual inspection, disintegration, colorimetry and TLC either as components of the GPHF MiniLab® or as individual tests. Overall, 4/39 (10%) studies were limited to visual inspection alone [33, 36, 49, 65]. In 7/39 (18%) studies, more than one screening test was employed; of which, five compared the MiniLab® with Raman Spectrometry and/or near infrared (NIR) [43–46, 66]. The CD-3 device, which analyses medicine packaging was reported in just one study [67] and another study employed MVHimagePCv8.exe Color Software which measures colour intensity of samples subjected to the colorimetric Fast Red TR test, using digital imagery [47].

Standard of reporting

In addition to the variation between studies in the outlets from which medicines were collected for analysis and the screening techniques employed, there was considerable variation in how results were reported. None of the included studies met all 23 criteria of the standard of reporting (see Fig. 4). Scores ranged from 17/23 (74%) as the highest [67] and 2/23 (9%) [47] as the lowest. Studies published before 2006 [10/39, (26%)] scored an average of 6.9 compared to 8.5 for those published after 2006. This marginal improvement may have been in response to the publication of the MiniLab® manual (instructions on testing procedures) and USP guidelines in 2006. The number of studies satisfying each of the quality of reporting assessment criteria are presented in Fig. 4.

Medicine storage and collection

Improper storage conditions have been suggested as a possible risk factor for deteriorating medicine quality over time, which if drugs are not stored adequately prior to analysis, could cause the proportion of poor quality medicines to be overestimated (misclassification bias) [68]. Nevertheless, reporting of storage conditions after collection was generally poor; only 4/39 (10%) studies stated maintaining appropriate storage conditions during transit from the outlet to the laboratory and less than half (15/39 (39%)) reported storage conditions in the laboratory prior to analysis [30, 65, 67, 69]. The scale of the surveys and number of samples analysed varied substantially between studies. USP guidelines for medicine sampling state that a minimum of 30 dosage units per location be collected, sufficient to carry out testing for identity and content of SAPI and dissolution [19]. Yet overall, 10/39 (26%) studies based their findings on a sample size of less than 30 [32, 35, 37–41, 47, 49, 52].

Visual inspection/packaging analysis

Visual assessment of medicine packaging and the tablet or capsule is an inexpensive approach but requires the original packaging from the manufacturer for accurate comparison. The GPHF MiniLab® manual provides guidelines to standardize visual inspection. In this review 9/39 (23%) studies did not state undertaking a visual assessment [31, 32, 46, 47, 52, 70–72]. Of those studies that did undertake visual inspection, 12 mentioned referring to MiniLab® guidelines [5, 28, 29, 34, 43, 45, 48, 66, 73–76]. Only 4/39 (10%) studies carried out packaging analysis (all from SE Asia) and reported comparison with a sample of the genuine packaging obtained from the medicine manufacturer [39, 65, 67, 77]. One study, explicitly stated contacting manufacturers for the original packaging without response [69].

Description of laboratory procedures (screening tests)

References standards are pure chemical compounds obtained from chemical manufacturing companies and are used by pharmacopeia such as USP as a basis for their official monographs for analysts to adopt. This review found that 15/39 (39%) studies stated using reference standards in the analytical process and reported on the source of the standard [30, 35, 38–42, 45, 46, 49, 65, 67, 76, 78, 79]. Of the 35/39 (89.7%) studies (excluding those that conducted visual inspection alone), 10/35 (29%) did not mention the source of the screening tests (and reagents), but simply named the device they were utilizing;

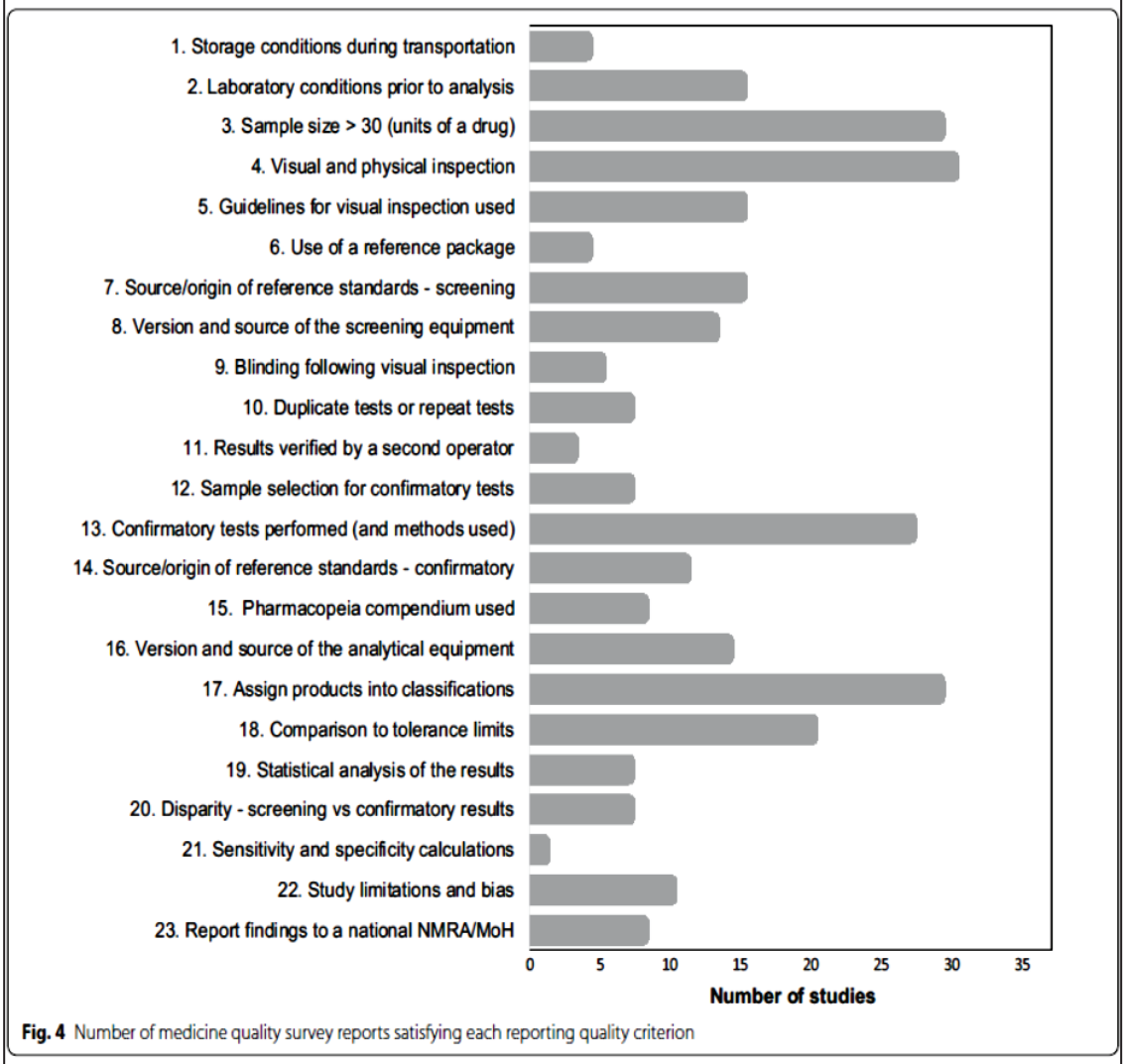


Fig. 4 Number of medicine quality survey reports satisfying each reporting quality criterion

MiniLab® or a Raman handheld device [28–32, 42, 45, 48, 51, 72].

Interpretation results from visual inspection, colorimetric and TLC tests are subjective and dependent on the visual acuity of the operator. A second operator to independently verify test results would enhance the validity of a study by minimizing the risk of operator error in results interpretation, particularly for the semi-quantitative TLC test in which there is a greater risk of misclassification bias. Overall, 31 studies used TLC, but only three reported using a second operator to verify results [38, 69, 75]. For 8/39 (21%) studies using visual inspection and/or colorimetry, a second operator would be unnecessary as results are more definitive in comparison to TLC.

USP guidelines for medicine quality testing using the MiniLab®, state that any samples of doubtful quality or 'failed' samples, as well as 5–10% of passed samples must be retested using disintegration and TLC techniques [19]. Devices such as the Raman handheld and CD3 are new additions to the market and at the time of the studies in which they undertaken, there was no mention of the need for test repetition. Of the studies that employed disintegration and TLC, just 7/30 (23%) reported repeat testing of samples [30, 43–45, 73, 75, 76]. Moreover, just 5/39 (13%) studies reported having blinded the operators to results from visual/packaging analysis or from screening tests, thus increasing the risk of performance (observer) bias [50, 51, 67, 70, 77]. In total, 7/39 (18%) studies discussed using a rudimentary strategy for selecting medicines from their initial sample to be analysed further by confirmatory tests (often to verify doubtful quality or failure of samples) [28–30, 67, 69, 74, 76]. The remaining studies either did not use confirmatory tests or the screening tests did not highlight any failing samples.

Confirmatory testing using pharmacopeia methods

In total, 9/39 (23%) studies did not employ confirmatory tests, hence their results simply provide an indication of medicine quality [31, 43–48, 66, 78]. A fairly wide range of confirmatory tests were applied in the remaining 30/39 (77%) studies, although three studies did not specify the test that had been carried out [30, 34, 75]. Tests assessing both the physical and chemical properties of a medicine were undertaken. For the former, this included friability (the tendency for a tablet to break), uniformity of mass (weight variation amongst samples from the same batch) and hardness tests. Chemical tests included HPLC or Mass spectrometry (MS) (to assess content of the SAPI) or dissolution (medicine bioavailability). Of the 27 studies that reported the specific type of confirmatory tests they utilized, 12 conducted physical tests and also undertook chemical testing in parallel [32–35, 37, 38, 40, 41, 52, 72]. The remaining studies (15/27 (56%)) used chemical tests alone, either LC/MS or dissolution apparatus. Studies conducted in the last 5 years used confirmatory tests only, suggesting either that more institutions have now acquired HPLC and dissolution equipment or there is greater recognition of their importance as highly accurate techniques.

Only 11/30 (37%) studies employing confirmatory tests stated the source of the reference standards obtained [35, 38–42, 49, 51, 65, 76, 77] and just 14 stated the manufacturer of the analytical equipment [5, 32, 35–41, 49, 51, 52, 65, 77]. In total, 7/27 (26%) studies that stated a using a specific type of confirmatory testing did not report using an international pharmacopeia [30, 50–52, 69, 76, 77]. Reference to the use of a pharmacopeia reassures the reader that ratified methods for testing medicines were employed.

In this review, 7/39 (18%) studies did not categorize failing medicines, reporting them simply as having 'failed the tests' or 'not compliant' without providing further details of the criteria used [32, 34, 37, 43, 66, 73, 74]. The remaining studies classified failing samples as counterfeit, falsified, fake, substandard, degraded and poor quality either alone, or in combination. In the absence of guidelines, no criteria for determining degraded medicines were provided. There are currently no universally agreed definitions for poor quality medicines which may account for the wide array of terms used in the included studies [80]. Yet, standardization for definitions is important as it enables regulatory authorities to plan appropriate action to address the problem of each specific type of poor quality medicine.

Tolerance limits refer to the standards listed in medicine monographs in pharmacopeia for the SAPI of a medicine. Medicines failing to meet these standards either by having a sub-optimal amount of SAPI or too much, would be considered to be of poor quality. Of the 27 studies that stated the specific type of confirmatory test employed, nine did not state tolerance limits for the medicines and of these [29, 30, 33, 34, 50, 51, 69, 77] eight studies still categorized the failing samples as falsified, counterfeit, poor quality and/or substandard. The remaining study only stated that samples had 'failed tests' [34]. Without stating tolerance limits to compare the SAPI in the sample against pharmacopeia standards, these categorizations are unsubstantiated.

Statistical treatment of results

A thorough analysis of obtained data should include a statistical analysis, including p values and/or confidence intervals which take account of the sampling variation in surveys, indicating the precision of any estimates obtained [81]. Of the included studies, only 7/39 (18%) [36, 50, 51, 65, 67, 69, 72] undertook a statistical analysis presenting their results with p values or confidence intervals.

Additionally, disparity between results from screening and confirmatory tests in terms of sensitivity and specificity of the screening test to classify medicines as poor quality, should be reported. For this study, the terms sensitivity and specificity are used in their statistical sense, as of a measure of the performance of binary classification tests differentiating between those medicines that are poor quality and good quality and how accurate these results are when compared to the 'gold standard' tests (HPLC and dissolution). Overall, 14/30 (47%) studies that stated using confirmatory tests, recorded a disparity with screening tests which had either overestimated or underestimated the quality of the samples [5, 28, 29, 32–34, 37–42, 49, 52, 67, 70, 71, 74, 76]. However, only 7/30 (23%) of these studies highlighted this disparity [5, 28, 34, 42, 67, 71, 76], and a sensitivity and specificity calculation was presented in just one study [28]. Thus, although authors have reported findings that demonstrate a lack of accuracy of the screening test, they have rarely described the reasons for inconsistency or as a minimum, drawn attention to the discrepancy.

Limitations and bias

Of the included studies, 15/39 (39%) did not discuss any potential limitations of the study design, sampling strategy or laboratory methods used [30, 32, 33, 35, 37–41, 46–48, 50, 52, 78]. Of the remaining 24 studies, 10 provided an account of limitations specifically relevant to the type of screening test used, of which, five studies included a discussion of the disparity between results from screening and confirmatory tests [5, 28, 29, 34, 65, 67, 69, 71, 74, 75].

Overall 16/39 (41%) studies discussed a potential risk of bias in their studies. Of these, 15 studies mentioned the risk of selection bias related to either the sampling strategy, a small sample size or in the sample selection for analysis by confirmatory tests [5, 28, 29, 31, 34, 36, 65–67, 69, 71, 72, 74, 75, 77]. The risk of operator error in performing a test incorrectly or misinterpreting results (misclassification bias) was cited by 3/16 (19%) studies [65, 66, 74]. In addition, 2/16 (13%) studies stated a concern of performance (observer) bias and the need to blind any additional operators involved in testing (or re-testing) medicine samples [51, 67].

Dissemination of findings

Overall, 9/39 (23%) studies stated that they had shared their findings (or intended to do so) with either the Ministry of Health or the relevant NMRA [28–30, 33, 36, 67, 69, 71, 73].

Discussion

In contrast to the extensive discourse in recent years on how medicine quality should be defined, much less attention has been paid to reporting of both the technologies used to assess medicine quality and the results obtained [80]. This review summarizes the current evidence on the reporting of findings from anti-malarial medicine quality surveys in LMICs that have employed screening technologies and provides guidance on how reporting could be improved for future studies. Our results highlight the great variation in study design, survey methods and laboratory procedures used. The lack of standardization hinders comparison between studies, and is a potential source of error and bias. The review reveals the need for procedures to be more comprehensively reported in a standardized manner, to more readily evaluate the accuracy of estimates of medicine quality obtained in surveys, and to compare results across studies. Medicine quality surveyors and researchers ought to state in detail, the analytical methods which they have used and provide an indication of the reliability of the results obtained [82]. Clear and thorough reporting on analytical methods and study findings should include the following aspects as a minimum; sampling strategies, specific details of screening and confirmatory test procedures, test repetition, blinding of operators, use of reference standards, and reporting on risk of bias to enable results to be interpreted with greater confidence.

Establishing conclusive evidence for the accuracy of commonly used screening tests is challenging as there is little information available on the precision of methods for detecting poor quality anti-malarials. The accuracy of the most frequently employed screening technique, the MiniLab® (TLC test), has been questioned as it has previously been shown to overestimate medicine quality for anti-malarials, producing false positive results when samples are compared to analysis by HPLC [5, 28, 83]. Indeed, the MiniLab® has been described as "only being able to detect grossly substandard or counterfeit medicines" [71]. Nevertheless, cost effective screening technologies have a key role in providing an indication of medicine quality and are especially useful in settings where confirmatory tests are not readily available. Yet, medicine quality surveys that elect to solely utilize screening technologies should be scrutinized thoroughly and regulatory decisions actioned after completing verification of suspect samples by confirmatory tests [84].

This review, has found that just under half (14/30 (47%)) of the studies reported a discrepancy in the results once confirmatory testing had been carried out subsequent to using screening tests. However, only the WHO multi-country study carried out a specificity and sensitivity calculation to explore the extent of the discrepancy [28]. There is a need to establish the precise accuracy of each of the screening techniques available for all medicines they test, and it should be mandatory for manufacturers of new technologies to report the sensitivity and specificity of the test, determined through both feasibility testing in a laboratory setting and piloting in the field.

Strengths and limitations of the review

The quality assessment score used in this review has suggested that reporting in anti-malarial medicine quality studies is not satisfactory; potentially limiting the ability of an NMRA to take action in the case of finding a poor quality medicine. However, there are two caveats to the criteria used. Firstly, if a study has not employed confirmatory tests it will inevitably be assigned a lower score as the study cannot fulfil 8 of the 23 criteria stipulated. Secondly, studies failing to provide pertinent information on the methods used, as well as those with a limited study design, would both obtain a low score. Nonetheless, this information is essential to have confidence in the accuracy of the results reported. A strength of the scoring criteria is that they do provide a broad indication of the rigour of the research design and the reliability of the results. The wide range in scores (2–17) in this review indicate that there is still considerable room for improvement in the reporting of medicine quality studies.

A review of the grey literature using keyword search terms in generic web search engines was not conducted. The majority of findings [36/39 studies (92%)] presented in this review are from academic peer-reviewed papers published in international journals and not from reports produced by NMRAs which are often the key organizations at country level conducting anti-malarial medicine quality surveys. Country specific medicine quality

reports from national surveys conducted by NMRAs or similar agencies may exist but are less accessible, as they are either published internally or for dissemination to funders and operational partners and may only be published on an *ad hoc* basis. The limited number of these types of report found in the process of the literature search did not meet the inclusion criteria.

Conclusions

The frequency with which medicine quality studies and surveys are being conducted by a diverse profile of organizations and academic institutions from LMICs, North America and parts of Europe has increased appreciably. Whilst a multidisciplinary approach to the field of medicine quality is both required and encouraged, researchers involved in these studies can differ in their disciplinary background (pharmacy, chemistry, medicine, epidemiology etc.), knowledge, and experience, placing an increased and urgent need for convergence toward an agreed approach to studies and surveys [84].

This review has found much heterogeneity across the included studies in terms of study design and consistency in reporting, which impacts on the generalizability of survey results and further perpetuates the lack of information on the accuracy of the most popular screening technologies. The introduction of reporting guidelines, such as the CONSORT and STROBE guidelines, have helped to standardize the reporting of clinical trials and epidemiological studies, and increased the clarity and scientific rigour of study design, facilitating the interpretation of results and comparison between studies. In contrast, there is little guidance on the reporting of findings from medicine quality surveys with the sole exception of the MEDQUARG checklist, applied in only one of the studies included in this review [69]. The MEDQUARG checklist provides guidance on sampling in medicine quality surveys. At country level, USP have provided guidance for conducting medicine quality surveys. Despite the availability of these two sets of guidelines the divergence in study designs limits the interpretation of findings and the comparison between studies.

It has also been highlighted here that the standard of reports is limited by a number of common weaknesses across studies. This includes small sample sizes (especially at the level of the confirmatory test), a lack of blinding of operators, limited results verification, and ambiguity in sample selection for confirmatory tests, all of which may bias results. A set of standardized guidelines would help to reduce variation and decrease the risk of bias in medicine quality studies. The authors propose that the measures for reporting the quality of a medicine quality survey in this review, should be used in conjunction with the MEDQUARG and USP guidelines, as a checklist for academics and programme managers in designing surveys and reporting results. This would facilitate the assessment of the reliability and accuracy of findings by national and international authorities (NMRAs, WHO, USP etc.), journal editors and peer reviewers.

Additional files

Additional file 1. Screening tests only. Included studies; screening tests only. Table representing studies that employed screening tests only that were included in the review and assessed for their standard using the criteria in the proposed template.

Additional file 2. Screening plus confirmatory. Included studies; screening tests plus confirmatory analysis. Table representing studies that employed screening tests plus confirmatory analysis that were included in the review and assessed for their standard using the criteria in the proposed template.

Abbreviations

ACT: artemisinin-based combination therapy; CONSORT: Consolidated Standards for Reporting Trials; DQSS: drug quality surveillance system; NMRA: National Medicine Regulatory Authority; GMP: good manufacturing practice; GPHF: Global Health Pharma Fund; HPLC: high performance liquid chromatography; LMICs: low-middle income countries; NIR: near infrared; SAPI: stated active pharmaceutical ingredient; STROBE: the strengthening the reporting of observational studies in epidemiology; TLC: thin layer chromatography; WHO: World Health Organization.

Authors' contributions

ML designed the review. ML and FEK undertook the systematic review. ML, FEK, HK and SC developed, reviewed and approved the criteria for reporting findings. ML wrote the first draft of the manuscript. ML, FEK, HK and SC revised the manuscript. All authors read and approved the final manuscript.

Author details

[1] London School of Hygiene and Tropical Medicine, London, UK. [2] Makerere University, Kampala, Uganda. [3] Uppsala University, Uppsala, Sweden.

Acknowledgements

Mirza Lalani is supported by the John Henry Memorial Fund and the Leverhulme Charities Trade Trust.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Received: 20 January 2017 Accepted: 9 May 2017
Published online: 15 May 2017

References

1. Owens S. Malaria and the millennium development goals. Arch Dis Child. 2015;100(Suppl 1):S53–6.
2. WHO. World malaria report 2015. Geneva: World Health Organization. 2015. http://www.who.int/malaria/publications/world-malaria-report-2015/report/en/. Accessed 3 Mar 2017.
3. Tabernero P, Fernandez FM, Green M, Guerin PJ, Newton PN. Mind the gaps-the epidemiology of poor-quality anti-malarials in the malarious world-analysis of the WorldWide Antimalarial Resistance Network database. Malar J. 2014;13:139.

4. Chaccour CJ, Kaur H, Mabey D, Del Pozo JL. Travel and fake artesunate: a risky business. Lancet. 2012;380:1120.
5. Lalani M, Kaur H, Mohammed N, Mailk N, van Wyk A, Jan S, et al. Substandard antimalarials available in Afghanistan: a case for assessing the quality of drugs in resource poor settings. Am J Trop Med Hyg. 2015;92:51–8.
6. Newton PN, Green MD, Fernandez FM. Impact of poor-quality medicines in the 'developing' world. Trends Pharmacol Sci. 2010;31:99–101.
7. Newton PN, Caillet C, Guerin PJ. A link between poor quality antimalarials and malaria drug resistance? Expert Rev Anti Infect Ther. 2016;14:531–3.
8. WHO. Prequalification of drugs factsheet. Geneva: World Health Organization. 2013. http://www.who.int/mediacentre/factsheets/fs278/en/. Accessed 7 Mar 2017.
9. Battersby A, Goodman C, Abondo C, Mandike R. Improving the supply, distribution and use of antimalarial drugs by the private sector in Tanzania. Malar Consort. 2003. http://researchonline.lshtm.ac.uk/2869426/1/antimalarials_final_draft_08_jul_03.pdf. Accessed 25 Apr 2017.
10. Jutand M, Salamon R. Lot quality assurance sampling: methods and applications in public health (in French). Rev Epidemiol Sante Publique. 2000;48:401–8.
11. Bloland PB, Kazembe PN, Watkins WM, Doumbo OK, Nwanyanwu OC, Ruebush TK 2nd. Malarone-donation programme in Africa. Lancet. 1997;350:1624–5.
12. Snell B. Inappropriate drug donations: the need for reforms. Lancet. 2001;358:578–80.
13. Malaria Operational Plan 2014, Senegal. United States Agency for International Development. 2014. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy14/senegal_mop_fy14.pdf?sfvrsn=10. Accessed 25 Apr 2017.
14. Ensuring the quality of medicines in resource-limited countries; an operational guide. United States Pharmacopeia. 2002. http://apps.who.int/medicinedocs/documents/s18424en/s18424en.pdf. Accessed 25 Apr 2017.
15. Measures to help protect patients from falsified medicines. European Medicines Agency. 2016. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/02/news_detail_002467.jsp&mid=WC0b01ac058004d5c1. Accessed 7 Mar 2017.
16. WHO. Counterfeit drugs. Geneva: World Health Organization. 1992. http://apps.who.int/iris/bitstream/10665/58358/1/WHO_DMP_CFD_92.pdf. Accessed 14 Jan 2017.
17. Report of the fifth meeting of the Member State mechanism on substandard/spurious/falselylabelled/falsified/counterfeit medical products. World Health Organization. 2017. http://apps.who.int/gb/ssffc/pdf_files/MSM5/A_MSM5_8-en.pdf. Accessed 12 Apr 2017.
18. WHO. Quality control laboratories. Geneva: World Health Organization. 2016. http://extranet.who.int/prequal/information/quality-control-laboratories. Accessed 25 Apr 2017.
19. Guidelines for Drug Sampling, USP DQI Drug Quality Monitoring Program. Use of the basic tests at the peripheral level. United States Pharmacopeia. 2006. http://pdf.usaid.gov/pdf_docs/PNADH150.pdf. Accessed 20 Feb 2017.
20. Jahnke R. A Concise quality control guide on essential drugs and other medicines: volume II on thin layer chromatographic tests. Global Pharma Health Fund. 2008. http://www.gphf.org/web/en/minilab/manuals.htm. Accessed 7 Mar 2017.
21. Newton PN, Lee SJ, Goodman C, Fernandez FM, Yeung S, Phanouvong S, et al. Guidelines for field surveys of the quality of medicines: a proposal. PLoS Med. 2009;6:e52.
22. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.
23. Nayyar GM, Breman JG, Newton PN, Herrington J. Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. Lancet Infect Dis. 2012;12:488–96.
24. Kovacs S, Hawes SE, Maley SN, Mosites E, Wong L, Stergachis A. Technologies for detecting falsified and substandard drugs in low and middle-income countries. PLoS ONE. 2014;9:e90601.
25. Almuzaini T, Choonara I, Sammons H. Substandard and counterfeit medicines: a systematic review of the literature. BMJ Open. 2013;3:e002923.
26. Schünemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ. 2008;336:1106–10.
27. Holger J. GRADE: grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ. 2008;336:1107.
28. WHO. Survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa. Geneva: World Health Organization. 2011. http://www.who.int/medicines/publications/WHO_QAMSA_report.pdf. Accessed 20 Feb 2017.
29. Survey of the quality of selected antimalarial medicines circulating in Madagascar, Senegal, and Uganda. United States Pharmacopeia. 2009. http://apps.who.int/medicinedocs/documents/s17069e/s17069e.pdf. Accessed 26 Feb 2017.
30. Monitoring the quality of antimalarial medicines circulating in Kenya division of Malaria Control and Pharmacy and Poisons Board. 2013. http://pharmacyboardkenya.org/downloads/?file=malaria_circular_three.pdf. Accessed 12 Apr 2017.
31. Bate R, Tren R, Mooney L, Hess K, Mitra B, Debroy B, et al. Pilot study of essential drug quality in two major cities in India. PLoS ONE. 2009;4:e6003.
32. Patel AK, Prajapati BG, Moria RS, Patel CN. In vitro evaluation of marketed antimalarial chloroquine phosphate tablets. J Vector Borne Dis. 2005;42:147–50.
33. Evans L 3rd, Coignez V, Barojas A, Bempong D, Bradby S, Dijiba Y, et al. Quality of anti-malarials collected in the private and informal sectors in Guyana and Suriname. Malar J. 2012;11:203.
34. Pribluda VS, Barojas A, Anez A, Lopez CG, Figueroa R, Herrera R, et al. Implementation of basic quality control tests for malaria medicines in Amazon Basin countries: results for the 2005–2010 period. Malar J. 2012;11:202.
35. Nair A, Strauch S, Lauwo J, Jahnke RWO, Dressman J. Are counterfeit or substandard anti-infective products the cause of treatment failure in Papua New Guinea? J Pharm Sci. 2011;100:5059–68.
36. Kaur H, Allan EL, Mamadu I, Hall Z, Ibe O, El Sherbiny M, et al. Quality of artemisinin-based combination formulations for malaria treatment: prevalence and risk factors for poor quality medicines in public facilities and private sector drug outlets in Enugu, Nigeria. PLoS ONE. 2015;10:e0125577.
37. Odeniyi MA, Adegoke OA, Adereti RB, Odeku OA, Itiola OA. Comparative analysis of eight brands of sulfadoxine-pyrimethamine tablets. Trop J Pharm Res. 2003;2:161–7.
38. Odunfa O, Adegoke O, Onaga I. Pharmaceutical equivalence of some commercial samples of artesunate and amodiaquine tablets sold in Southwestern Nigeria. Trop J Pharm Res. 2009;8:491–9.
39. Affum AO, Lowor S, Osae SD, Dickson A, Gyan BA, Tulasi D. A pilot study on quality of artesunate and amodiaquine tablets used in the fishing community of Tema, Ghana. Malar J. 2013;12:220.
40. El-Duah M, Ofori-Kwakye K. Substandard artemisinin-based antimalarial medicines in licensed retail pharmaceutical outlets in Ghana. J Vector Borne Dis. 2012;49:131–9.
41. Ofori-Kwakye K. Quality of artesunate tablets sold in pharmacies in Kumasi, Ghana. Trop J Pharm Res. 2008;7:1179–84.
42. Osei-Safo D, Agbonon A, Konadu DY, Harrison JJEK, Edoh M, Gordon A, et al. Evaluation of the quality of artemisinin-based antimalarial medicines distributed in Ghana and Togo. Malar Res Treat. 2014;2014:12.
43. Bate R, Hess K. Anti-malarial drug quality in Lagos and Accra—a comparison of various quality assessments. Malar J. 2010;9:157.
44. Bate R, Jin GZ, Mathur A. Does price reveal poor-quality drugs? Evidence from 17 countries. J Health Econ. 2011;30:1150–63.
45. Bate R, Mooney L, Milligan J. The danger of substandard drugs in emerging markets: an assessment of basic product quality. Pharmacologia. 2012;3:46–51.
46. Bate R, Tren R, Hess K, Mooney L, Porter K. Pilot study comparing technologies to test for substandard drugs in field settings. Afr J Pharm Pharmacol. 2009;3:165–70.
47. Nyarko EA, Nettey H. Quality assessment of artemether/lumefantrine tablets sampled from pharmacies in Accra, using the MVHimagePCv8.exe Color Software. Pharmacol Pharm. 2013;4:567–72.
48. Ochekpe N, Agbowuro A, Attah S. Correlation of price and quality of medicines: assessment of some artemisinin antimalarials in Nigeria based on GPHF minilab. Int J Drug Dev Res. 2010;2:211–8.

49. Atemnkeng MA, De Cock K, Plaizier-Vercammen J. Quality control of active ingredients in artemisinin-derivative antimalarials within Kenya and DR Congo. Trop Med Int Health. 2007;12:68–74.
50. Dondorp AM, Newton PN, Mayxay M, Van Damme W, Smithuis FM, Yeung S, et al. Fake antimalarials in Southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials. Trop Med Int Health. 2004;9:1241–6.
51. Hall KA, Newton PN, Green MD, De Veij M, Vandenabeele P, Pizzanelli D, et al. Characterization of counterfeit artesunate antimalarial tablets from southeast Asia. Am J Trop Med Hyg. 2006;75:804–11.
52. Hebron Y, Tettey JN, Pournamdari M, Watson DG. The chemical and pharmaceutical equivalence of sulphadoxine/pyrimethamine tablets sold on the Tanzanian market. J Clin Pharm Ther. 2005;30:575–81.
53. Minzi OM, Marealle IA, Shekalaghe S, Juma O, Ngaimisi E, Chemba M, et al. Comparison of bioavailability between the most available generic tablet formulation containing artemether and lumefantrine on the Tanzanian market and the innovator's product. Malar J. 2013;12:174.
54. WHO. Basic tests for drugs. Geneva: World Health Organization. 1998. http://whqlibdoc.who.int/publications/1998/9241545135.pdf. Accessed 7 Mar 2017.
55. WHO. Guidance for inspection when pharmaceutical products are suspected to be counterfeit, spurious or substandard. Geneva: WHO Technical Report Series, World Health Organization. 1999. http://apps.who.int/medicinedocs/en/d/Jh1792e/21.10.html#Jh1792e.21.10. Accessed 7 Mar 2017.
56. WHO. Guidelines to develop measures to combat "counterfeit" drugs. Geneva: World Health Organization. 1999. http://whqlibdoc.who.int/hq/1999/WHO_EDM_QSM_99.1.pdf. Accessed 20 Feb 2017.
57. GPHF Minilab. Global Pharma Health Fund. 2012. http://www.gphf.org. Accessed 25 Apr 2017.
58. Ricci C, Nyadong L, Yang F, Fernandez FM, Brown CD, Newton PN, et al. Assessment of hand-held Raman instrumentation for in situ screening for potentially counterfeit artesunate antimalarial tablets by FT-Raman spectroscopy and direct ionization mass spectrometry. Anal Chim Acta. 2008;623:178–86.
59. Weaver AA, Reiser H, Barstis T, Benvenuti M, Ghosh D, Hunckler M, et al. Paper analytical devices for fast field screening of beta lactam antibiotics and antituberculosis pharmaceuticals. Anal Chem. 2013;85:6453–60.
60. Hajjou M, Qin Y, Bradby S, Bempong D, Lukulay P. Assessment of the performance of a handheld Raman device for potential use as a screening tool in evaluating medicines quality. J Pharm Biomed Anal. 2013;74:47–55.
61. Yoon WL, Jee RD, Charvill A, Lee G, Moffat AC. Application of near-infrared spectroscopy to the determination of the sites of manufacture of proprietary products. J Pharm Biomed Anal. 2004;34:933–44.
62. Martino R, Malet-Martino M, Gilard V, Balayssac S. Counterfeit drugs: analytical techniques for their identification. Anal Bioanal Chem. 2010;398:77–92.
63. Weaver AA, Lieberman M. Paper test cards for presumptive testing of very low quality antimalarial medications. Am J Trop Med Hyg. 2015;92:17–23.
64. Wilson BK, Kaur H, Allan EL, Lozama A, Bell D. A new handheld device for the detection of falsified medicines: demonstration on falsified artemisinin-based therapies from the field. Am J Trop Med Hyg. 2017. doi:10.4269/ajtmh.16-0904.
65. Yeung S, Lawford HL, Tabernero P, Nguon C, van Wyk A, Malik N, et al. Quality of antimalarials at the epicenter of antimalarial drug resistance: results from an overt and mystery client survey in Cambodia. Am J Trop Med Hyg. 2015;92:39–50.
66. Bate R, Mathur A. The impact of improved detection technology on drug quality: a case study of Lagos Nigeria. AEI Econ Policy. 2011. doi:10.2139/ssrn.2212974.
67. Tabernero P, Mayxay M, Culzoni MJ, Dwivedi P, Swamidoss I, Allan EL, et al. A repeat random survey of the prevalence of falsified and substandard antimalarials in the Lao PDR: a change for the better. Am J Trop Med Hyg. 2015;92:95–104.
68. Langner MD, Maibach HI. Many common drugs in dermatology are light, temperature, or moisture-sensitive. Skin Ther Lett. 2009;14:3–5.
69. Visser BJ, Meerveld-Gerrits J, Kroon D, Mougoula J, Vingerling R, Bache E, et al. Assessing the quality of anti-malarial drugs from Gabonese pharmacies using the MiniLab(R): a field study. Malar J. 2015;14:273.
70. Minzi OM, Moshi MJ, Hipolite D, Massele AY, Tomson G, Ericsson O, et al. Evaluation of the quality of amodiaquine and sulphadoxine/pyrimethamine tablets sold by private wholesale pharmacies in Dar Es Salaam Tanzania. J Clin Pharm Ther. 2003;28:117–22.
71. Risha PG, Msuya Z, Clark M, Johnson K, Ndomondo-Sigonda M, Layloff T. The use of Minilabs to improve the testing capacity of regulatory authorities in resource limited settings: tanzanian experience. Health Policy. 2008;87:217–22.
72. Syhakhang L, Lundborg CS, Lindgren B, Tomson G. The quality of drugs in private pharmacies in Lao PDR: a repeat study in 1997 and 1999. Pharm World Sci. 2004;26:333–8.
73. Diop Y. Contrôle de la qualité des antipaludiques au niveau de cinq sites sentinelles de surveillance épidémiologique du paludisme. Société des Experts Chimistes de France. 2008:55–62.
74. Phanouvong S, Raymond C, Krech L, Dijiba Y, Mam B, Lukulay P, et al. The quality of antimalarial medicines in western Cambodia: a case study along the Thai–Cambodian border. Southeast Asian J Trop Med Public Health. 2013;44:349–62.
75. Tipke M, Diallo S, Coulibaly B, Storzinger D, Hoppe-Tichy T, Sie A, et al. Substandard anti-malarial drugs in Burkina Faso. Malar J. 2008;7:95.
76. Vijaykadga S, Cholpol S, Sitthimongkol S, Pawaphutanan A, Pinyoratanachot A, Rojanawatsirivet C, et al. Strengthening of national capacity in implementation of antimalarial drug quality assurance in Thailand. Southeast Asian J Trop Med Public Health. 2006;37(Suppl 3):5–10.
77. Sengaloundeth S, Green MD, Fernandez FM, Manolin O, Phommavong K, Insixiengmay V, et al. A stratified random survey of the proportion of poor quality oral artesunate sold at medicine outlets in the Lao PDR—implications for therapeutic failure and drug resistance. Malar J. 2009;8:172.
78. Basco LK. Molecular epidemiology of malaria in Cameroon. XIX. Quality of antimalarial drugs used for self-medication. Am J Trop Med Hyg. 2004;70:245–50.
79. Bertoldi AD, Barros AJ, Hallal PC. Generic drugs in Brazil: known by many, used by few. Cad Saude Publica. 2005;21:1808–15.
80. Clift C. Combating counterfeit, falsified and substandard medicines: defining the way forward? Chatham House. 2010. http://www.gphf.org/images/downloads/library/chathamhouseproject2010.pdf. Accessed 26 Feb 2017.
81. Kirkwood B, Sterne J. Essential medical statistics. 2nd ed. Oxford: Wiley; 2003.
82. Editorial. Observational studies: getting clear about transparency. PLoS Med. 2014; 11:e1001711.
83. Fadeyi I, Lalani M, Mailk N, Van Wyk A, Kaur H. Quality of the antibiotics-amoxicillin and co-trimoxazole from ghana, Nigeria, and the United Kingdom. Am J Trop Med Hyg. 2015;92:87–94.
84. Kaur H, Clarke S, Lalani M, Phanouvong S, Guerin P, McLoughlin A, et al. Fake anti-malarials: start with the facts. Malar J. 2016;15:86.
85. Primo-Carpenter J, McGinnis M. Media reports on medicine quality: focusing on USAID-assisted countries by the promoting the quality of medicines program. United States Agency for International Development. 2009. http://www.usp.org/pdf/EN/dqi/ghcDrugQualityMatrix.pdf. Accessed 26 Feb 2017.
86. Tabernero P, Newton PN. The WWARN antimalarial quality surveyor. Pathog Glob Health. 2012;106:77–8.

Chapter 5: An evaluation of a new screening test for assessing the quality of artemisinin based medicines

5.1 Introduction

Poor quality medicines are those that do not comply with pharmacopeia tolerance limits and may contain sub-therapeutic or a greater amount of the stated active pharmaceutical ingredient (SAPI) resulting in treatment failure, the propagation of drug resistance (in the case of anti-infectives) or an increase in adverse effects. [1, 2] Focussing on antimalarial medicines, a recent review indicated that 30.1% (2,813) of 9,348 antimalarial medicines sampled in low-middle income countries (LMICs) failed chemical/packaging quality. [3] This is of concern in LMICs who may have minimal regulatory and technical capacity to control and monitor the quality of medicines entering and circulating nationally. Indeed, the World Health Organization (WHO) estimated that 30% of countries in Latin America, Asia and Africa had 'no medicine regulation or a capacity that hardly functions.' [4] Estimates for the proportion of countries with adequate technical capacity are lacking. In the context of medicines quality, an effective medicines quality assurance system (MQAS) requires robust regulation that can prevent poor quality medicines entering a country and the capability to undertake post-marketing surveillance that detects poor quality medicines and acts to remove such medicines from national medicine supply chains.

A medicines quality surveillance system (MQSS) is an integral component of a MQAS and relies upon adequate technical capacity including; 1) a medicines quality control laboratory (MQCL) with equipment and expertise to carry out confirmatory testing (as listed in drug monographs in pharmacopeia), 2) screening technologies employed in sentinel sites to assess the quality of a larger volume of medicines and 3) effective post-marketing surveillance with periodic medicines quality surveys using robust sampling techniques. Hence, the quality of medicines available cannot be assured (even where regulation operates effectively) unless adequate technical capacity is available.

MQSS in LMICs employ screening devices at the preliminary stage for medicine quality assessment to identify those medicines that need more detailed (and expensive) laboratory investigation. Some of these devices are handheld, simple to use and relatively inexpensive, making them suitable for screening large volumes of medicines. However, screening devices only provide an indication of the quality of a medicine and are useful in detecting falsified or grossly substandard medicines (with an absence of or very low SAPI) but cannot identify

substandard medicines. [5-7] Screening tests can be employed at any point of the distribution chain from entry of a consignment of medicines at the port to its point of sale as well as in laboratories as part of routine post marketing surveillance activities such as periodic medicines quality surveys. Subsequent to screening tests, medicines should always be analysed using confirmatory tests following methods described in an international pharmacopeia so as to obtain a definitive result on the quality of a medicine in terms of its content in comparison to tolerance limits for the medicine stated in its drug monograph. [8] However, medicine quality analysis using confirmatory methods is expensive, resource intensive and requires engagement at the level of the national government, all of which maybe seldom available in LMICs. [9] Thus, by default, screening technologies may play a pivotal role in the surveillance of medicines quality especially as the majority of LMICs have limited regulatory capacity to assure the quality of medicines entering a country coupled with, in some LMICs, multiple entry points for medicines (official and unofficial) which in turn increases the reliance upon post-marketing surveillance. Thus, the capability to analyse medicine quality outside of an established laboratory setting is a necessity. [10]

The merits of screening technologies currently available on the market have been outlined in the introduction to section 2. This chapter focusses upon the evaluation of a new screening test comprising two new screening assays, namely the artemisinin derivative test (ADT) which specifically detects the artemisinin derivative (AD[‡]) component and is thus useful in determining the quality of artemisinin based medicines in both their monotherapy and combination formulations. This chapter also assesses the performance of the ADT against the currently more widely utilised technology namely the Global Pharma Health Fund (GPHF) MiniLab®, reportedly available in around 95 countries globally, the vast majority of which are LMICs. [11] The MiniLab® is also promoted for use by the United States Pharmacopeia (USP) Poor Quality Medicines Programme, as a key component of a MQSS and is currently the only screening technology used as part of periodic medicines quality surveys in several LMICs. [11, 12]

[‡] In this chapter the term ADs encompass artemisinin derivatives in both their monotherapy (e.g. dihydroartemisinin and combination therapy forms (dihydroartemisinin-piperaquine). ACTs refer to artemisinin combination therapies only in which the artemisinin derivative is partnered with another drug.

5.1.1 The GPHF MiniLab®

The GPHF MiniLab® is a medicine quality screening toolkit, containing both qualitative and quantitative testing techniques. The qualitative tests include visual inspection and tablet/capsule disintegration and the quantitative test is a version of thin layer chromatography (TLC). [13] According to the manufacturer's technical specifications, the TLC component of the MiniLab® provides a semi-quantitative analysis of medicines content (see figure 5.1) in which a spot of the medicine sample is applied to a TLC plate and should migrate at the same rate as the reference standard of the SAPI. If the spot formed by the sample is obviously different to the reference spot in distance travelled, shape and size this may indicate a poor quality sample. This is shown in figure 5.1 where 'Run no. 3' represents a sample of poor quality dihydroartemisinin and is visibly different in shape and size in comparison to the other three reference samples. Additionally, the TLC test must show that the sample contains more than 80% SAPI to be considered as a 'pass' according to MiniLab® guidelines. This is represented in figure 5.1 as 'Run no. 4', lower working reference standard of dihydroartemisinin representing 80% SAPI. [14]

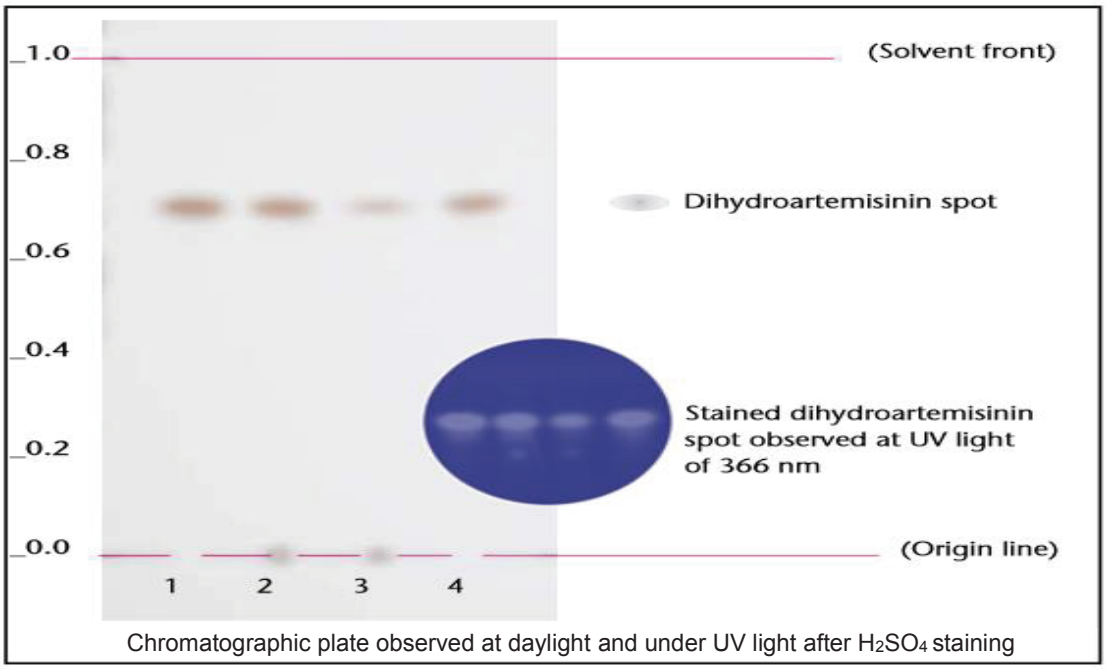


Figure 5.1: Image of a TLC run for a sample of dihydroartemisinin
Run No.1: Upper working standard representing 100% of total dihydroartemisinin. Run No.2: A drug product of good quality with acceptable drug content. Run No.3: A drug product of poor quality with unacceptable low drug content. Run No.4: Lower working standard representing 80% of total dihydroartemisinin. Source: GPHF MiniLab® manual (2010).

5.1.2 Artemisinin Derivative Test

The ADT comprises two simple assays developed at the London School of Hygiene and Tropical Medicine (LSHTM) to detect the artemisinin component of a monotherapy or combination formulation containing an artemisinin derivative and have not as yet been formatted into a kit for sale. The assays have been patented by LSHTM[§], which was granted in 2013.

These colorimetric assays utilise TLC silica gel sheets and either 2,4 dinitrophenylhydrazine (DNP) or 4-Benzoylamino-2, 5-dimethoxybenzenediazoniumchloride hemi (zinc chloride) salt (Fast Blue Salt – FBS) as the reagents to detect ADs. The principal of the test involves dissolving the pulverized tablet in methanol and applying a very small amount (5 µl x 2) of the resulting solution to a TLC sheet followed by either of the reagents (5 µl) and allowing the reaction to proceed at room temperature. The reaction(s) will produce a pink colour with the DNP or blue colour with FBS if an AD is present in the sample. Both colours should appear within 40 minutes. The test comprises two assays so as to provide corroborative evidence of the detection of an AD. During product testing no medicines on the WHO essential medicines list or non-AD antimalarials or excipients produced a pink colour with DNP (aside from the ADs), only the antibiotic erythromycin did produce a blue colour (similar to the ADs) with the FBS reagent. Erythromycin did not produce the pink colour when tested with DNP.

The ADT is chromatographic and colorimetric and provides an alternative to the GPHF MiniLab® for screening the quality of ADs (artemether, artesunate and dihydroartemisinin only). The development of the assays at LSHTM, demonstrated total specificity for ADs. [15] In addition, the test is also capable of detecting concentrations of ADs in formulations as low as 10% of the SAPI (figure 5.2).

[§] Kaur H; Ioset JR. Assay, kit and apparatus for detection of artemisinin derivatives. UK Intellectual Property Office, 2007; WO2007077444 (A1. Date of publication and mention of the grant of the patent: 22.05.2013 Bulletin 2013/21

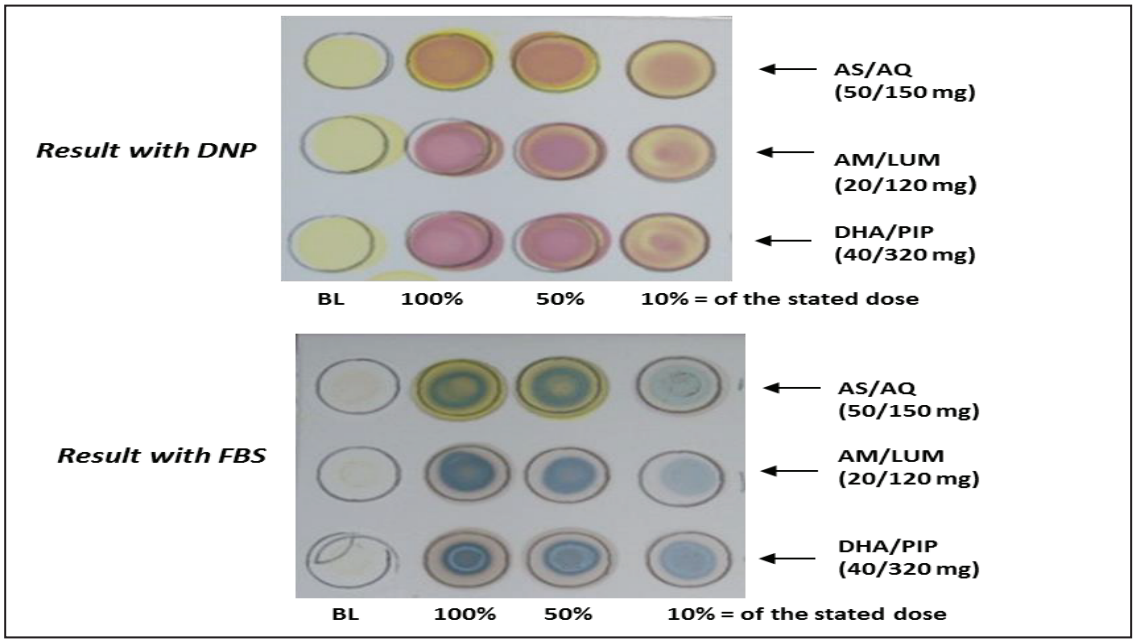


Figure 5.2: Detection of the artemisinin derivative component from 100% (which is the tablet containing the correct amount of the SAPI on the packet) down to 50% and 10% (which will imply that the product is substandard or grossly substandard) in formulations of artesunate/amodiaquine (AS/AQ;100% = 50 mg, 50% =25 mg and 10% = 5 mg), artemether/lumefantrine (AM/LUM, Coartem®; 100% = 20 mg, 50% =10 mg and 10% = 2 mg), and dihydroartemisinin/piperaquine (DHA/PIP, Duocortexin®; 100% = 40 mgs, 50% =20 mg and 10% = 4 mg). BL = Methanol as blank 100% = each tablet dissolved in 2 mL methanol corresponds to the acceptable dose; 50% = each tablet dissolved in 4 mL methanol corresponds to a substandard dose; 10% = each tablet dissolved in 20 mL methanol corresponds to a grossly substandard medicine.

The ADT is rapid, simple to use, handheld, inexpensive and requires no previous laboratory experience. Nonetheless, as with the MiniLab®, it relies on a subjective assessment for results interpretation. Comparison of practical aspects of the GPHF Minilab® (TLC) and ADT are listed in table 5.1 below.

Table 5.1: A comparison of the practical aspects of the MiniLab® TLC test and the ADT test for the screening of artemisinin derivatives

	GPHF MiniLab®® (TLC)	ADT
Time for assay preparation (for one sample)	Up to 30 minutes	5 minutes
Time (minutes) for development of results	30 minutes	40 minutes minimum
Total time per test	60 minutes	45 minutes minimum
Reagents/solvents required	Sulphuric acid solution 96% Ethyl acetate Methanol Ammonia solution 25% Acetone Glacial acetic acid Toluene	Methanol Dinitrophenylhydrazine (DNP assay) 4-Benzoylamino-2, 5-dimethoxybenzenediazonium-chloride hemi (zinc chloride) salt (FBS assay)
Test result	Needs a UV lamp to visualise	The pink colour (DNP assay) or Blue colour (FBS assay) are visible to the naked eye
Size	Large suitcase (40Kg)	To be formatted – size equivalent to pregnancy testing kit (15cm x 8cm x 2cm) and weight < 0.5 kg
Interpretation of results	Relies on subjective assessment	Relies on subjective assessment
Training	Formal training course required Laboratory experience is advantage	Minimal training No laboratory experience needed

We explored aspects of the test that had not been assessed during initial product testing. Firstly, just a handful of individuals at LSHTM had used the ADT in controlled laboratory conditions. Secondly, an instruction manual for the test had not been designed nor had a detailed test procedure or reference guidance on results interpretation (e.g. colour chart) been produced. Finally, for the ADT to be used in malaria endemic countries it required feasibility testing by individuals who had no prior knowledge of the test. A field evaluation of the test included an assessment of its practical utility, usefulness and acceptability.

Design of a manual for the ADT test

A manual (see supplementary file 1) was designed by us and included the assay procedures, interpretation of results, a colour chart, bench aids (outlining test procedure, steps 1-4 as in figure 5.3) and a summary description of the laboratory investigations based on the published work by the inventors of the test, Ioset and Kaur. [15] The manual was designed to be similar in structure and language to the TLC test procedures of the MiniLab® manual so as to be simple to follow for the laboratory technicians, given their experience of having previously

used the MiniLab®. The manual included a detailed description of various aspects of the test (illustrated in figure 5.3 below) including; a list of equipment, the test procedure (steps 1 and 2; sample and TLC plate preparation), spotting of test solution (step 3), development of results (step 4) and results interpretation (step 5). The manual also included a bench aid which provided a concise summary of steps 1-5.

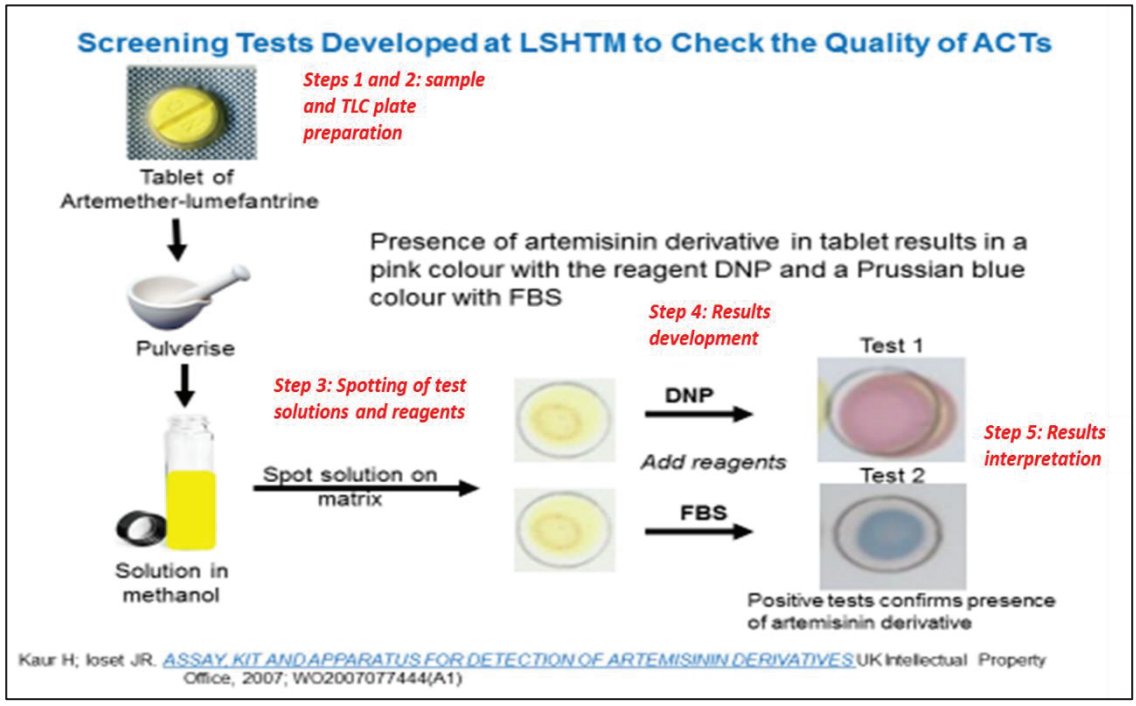


Figure 5.3: ADT test developed at LSHTM to check the quality of artemisinin based medicines
The text in red shows the major steps for carrying out the test: steps 1 and 2 - preparation of the sample and TLC plate; step 3 - spotting of solution on matrix on TLC plate; step 4 - development of the results; step 5 - interpretation of resulting colours.

To enable step 5 (results interpretation) a colour chart (included in the manual) was designed to reflect the range of depth of colours produced using samples of ACTs collected from multi-country medicine quality surveys that had already been tested using confirmatory content analysis by High Performance Liquid Chromatography with photodiode array detector (HPLC-PDA) at LSHTM. [16] All ACTs were solubilised in methanol and diluted to obtain solutions with concentrations of 10, 40 and 100 % SAPI as this produced the best distinguishable colours when viewing the analysis results of the ADT.

This study aimed to evaluate the practical utility of the ADT, perceptions of its potential usefulness and acceptability following 'field' testing in an LMIC. It assessed the performance of the ADT in the hands of laboratory technicians, who had no prior knowledge of this test, at the Laboratoire Nationale de Controle de Medicaments (LNCM) in Senegal. This approach was

designed to establish the acceptance of the test by laboratory technicians in malaria endemic countries for use as a component of a MQSS.

This study was conducted through three specific objectives:

1. To assess the ease of use and accuracy of the ADT for detecting the artemisinin derivative component of the formulation when used by laboratory technicians in the field.

2. To explore the acceptability and perceived usefulness of the ADT, and its potential role in a national system to monitor the quality of ACTs.

3. To compare the performance of the ADT and the GPHF-MiniLab® TLC test in terms of their accuracy when used by laboratory technicians in the field.

5.2 Methods and results

5.2.1 Study Setting and participant characteristics

The study was undertaken at the LNCM in Dakar, Senegal in February 2014 over the course of five days. All laboratory technicians employed by the LNCM (in Dakar) were invited to participate in the study. Senegal was chosen as an appropriate study site as a national MQSS has been in operation since around 2001. This provided an opportunity to assess the utility and role of this new screening test within a functioning surveillance system. Furthermore, the laboratory technicians at the LNCM were experienced users of the MiniLab® in the screening of samples collected as part of regular medicines quality surveys which had been ongoing in the country since around 2009 [17] with ad hoc use of the technology for a few years preceding the commencement of formal field surveys.

Ethical approval for the undertaking of this study was granted by the London School of Hygiene and Tropical Medicines Research Ethics Committee (see annex 1) and National Council for Health Research, Senegal (annex 2).

Information on age, gender, level of education, length of time at LNCM etc. of the participating technicians was collected. Eight LNCM technicians participated in the study; three males and five females, aged 30-52. With the exception of one technician, all had undertaken further education (diploma or university degree) after the completion of formal schooling. The period of employment at the LNCM ranged between 1-16 years. The average number of years of

experience in using the MiniLab® was five. Furthermore, all participating technicians had used the MiniLab® for testing ACTs in the three months prior to this study.

5.2.2 Study materials

Samples of ADs for testing were provided by the LNCM from a repository of medicines previously collected as part of routine medicine quality surveys conducted nationally. The laboratory manager stated that these samples had undergone HPLC analysis at the LNCM and confirmed to be of acceptable quality. MiniLab® equipment (for the TLC test only) and other materials required for the study were provided by the LNCM and, the two reagents and TLC plates for the ADT, were provided by Dr Kaur at LSHTM. A full list of equipment and procedures for the testing of ACTs using the MiniLab® is available in the GPHF MiniLab® manual. [14] The ADT test procedure and list of equipment was included as part of the aforementioned manual complied by myself. As Senegal is a francophone country, French versions of both manuals were provided to the study participants.

5.2.3 Study description

The test evaluation consisted of two laboratory exercises; i) an assessment of the practical utility of the ADT and ii) an evaluation of the test performance of both the ADT and the MiniLab®. Two focus group discussion (FGD) explored the perceptions of utility, acceptability and usefulness of the test. The outcomes of these exercises are structured as follows; 1) methods and results of the two exercises assessing the practical utility of the ADT and 2) methods and results of the evaluation of test performance of the ADT and the MiniLab®. Both these methods and results sections also include relevant data from the FGDs.

Studies evaluating other screening approaches (primarily early detection for the screening of disease and infection) were consulted to inform this investigation and it was found that operator agreement in the interpretation of results and adherence to instructions is enhanced by consistency in training. [18] For example, a study assessing the measurement of waist circumference as part of diagnostic criteria of metabolic syndrome was subject to significant inter-operator variability which the authors reported may potentially lead to misclassifying patients. Variability was minimised through standardised and consistent training of health professionals on how best to measure waist circumference. [19] Another study evaluating assays to detect antibodies of the Hepatitis C virus found that a lower level of agreement between operators performing a particular assay was a result of the assay being operated by both less experienced users and more knowledgeable laboratory medical technologists with the latter group more likely to interpret results correctly. [20]

Therefore, prior to undertaking this evaluation, the researcher (ML) liaised with key personnel at the LNCM to gain an understanding of local approaches to training on new laboratory tests. This learning informed the outlining of the ADT training programme and production of the test manual. The researcher (ML) then delivered a training programme consisting of a test demonstration, followed by an opportunity for the technicians to carry out the test under observation on ADs (provided by the LNCM) with feedback from the researcher. This training was not part of the evaluation and was conducted prior to the formal commencement of the study.

Two FGDs were held with participants one before and one after the laboratory testing of samples using the two screening tests. The FGD guides (see annex 8 and 9) were designed on the basis of themes relating to the practical utility of both screening tests and the usefulness and acceptability of the ADT. The first FGD assessed the perceptions of MiniLab® technology. The second FGD focussed on the participant experience of using the ADT alongside the MiniLab® test under operational conditions. Overall findings from the evaluation of the practical utility of the ADT and evaluation of performance of the two screening assays were shared prior to commencement of the second FGD. Where appropriate, responses garnered from questionnaires completed by technicians after the each of the two exercises undertaken as part of the evaluation of the practical utility of the ADT, were used as points of discussion for the second FGD. A research assistant facilitated the FGDs in French and also assisted with completion of questionnaires. The FGDs were audio-recorded, then transcribed verbatim in French before being translated into English.

1. Assessment of the practical utility of the artemisinin derivative test

The participants undertook two practical laboratory based exercises and completed a questionnaire after each exercise.

Exercise 1: Test procedure

This exercise aimed to assess the ability of each of the technicians to adhere to the test procedure. The first four steps of the test described previously in this chapter were assessed. This exercise did not evaluate step 5 of the test procedure - interpretation of the resultant colour reaction, or decision made following each of the test results. Each technician performed the ADT using a sub-set of ACT samples (n=10) comprising artemether-lumefantrine (AL) and artesunate-amodiaquine (AS-AQ) as these were the most commonly used ACTs in Senegal at the time of the fieldwork. Technicians were provided with all necessary equipment for the test,

the samples of ACTs, the manual (including the colour chart), and bench aid outlining the test procedure. They were assessed on their proficiency in conducting the test based on the procedure listed in the manual. A checklist of 16 actions (table 5.2) was created to gauge their ability to adhere to the test procedure. Each action was marked with a tick to indicate when it was carried out correctly, incorrectly or omitted.

Table 5.2: Checklist of actions for assessing the adherence to ADT procedures

Test procedure action	Description
1	Sample preparation (1); pulverise and dissolve in 10 ml of methanol
2	Sample preparation (2): Sonicate for appropriate length of time (approx. 5 minutes) depending on pulverisation
3	Sample preparation (3): Appropriate tablet breakdown/sedimentation and use of centrifuge if required
4	Sample preparation (4): Appropriate labelling of sample (vial or Eppendorf tube)
5	TLC preparation (1): Draw square or circular shapes roughly $1cm^2$ or 1cm in diameter
6	TLC preparation (2): Correct labelling of squares/circles
7	Spotting (1): Drawing up of supernatant
8	Spotting (2): Correct spotting of methanol within square/circle (2x5µl) (volume)
9	Spotting (3): Correct spotting of tab within square/circle (2x5µl) (volume)
10	Spotting (4): Correct spotting of DNP to within square/circle (1x5µl) (volume)
11	Spotting (5): Correct spotting of FBS to within square/circle (1x5µl) (volume)
12	Development (1): Correct storage of plate away from sunlight
13	Development (2): Plate read after 40 minutes
14	Development (3): Appearance of plate after testing and development
15	Additional steps (1): Pipette replaced after spotting of each methanol/sample
16	Additional steps (1): Pipette replaced after spotting of DNP

A questionnaire (annex 6) on initial perceptions of the ease of use of the test was given to each technician to complete after step 4 (the colour development). The questionnaire included a 1-5 scale to rate specific aspects of the assays such as the ease of carrying out each action as well as broader open and closed questions relating to their overall perceptions of the test e.g. difficulties encountered with the assays and aspects of the test that they favoured.

Each participant consecutively undertook the assessment conducting the test following the instructions outlined in the manual. For each sample tested, the researcher observed and recorded whether each of the 16 actions was performed correctly, scored as 1= action performed correctly or 0= action incorrect or omitted. For each technician, a total score out 10 (representing the total number of samples tested) was assigned for each of the 16 steps

(maximum score 160). Any incorrect or omitted action at an early stage in the testing process would be expected to have an impact on the latter steps of the procedure i.e. result and interpreting the result of the colour produced for each assay.

Technicians scored lowest on actions 4 and 6 which involved the labelling of sample vials and the test card (TLC plate) (see bar graph and annex 5). Overall, 50% and 37.5% of technicians either omitted or performed actions 4 and 6 incorrectly. There were no obvious reasons for this issue to arise when explored during the FGDs. Scores ranged from 120 (technician 2) to 158 (technicians 4 & 6) with an average technician score of 143 (calculated from totalling all technician scores and dividing by number of technicians (n=8)). Time to completion for all 10 samples ranged from 33 mins to 90 minutes. The average length of time to complete the tests (not including the time taken for the colours to develop) was 58.5 minutes (around 6 minutes per sample). Technician 6 had been in post at the LNCM for 16 years. Technician 4 had the most advanced academic qualifications with a Master's degree in Analytical Chemistry from UCAD.

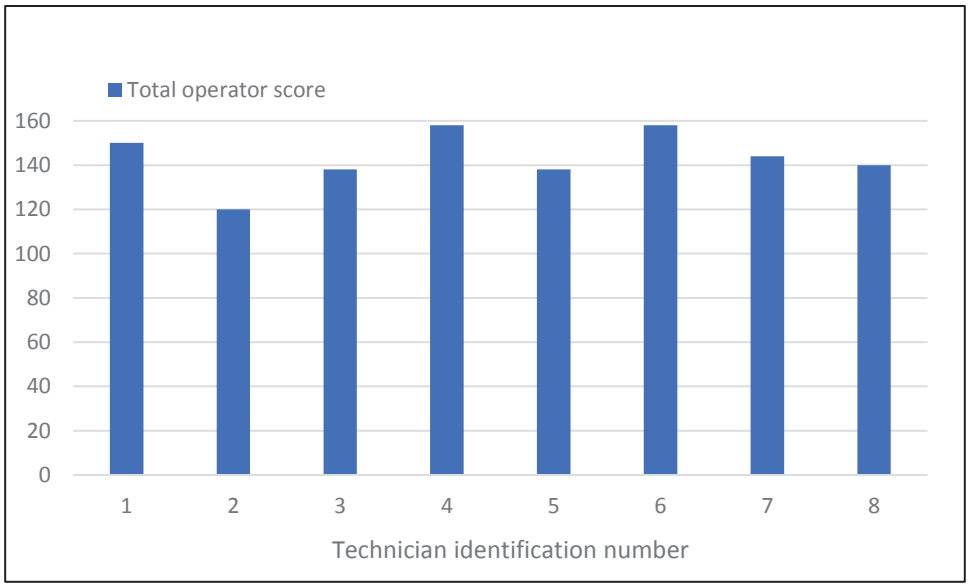


Figure 5.4: Bar graph representing total score for each technician for adherence to test procedure

The questionnaire administered to each technician after the exercise requested a rating of 1-5 (1= very difficult to use, 5 = very easy to use) of various aspects of the test procedure. The results suggested that overall the test procedure was simple to follow, illustrated by the average rating of 5 which was assigned to several aspects of the test including content of the training manual, the bench aids, preparation of sample and TLC plate, spotting of solution/reagents and the development of test results. The technicians were also encouraged by the negligible risk of reagent toxicity, as a result of using minute volumes.

'It is a rapid test, the interpretation is easy, it does not necessitate many toxic solvents, and with good organization it can be done very easily. I do not need to be a laboratory person to use it.' Technician

A few technicians suggested the time taken for results to develop as a limitation of the test. The appearance of the pink and blue colour indicating the presence of an AD may take up to 40 minutes. The technicians mentioned that after around 40 minutes both blue and pink colours had appeared but to view the true depths of colours took a few hours. Nonetheless, they suggested a longer development time was offset by a swift preparation time.

Exercise 2: Results Interpretation

This exercise focussed on step 5 of the test and aimed to establish the extent to which each technician correctly interpreted results from the ADT and their resulting decision in sending a sample for confirmatory testing. For this exercise each technician was provided with a pre-prepared standardised set of results i.e. images from colours produced by AD samples following testing by the ADT. Hence, all technicians examined the same set of results.

To aid in the interpretation of the test results, technicians were requested to refer to the colour chart included in the ADT manual. An extract from the chart is presented in figure 5.5 below.

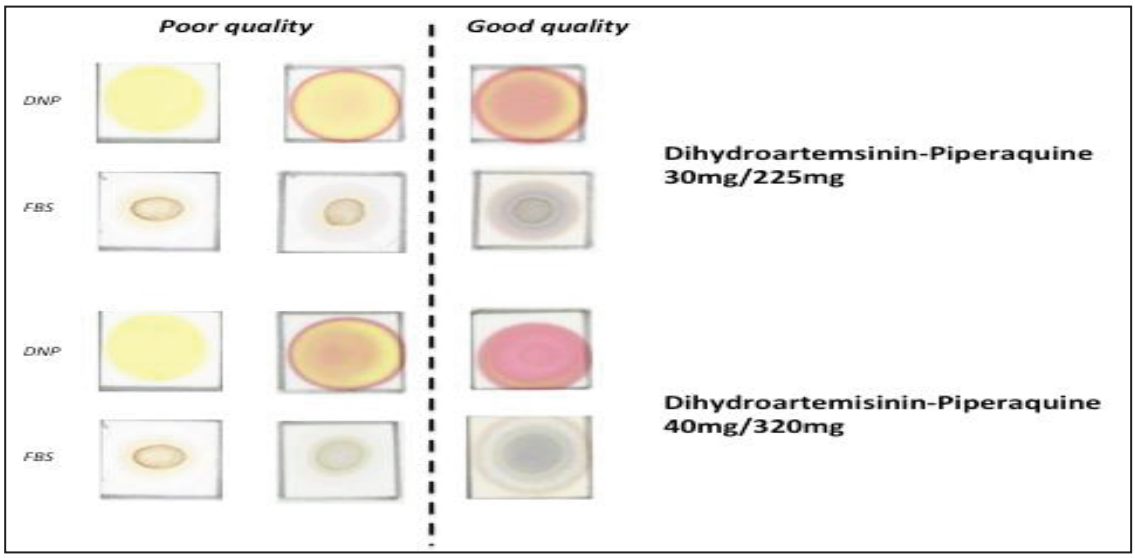


Figure 5.5: Extract from colour chart showing dihydroartemisinin-piperaquine included as part of the ADT manual. Poor quality samples produce pale pink or pale blue/grey colours (some SAPI) or there is an absence of those colours (absence of SAPI).

The technicians were requested to interpret the colours produced following the testing of ACTs at LSHTM. The colours from samples included in this exercise were selected purposively,

to include acceptable pharmacopeial quality and poor quality ACTs containing artemether, artesunate and dihydroartemisinin. The ACTs used for this exercise had all been previously tested at LSHTM using HPLC-PDA and were of acceptable pharmacopeial quality. The poor quality samples were created by Dr Kaur at LSHTM by diluting acceptable pharmacopeial quality ADs to create samples with some API (pale pink and blue colours) and methanol alone to create samples with zero SAPI. The resulting colours were subsequently photographed, and the images provided to the technicians for interpretation. The approach used in this exercise is similar to that used for evaluating the interpretation of results by operators for rapid diagnostic tests (RDTs) for detecting malaria parasites, whereby participants are blinded to the identity of the samples and only provided with the results. [21]

Participants were requested to record their results including whether the colour produced represented (i) an acceptable pharmacopeial quality AD or (ii) poor quality AD that should be sent for confirmatory testing (by pharmacopeia methods). Furthermore, technicians were requested to state on the recording sheet for each of the ten colours a level of confidence between 1 (no confidence) – 5 (very confident) in their decision to send the sample for confirmatory testing (or not). A questionnaire (annex 7) on initial perceptions of the ease of interpretation of test was provided after the exercise. The questionnaire included a 1-5 scale for technicians to rate specific aspects of step 5 of the test (results interpretation) e.g. clarity of colours (images), ease of categorisation (acceptable/poor quality) etc. Broader open and closed questions were also included and related to their overall perceptions of interpreting results such as which colour they preferred to interpret and the extent in their confidence of making a decision in sending a sample for confirmatory testing (or not).

The proportion of correct answers (see table 5.3) ranged from 37.5% (3/8 technicians) for colours 7 and 9 (poor quality ACT, some API) to 100% for colours 1 and 8 (acceptable pharmacopeial quality ACT). Furthermore, the mean confidence ranged from 4.0 (colour 5, acceptable pharmacopeial quality ACT) to 4.9 (colours 1 & 8, acceptable pharmacopeial quality ACT). Of the five colours (1, 3, 5, 8 and 10) representing acceptable pharmacopeial quality samples of ACTs, only two colours (1 & 8) were correctly identified by all technicians. The mean confidence of 4.9 for each of these colours indicated that the technicians had a high level of confidence in their decision to not send the sample for confirmatory testing. The remaining five colours of ACT samples (2, 4, 6, 7 and 9) represented poor quality samples. Colours 2 and 6 (zero SAPI) were correctly identified by 62.5% and 75% of technicians. Of the poor quality (some API) colours, two colours (7 & 9) received the lowest proportion of correct answers (37.5%) as these were misinterpreted as acceptable pharmacopeial quality. These

colours were obtained from quality assured ACTs that were intentionally diluted to contain some API, hence pale colours (blue and pink). The mean confidence for each these colours was 4.1 indicating that some of the technicians were less confident in their decision to send the sample for confirmatory testing or not. The lowest confidence mean was for image 5, an acceptable pharmacopeial quality ACT, yet only one technician incorrectly identified this sample as poor quality.

Technician 1 correctly identified each sample whereas technicians 3 and 5 only managed to achieve scores of 4/10 (40%). Overall, the average score for all technicians was 55% (5.5/10), suggesting the result interpretation of the ADT (step 5) is less straightforward than undertaking the preparation of the sample (steps 1-4).

Table 5.3: Summary of results from results interpretation exercise
Blue colours are produced from samples tested using FBS (3, 7, and 10). Pink colours are produced from samples tested using DNP (1, 4, 5, 8, 9). Deep blue and pink colours represent acceptable pharmacopeial quality (APQ) drugs. The pale pink and blue colours represent poor quality samples (with some SAPI). The absence of colour produced in no. 2 and 6 show that they do not contain any SAPI and are falsified. (** Mean Confidence obtained from average of individual confidence scores (out of a maximum total of 5) from each technician as follows: for each colour (sample) the confidence scores provided by each technician were totalled and then divided by the number of technicians (n=8).)

Colour number	1	2	3	4	5	6	7	8	9	10
Quality of ACT sample and colour produced	APQ 	Poor quality (zero SAPI) 	APQ 	Poor quality (some SAPI) 	APQ 	Poor quality (zero SAPI) 	Poor quality (some SAPI) 	APQ 	Poor quality (some SAPI) 	APQ 
Send for confirmatory testing	No	Yes	No	Yes	No	Yes	Yes	No	Yes	No
Proportion of technicians correctly identifying colour (%)	100 (8/8)	62.5 (5/8)	75 (6/8)	62.5 (5/8)	87.5 (7/8)	75 (6/8)	37.5 (3/8)	100 (8/8)	37.5 (3/8)	75 (6/8)
Mean Confidence **	4.9	4.9	4.8	4.5	4	4.6	4.1	4.9	4.1	4.4

Results from the questionnaire showed that the average rating on different aspects of results interpretation (step 5 of the test) were quite high overall (4/5 or 5/5 for all aspects) despite quite low scores achieved by some of the technicians. Overall the results showed a propensity for some technicians to incorrectly classify colours from samples of poor quality ACTs with some API (that would be regarded as substandard medicines) as acceptable pharmacopeial quality and worryingly high levels of confidence, even in the incorrect decisions made. This

inconsistency between perception and actual results from using the test was best exemplified by a finding from the questionnaire responses which showed an average rating of 5 for 'overall confidence in decisions made.' The free text responses from the questionnaire suggested that most 'preferred' the pink colour as it was more discernible than the blue.

Responses from the FGDs suggested that the technicians thought that the acceptable pharmacopeial quality colours were easily identified. All stated they were less certain about the pale pink or blue colours (4, 7 & 9, with some API) as this caused confusion as to whether to classify them as acceptable pharmacopeial quality or poor quality and hence, whether to send for confirmatory testing. The average score of acceptable pharmacopeial quality samples was much higher than the poor quality samples, 87.5% compared to 45.8%. Indeed, one technician suggested that given the uncertainty over the depth of colours, the test specificity and sensitivity needed to be established for when the 'KIT' of the test is formatted. Another technician also highlighted that samples with more API (exceeding pharmacopeia tolerance limits) would also be substandard and that these would not be identified by the test as the colour maybe very deep and assumed to be of acceptable quality. Moreover, some felt that due to the variation in both colours in terms of depth it would be difficult to quantify the API in a sample. One suggested that an acceptable pharmacopeial quality sample could be validated by providing a colour chart with colours representing an API of between 80% and 100%. Another technician felt that the creation of a more comprehensive colour chart with all the reference standards for commercially available ARDs would simplify interpretation.

> *'We cannot quantify the active ingredient in a sample based on the image. The image shows us if the active drug is there or not, nothing else. The deeper it is the better quality of drug but it is difficult to be accurate.'* Technician

Further insights from focus group discussions on the acceptability and usefulness of the ADT

Technicians believed the test would be very useful for the MQSS in light of obtaining a visual result in the form of easily identifiable colours. It was suggested that the test could be used by drug inspectors to perform spot checks or follow up reports of poor quality medicines, or at the point of care where a treatment provider at a health facility level doubted the quality of an ACT. The technicians acknowledged that despite the test's merits (rapid sample preparation, ease of use etc.) ultimately, its use in Senegal would be determined by their superiors but it's relatively low material cost and portability may appeal to the Ministry of Health (MoH). With respect to usefulness and acceptability of the test, no limitations were identified.

'In the regional hospitals, we have treated patients with artemether lumefantrine and in 5 or 10 we did not see any improvement. If we had this test we can immediately contact the regional inspector who can come and do this test rapidly and take a decision. I think this test is for that, an urgent case.' Technician

2. Evaluation of the performance of the artemisinin derivative test and the MiniLab® TLC test

Samples of ADs (comprising dihydroartemisinin as monotherapy and as part of various ACTs, including artemether-lumefantrine and artesunate-amodiaquine) collected in Senegal through routine medicine quality surveys were tested by each method: ADT and MiniLab® TLC test. At the time of the study in 2014, artemether-lumefantrine and artesunate-amodiaquine were first-line medicines for the treatment of uncomplicated *P.falciparum* malaria in Senegal. [22] Furthermore, ACTs had been adopted as first-line treatment by 14 countries in West Africa.[23] The testing of the samples was carried out by each laboratory technician participating in the evaluation (20 samples tested by each screening test, n=40). The performance of each test when carried out by local technicians under the environmental conditions typically found in LIMCs, was evaluated. Technicians were provided with samples of acceptable pharmacopeial quality and poor quality ADs to reflect a possible broad spectrum of the artemisinin based formulations available in Senegal. Acceptable pharmacopeial quality ADs provided by the LNCM were diluted by ML and the LNCM laboratory manager to create poor quality samples with some API. This was necessary as no substandard or falsified ADs were available at the LNCM for testing. The samples provided comprised AD tablets crushed and dissolved in methanol. This is the preliminary step in test procedures for ADs when using both the MiniLab® and the ADT.

To reduce response bias, the technicians were blinded to the identity of the samples by labelling sample bottles 1-20 for the ADT and samples labelled as 21-40 for the MiniLab® (see table 5.4 and 5.5 below). To enable the technicians to carry out the appropriate test procedure for the ADs with the MiniLab® (which differs slightly depending on the AD) for each sample, they were provided with the name of the medicine and dosage e.g. artemether-lumefantrine 20mg. No information on the quality of the sample was provided. The samples provided contained ADs of varying available dosages. Overall, 5/20 samples were diluted to create poor quality medicines with some SAPI (10% and 40%). Paracetamol (white tablet) and amodiaquine (yellow tablet) were selected to represent dihydroartemisinin (white tablet) and artesunate-amodiaquine (yellow tablet, due to the yellow amodiaquine component). These negative non-AD controls represented the falsified (zero SAPI) ADs. They were labelled as dihydroartemisinin

40mg (n=1) and artesunate-amodiaquine 50mg (n=2) so as to blind the technicians to their actual identity.

Participants were encouraged to follow the procedures outlined in the ADT manual. Use of the MiniLab® manual was optional as all participants were familiar with the outlined procedures. The evaluation of the performance of the two screening methods was undertaken separately. First, the technicians undertook testing of the samples using the ADT. Once this was completed they tested samples using the MiniLab®. Observation of adherence to test procedures was not undertaken for either test. In terms of classifying the results, the participants were asked to make a dichotomous decision; pass or fail for the MiniLab® (based on the 80% pass mark from TLC) and whether they would send a sample for confirmatory analysis (or not), for the ADT (further testing was unnecessary for the ADT if the appropriate depth colour was observed).

Results from Performance of ADT

All samples containing zero SAPI ((1, 6 and 17) poor quality representing a falsified medicine) were correctly identified by all the technicians and sent for confirmatory testing. Only half of the samples of acceptable pharmacopeial quality ADs (6/12) that contained the correct SAPI (samples 2, 5, 13, 15, 16, 18), were correctly identified by all technicians as not requiring confirmatory testing (table 5.4). The samples that contained some SAPI (with pale pink or blue colour) were less likely to be correctly allocated, a challenge highlighted by many technicians in the result interpretation exercise. Of the five 'some SAPI' samples, only sample 12 of AL 20mg (containing 10% SAPI) was correctly allocated as requiring further testing by all technicians. The three samples with 40% SAPI were the least likely to be classified correctly; sample 8 (25% of technicians), sample 10 (37.5%) and sample 14 (12.5%). These 'some SAPI' samples were more frequently misclassified as acceptable pharmacopeial quality, not needing to be sent for further investigation.

Technicians were also requested to provide a level of confidence (1= low confidence, 5= high confidence) in whether they were making the correct decision to send the sample for confirmatory testing (or not). The highest mean confidence of 5.0 was for each of samples 1, 4, 15, 18 & 20. Sample 1 was amodiaquine (zero SAPI) and the other samples (4,5, 18 & 20) were of acceptable pharmacopeial quality ADs. The lowest confidence mean was 4.3 for each of samples 3 & 8, both of which were poor quality (some SAPI) artesunate-amodiaquine. Of interest, the lowest scoring sample (14 - only correctly allocated by one technician) had a relatively high confidence mean of 4.9 suggesting that technicians had a high level of confidence in their incorrect decision.

Table 5.4: Summary of results from test performance of the ADT
Proportion (%) represents responses correctly categorised by sample e.g. 37.5% indicates only 3 out of 8 technicians recorded the correct response. The mean confidence was obtained from the average of individual confidence scores out of a total of 5 from each technician as follows: for each colour (sample) the confidence scores provided by each technician were totalled and then divided by the number of technicians (n=8). APQ = acceptable pharmacopeial quality

Sample No.	Sample provided for screening (n=20)		Correct classification		Proportion of samples classified correctly (%)	Mean confidence
	AD type and dosage	SAPI	Quality	Confirmatory testing required		
1	Amodiaquine	No AD	Poor quality	Yes	100 (8/8)	5.0
2	Artemether-Lumefantrine 20mg	Correct SAPI	APQ	No	100 (8/8)	4.9
3	Artesunate-Amodiaquine 50mg	10% SAPI (diluted)	Poor quality	Yes	62.5 (5/8)	4.3
4	Artemether-Lumefantrine 20mg	Correct SAPI	APQ	No	87.5 (7/8)	5.0
5	Artesunate-Amodiaquine 100mg	Correct SAPI	APQ	No	100 (8/8)	4.9
6	Amodiaquine	No AD	Poor quality	Yes	100 (8/8)	4.8
7	Artemether-Lumefantrine 20mg	Correct SAPI	APQ	No	75 (6/8)	4.4
8	Artesunate-Amodiaquine 50mg	40% SAPI (diluted)	Poor quality	Yes	25 (2/8)	4.3
9	Artemether-Lumefantrine 20mg	Correct SAPI	APQ	No	50 (4/8)	4.9
10	Dihydroartemisinin 40mg	40% SAPI (diluted)	Poor quality	Yes	37.5 (3/8)	4.5
11	Artesunate-Amodiaquine 50mg	Correct SAPI	APQ	No	75 (6/8)	4.5
12	Artemether-Lumefantrine 20mg	10% SAPI (diluted)	Poor quality	Yes	100 (8/8)	4.5
13	Artemether-Lumefantrine 80mg	Correct SAPI	APQ	No	100 (8/8)	4.9
14	Artemether-Lumefantrine 80mg	40% SAPI (diluted)	Poor quality	Yes	12.5 (1/8)	4.9
15	Artesunate-Amodiaquine 100mg	Correct SAPI	APQ	No	100 (8/8)	5.0
16	Dihydroartemisinin 40mg	Correct SAPI	APQ	No	100 (8/8)	4.9
17	Paracetamol	No AD	Poor quality	Yes	100 (8/8)	4.9
18	Dihydroartemisinin 40mg	Correct SAPI	APQ	No	100 (8/8)	5.0
19	Artesunate-Amodiaquine 50mg	Correct SAPI	APQ	No	62.5 (5/8)	4.8
20	Artemether-Lumefantrine 20mg	Correct SAPI	APQ	No	87.5 (7/8)	5.0
					Overall mean = 78.8%	Overall mean= 4.8

Performance of the GPHF MiniLab®

Of the 12 samples of acceptable quality, seven (22, 23, 25, 26, 30, 36, 37) were correctly identified and categorised as a pass (table 5.5) by all technicians. Of the three samples (24, 35, 40) that contained zero SAPI only one individual technician incorrectly allocated sample 35, the remainder were correctly categorised. Poor quality samples that contained some SAPI were often allocated incorrectly. Indeed, only sample 38 (artesunate-amodiaquine 50mg, 10% SAPI) was correctly allocated as a fail by all technicians. The remaining samples were incorrectly allocated as being of acceptable pharmacopeial quality and hence passed (confirmatory testing not required); sample 27 (50% of technicians), sample 29 (75%), sample 31 (37.5%) and sample

33 (75%). The lowest score was for sample 31 of dihydroartemisinin which contained 40% SAPI (poor quality).

Samples 22, 26 & 36 were all acceptable pharmacopeial quality and each had the highest mean confidence of 5.0. The lowest confidence mean (4.0) was for sample 31 (dihydroartemisinin 40mg with 40% SAPI) which also had the lowest score in terms of correct classification as a 'fail.'

Table 5.5: Summary of results from test performance of the GPHF MiniLab®

Sample No.	Sample provided for screening (n=20)		Correct classification		Proportion of samples classified correctly (%)	Mean confidence
	AD type and dosage	SAPI	Quality	Pass/Fail		
21	Artemether-Lumefantrine 20mg	Correct SAPI	APQ	Pass	75	4.9
22	Artesunate-Amodiaquine 50mg	Correct SAPI	APQ	Pass	100	5.0
23	Dihydroartemisinin 40mg	Correct SAPI	APQ	Pass	100	4.6
24	Paracetamol	No AD	Poor quality	Fail	100	4.5
25	Dihydroartemisinin 40mg	Correct SAPI	APQ	Pass	100	4.6
26	Artesunate-Amodiaquine 100mg	Correct SAPI	APQ	Pass	100	5.0
27	Artemether-Lumefantrine 80mg	40% SAPI (diluted)	Poor quality	Fail	50	4.5
28	Artemether-Lumefantrine 80mg	Correct SAPI	APQ	Pass	87.5	4.9
29	Artemether-Lumefantrine 20mg	10% SAPI (diluted)	Poor quality	Fail	75	4.4
30	Artesunate-Amodiaquine 50mg	Correct SAPI	APQ	Pass	100	4.8
31	Dihydroartemisinin 40mg	40% SAPI (diluted)	Poor quality	Fail	37.5	4.0
32	Artemether-Lumefantrine 20mg	Correct SAPI	APQ	Pass	87.5	4.6
33	Artesunate-Amodiaquine 50mg	40% SAPI (diluted)	Poor quality	Fail	75	4.6
34	Artemether-Lumefantrine 20mg	Correct SAPI	APQ	Pass	87.5	4.8
35	Amodiaquine	No AD	Poor quality	Fail	87.5	4.5
36	Artesunate-Amodiaquine 100mg	Correct SAPI	APQ	Pass	100	5.0
37	Artemether-Lumefantrine 20mg	Correct SAPI	APQ	Pass	100	4.9
38	Artesunate-Amodiaquine 50mg	10% SAPI (diluted)	Poor quality	Fail	100	4.8
39	Artemether-Lumefantrine 20mg	Correct SAPI	APQ	Pass	62.5	4.9
40	Amodiaquine	No AD	Poor quality	Fail	100	4.5
					Overall mean = 86.3%	Overall mean= 4.7

Comparison of performance of both screening tests

The average proportion of responses correctly categorised for each sample is slightly higher for the MiniLab® than the ADT (table 5.6) which may be attributable to the differing level of experience of using the two technologies. Prior to this exercise the technicians used the ADT on just two occasions yet they had an average of 5 years of experience of using the MiniLab®. Despite greater familiarity with the MiniLab® there was marginally less confidence in the results obtained with it than with the ADT.

The average proportion of correctly allocated responses for acceptable pharmacopeial quality SAPI was slightly higher for the MiniLab®, although for both tests, proportions were quite low overall for the 'some SAPI' samples. The ADT showed marginal advantage over the MiniLab® in allocating poor quality ARDs (zero SAPI) for confirmatory testing. Generally, for both tests, technicians appear to be more confident in detecting samples of acceptable pharmacopeial quality as opposed to samples of poor quality (both some and zero SAPI).

Table 5.6: Results summarised by quality of AD for both screening tests
(The results presented here were not subject to statistical testing due to a small sample size)

Quality of sample	Acceptable pharmacopeial quality		Poor quality (some SAPI)		Poor quality (zero SAPI)		Overall performance	
Screening Test	GPHF MiniLab®	ADT	GPHF MiniLab®	ADT	GPHF MiniLab®	ADT	GPHF MiniLab®	ADT
Average proportion of responses correctly catergorised by sample (%)	91.7	86.4	67.5	47.5	95.8	100	86.3	78.8
Confidence mean	4.8	4.8	4.4	4.9	4.5	4.5	4.7	4.8

Practical utility of the MiniLab® - operator error

Overall, the findings suggested a high level of confidence in the results obtained when using the MiniLab® even when these decisions were incorrect. Nonetheless, the notion of operator error was a prominent emerging theme from the FGDs with technicians believing that the MiniLab® was at higher risk of error at two stages of the testing process. Firstly, sample preparation consists of several steps, and technicians mentioned that a lack of adherence to test procedures might lead to erroneous results. Secondly, some technicians believed that a sample could be misclassified as a 'pass' when it was in fact doubtful or a 'fail' (and vice versa)

because the test operator had misinterpreted the result. This was shown to be the case in this study with some of the 40% SAPI samples allocated incorrectly as a pass and hence deemed to be of acceptable quality. MiniLab® TLC instructions for all ADs are quite specific and state that spots from reference standards and the sample must correspond in terms of size, intensity, shape and distance travelled. This aspect of the test relies upon the subjective judgement of the operator and the technicians suggested that this could potentially lead to misclassification error and be the most common reason for any inter-operator variability.

Technicians stated that the colorimetric basis of the ADT made it easier to interpret the results. Identification of the correct colour to indicate the presence of an ART may reduce the risk of misclassification error. That said, test performance results in this study were to the contrary and the 'some SAPI (poor quality) samples' were more often classified correctly by the MiniLab® than the ADT (67.5% vs 47.5%) which may have been due to the technician's greater experience of using the MiniLab®.

Sensitivity and specificity of the two tests

Sensitivity and specificity parameters were realised as key attributes of screening tests as stated in the introduction to this section. Indeed, in the context of medicine quality screening a test ought to be highly sensitive and produce minimal 'false passes' i.e. pass the lowest proportion of poor quality medicines as is possible. The comparison with the gold standard in table 5.7 refers to the samples being of acceptable pharmacopeial quality following analysis by HPLC at the LNCM.

Table 5.7: Sensitivity and specificity of the GPHF MiniLab® and the ADT

	Gold Standard (HPLC)		
GPHF MiniLab®- pass or fail	***Pass***	***Fail***	***Total***
Pass	**88 (86.3%)**	8	96
Fail	14	**50 (86.2%)**	64
Total	102	58	160
ADT – send for confirmatory testing	***Pass***	***Fail***	***Total***
No	**83 (81.3%)**	13	96
Yes	19	**45 (77.6%)**	64
Total	102	58	160

The MiniLab® demonstrated a sensitivity of 86.3% (95% Cl, 78.0 %, 92.3%) and a specificity of 86.2 (95% Cl, 74.6%, 93.9%). In comparison, the ADT sensitivity was 81.3% (95% Cl, 72.5%,

88.4%) and specificity 77.6% (95% CI, 64.7%, 87.5%). The results suggest the MiniLab® is marginally more accurate than the ADT. In light of these findings, it was reassuring that during the FGDs the technicians acknowledged the importance of pharmacopeia methods and not relying solely on results from screening tests.

Practical comparisons of the two tests

Technicians described some of the positive and negative aspects about the MiniLab®. They mentioned that that once familiarity with test procedures was acquired, the MiniLab® was quite simple to operate. Another suggested advantage of the MiniLab® was its capability to test a wide range of medicines.

There was debate regarding the amount of time taken to prepare and analyse samples, with some technicians suggesting the testing time was comparable between the two tests and others stating that the MiniLab® took up to 30 minutes longer (per sample). Overall the technicians thought the preparation phase of the MiniLab® was lengthy but the transition to the results phase was quite quick. Personal experience of the two tests corroborates the view of a lengthier testing time overall with the MiniLab®. Furthermore, overall, the evaluation of the performance of the ADT was completed by the technicians more quickly in comparison to the MiniLab® evaluation. The hazardous nature of some reagents, lack of portability and the need to use a development chamber and fume cupboard, were identified as limitations of the MiniLab®. These characteristics limit its suitability for use in peripheral laboratories that are less well-equipped and in field surveys. For ADs, the technicians felt that overall, the ADT was a more preferable test to use than the MiniLab® especially in non-laboratory settings as it was quicker (in sample preparation), simpler to use, potentially lower in cost, more portable (handheld), safer and easier to interpret its results.

5.3 Discussion

The key attributes of screening tests make them a potentially integral component of post-marketing surveillance activities. Given the large number of samples a screening test is likely to screen, it ought to be inexpensive to purchase and maintain, easy to use and portable (preferably handheld). [15, 24-27] Additionally, an ideal medicine quality screening test ought to be highly sensitive and produce minimal 'false' passes. Whilst the utilisation of screening tests as part of a MQSS is important, the accuracy of the results they provide must be better understood. All new tests that are developed must to be evaluated against confirmatory

methods as well as the most utilised screening test such as the MiniLab® to identify their relative merits and drawbacks in comparison with existing technologies.

This chapter presents a study that aimed to evaluate the practical utility of the ADT as well as perceptions of its usefulness and acceptability following 'field' testing in an LMIC. It evaluated the performance of the test by a small sample of first time users with no prior familiarity, in its intended LMIC setting within the specific context of use by laboratory technicians in the national MQCL in Senegal, who are routinely engaged in medicine quality surveillance. In initial product testing under controlled laboratory conditions at LSHTM, the ADT was shown to specifically detect ADs (in monotherapy and combination treatments) producing distinct pink and blue colours. [15] In comparison, the MiniLab® produces generic spots for the ADs that lack a characteristic colour. The study findings suggest the laboratory technicians found it to be marginally easier to distinguish a poor quality sample with zero SAPI (absence of colour), with the ADT than with the MiniLab®. In contrast, the MiniLab® was slightly superior in detecting acceptable pharmacopeial quality AD samples.

Furthermore, the MiniLab® was also shown to be somewhat superior in detecting the 'some SAPI' samples i.e. less likely than the ADT to classify them incorrectly as acceptable pharmacopeial quality samples. The reason for this may partly be attributed to the previous experience of using the MiniLab® by the technicians, who did report some confusion in appreciating the resulting colour from the ADT. This may explain the slightly inferior sensitivity and specificity of the ADT (81.4% and 77.6%) in epidemiological terms compared to the MiniLab® (86.3% and 86.2%). The MiniLab® has previously been reported to overestimate (false passes) [28, 29] and underestimate the quality of a medicine (false fails) [28] and is thought to be ''only capable of detecting counterfeit (zero SAPI) or grossly substandard (very low SAPI) medicines.'' [7] This was also found in this study as the three samples with some SAPI (40%) scored an average of 52.4% in terms of their correct classification. This average score was even lower for the ADT at just 25%. The detection of medicines containing the correct active ingredients, but at sub-therapeutic concentrations, thus remains a challenge for assessing medicine quality using screening tests in general.

Hence, these findings confirm that TLC chromatographic screening tests can detect acceptable quality, very poor quality (with very low SAPI) and medicines with zero SAPI the majority of the time but risk allowing medicines with some SAPI (between 40% and 80 % SAPI) to 'pass' meaning that substandard medicines [30] may continue to circulate in a country. The impact of substandard antimalarials has been purported as detrimental to public health due to

inadequate treatment of infection, resulting in recrudescence with the risk of progression to severe disease. This in turn increases the burden on already strained health systems, wasting valuable financial and human resource. [9] Neither screening test can give definitive results on the amount of SAPI in a sample, and both are also at risk of operator error due to their reliance upon a subjective judgement which may lead to misclassification of medicines with some API as acceptable quality, when they are in fact substandard. This suggests that the fallibility of these screening tests may be a risk factor for the persistence of substandard medicines in a country. This is particularly concerning in light of recent findings of a higher prevalence of substandard as opposed to falsified antimalarial medicines detected using confirmatory tests.[31-33]

Operator error has been documented as a problem in the diagnosis of infectious diseases using RDTs. In the case of HIV, RDT over interpretation by test users who viewed a weak reactive test as a HIV positive result led to misdiagnosis in some cases. [34] An apparent low specificity of some malaria RDTs has been attributed to misinterpretation of results by operators leading to a higher number of false positive results whereby individuals without malaria are thought to have infection and hence are inappropriately treated. [35] Additionally, in both these studies a lack of adherence to the test methodology was cited as a potential reason for error. Strict adherence to test instructions is vital when using point of care tests. [36] In our study, the MiniLab® procedures carried out by the technicians were not observed. Observation of the ADT procedure in exercise 1 found that only one technician failed to adhere correctly to the procedure and in that instance the test did not work. Technician's also citied inter-operator variability as a risk factor for erroneous results with the MiniLab®. A kappa value for inter-operator variability could not be calculated due to multiple operators. Even so, the data suggests that variability does exist in this sample of technicians although it is difficult to associate with the personal characteristics of the technician.

However, the issues highlighted here concerning operator error may be because of a key limitation of both tests, the need for a subjective judgement; on the intensity of a colour reaction for the ADT and an assessment of the distance travelled by the spot on the TLC plate or the variation in its shape, size etc. for the MiniLab®. Moreover, the vagueness of results as identified by the technicians from the 'some API' samples (substandard) in this study for both tests led to some of these samples being misclassified as acceptable quality. The findings from this study further demonstrate the need for caution when interpreting results from these two screening tests with any doubt about the quality of a medicine sample resulting in its referral for confirmatory testing.

My research also found that the MiniLab® and the ADT have similar attributes, yet they are quite different in terms of foreseeable roles within a MQSS. The former has been reported as a feasible technology for use outside of the laboratory [11] which is contrary to personal experience and to the findings from the FGDs in this study. The use of hazardous reagents, the need for essential but less portable equipment (with a total weight of 40 kg, bottles of reagents and storage jars), the requirement to undergo training as well as some prior experience of laboratory work suggest that this technology is best utilised in a laboratory environment. The MiniLab® also comes with a supply of solvents that need to be stored in a cool dry place. The ADT due to its ease of use, just two reagents and equipment (pipette and TLC sheet) has the potential to be formatted into an almost pocket-sized kit, which will enable its application in peripheral regional laboratories that lack technical equipment or regular power supply or for use by laboratory technicians in field surveys. They could also be used at the point of care in health care facilities and deployed when a treatment provider suspects a poor quality AD. At the point of entry (land borders or road checkpoints), the ADT could simply be utilised to implement spot checks of ADs for their quality. However, the MiniLab® is capable of screening the quality of around 85 essential medicines whereas the ADT specifically detects ADs only.

An appraisal of the other currently available screening technologies is discussed in Section 2. It appears that the most of the new screening devices entering the market are quite similar to the ADT in their design principles; easy to use, handheld and in some cases inexpensive allowing the screening of a large volume of samples rapidly. They have also been designed to be used outside of laboratory settings with some such as the Counterfeit Detection Device (CD3+) being employed to check the quality of medicines at the point of entry into a country.[25] A key commonality amongst all new and existing screening devices is their capability in detecting very low SAPI or zero SAPI medicines (grossly substandard or falsified medicines), yet, their common weakness is the inability to detect ‘some SAPI’ (substandard) medicine. Moreover, there is a dearth of information on their accuracy in terms of their sensitivity and specificity [5] the former of which is crucial given their proposed use in non-laboratory settings and especially where confirmatory testing maybe absent.

5.3.1 Study limitations

The ADT has been designed to be used in both laboratory and non-laboratory settings, yet, in this study only laboratory technicians performed the test in the context of an adequately equipped national reference laboratory. Prior to being deployed more widely, the ADT will need to be formatted into a kit and piloted with individuals who have minimal recent

laboratory experience. It would also need to be evaluated to determine its feasibility, practicality and accuracy when used by those working in different sectors such as medicines regulation (drug inspectors), healthcare (treatment providers) and customs (border officials). Nonetheless, the ADT has been piloted by individuals who had no prior knowledge of this test and in a different context in terms of environment, language and prior training. In further product testing at LSHTM it was found that increasing humidity and temperature (replicating environmental conditions such as those in the tropics) slightly accelerated the development of the pink and blue colours. This was not observed in the laboratory in Dakar despite the room temperature being warmer and the air more humid. The environment in the laboratory in Dakar more closely represents that of other malaria-endemic LMICs. Even so, at the time of the study it was winter in Dakar and so it would be expected that future use of the test would be in conditions with higher temperatures and humidity than those experienced during this study.

The presence of the researcher (ML) at all times during the study may have skewed the perceptions of the technicians to a more favourable view of the ADT test and may account for a high level of confidence in interpretation of ADT test results. This is a form of social desirability bias [37] whereby an individual provides responses they perceive the researcher wants to hear or those that are socially and morally acceptable, although, for the second FGD (focus on perception of the ADT), the researcher (ML) was absent.

Routine practice in Senegal when using the MiniLab® is to repeat the screening of samples that fail or are of dubious quality. On repeat testing, if the sample 'fails' or if it is still considered to be of dubious quality it would be retested with the MiniLab® by a different operator. In the evaluation of the performance of both screening tests, technicians did not repeat the screening of samples that they identified as poor quality nor were the results subjected to verification by a second operator. It is concevible that had the technicians repeated tests on the samples that they identified as poor quality they may have changed their decesion as to whether they send the sample for confirmatory testing or not, potentially increasing the proportion of correct results obtained from using both tests.

An additional limitation in the evaluation of the two screening tests exercise, was that the techncians were provided with already solubilised samples. The process of crushing and dissolving a sample in an approriate solvent would normally be carried out by the technician. It is not known whether this may have affected the results.

5.4 Conclusion

The ADT is a potentially useful screening test in detecting acceptable, very poor quality or zero SAPI ADs, but its ability to identify substandard (between 40% and 80% API) ADs is limited. The ADT could be used in a malaria endemic country for proactive point of care testing and at the point of entry into a country for specifically testing ACTs. Their ease of use, potential low cost and handheld design may appeal to MoHs. It must also be emphasised that as with all screening tests, identified suspect medicines should be subjected to confirmatory testing based on pharmacopeia methods to confirm actual SAPI. Screening followed by confirmatory testing is an integral part of a national MQSS, as is the case in Senegal where all medicines collected as part of routine medicine sampling surveys are first tested by the MiniLab® and any failing or doubtful quality samples are then analysed by HPLC. Technical capacity in LMICs to perform confirmatory testing must be also strengthened and screening technologies should work in tandem with well-equipped national and peripheral laboratories to ensure that poor quality medicines can be swiftly detected, and valid findings passed on to the appropriate national and international authorities to take regulatory action.

5.5 Suggestions for formatting the artemisinin derivative test and the use of the GPHF MiniLab®

In order for the ADT to be used in a malaria endemic country as part of a MQSS a few improvements are required. These are listed below along with broader suggestions for consideration by MQSS' in all LMICs with regard to the MiniLab®.

- A more extensive colour chart for the ADT needs to be created with focus upon how an acceptable pharmacopeial quality AD colour appears following testing, to help reduce misclassification. There is also a requirement to clarify the instructions on sending a sample for confirmatory testing in that any doubts about depth of colour should result in a sample being sent for HPLC analysis. The suggestion of adding resulting colours for 80% and 100% as a comparator may help in this regard. Furthermore, the colour chart should contain the resulting colours for all commercially available AD reference standards and be updated on a regular basis. To assist operators of the test in the interpretation of results, the colour chart could be further sophisticated by exploring colour pixel technology which can detect the depth of colour.

- The ADT should be piloted in non-laboratory settings with individuals with little or no laboratory experience in order to assess its suitability for use by boarder officials, treatment providers, etc.
- The best use of the ADT maybe external to the traditional laboratory network of a MQSS and/or as part of the MiniLab® kit for the testing of ACTs only, for example when used for field surveys and post-marketing surveillance, for point-of-entry screening by land border customs officials, or to confirm medicine quality at point-of-care by treatment providers prior to supplying or selling ADs to patients.
- Although already widely used, the MiniLab® could also benefit from further evaluation alongside confirmatory testing using pharmacopeia methods to establish its true sensitivity and specificity and to determine how this varies between medicines, operators and contexts.
- Where feasible, regular retraining on the MiniLab®, even on an informal basis must take place with an emphasis on results interpretation. This could be coupled with observation of operators to ensure the test procedure is correctly adhered to.

5.6 References

1. Newton PN, Caillet C, Guerin PJ. A link between poor quality antimalarials and malaria drug resistance? *Expert Rev Anti Infect Ther*. 2016;14(6):531-3.
2. Holmes AH, Moore LS, Sundsfjord A, Steinbakk M, Regmi S, Karkey A. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet (London, England)*. 2016;387.
3. Tabernero P, Fernandez FM, Green M, Guerin PJ, Newton PN. Mind the gaps--the epidemiology of poor-quality anti-malarials in the malarious world--analysis of the WorldWide Antimalarial Resistance Network database. *Malaria journal*. 2014;13:139.
4. Assessment of medicines regulatory systems in sub-Saharan African countries: an overview of findings from 26 assessment reports Geneva, Switzerland: World Health Organization 2010. http://apps.who.int/medicinedocs/documents/s17577en/s17577en.pdf. [cited 12th May 2016]
5. Lalani M, Kitutu FE, Clarke SE, Kaur H. Anti-malarial medicine quality field studies and surveys: a systematic review of screening technologies used and reporting of findings. *Malaria journal*. 2017;16(1):197.
6. Hajjou M, Qin Y, Bradby S, Bempong D, Lukulay P. Assessment of the performance of a handheld Raman device for potential use as a screening tool in evaluating medicines quality. *J Pharm Biomed Anal*. 2013;74:47-55.
7. Risha PG, Msuya Z, Clark M, Johnson K, Ndomondo-Sigonda M, Layloff T. The use of Minilabs to improve the testing capacity of regulatory authorities in resource limited settings: Tanzanian experience. *Health Policy*. 2008;87(2):217-22.
8. Guidelines for Drug Sampling, USP DQI Drug Quality Monitoring Program. Use of the Basic Tests at the Peripheral Level. Rockville: United States Pharmacopeia 2006. http://pdf.usaid.gov/pdf_docs/PNADH150.pdf. [cited 20th Feburary 2017]
9. Newton PN, Green MD, Fernandez FM. Impact of poor-quality medicines in the 'developing' world. *Trends in Pharmacological Sciences*. 2010;31(3):99--101.
10. Ranieri N, Tabernero P, Green MD, Verbois L, Herrington J, Sampson E, et al. Evaluation of a new handheld instrument for the detection of counterfeit artesunate by visual fluorescence comparison. *The American journal of tropical medicine and hygiene*. 2014;91(5):920-4.
11. GPHF Minilab. Frankfurt, Germany: Global Pharma Health Fund 2012. www.gphf.org. [cited 25th April 2017]
12. Promoting the Quality of Medicines in Developing Countries (PQM). United States Pharmacopeia https://www.usp-pqm.org/. [cited 18th March 2018]
13. Guidelines to develop measures to combat "counterfeit" drugs. Geneva: World Health Organisation Medicines DoEDaO; 1999. http://whqlibdoc.who.int/hq/1999/WHO_EDM_QSM_99.1.pdf. [cited 20th February 2017]
14. Jahnke R. A Concise Quality Control Guide on Essential Drugs and other Medicines: Volume II on Thin Layer Chromatographic Tests. Frankfurt: Global Pharma Health Fund 2008 Contract No.: Volumes I-III. http://www.gphf.org/web/en/minilab/manuals.htm. [cited 7th March 2017]
15. Ioset JR, Kaur H. Simple field assays to check quality of current artemisinin-based antimalarial combination formulations. *PLoS One*. 2009;4(9):e7270.
16. Kaur H. Analysing the quality and authenticity of ACT drugs. London: ACT consortium 2015. http://www.actconsortium.org/projects/9/analysing-the-quality-and-authenticity-of-act-drugs. [cited 5th May 2017]
17. Survey of the Quality of Selected Antimalarial Medicines Circulating in Madagascar, Senegal, and Uganda. United States Pharmacopeia United States Pharmacopeia U;

2009 November 2009. Report No. http://apps.who.int/medicinedocs/documents/s17069e/s17069e.pdf. [cited 26th February 2017]
18. Bartlett J, Frost C. Reliability, repeatability and reproducibility: analysis of measurement errors in continuous variables. *Ultrasound in obstetrics & gynecology*. 2008;31(4):466-75.
19. Panoulas VF, Ahmad N, Fazal AA, Kassamali RH, Nightingale P, Kitas GD, et al. The inter-operator variability in measuring waist circumference and its potential impact on the diagnosis of the metabolic syndrome. *Postgrad Med J*. 2008;84(993):344-7.
20. Smith BD, Drobeniuc J, Jewett A, Branson BM, Garfein RS, Teshale E, et al. Evaluation of Three Rapid Screening Assays for Detection of Antibodies to Hepatitis C Virus. *The Journal of Infectious Diseases*. 2011;204(6):825-31.
21. Maltha J, Gillet P, Bottieau E, Cnops L, van Esbroeck M, Jacobs J. Evaluation of a rapid diagnostic test (CareStart Malaria HRP-2/pLDH (Pf/pan) Combo Test) for the diagnosis of malaria in a reference setting. *Malaria journal*. 2010;9:171.
22. Malaria Operational Plan 2014, Senegal. United States: United States Agency for International Development 2014. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy14/senegal_mop_fy14.pdf?sfvrsn=10. [cited 25th April 2017]
23. World Malaria Report 2015. Geneva: World Health Organization 2015. http://www.who.int/malaria/publications/world-malaria-report-2015/report/en/. [cited 3rd March 2017]
24. Wilson BK, Kaur H, Allan EL, Lozama A, Bell D. A New Handheld Device for the Detection of Falsified Medicines: Demonstration on Falsified Artemisinin-Based Therapies from the Field. *The American journal of tropical medicine and hygiene*. 2017;96(5):1117-23.
25. Batson JS, Bempong DK, Lukulay PH, Ranieri N, Satzger RD, Verbois L. Assessment of the effectiveness of the CD3+ tool to detect counterfeit and substandard anti-malarials. *Malaria journal*. 2016;15:119.
26. Weaver AA, Lieberman M. Paper test cards for presumptive testing of very low quality antimalarial medications. *The American journal of tropical medicine and hygiene*. 2015;92(6 Suppl):17-23.
27. Ricci C, Nyadong L, Yang F, Fernandez FM, Brown CD, Newton PN, et al. Assessment of hand-held Raman instrumentation for in situ screening for potentially counterfeit artesunate antimalarial tablets by FT-Raman spectroscopy and direct ionization mass spectrometry. *Anal Chim Acta*. 2008;623(2):178-86.
28. Survey of the Quality of Selected Antimalarial Medicines Circulating in Six Countries of Sub-Saharan Africa. Geneva: World Health Organization 2011. http://www.who.int/medicines/publications/WHO_QAMSA_report.pdf. [cited 20th February 2017]
29. Fadeyi I, Lalani M, Mailk N, Van Wyk A, Kaur H. Quality of the antibiotics-amoxicillin and co-trimoxazole from ghana, Nigeria, and the United kingdom. *The American journal of tropical medicine and hygiene*. 2015;92(6 Suppl):87-94.
30. Substandard/Spurious/falsely-labelled/falsified/counterfeit (SSFFC) medicines: Frequently asked questions. Geneva: World Health Organization 2016. http://www.who.int/medicines/services/counterfeit/faqs/SSFFC_FAQ_print.pdf. [cited 30th September 2016]
31. Yeung S, Lawford HL, Tabernero P, Nguon C, Wyk A, Malik N. Quality of antimalarials at the epicenter of antimalarial drug resistance: results from an overt and mystery client survey in Cambodia. *The American journal of tropical medicine and hygiene*. 2015;92.

32. Kaur H, Allan EL, Mamadu I, Hall Z, Ibe O, El Sherbiny M, et al. Quality of artemisinin-based combination formulations for malaria treatment: prevalence and risk factors for poor quality medicines in public facilities and private sector drug outlets in Enugu, Nigeria. *PLoS One*. 2015;10(5):e0125577.
33. Team ACTCDQP, Team IS. Quality of Artemisinin-Containing Antimalarials in Tanzania's Private Sector-Results from a Nationally Representative Outlet Survey. *Am J Trop Med Hyg*. 2015.
34. A report on the misdiagnosis of HIV status. Geneva: World Health Organization 2014. http://apps.who.int/iris/bitstream/10665/180231/1/WHO_HIV_2015.33_eng.pdf. [cited 20th February 2017]
35. Chinkhumba J, Nyanda M, Skarbinski J, Mathanga DP. Performance of Two Malaria Rapid Diagnostic Tests in Febrile Adult Patients with and without Human Immunodeficiency Virus-1 Infection in Blantyre, Malawi. *The American journal of tropical medicine and hygiene*. 2012;86(2):199-202.
36. Rennie W, Phetsouvanh R, Lupisan S, Vanisaveth V, Hongvanthong B, Phompida S, et al. Minimising human error in malaria rapid diagnosis: clarity of written instructions and health worker performance. *Trans R Soc Trop Med Hyg*. 2007;101(1):9-18.
37. Grimm P. Social desirability bias. *Wiley International Encyclopedia of Marketing*. 2010.

Chapter 6: Reflections, implications and conclusions

Addressing the problem of poor quality medicines remains a challenge for many low-middle income countries (LMICs), compounded by limited regulatory and technical capacity at the national level. This thesis has examined the national surveillance system for assuring and monitoring the quality of medicines in Senegal, through a series of studies using differing methodological approaches to examine several facets of medicines quality surveillance systems (MQSS) with the aim to identify challenges to these component parts, how they could be addressed and thus how the system as a whole could be strengthened. The evidence presented also considers how the quality of information generated by future studies and surveys of medicine quality in LMICs could be improved. This final chapter reflects upon the implications of my findings for current and future medicines quality related research in LMICs. Suggestions are provided for certain components of surveillance systems that require specific focus to improve functionality and effectiveness as well as considering priority areas for medicines quality related policy.

6.1 External risk factors for poor quality medicines

Chapter 2 discussed the internal risk factors for poor quality medicines that can be acted upon by national governments using findings from interviews in Senegal with the MQSS stakeholders including representatives of the key authorities responsible for the system and treatment providers. Here I reflect on the external risk factors for poor quality medicines, which are beyond the sphere of influence of individual countries, their governments and National Medicines Regulatory Authorities (NMRAs). External factors include the high cost of medicine to the consumer, medicine shortages, substandard manufacturing practices and trade in fraudulent products as well as limited funding for medicines quality assurance at a global level and the role of multiple actors.

Firstly, medicines are commodities, manufactured and marketed by pharmaceutical companies who have internal quality assurance and control processes, which provides them with confidence in the quality of the medicines they release onto the market. Nevertheless, there is variation in manufacturing competence and in quality assurance. Thus, schemes like WHO prequalification provide purchasers of medicines from accredited manufacturers (with Good Manufacturing Practice certification) with a degree of confidence that these medicines have met minimum standards for quality. Pharmaceutical companies and manufacturers are less involved in controlling medicines quality once medicines enter national distribution chains [1]

as these then become the responsibility of a NMRA. Even so, in resource constrained LMICs in particular, where regulatory and technical capacity is lacking, this raises questions regarding the corporate moral or social responsibility of pharmaceutical companies and manufacturers. Could manufacturers and pharmaceutical companies provide more assistance to support national surveillance systems? For example, based on findings in Senegal discussed in chapter 2, a lack of drug reference standards was identified as a potential weakness of the MQSS by representatives of the national medicine quality control laboratory (MQCL). Drug reference standards are essential in confirming the quality of a medicine and are thus, integral to the medicine quality analysis process. Without them, results on the quality of a medicine are meaningless, yet, their procurement cost was often seen as prohibitive. Pharmaceutical companies could reduce the cost of drug reference standards when being purchased by LMICs either through differential pricing mechanisms or donation. Pharmaceutical companies could also offer consultation for the development of medicine quality control and assurance processes and training on the utilisation of pharmacopeia methods.

Secondly, medicines quality assurance is underfunded at an international level which is perhaps best exemplified by the WHO prequalification scheme itself being unable to secure sustained funding, although there is an element of cost-recovery, by charging the manufacturer a fee when applying for pre-qualification status. [2] WHO prequalification has evolved over the last decade or so within the context of reports of the existence of poor quality medicines (especially in LMICs) and from recognition of the weaknesses of national systems for monitoring medicines quality. Assuring medicines quality at source is more cost-effective than building capacity for medicines quality monitoring and control in resourced constrained countries as there are fewer locations in which medicines are manufactured or distributed (at the international/national level) compared to the vast numbers of outlets/facilities from which they are sold or supplied to the public. Of further relevance, is the Affordable Medicine Facility for Malaria (AMFm) pilot initiative which along with the WHO prequalification scheme aimed to supply quality assured ACTs to the regulated sectors in LMICs. [3, 4] AMFm also successfully encouraged pharmaceutical companies to reduce the cost of ACTs, to make them affordable to consumers in malaria endemic countries, reducing the availability and market share of artemisinin based monotherapies and other less effective antimalarial medicines.

Thirdly, my data presented in this thesis from interviews, especially with treatment providers highlighted a national problem of medicine shortages. This is a pervasive global challenge and not just an issue for Senegal or other LMICs. [5] Medicines shortage is a multifaceted issue

with numerous contributory causes, ranging from manufacturing problems (e.g. lack of raw material), acute demand (e.g. epidemics), external political and economic factors (poor financial incentives for manufacturers, changes in reimbursement and changes in regulatory requirements) or marketing, procurement, and supply chain management practices. [6] Medicine shortages are a risk factor for poor quality medicines as market gaps may be filled by opportune counterfeiters who sell counterfeit or substandard versions of the authentic medicines in short supply, at a lower price. [5]

Finally, a variety of different actors are involved in assessing medicines quality including the WHO, pharmaceutical companies, academic institutions, international development agencies, and among these exist a range of professions and disciplines such as chemists, pharmacists, lawyers, politicians and academics. Whilst this heterogeneity possibly strengthens the pursuit of achieving minimum standards for medicines quality it may have also contributed to the protracted discussion that delayed agreement on definitions. [1] Furthermore, the inclusion of many interest groups with differing priorities leads to an increased risk of inconsistency in approaches to assessing medicines quality, as highlighted in chapter 4 whereby a lack of standardisation of study designs and reporting may render findings unreliable.

These external factors demonstrate the need for international cooperation and a national system for assuring medicines quality to reduce the likelihood of poor quality medicines entering and circulating within a country.

6.2 The gaps in knowledge on medicines quality at a national level

6.2.1 Medicines quality and the informal health sector

Findings presented in chapter 2 indicated that in Senegal, there was confidence among most stakeholders about the quality of medicines available in the public and regulated private sectors which was based on the perception of a robust regulatory system and adequate technical capacity to assure and control medicines quality nationally. Nonetheless, the ability of the MQAS to protect the public from the risk of poor quality medicines was perceived to be undermined by the presence of what was described as a large unregulated informal sector, and the absence of surveillance of medicines sold in this sector.

Based on the interview findings and the evidence from the current literature presented in this thesis, the informal sector is possibly the single largest risk factor for poor quality medicines in Senegal (and LMICs in which there is a high proportion of unregulated medicine outlets and sellers) due to a lack of regulatory oversight and improper medicines storage. Yet, the extent

of this risk is unknown as there is little information in terms of the prevalence of poor quality medicines available in this sector. Estimates for the proportion of the population accessing the informal sector in Senegal are not available but a recent study undertaken in 3 districts in Ghana found that of 11,089 individuals surveyed, 31% chose to use informal health care services. [7] While this thesis advocates for the use of screening technologies in LMICs especially where technical capacity is limited, their impact would be minimal in countries where an extensive unregulated informal medicine sector accessed by a large proportion of the population exists. Nevertheless, the interview findings suggest that the doubts raised about the quality of medicines available through informal outlets, were perceptions based on anecdotal reports of poor quality medicines, not on empirical evidence. In the absence of empirical data, this widely accepted narrative can remain little more than an unproven belief.

Private providers (non-governmental facilities) play a vital role in expanding access to treatment in settings with limited public health infrastructure as they are geographically convenient, have longer opening hours and are less frequently affected by medicine stock outs. Treatment seeking for medicines from the private sector is prominent in sub-Saharan Africa and Senegal is unlikely to be an exception. Indeed, a study mapping treatment-seeking rates in malaria endemic countries estimated that just under half of those seeking treatment would visit a government facility in the WHO West African region (48.91%). [8] There is a discernible difference between private sector providers, such as the private pharmacies in Senegal and informal medicine sellers, as the former are regulated by the NMRA and the latter are essentially unregulated. A key issue raised during interviews with stakeholders of the MQSS was the risk of legitimising informal sector trade if the quality of medicines from the sector was reported, although, this does not fully excuse the lack of surveillance. There also appeared to be socio-cultural and political reasons for not tackling the informal sector which could be unique to Senegal. Nevertheless, these findings serve to illustrate how moral and political considerations can play a key role in shaping surveillance systems, the research that is undertaken, and the resulting data available.

Due to the location of informal medicines sellers in open markets in Senegal, it could be more challenging to implement regulatory and surveillance procedures when compared to the fixed locations of pharmacies and clinics. Even so, where fixed locations for informal medicine sellers exist, traders could be encouraged to consider formalising their business, through accreditation systems for drug shops such as those implemented in Uganda and Tanzania. [9, 10] This would enable the NMRA to monitor some of these previously less regulated outlets

including monitoring their supply of medicines and even their participation in medicine quality surveys to provide a more representative picture of medicines quality.

In light of this somewhat limited knowledge, there is a need to gain a better understanding of the informal medicines sector and the quality of medicines they sell both in Senegal and other LMICs. The assessment of medicines quality in the informal sector should be an urgent priority for research and should include periodic surveys for assessing medicines quality, as well as documenting the risk factors that are likely to affect quality, such as exposure to sunlight and high temperatures which are particular relevant to medicines sold via open market stalls. In addition, studies exploring the perceptions of informal sellers of the quality of the medicines they sell and their awareness and knowledge of the impact of poor quality medicines (and their general health knowledge) is required so that appropriate measures can be implemented. If there is evidence of the availability of poor quality or unregistered medicines in this sector punitive approaches such as legal action to shut down informal sector outlets or markets, financial penalties or even the conviction of individual traders could be taken. These measures may be challenging to implement in Senegal for political reasons and hence more pragmatic approaches are required. This may include education, training and communication campaigns targeting informal sector traders to raise awareness of the risks of obtaining medicines from unauthorised sources and storing medicines inappropriately as both increase the likelihood of poor quality medicines being available within this sector. Additionally, public health communication strategies that encompass information on medicines quality, should advocate for obtaining medicines from the regulated sectors whilst also warning of the potential risk of purchasing medicines from the informal sector (as their quality cannot be verified) which is a comparable approach to the previous 'Street drugs kill' campaign conducted in Senegal in 2009. [11]

6.2.2 The effectiveness of medicines quality assurance in low-middle income countries

At a national level, medicines quality assurance relies on adhering to the infrastructure for medicines regulation and medicines quality monitoring and control, set against the backdrop of an adequately functioning and operating health system. Regulation is recognised as the key component for an effective medicines quality assurance system (MQAS). [12, 13] Even with adequate technical capacity, including robust sampling strategies and a well-equipped MQCL, stringent medicines regulation is required to ensure that medicines that enter the distribution chain are of acceptable pharmacopeial quality and that tangible action can be taken when poor quality medicines are detected.

This thesis has outlined several core functions of medicines regulation in the context of the MQAS: 1) authorisation of manufacturers/wholesalers and the medicines they produce/distribute, 2) medicines quality sampling at the point of entry, 3) inspection of distributors (national wholesalers, health facilities, pharmacies and drug outlets) to assess their compliance with storage and national medicines policy guidelines, 4) implementation of robust sampling strategies as part of post-marketing surveillance activities, 5) information sharing with other relevant national and international agencies, 6) close coordination with MQCLs and 7) action based on findings from medicine quality surveys to include withdrawal of affected batches and enforcement of laws based on a legal medicines regulatory framework against producers and distributors of poor quality medicines.

In Senegal, most of the key functions of medicines regulation relating to medicines quality were in place including authorisation, inspection, sampling through post-marketing surveillance, information sharing and action through the removal of affected medicines batches. Furthermore, working towards WHO prequalification accreditation was perceived to be a major step in enhancing national technical capacity, enabling the MQSS to broaden their control activities to include sampling at the point of entry. A sound regulatory system underpinned by a willingness amongst key actors to develop aspects relating to medicines quality control provides the basis for an effectively functioning national MQAS in Senegal, which is encouraging when compared to many LMICs in which regulatory and technical capacity is most often lacking.

However, a key challenge in many LMICs is the ability of the MQAS (and regulatory system) to act on findings from surveys or ad hoc detection of poor quality medicines in terms of apprehending producers and distributors of such medicines and enacting judicial processes based on a legal framework, which may not exist. Recently standardised definitions for medicines quality [14] may provide Member States with the basis for creating a legal framework to prosecute those who produce and distribute poor quality medicines within a country. Indeed, in many countries, prosecution of those who violate medicines regulatory law is non-existent at present and would require cooperation and a shared mandate between several national agencies including health, customs, law enforcement and judiciary. [15] This is a key step in assuring medicines quality by deterring those who intend to produce and distribute poor quality medicines with penalties proportionate to the crime.

Another gap in the knowledge of medicines quality assurance is a lack of information on the effectiveness of medicines regulation and medicines quality monitoring and control in LMICs. A

WHO report (2010) that presented an assessment of medicines regulation in 26 countries in sub-Saharan Africa reported that whilst 17 had a national MQCL, only 5/26 had the five key functions of medicine regulation. [16] Through the examination of the MQAS in Senegal which has been in place since around 2001, this thesis has sought to address this knowledge gap. When examined in relation to the health systems building blocks, [17] Senegal possesses all the basic components required to operate a system to control the quality of medicines circulating in the country. This includes a sound governance structure with engagement from several agencies including: the NMRA, organisations responsible for the supply of medicines and the control of medicines quality, as well as support from an external agency. Additionally, there is a functioning MQSS with adequate technical capacity that undertakes regular sampling of important medicines classes (primarily antimalarials, anti-tuberculosis medicines, antiretrovirals and oral contraceptives) and is committed to improving technical approaches for medicines quality assurance. There is also continued financial and technical support from United States Pharmacopeia (USP) who are responsible for enhancing technical and logistical capacity for medicines quality.

Whilst the findings presented in this thesis have highlighted several key elements a country requires to effectively control the quality of medicines nationally, there are some limitations in the scope of the data presented associated with medicines regulation and quality assurance. This thesis has focussed on the surveillance aspects of a medicines quality control system not the MQAS as a whole. Hence, future research on MQAS could focus on providing an updated account of medicines regulation to enable appropriate external agencies (WHO and USP), academic institutions, international non-governmental organisations and even established and well performing NMRAs from neighbouring countries to support and develop regulation in countries where it is less effective or even absent. Additionally, research could explore a potential association between medicines regulation (including technical capacity) and medicines quality in a country to understand how effective regulation, assurance and control ought to be, to reduce the likelihood of poor quality medicines circulating.

Support for building regulatory capacity is provided by USP in countries within which their Poor Quality Medicines programme operates. USP have successfully instituted an initiative in several countries that focuses on medicines registration with sampling at point of entry and routine sampling as part of post-marketing surveillance to identify unregistered medicines, for which there may be little data on their quality as they will not have been subjected to regulatory processes. [18] However, whilst USP state that they provide support for building regulatory capacity, their primary focus is on providing resources to build technical capacity

such as equipping laboratories to achieve WHO prequalification accreditation, as has been the case with their activities in Ethiopia, Ghana, Nigeria, and Kenya in recent years. [19] Technical capacity is paramount for the operation of an effective MQSS but must be underpinned by a robust medicines regulatory system which is integral to assuring medicine quality.

6.2.3 Clinical and public health impact of substandard medicines

To date, the agenda around medicines quality has been dominated by the legal and technical dimensions, and my research has identified the need for an in-depth understanding of the clinical impact of substandard medicines at the population level in LMICs, which remains largely unknown. In other words, what proportion of children treated for fever receive a substandard antimalarial? The answer to this question depends not only on the proportion of medicines that are substandard, but also the number of individuals who are at risk of being exposed to substandard medicines. What is the clinical implication on an individual of consuming a substandard (subtherapeutic) medicine? What are the public health implications of the widespread or repeated consumption of substandard medicines? A recent WHO study using impact modelling estimated that incremental deaths in sub-Saharan Africa due to substandard and falsified antimalarials may have comprised up to 5% of total malaria deaths between 2007-2016. [20] There is also a posited (but unproven) association between substandard antimalarials and drug resistance [2] which may have in part emerged from the literature on the development of artemisinin resistance in Southeast Asia from where the first reports of the problem with poor quality antimalarials were published. [21]

From a technical perspective, substandard medicines are those that do not meet the criteria outlined in a drug monograph, either exceeding or not meeting tolerance limits for their SAPI. Medicines with SAPI below the tolerance limit are a concern for health because they will not result in an effective cure, hence, the problem of poor quality medicines goes beyond the need to detect just fakes. Furthermore, there is little understanding of the clinical impact on the individual or the implications for public health from consuming substandard (subtherapeutic) medicines that range from those that have some of the SAPI (e.g. 40%) to those that just fail to meet tolerance limits (e.g. < 80%). This group of substandard medicines will not be detected by the currently available screening technologies.

6.2.4 The role of screening technologies

Whether evidence on the quality of medicines is sufficiently reliable and robust to inform effective public health action, depends on (i) the robustness of the surveys used to collect samples for evaluation and whether they are representative of the medicines which are most

used by patients; as well as on (ii) the quality of the laboratory techniques employed to evaluate them. The second section of the thesis examined both of these parameters and both were found wanting. Both the artemisinin derivative test (ADT) and the MiniLab® were shown to be capable of detecting falsified and grossly substandard (10% API) artemisinin based medicines. The ADT has also previously shown capability in distinguishing between 10% (grossly substandard) and 50% (substandard) SAPI of the tested artemisinin based medicine (figure 5.2, chapter 5). However, in this study, both tests were shown to be less likely to detect substandard samples or differentiate between acceptable pharmacopeial quality and substandard samples (especially those of 40% API) which is a key limitation of screening tests for antimalarials and other medicine classes. [22] Furthermore, it was found that the competence of the operator in carrying out test procedures and interpreting the results affected the accuracy of the tests with Inter-operator variability having previously been cited as limiting the accuracy of screening tests. [23]

The key attributes of a screening tests described in section 2 can be categorised as i) test performance versus the gold standard method of analysis and effective performance in field conditions, and ii) practical considerations (utility and cost). Further evaluations of test performance in comparison to the gold standard are required for all screening tests. In particular, essential information is required on the test parameters of sensitivity and specificity in the hands of different operators in the countries in which they are likely to be utilised. Aside from laboratory staff, this may also include groups such as customs officials and treatment providers. The results obtained will provide a clearer indication on the accuracy of these technologies in the hands of those most likely to use them, as well as in the situational context of field surveys in the tropics.

Furthermore, policy makers deliberating on the potential role of screening tests may consider their individual practical attributes (portability, preferably handheld, ease of use and cost) before approving their use as part of a MQSS. Nonetheless, there is a limited understanding of the precise strategy in implementing screening technologies, in medicines quality analysis and more generally as part of a MQSS at scale. Hence, a series of pilot studies will be required to establish the effectiveness of the technologies in detecting poor quality medicines at country level as well as the ability to integrate them into a MQSS and the wider health system. A potential strategic approach to implementation using the devices mentioned in this thesis could be as follows; 1) employing screening tests such as paper test cards, ADT or CD3 at border points, health facilities and pharmacies to both assess quality at the point of entry and point of care as part of routine surveillance, 2) use of the MiniLab® in peripheral laboratories

specifically for medicines quality surveys and 3) final decisions for regulatory action made following confirmatory testing using pharmacopeia methods.

Introducing screening tests at the service delivery level in a health system (at the point of care) or at the point of entry (outside of the current scope of a MQSS) will require additional research and evaluation centred on the accuracy of a test, in the hands of individuals with less laboratory experience such as treatment providers, pharmacists, medicine sellers and customs officials. Recent publications have discussed relevant examples of the barriers and facilitators to the roll out of rapid diagnostic tests for infectious diseases in sub-Saharan Africa such as end user beliefs, attitudes, perceptions, and satisfaction, as well as the competency of individuals in carrying out and interpreting results from a test. [24, 25] Similar considerations also apply when planning wider scale implementation of screening tests for assessing medicines quality and aspects such as the practical utility and usefulness of a test are likely to affect perceptions of its acceptability among users.

6.2.5 The need for good evidence: systematic and rigorous medicines quality studies

This thesis advocates for the use of more systematic and rigorous methods and standardised reporting of results in future medicine quality studies, following the reporting template that we produced and presented in chapter 4. This includes employing more representative approaches to sampling (including larger sample sizes), blinding of operators, verification of results (using a second operator, especially for screening tests), clarity in sample selection for confirmatory testing and the detailed reporting of other aspects within individual studies that may contribute to error and bias, and which need to be considered when interpreting the findings of a study.

The introduction of reporting guidelines, such as CONSORT and STROBE, have assisted in standardising the reporting of clinical trials and epidemiological studies, increasing clarity and scientific rigour of study design as well as facilitating the interpretation of results and comparison between studies. In contrast, there is little guidance on the reporting of findings from medicine quality surveys with the sole exception of the MEDQUARG checklist. [26] In the absence of universally recommended guidelines, combining our published template with current guidelines for medicines quality studies such as those published by MEDQUARG and USP [27] will help academics, NMRAs and operators of a MQSS with guidance on the criteria that need to be satisfied when undertaking a medicines quality survey. Additionally, a standardised approach to survey design and reporting would enable the assessment of the reliability and generalisability of survey findings. The lack of standardisation limits comparisons

between studies. This casts doubt on the current empirical evidence for medicines quality including that of antimalarials and hence, the scale of the problem of poor quality antimalarials globally, nationally or regionally within countries is difficult to assess.

Regardless of the quality of data on medicine quality, there remain significant geographical gaps in terms of the information available for certain countries and areas within countries. The WWARN antimalarial drug quality surveyor is a useful tool that has sought to pool existing antimalarial quality data from published sources and does, in part, address this gap. [28] However, national surveys conducted by NMRAs are seldom published and even data from countries in which the USP Poor Quality Medicines programme is active are not widely available. The sharing of national medicines quality survey data would be helpful to identify which countries (or areas within countries) are prone to the circulation of poor quality medicines, enabling further investigation by national agencies, USP, and WHO. Such data may also direct the efforts of academic institutions towards elucidating the most urgent gaps in understanding. Data from surveys can identify the sectors that are most at risk of poor quality medicines as well as the specific classes of medicines, origin and type of medicines which are compromised. Such surveys can also identify the places in which further assessment is most urgently needed to examine key internal factors that perpetuate poor medicines quality at a national level; weak medicines regulatory system, inadequate technical capacity, inability to apprehend and act against producers of poor quality medicines and inadequate medicines storage.

In addition to improvements in survey methodology and reporting, there is a need to recognise that the picture of the risk presented by poor quality medicines would remain incomplete if surveys do not include all sources of treatment, i.e. all points of consumer access to medicines, in that country. As highlighted by MQSS stakeholders interviewed in Senegal, the sale of drugs in unregulated street markets present a particular set of challenges for medicines quality surveillance and regulatory action and can be overlooked in surveys. Thus, in countries with a vibrant informal sector, these regulatory challenges to assuring medicine quality make it more imperative (not less) that medicine quality surveys include sampling from unregulated providers.

6.3 Redefining medicine quality

In order to compare data obtained from research undertaken in different settings, as well as consistency in the survey methodologies used, there is a need for medicine quality to be

defined in the same manner in every country. Moreover, universally accepted definitions are an important first step in creating a global legal framework for law enforcement and judicial processes against those that produce and distribute falsified medicines. For many years international agreement on the definitions for medicines quality has been lacking. It was not until 2017 that the World Health Assembly Member State mechanism reached consensus, classifying medicines quality into three categories; substandard, falsified and unregistered/unlicensed medicines. [29]

Whilst substandard and falsified medicines fit a technical paradigm, whereby the former may contain too little or too much of the stated active pharmaceutical ingredient (SAPI) and the latter may contain zero SAPI, the wrong SAPI and incorrect labelling of the medicines packaging (deliberately misrepresenting the medicine), the terms 'unregistered or unlicensed' largely fit the legal paradigm. [30] Unregistered/unlicensed medicines are those that have bypassed the regulatory system within a country and hence do not meet the criteria for approval or licensing granted by a NMRA. [29] Therefore, the presence of unregistered/unlicensed medicines in a country may raise suspicion and prompt an NMRA to take action against distributors and sellers of such medicines although this does not necessarily mean that these medicines are of poor quality. The proportion of unregistered/unlicensed medicines in a country may also indicate the extent to which the NMRA is effectively enacting regulatory mechanisms by controlling medical products entering and being distributed in the country. Overall, these recently agreed definitions appear to be intended to provide the impetus for action to be taken against producers, distributors and sellers of poor quality medicines. However, a legal framework that is universally agreed and accepted by member states, pharmaceutical companies and legal entities, obligating all parties to work together to apprehend and prosecute individuals who violate laws centred on the production and distribution of poor quality medicines does not exist, as yet. [1] This much needed universally agreed legal framework would provide a foundation upon which NMRAs, customs and law enforcement agencies could collaborate at inter and intra country level to take action against those who contravene medicine regulatory (and quality) laws strengthening the credibility of a MQAS.

The recently agreed definitions whilst standardising the way in which medicines quality is framed, still require further adaptation to encompass the clinical and public health outcomes of consuming substandard as well as falsified medicines which would connect the technical and clinical paradigms, increasing their relevance to national NMRAs, policymakers and health professionals. My research findings showed that at a country level, health system stakeholders

described medicine quality in terms of a clinical paradigm centred on the health outcomes of consuming a poor quality medicine; the effectiveness of a medicine in treating physical symptoms. The terms falsified, counterfeit and substandard most commonly used to describe medicines that have failed quality assessment in the academic literature, were rarely mentioned by interviewees. The perceptions of medicines quality presented from findings in this thesis are therefore, in stark contrast to the technical and legal paradigms within which medicine quality is defined on a global level amongst academics, international policy-makers and pharmaceutical companies. Perceived factors that determined medicine quality also included its origin, type (generic or brand) and its cost. This is hardly surprisingly, since in the absence of screening tests at the point of care, a provider can only judge medical products on these parameters.

The perceptions of health professionals and consumers are also important in terms of access to affordable essential medicines. The negative perceptions of generic medicines amongst medicine regulators and treatment providers presented in chapter 3, remain of some concern in light of the premise of global initiatives such as the existing WHO Essential Medicines list and recently concluded AMFm pilot which aimed to increase access to affordable and clinically useful medicines to LMICs. [3, 31] Generic medicines which are considerably cheaper than their brand name counterparts, comprise a significant proportion of the medicines available through these initiatives. Yet, they are perceived to be of inferior quality despite AMFm medicines being quality assured and the WHO prequalification status of several medicines on the WHO Essential Medicines list. The consumer's preference for a brand name medicine, means that they are often willing to pay a higher cost. This is problematic in LMICs where large swathes of the population are impoverished, and the cost of medicine is often prohibitive and could expose the population to the risk of counterfeit brand name medicines infiltrating the market, which counterfeiters will supply for a lower price in comparison to the authentic product.

Scepticism about the quality of generic medicines will exist until there is sound empirical evidence to suggest otherwise. Therefore, MQSS and other agencies that carry out medicine quality studies and surveys should specifically categorise results in order to differentiate between generic and brand medicines when reporting their findings on the quality of medicines in their sample. In light of the findings presented in chapter 3, it can be deduced that if a generic medicine is proven to be of acceptable pharmacopeial quality then such information should be disseminated to health professionals, treatment providers and consumers as they have all been shown to be dubious about the quality, efficacy and safety of

generics. [32-37] Ultimately, to achieve the specific component of Sustainable Development Goal 3 'access to affordable safe and quality assured medicines,'[38] there is a need for greater advocacy to address the negative and somewhat unfounded perceptions of generic medicines (based on a lack of empirical evidence) on behalf of the WHO, pharmaceutical companies, NMRAs and even health professionals to ensure affordable access to essential medicines.

6.4 Focussing priorities

The multifaceted and complex nature of medicines quality spanning several disciplines and actors has been presented in this thesis. It is recognised that medicines quality may not attract substantial funding in the near future if the current funding trajectory remains on course. Medicines quality is unlikely to become a national public health priority in LMICs as there are other more pressing issues such as the ongoing focus on treatment and prevention of communicable diseases as well as emerging concerns of the growing burden of non-communicable diseases. [39] Hence, a pragmatic approach that focusses on 'quick wins' with minimal resources could be considered for countries in which a MQSS is in its infancy or lacking altogether. Some suggestions for evolving or developing medicines quality surveillance in resource constrained settings that may be relatively straightforward to implement are outlined below.

1. Partnership building

A key strength of the MQAS in Senegal was the presence of an established coordinating committee created by the MoH for monitoring the quality of antimalarial medicines nationally which comprised representatives of the NMRA, the national MQCL, the national malaria control programme, USP (as an implementing partner of USAID) and the central medical stores (the national distributor of medicines to public sector health facilities). An integral aspect that formed the basis of the confidence of medicines quality in Senegal amongst most of the interviewees, was a shared collaborative commitment to medicines quality assurance and a degree of pride in the manner in which the MQSS had developed in recent years. These findings underline the value of partnership building within nations.

Moreover, where possible, national governments could allocate a capitated budget to a collaborative partnership between MQSS authorities, holding them accountable for medicines quality assurance nationally, although this assumes that governance arrangements are in place and funders such as USP are willing to support such an approach. This is a potentially important lesson for existing and nascent MQSS in other LMICs, whereby autonomy and

accountability may act as drivers for increasing engagement and empowerment of stakeholders in medicines quality activities. It also reflects some of the recommendations by the WHO following assessment of regulatory systems in sub-Saharan Africa, in which they state the importance of providing NMRAs autonomy, with a sufficient budget to allocate resources to conduct medicines regulation so as to improve regulatory capacity, system efficiency and effectiveness. [16] Expanding this partnership to include the private health sector in Senegal primarily represented by the pharmacist professional body would enable better engagement with a key health system stakeholder, strengthening the MQSS.

Building regional, continental or even international partnerships should be considered. Given USP's role in several sub-Saharan countries, the formation of a regional medicine quality forum may encourage data and knowledge sharing. Furthermore, resources could be shared or pooled by neighbouring countries. For example, attaining WHO prequalification status for the MQCL in Senegal could benefit the Western Sahel region with the quality control of medicines and other products undertaken in one country, minimising the need to build expensive technical capacity in every neighbouring country, where resources and health system infrastructure may be more limited.

2. Strengthening post marketing surveillance

If medicines regulation is robust and effective in limiting the import and distribution of poor quality medicines, post-marketing surveillance should amount to no more than addressing medicine quality issues as they arise and would involve; 1) responding to reports of the detection of a poor quality medicine, 2) taking action by withdrawing affected batches, 3) carrying out additional surveys to assess the extent of the problem for the medicine in question and 4) if appropriate, raising concerns with the manufacturer (if the medicine was substandard) or enacting legislative procedures (if the medicine was falsified), which may include apprehending and prosecuting sellers, distributors and producers. [39] Therefore, post-marketing surveillance could rely on passive reporting by treatment providers without the need for field surveys to sample and test medicines from points of sale. Nonetheless, there may be a few countries in sub-Saharan Africa that can employ a primarily active approach whereby there is no periodic sampling, reports of suspect quality medicines are pursued and investigated to locate the source and all affected batches are identified and withdrawn from circulation. This can be easier when medicines quality nationally is well controlled, and reports of medicines of suspect quality are rare. In countries employing an active approach, a virtuous cycle can develop in which instances of poor quality medicines entering circulation are infrequent and when they arise are removed from distribution chains swiftly whilst

maintaining a constant state of vigilance. This 'end state' for MQSS' whereby treatment providers are fully engaged in the reporting of medicines of suspect quality is possibly a model that most MQSS' should strive toward.

Surveillance of medicines quality even on a limited scale is better than none and undertaking regular medicines quality surveys to build the knowledge base of medicine quality in a country would be an acceptable approach to surveillance as an initial step towards creating a functional and effective MQSS. A minimum requirement would be to collect medicine samples following representative sampling using a randomised approach and testing with a fully validated commercially available screening tests in sentinel sites, followed by confirmatory testing at a MQCL with appropriate gold standard (HPLC) equipment. These steps would ensure that, at the very least, the data produced on medicines quality is reliable and could be used to advocate to governments or external funders with evidence-based findings for further investment in technical and regulatory capacity.

3. Utilising the existing health infrastructure

The absence of a well-developed primary care structure in LMICs means that the public are particularly reliant on pharmacies and drug shops that are often geographically easier to access. Issues of medicine stock outs and long queues for treatment at government health centres also encourage patients to seek medicines from alternative providers. Drug shops and pharmacies are seen as offering a quicker and more convenient service. [40, 41] Therefore, pharmacists and drug shop operators are often the primary point of care and have an important, yet seemingly unrecognised role in the health system [42] despite a large proportion of the population in sub-Saharan Africa seeking treatment from the private sector – both regulated providers e.g. pharmacists and less regulated medicines sellers e.g. drug shop owners or market traders. [8] In light of their extensive knowledge on the safety, efficacy and quality of medicines, pharmacists are ideally placed to play an active role in the surveillance of medicines quality by identifying falsified products or those that may bypass usual supply chains (e.g. unregistered medicines) and documenting cases of treatment failure in patients. In Senegal there an abundance of regulated pharmacies with qualified and accredited pharmacists, [43] offering an existing infrastructure for the provision of medicines information, medicines quality surveillance and pharmacovigilance.

However, in Senegal there was a noticeable disconnect between the strategic/operational levels in the health system and the provider level (both public and private, but especially with pharmacists). It is suggested that health systems in LMICs ought to engage better with

treatment providers and recognise the significance of their role at the point of care and in the specific context of medicines regulation and quality assurance, as the 'frontline' in a system for surveillance and monitoring. Indeed, pharmacists in some LMICs are already involved in pharmacovigilance systems (through reporting of adverse medicines reactions and issues of product safety). [44] Without the engagement of pharmacists and other treatment providers as active stakeholders in a MQSS, gaps in medicine quality data will continue to exist.

Additional training of treatment providers on medicines quality and particularly the use of screening tests (implemented in health facilities and pharmacies) may provide a MQSS with a potentially significant resource in post marketing surveillance. Alternatively, where resources are limited, treatment providers could be educated in the visual identification of poor quality medicines (especially falsified versions) without the need for tests or devices. Visual inspection at the point of care could act as a first line in post-marketing surveillance in a MQSS. Moreover, establishing an effective feedback mechanism for treatment providers to report a medicine of suspect quality (with or without screening tests) would further develop the effectiveness of a MQSS. Information sharing between treatment providers and the MQSS could be enhanced using recent advances in mobile phone technology. Implementing a medicine quality alert system using mobile communication systems whereby a treatment provider can directly send details to the NMRA of the suspected quality of a medicine would result in a more efficient use of established resources. [45] Moreover, if such an alert system were to operate effectively it may limit the need for regular medicine quality surveys, whilst also strengthening post marketing surveillance.

The selection of appropriate strategies for medicines quality assurance and control is dependent upon the specific country context. Contributory factors such as the resources available (especially financial investment), the effectiveness of the national medicines regulatory system, the robustness of the medicines supply chain and capability of the national MQCL, to produce valid and reliable results may determine selection of the best overall approach for medicines quality assurance and control at a given point in time. Strategies for assuring and controlling medicines quality must also consider the main sources of treatment and types of providers accessed by the patient population, especially the existence of an informal sector of uncertain scale, selling medicines of unknown quality which may potentially render a MQSS ineffective if not addressed. Further strategic considerations for medicines quality assurance and control may include investment in medicines regulation, passive and active approaches to detecting poor quality medicines and the most appropriate sampling technique and validated screening technology to employ (though these should always be used

alongside authorised pharmacopeia methods to provide robust evidence on medicines quality). Together these components form the basis of a MQSS strategy which has a specific role in a national health system; enabling the MQSS to fulfil its remit, namely to minimise the circulation of poor quality medicines and in instances where such medicines are detected, ensure that they are withdrawn from circulation promptly to limit their impact on public health.

6.5 References

1. Attaran A, Barry D, Basheer S, Bate R, Benton D, Chauvin J, et al. How to achieve international action on falsified and substandard medicines. *BMJ*. 2012;345:e7381.
2. Pisani E. Antimicrobial resistance: what does medicine quality have to do with it? Review on antimicrobial resistance. 2015. http://amr-review.org/sites/default/files/ElizabethPisaniMedicinesQualitypaper.pdf. Accessed 12th May 2016.
3. Tougher S, Ye Y, Amuasi JH, Kourgueni IA, Thomson R, Goodman C, et al. Effect of the Affordable Medicines Facility—malaria (AMFm) on the availability, price, and market share of quality-assured artemisinin-based combination therapies in seven countries: a before-and-after analysis of outlet survey data. *The Lancet*. 2012;380(9857):1916-26.
4. World Health Organization Prequalification programme. A United Nations programme managed by WHO. Geneva: World Health Organization 2016. http://www.apps.who.int/prequal/. [cited 12th May 2016]
5. Ventola CL. The drug shortage crisis in the United States: causes, impact, and management strategies. *Pharmacy and Therapeutics*. 2011;36(11):740.
6. Fox ER, Birt A, James KB, Kokko H, Salverson S, Soflin DL. ASHP Guidelines on Managing Drug Product Shortages in Hospitals and Health Systems. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists*. 2009;66(15):1399-406.
7. Fenny AP, Asante FA, Enemark U, Hansen KS. Treatment-Seeking Behaviour and Social Health Insurance in Africa: The Case of Ghana Under the National Health Insurance Scheme. *Global Journal of Health Science*. 2015;7(1):296-314.
8. Battle KE, Bisanzio D, Gibson HS, Bhatt S, Cameron E, Weiss DJ, et al. Treatment-seeking rates in malaria endemic countries. *Malaria journal*. 2016;15(1):20.
9. Rutta E, Liana J, Embrey M. Accrediting retail drug shops to strengthen Tanzania's public health system: an ADDO case study. 2015;8:23.
10. Clarke S. Introducing rapid diagnostic tests (RDTs) into the public & private health sectors in Uganda: a randomized trial to evaluate impact on antimalarial drug use. ACT Consortium 2012. http://www.actconsortium.org/pages/project-3.html. [cited 12th October 2012]
11. Senegal Health Authorities Organize Campaign against “Street Drugs” with Participation of USP, USAID, and other International Groups. The Standard. 2009:11.
12. Newton PN, Green MD, Fernandez FM. Impact of poor-quality medicines in the 'developing' world. *Trends in Pharmacological Sciences*. 2010;31(3):99--101.
13. Effective medicines regulation: ensuring safety, efficacy and quality. Geneva: World Health Organization 2003. http://apps.who.int/medicinedocs/pdf/s4921e/s4921e.pdf. [cited 18th March 2018]
14. WHO member state mechanism on substandard/spurious/falselylabelled/falsified/counterfeit (SSFFC) medical products: Working definitions. Geneva: World Health Organisation 2017 http://www.who.int/medicines/regulation/ssffc/A70_23-en1.pdf?ua=1. [cited 21st July 2017]
15. Attaran A. Stopping murder by medicine: introducing the model law on medicine crime. *The American journal of tropical medicine and hygiene*. 2015;92.
16. Assessing National Medicines Regulatory Systems. World Health Organisation 2010. http://www.who.int/medicines/areas/quality_safety/regulation_legislation/assesment/en/. [cited 11th March 2017]
17. Everybody's Business: Strengthening Health Systems to Improve Health Outcomes: WHO's Framework for Action. . Geneva: World Health Organisation 2007.

http://www.who.int/healthsystems/strategy/everybodys_business.pdf. [cited 7th March 2013]
18. Africa and the Middle East: Our work in the region. United States: United States Pharmacopeia 2017. http://www.usp-pqm.org/where-we-work/Africa-MiddleEast. [cited 16th May 2017]
19. Prequalification of quality control laboratories. Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies (Technical report series, no. 961). Geneva: World Health Organization; 2011.
20. A study on the public health and socioeconomic impact of substandard and falsified medical products. Geneva: World Health Organization 2017. http://www.who.int/medicines/regulation/ssffc/publications/Layout-SEstudy-WEB.pdf?ua=1. [cited 29th March 2018]
21. Newton PN, Caillet C, Guerin PJ. A link between poor quality antimalarials and malaria drug resistance? *Expert review of anti-infective therapy*. 2016(just-accepted).
22. Kaur H, Clarke S, Lalani M, Phanouvong S, Guerin P, McLoughlin A, et al. Fake anti-malarials: start with the facts. *Malaria journal*. 2016;15(1):86.
23. Maxim LD, Niebo R, Utell MJ. Screening tests: a review with examples. *Inhalation toxicology*. 2014;26(13):811-28.
24. Kirwan DE, Cárdenas MK, Gilman RH. Rapid implementation of new TB diagnostic tests: is it too soon for a global roll-out of Xpert MTB/RIF? *The American journal of tropical medicine and hygiene*. 2012;87(2):197-201.
25. Asiimwe C, Kyabayinze DJ, Kyalisiima Z, Nabakooza J, Bajabaite M, Counihan H, et al. Early experiences on the feasibility, acceptability, and use of malaria rapid diagnostic tests at peripheral health centres in Uganda-insights into some barriers and facilitators. *Implementation Science*. 2012;7(1):5.
26. Newton PN, Lee SJ, Goodman C, Fernandez FM, Yeung S, Phanouvong S, et al. Guidelines for field surveys of the quality of medicines: a proposal. *PLoS medicine*. 2009;6(3):e52.
27. Guidelines for Drug Sampling, USP DQI Drug Quality Monitoring Program. Use of the Basic Tests at the Peripheral Level. Rockville: United States Pharmacopeia 2006. http://pdf.usaid.gov/pdf_docs/PNADH150.pdf. [cited 20th Feburary 2017]
28. Tabernero P, Newton PN. The WWARN Antimalarial Quality Surveyor. *Pathogens and Global Health*. 2012;106(2):77-8.
29. Report of the fifth meeting of the Member State mechanism on substandard/spurious/falselylabelled/falsified/counterfeit medical products. Geneva: World Health Organisation 2017. http://apps.who.int/gb/ssffc/pdf_files/MSM5/A_MSM5_8-en.pdf. [cited 12th April 2017]
30. Substandard/Spurious/falsely-labelled/falsified/counterfeit (SSFFC) medicines: Frequently asked questions. Geneva: World Health Organization 2016. http://www.who.int/medicines/services/counterfeit/faqs/SSFFC_FAQ_print.pdf. [cited 30th September 2016]
31. WHO Essential Medicines and Health Products - Annual Report 2015. Geneva: World Health Organisation 2015. http://www.who.int/medicines/publications/emp_annual-report2015/en/. [cited 25th February 2017]
32. Dunne SS, Shannon B, Cullen W, Dunne CP. Beliefs, perceptions and behaviours of GPs towards generic medicines. *Family Practice*. 2014;31(4):467-74.
33. Bertoldi AD, Barros AJ, Hallal PC. Generic drugs in Brazil: known by many, used by few. *Cad Saude Publica*. 2005;21(6):1808-15.

34. Chaudhuri S, Mackintosh M, Mujinja PGM. Indian generics producers, access to essential medicines and local production in Africa: an argument with reference to Tanzania. *European Journal of Development Research*. 2010;22.
35. Shrank WH, Liberman JN, Fischer MA, Girdish C, Brennan TA, Choudhry NK. Physician perceptions about generic drugs. *Ann Pharmacother*. 2011;45(1):31-8.
36. Patel A, Gauld R, Norris P, Rades T. Quality of generic medicines in South Africa: perceptions versus reality - a qualitative study. *BMC health services research*. 2012;12:297.
37. Wong ZY, Hassali MA, Alrasheedy AA, Saleem F, Yahaya AH, Aljadhey H. Patients' beliefs about generic medicines in Malaysia. *Pharm Pract (Granada)*. 2014;12(4):474.
38. World Health Statistics 2016: Monitoring Health for the SDGs Sustainable Development Goals. Geneva, Switzerland: World Health Organization 2016. http://www.who.int/gho/publications/world_health_statistics/2016/en/.
39. Ebrahim S, Pearce N, Smeeth L, Casas JP, Jaffar S, Piot P. Tackling non-communicable diseases in low-and middle-income countries: is the evidence from high-income countries all we need? *PLoS medicine*. 2013;10(1):e1001377.
40. Goodman C, Brieger W, Unwin A, Mills A, Meek S, Greer G. Medicine sellers and malaria treatment in sub-Saharan Africa: what do they do and how can their practice be improved? *The American journal of tropical medicine and hygiene*. 2007;77(6 Suppl):203-18.
41. Ladner J, Davis B, Audureau E, Saba J. Treatment-seeking patterns for malaria in pharmacies in five sub-Saharan African countries. *Malaria journal*. 2017;16(1):353.
42. Azhar S, Hassali MA, Ibrahim MIM, Ahmad M, Masood I, Shafie AA. The role of pharmacists in developing countries: the current scenario in Pakistan. *Human Resources for Health*. 2009;7(1):54.
43. Patterson D. Pharmacy in Senegal: Gender, Healing, and Entrepreneurship: Indiana University Press; 2015.
44. Olsson S, Pal SN, Dodoo A. Pharmacovigilance in resource-limited countries. *Expert Review of Clinical Pharmacology*. 2015;8(4):449-60.
45. Global Surveillance and Monitoring System for Substandard and Falsified Medical Products Geneva: World Health Organization 2017. http://www.who.int/medicines/regulation/ssffc/publications/GSMS_executive_Summary.pdf?ua=1. [cited 29th March 2018]

Annex 1 – Ethics approval; London School of Hygiene and Tropical Medicine Research Ethics Committee

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Mirza Lalani
Research Degree Student
CR / ITD
LSHTM

4 April 2013

Dear Mr Lalani,

Study Title: **Surveillance approaches to detect the quality of Artemisinin Combination Therapy drugs for Malaria Control in Senegal**

LSHTM ethics ref: **6330**
LSHTM amend no: **403**

Thank you for your application of 18 March 2013 for the amendment above to the existing ethically approved study and submitting revised documentation. The amendment application has been considered by the Observational Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above amendment to research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval for the amendment having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
LSHTM amendment application	n/a	18/03/2013
Protocol including Information sheets and Consent forms	1.2	15/03/2013

After ethical review

Any further changes to the application must be submitted to the Committee via an E2 amendment form. The Principal Investigator is reminded that all studies are also required to notify the ethics committee of any serious adverse events which occur during the project via form E5. At the end of the study, please notify the committee via form E5.

Yours sincerely,

[redacted]

Professor John DH Porter
Chair
ethics@lshtm.ac.uk
http://intra.lshtm.ac.uk/management/committees/ethics/

Annex 2 – Ethics approval; National Council for Health Research, Senegal

045

REPUBLIQUE DU SENEGAL
Un Peuple – Un But – Une Foi

MINISTERE DE LA SANTE
ET DE L'ACTION SOCIALE

DIRECTION DE LA PLANIFICATION
DE LA RECHERCHE ET DES STATISTIQUES

N°_____MSAS/DPRS/CNERS

Dakar, le 08 AVR 2013

NERS
SENEGAL
Comité National d'Ethique pour la Recherche en Santé

Le Coordonnateur

AVIS ETHIQUE ET SCIENTIFIQUE

Protocole : SEN 13/05 : intitulé « Surveillance de la qualité des combinaisons thérapeutiques à base d'artémisinine dans la lutte contre le paludisme au Sénégal » du service de la Parasitologie Mycologie.

Professeur,

Les réponses que vous avez fournies suite aux commentaires qui vous ont été adressés à l'issue de l'examen du protocole sus mentionné le 07 février 2013, ont été jugées satisfaisantes par le CNERS qui émet en conséquence un avis éthique et scientifique favorable pour vous permettre de dérouler votre projet.

Toutefois, il vous recommande, en respect des principes de Bonnes Pratiques de Recherche, de bien vouloir prendre des dispositions pour le tenir informé du démarrage et de la conduite de la présente étude à travers des lettres d'information, des rapports d'étape et de fin de projet.

Cet avis est annuel et son renouvellement est assujetti à la fourniture d'un rapport et d'une demande de prolongation adressée au CNERS.

Je vous prie de croire, **Professeur,** à l'expression de ma considération distinguée et de mes encouragements renouvelés.

Professeur Omar GAYE
Département Parasitologie Mycologie / UCAD

[redacted]

Annex 3 - Interview Guide for MQSS authority representatives and other stakeholders (chapter 2/3)

Topics of interest	Questions	Comments
Background	***1. Key informant profile:*** What is your role within the organisation? How long have you been in this role? ***2. MQSS background and rationale*** Historical aspects: • Were you involved in any aspect of medicine quality monitoring before the MQSS was formally established? If yes, what did you do? • When did your organisation become involved in the MQSS? • In your opinion what were the reasons behind the creation of the MQSS and who were the main actors involved? How has the MQSS changed since its inception? *Probe:* • *What are these changes?* • *Perceptions relating to whether these changes are thought of as good or bad?* • *What have been the main challenges for the MQSS in this time?* • *Which medicines does the MQSS focus upon for monitoring and why were these selected?*	Ease the interviewee into the discussion.
Roles and responsibilities	***3. Perceived roles and responsibilities*** Have you as an individual had any previous roles with the MQSS? What are your specific responsibilities in relation to the MQSS? What is the role of your organisation within the MQSS? Please describe any challenges you have faced in fulfilling this role? *Probe:* • *Have they had any guidance in this role?* • *If so, from whom?* • *Where or who would they go to for guidance?* In your opinion, how central is your organisation in the functioning of the MQSS?	Obtain written documentation where possible e.g. organogram of structure of MQSS and any documents stating roles and responsibilities of authorities with the MQSS.

	Please briefly describe the roles and responsibilities you perceive of the other organisations central to the functioning of the MQSS. *Probe:* • *How do these roles and responsibilities relate to your organisation?* How do you communicate with the other MQSS authorities? *Probe:* • *Regular communication?* • *Who with in terms of specific person(s)? Who is the main point of contact in each of the authorities?* • *How often?* What challenges, if any, are faced when coordinating with these other authorities?	
General health system aspects	***4. Information Flow*** Please describe how information flows within the MQSS? *Probe:* • *How does this information flow operate?* • *What are the different parts of it? (further probes on reporting, performance and data gathering)* • *Are there any problems relating to this?* • *If so how could they be overcome?* ***5. Financing*** What is the main source of funding for your organisation for MQSS related activities? *Probe:* • *Are there any additional sources of funding?* • *Is the total level of funding adequate for the efficient operation of the MQSS?* • *If extra funding were available what aspects of the MQSS could be improved?* ***6. Human Resources*** In your opinion do you have an adequate number of staff with appropriate training or qualifications within the MQSS? *Probe :* • *If not, where in the system are more qualified staff needed?* • *Who is involved in training them?*	
Strengths and weaknesses	***7. Perceived strengths and weakness of MQSS?*** What do you see as the main strengths of the MQSS? What aspects do you believe the MQSS could improve upon? Of these aspects you have mentioned which are the most simple to change and which are the most difficult and why?	

	8. *Perceived Strengths/Weaknesses of organisation* In terms of medicine quality monitoring what are the main challenges for your organisation? In your opinion, how could your organisation play a greater or better role in the MQSS?	
QAMSA Study	***9. Discussion on findings of QAMSA study:*** Are you aware of the QAMSA study? Please describe the reaction and any discussions that took place following the QAMSA report in 2010? To what extent were the findings from the QAMSA report a source of concern or not? *Probe:* • *Did they have follow up meeting with WHO/USP regarding findings?* • *What was the response from the findings amongst various authorities in the MQSS?* Do you feel that the QAMSA report led to any changes in the MQSS or in medicines regulation or not? *Probe:* • *If so what specific aspects of the findings led to the changes?* • *What were these changes?*	Keep copy of report in French to show the interviewee if needed.
Poor quality medicines	***10. Perceived situation of poor quality medicines*** Moving to the situation as it is currently in Senegal. How confident are you about the quality of medicines available currently in Senegal? To what extent do poor quality medicines pose a risk to public health in Senegal if at all? *Probe: If interviewee acknowledges existence of poor quality medicines:* • *Which medicine have been found to be of poor quality?* • *Have the sampled poor quality medicines been fake (SFFC)(no API), substandard or degraded?* • *Where in Senegal have the poor quality medicines been found? Sector (public, private, informal), geographical location, urban/rural?* Can you describe a previous example of what happened when a poor quality medicine was suspected in Senegal? *Probe:* • *What are the procedures in place?* • *What action was taken and by whom?* • *Have poor quality ACTs been detected?* • *Do you consider these actions as adequate?* • *What else could have been done?*	.

	11. Risk factors In your opinion what factors do you consider, increase the risk of poor quality medicins in Senegal? *Probe:* • *Source of ACTs (country in manufacture, country of import)?* • *Impact of ACT stock outs in Senegal?* • *ACT costs?* • *Medicine regulation?* • *Sampling and detection?* In your opinion how can the MQSS specifically work to assure the quality of all medicines in Senegal? To what extent does the current MQSS provide you with confidence with regard to the quality of medicines available in Senegal?	
Medicines supply and regulation	***12. Supply Chain*** Apart from the CMS do public and private sector pharmacies purchase medicines (especially ACTs) from elsewhere? Supply chains: • What are the main levels of the supply chain in Senegal? • Who are the main actors at each level of the supply chain and what are their roles? In your opinion at which point(s) of the supply chain, if any, is there a risk of poor quality medicines appearing? *Probe:* • *Which parts of the supply chain structure are most vulnerable?* • *How could they be improved?* ***13. Medicines regulation*** What is the role of medicine regulation in Senegal? Does medicine regulation differ between the public, private and informal sectors? If so, how? How is medicine regulation linked to the MQSS? *Probe:* • *Does interviewee see them as intrinsically connected or are they two separate 'systems' each regulator is involved with?* Does the quality of medicines differ between sectors? If so why? *Probe:* • *Specifically role of unregistered drug outlets/informal sector in Senegal on medicine quality and regulation?*	Obtain documentation relating to levels of supply chain in Senegal: wholesale, NGO etc Obtain documentation relating to levels of registration and/or classification of pharmacies in Senegal

	• *Where do informal sector buy their medicines from? (if known)* What is the role of a drug inspector in Senegal? *Probe:* • *How many inspectors are there?* • *How often do they inspect?* • *Do they inspect the informal sector?* • *Do drug inspectors have any linkages to the MQSS?* If unanswered in previous questions: What are the most common challenges faced in terms of medicines regulation in Senegal?	
Medicine quality analysis and sampling	***14. Sampling*** Where do you collect/sample medicines from? *Probe:* • *How do you collect medicines? (sampling strategies, samples sizes)* • *How often? (timings)* • *Where from? (sampling frame and locations)* To what extent are you confident that the current sampling strategy provides the reassurance that any medicine supplied to a member of the public in Senegal is probably safe and of acceptable quality? *Probe:* • *Do you have confidence in current strategy?* • *Does sampling strategy need improvement? Why? How could it be improved?* Why were the sentinel sites where medicine quality laboratories are located, chosen? *Probe:* • *Are the areas in nearest proximity to the sentinel sites only areas sampled or others as well?* **15. *Medicine quality analysis*** What is the definition of a poor quality medicine in terms of results obtained from analysis? Please describe current techniques used in Senegal for medicine quality analysis and how they are used? *Probe:* • *How various techniques fit into the current MQSS for detection of poor quality medicines?* • *Ask them to provide an example of what happens to a sampled medicines in terms of analysis? Why are these steps/procedures taken?* For each technique: • What do you see as the main advantages of this technique? • Do you find any limitations with this technique?	Obtain written documentation if possible for strategies; sampling sizes, frames locations and timing of collection etc. Obtain previous reports of sampling and collection activities.

	To what extent do the current techniques provide you with the answers you need? Can you describe a previous example of what happened when a poor quality medicine was suspected in Senegal? *Probe:* • *What are the procedures in place?* • *What action was taken and by whom?* • *Have poor quality ACTs been detected?* • *Do you consider these actions as adequate?* • *What else could have been done?* What happens to the findings from medicine quality sampling and analysis collections? *Probe:* • *Who do they report the findings to?* • *Why do they report them to that agency?* • *Do they publish the findings?* • *Do they investigate the sources of the poor quality medicine?* In your opinion how can the MQSS specifically work to assure the quality of all medicines in Senegal? To what extent does the current MQSS provide you with confidence with regard to the quality of medicines available in Senegal?	
	Is there anything you would like to add? Have you any questions for me?	

Annex 4 - Interview guide for treatment providers (chapter 2/3)

Areas of interest	Questions	Comments
Background	***1. Key informant profile*** What is your role at this outlet/facility and what are you responsible for? How long have you worked here? What training have you or anyone else at this outlet received relating to malaria? *Probe:* • *clinical diagnosis, RDTs* • *malaria drug treatment* • *ACTs* ***2. Malaria situation*** I am interested in discussing malaria treatment with you. In your opinion what is the current situation with regard to drug treatment for malaria in Senegal? How and why has this situation changed in recent years? How do you diagnose patients that you suspect have malaria? What would you normally prescribe them for malaria infection? *Probe:* • *What is the first line medicine normally prescribed or sold?* • *What is the second line medicine?* • *What is the brand of medicines supplied?* • *Why are these medicines prescribed or sold?* • *In what situation may you prescribe or sell another medicine?* • *What is the first line medicine recommended for treatment of malaria* • *If this is different to the one mentioned above as the one normally prescribed – then ask why the difference* In your experience have any of the patients whom you have treated for malaria then returned here in subsequent days or weeks with malaria like symptoms? *Probe:* • *How often does this occur? (if at all)* • *In your opinion what is the reason for this?*	Purpose of this section is to ease the interviewee into the interview.

Medicine procurement and quality	***3. Medicine (ACT) procurement*** Who decides which medicines to stock? (specifically ACTs) *Probe :* • *Are there guidelines for this?* • *Where are these guidelines from?* • *Ask them to describe circumstances in which they have not adhered to guidelines In the past if applicable.* Where are medicines bought from normally? Do you ever obtain medicines from other sources? *Probe:* • *When was the last occasion they did this?* • *How often?* • *Why?* What influences your decisions when buying medicines? *Probe:* • *Cost* • *Availability* • *National policy* • *Quality* *If quality is mentioned why is it important to them? Would quality override any of the other influences on medicine procurement?* ***4. Medicine quality perceptions*** How can you know a medicine is of acceptable quality? What can affect the quality of a medicine? How confident are you in the quality of medicines available here in this facility/outlet? Have you had any reason to doubt medicine quality in the past? *Probe* • *If yes, what made you suspect the medicine?* • *If no, how would you recognise a poor quality medicine?* What about the quality in Senegal generally? *Probe:* • *If medicine quality is a concern, why is it a concern?* • *Is medicine quality a concern or consideration for patients?* • *Probe specifically on antimalarials or ACTs* • *What course of action would they/or did they take if they suspected a medicine was of poor quality*?	

	5. Medicine Quality Surveillance Do you know if the government has a system in place to check on the quality of medicines? *Probe:* • *If yes, what do they understand to be the main function of this system and does it fulfil its role?* • *Do they have any interaction with the system?* How would it assist you in your role as a treatment provider to be able to test the quality of a medicine? How confident are you that the government is able to ensure that the medicines you supply to patients are of good quality?	
	Is there anything else you would like to add? Have you any questions for me?	

Annex 5 - Sub-study 1: detailed results of ADT test procedure (chapter 5)

Test procedure action	Technician								Average score	Description
	1	2	3	4	5	6	7	8		
1	10	10	10	10	10	10	10	10	10	Sample preparation (1); pulverise and dissolve in 10 ml of methanol
2	10	0	0	10	10	10	10	10	7.5	Sample preparation (2): Sonicate for appropriate length of time (approx. 5 mins) depending on pulverisation
3	10	10	10	10	10	10	10	10	10	Sample preparation (3): Appropriate tablet breakdown/sedimentation and use of centrifuge if required
4	0	10	10	10	0	10	0	0	5	Sample preparation (4): Appropriate labelling of sample (vial or Eppendorf tube)
5	10	10	10	10	10	10	10	10	10	TLC preparation (1): Draw square or circular shapes roughly $1cm^2$ or 1cm in diameter
6	10	10	0	10	0	10	10	0	6.3	TLC preparation (2): Correct labelling of squares/circles
7	10	10	10	10	10	10	10	10	10	Spotting (1): Drawing up of supernatant
8	10	10	10	10	10	10	7	10	9.6	Spotting (2): Correct spotting of methanol within square/circle (2x5µl) (volume)
9	10	10	10	10	10	10	10	10	10	Spotting (3): Correct spotting of tab within square/circle (2x5µl) (volume)
10	10	0	10	10	10	10	10	10	8.8	Spotting (4): Correct spotting of DNP to within square/circle (1x5µl) (volume)
11	10	0	9	9	10	9	7	10	8	Spotting (5): Correct spotting of FBS to within square/circle (1x5µl) (volume)
12	10	10	10	10	10	10	10	10	10	Development (1): Correct storage of plate away from sunlight
13	10	10	10	10	10	10	10	10	10	Development (2): Plate read after 40 minutes
14	10	0	9	9	8	9	10	10	8.1	Development (3): Appearance of plate after testing and development
15	10	10	10	10	10	10	10	10	10	Additional steps (1): Pipette replaced after spotting of each methanol/sample
16	10	10	10	10	10	10	10	10	10	Additional steps (2): Pipette replaced after spotting of DNP
Total technician score	150	120	138	158	138	158	144	140	143	
Time taken to complete test (mins)	33	45	60	60	50	90	55	75	58.5	

Annex 6 - Sub study 1: test procedure questionnaire (chapter 5)

PARTICIPANT DETAILS					
Participant name:	**Participant code:** **|____|____|**				
Date of interview:	**Name of interviewer:**				
ADT RATING: ***1 = very difficult to use, 5 = very easy to use***					
Training Manual	**1**	**2**	**3**	**4**	**5**
Test instructions (bench aid)	**1**	**2**	**3**	**4**	**5**
Ease of preparing sample	**1**	**2**	**3**	**4**	**5**
Ease of preparing TLC plate	**1**	**2**	**3**	**4**	**5**
Ease of spotting test solution and reagents	**1**	**2**	**3**	**4**	**5**
Number of steps to carry out ADT	**1**	**2**	**3**	**4**	**5**
Time to wait for results (1= too long, 5= appropriate length of time)	**1**	**2**	**3**	**4**	**5**
Ease of interpreting test results	**1**	**2**	**3**	**4**	**5**
FURTHER QUESTIONS					
How easy is this test to use? **What specific difficulties did you encounter when using this test?** **What did you like most about this test? (What are its strengths?)** **What are the main challenges of this test?** **Will this test make your work easier? Give reasons for you answer.** **What challenges do you foresee in using this test in the field?** **Do you have any recommendations on how this test could be improved?** **Have you used a similar test in the past? (if so please state)** **Do you have any additional comments?**					

Annex 7 - Sub-study 2: results interpretation questionnaire (chapter 5)

TECHNICAN DETAILS					
Participant name:	**Participant code:** |___|___|			
Date of interview:	**Name of interviewer:**				
ADT RATING: ***1 = very difficult to use, 5 = very easy to use***					
Colour chart and instructions for use	**1**	**2**	**3**	**4**	**5**
Instructions for results interpretation	**1**	**2**	**3**	**4**	**5**
Clarity of pictures (not clear =1, very clear = 5)	**1**	**2**	**3**	**4**	**5**
Influence of light in laboratory (great influence =1, no influence =5)	**1**	**2**	**3**	**4**	**5**
Ease of results categorisation and interpretation	**1**	**2**	**3**	**4**	**5**
Confidence in decision made (no confidence = 1 **,** very confident =5)	**1**	**2**	**3**	**4**	**5**
FURTHER QUESTIONS					
How easy did you find test the results to interpret? **How confident would you be in making a decision in sending for further testing or not?** **Which colour is easier to interpret and why?** **What difficulties did you encounter in interpreting the results?** **Which is easier to interpret results from the MiniLab® or this test?** **What are your thoughts on the difference between pictures for poor quality and acceptable pharmacopeial quality (good quality)?** **Do you have additional comments?**					

Annex 8 - Focus group guide 1; prior to laboratory exercises (chapter 5)

Topics of interest	Questions	Comments
Background	Please discuss your role and your responsibilities as a technician in the context of the MQSS? *Probe:* • *Why or how did you start working in medicine quality?* • *Do you all do the same work?* • *Do they enjoy their work in comparison to other lab work they have done? Why?* • *What is the range of experience of the technicians in terms of working within the MQSS?*	Purpose of this section is to ease the participants into discussion This section will provide some useful information relating to the background of the technicians – Education, training (self or taught), taught by whom, experience, satisfaction.
Medicine quality analysis	How do you assess the quality of a medicine? *Probe:* • *Screening technique i.e. MiniLab®* • *What are the methods and procedures undertaken or followed?* • *How do they interpret the results from analysis?* • *How confident are they in their decision making?* • *Action taken if medicine fails* What are the main challenges you face when deciding if a medicine is of acceptable pharmacopeial quality or not? Tell me more about the current techniques you use for medicine quality analysis? *Probe:* • Strengths? Challenges? • *Ease of use?* • *Practicalities e.g. time of assay, use of hazardous substances/reagents* • *If not already covered above then ask about the reliability of the results* If there was anything you could change about the MiniLab, what would it be and why? Tell me more about the laboratory here and others in Senegal you have worked in: (MQ specifically) Probe: • *Equipment – functioning? Quality? Enough?*	Relates to what they actually do – will allow comparison about how closely their actual work practices align with guidelines.
Quality of medicines	What is an acceptable pharmacopeial quality medicine? *Probe:* • *Who ultimately decides what an acceptable pharmacopeial quality medicine in the field is?*	The responses here ought to relate to what they perceive in relation to their work – what they are taught/have learnt.

	• *What are main risk factors for poor quality medicines?* Describe your general findings in terms of the quality of medicines in Senegal? *Probe:* • *How has medicine quality changed in their experience?* • *Ask for examples of when they have found poor quality medicines in Senegal.* • *Which medicines do they find fail the most and why?*	However, perhaps more personal perspectives on this definition can also be elicited.
Additional questions	Please tell me about any other aspects of your role as a technician, the medicine quality analysis technology or medicine quality in general. Is there anything else you would like to add? Have you any questions for me?	In this section try and identify anything relevant that may have been missed

Annex 9 - Focus group guide 2; post laboratory exercises (chapter 5)

Topics of interest	Questions	Comments

Acceptance of ADT test	Tell me about your thoughts regarding the test?
	Probe:
	• *What did you like about the test?*
	  ○ *Manual/instructions*
	  ○ *Preparation of sample/plates*
	  ○ *Spotting*
	  ○ *Reagents not being toxic*
	  ○ *Rapid*
	• *What are the main challenges of the new test?*
	  ○ *Time to wait for results*
	  ○ *Confusion of FBS/DNP where to spot*
	  ○ *Can it be used in the field – less laboratory equipment*
	
	What do you see as the main advantages of the new test?
	○ What did you like best?
	
	How confident are you in the results obtained and in interpretation?
	Probe:
	• *How confident are they in the decision made?*
	• *Which colour did they prefer to interpret?*
	• *Which images were hard to interpret?*
	
	If there was anything you could change about the ADT what would it be and why?
		Principal researcher not present. Please reassure staff that they should be open and candid about views and perceptions of the test.
		
		Use responses from questionnaires relating to ease of use and results interpretation.

Perceived usefulness	How well would this test fit into your everyday work of screening medicine quality? *Probe:* • *Can this test be a viable alternative to the MiniLab® for ACT screening? Why?* • *How will the test be perceived among colleagues and their superiors?* Do you find the test useful in terms of identifying medicines of good or poor quality? Do you think this is a useful screening test and why?	
ADT and Minilab comparison	Which test did you find easier to use and interpret the results for ACT analysis and why?	
Additional questions	What other aspects of the test (including the training manual) need to be considered prior to it being used by others for ACT screening in Senegal? Is there anything else you would like to add? Have you any questions for me?	Try and raise any recurring points raised from questionnaires not captured in this guide.

Supplementary File 1: ADT manual, including colour chart and bench aid (chapter 5)

The ADT
(Artemisinin Derivative Test)

Mirza Lalani

Introduction

Numerous recent reports can be found of discoveries of poor quality medicines globally. Currently Artemisinin Combination Therapies (ACTs) are recommended treatment for uncomplicated *P.falciparum* malaria by the World Health Organisation. By 2008 77 out of 86 malaria endemic countries had an active treatment policy stating that ACTs should be used to treat *P.falciparum* malaria. [1] The increase in demand for ACTs places them at the inevitable risk of being counterfeited or produced at lower cost using poor manufacturing practices. The first documented case of poor quality artemisinin was in 1999 in Cambodia where a nationwide survey found that 71% of 133 drug outlets stocked 'fake' artesunate. [2] Subsequently in recent years there has been a proliferation of poor quality antimalarials in Southeast Asia. [3-5] There have also been reports of the detection of poor quality artemisinin in sub-Saharan Africa and this appears to be a growing problem in some parts of West Africa in particular. [6-13] Based on this evidence, regular testing to ensure that ACTs are of acceptable pharmacopeial quality is vital in ensuring success of recent malaria control programmes to continue.

Need for ADT test

To assure quality of artemisinin derivative based medicines (ADs), medicine quality surveillance systems require appropriate laboratory facilities with, at the very least, adequate technical capacity. The gold standard for medicine quality content analysis is High Performance Liquid Chromatography (HPLC), which is an accurate, precise and specific analytical technique. [14] However, HPLC equipment has a relatively high capital and maintenance cost and reagents are also expensive. Furthermore, it requires a high level of technical expertise to operate. For these reasons it is only available at a limited number of reference laboratories and cannot be implemented for routine analysis in the field.

The GPHF MiniLab® is a screening test that provides a rapid and simple assessment of medicine quality and therefore plays an important role in the monitoring of medicine quality in resource poor settings. [15] However, it has been reported that the MiniLab® can only detect grossly substandard and counterfeit medicines. [16] Therefore, the MiniLab® cannot be relied upon unequivocally for medicines quality monitoring systems and for definitive results precise analytical methods such as HPLC need to be utilised.

To address the need for a reliable, affordable and accurate test that is readily portable and can be used at the point of screening, two simple colorimetric assays have been developed by Ioset and Kaur [17] that require minimal training and equipment and are specifically for the detection of the presence of ADs in ACTs and thus for determining the quality of ACTs.

Application and content of test

The ADT test includes two simple to use, rapid and reproducible assays that have been developed for the detection of ADs, not only in mono formulations but also in combination therapies (ACTs). These colorimetric assays utilise thin layer chromatography (TLC) silica gel sheets and either 2,4 dinitrophenylhydrazine (DNP) or 4-Benzoylamino-2, 5-dimethoxybenzenediazonium-chloride hemi (zinc chloride) salt (Fast Blue Salt – FBS) as the reagents to detect the ADs. The principal of the test involves dissolving the pulverized tablet in

methanol and applying a very small amount of the resulting solution to a TLC sheet followed by either of the reagents and allowing the reaction to proceed at room temperature. If ADs are present in the sample the reaction(s) will produce a pink colour with the DNP or blue colour with FBS. Both colours will appear within 40 minutes.

A complete validation of the two developed assays has been undertaken in the laboratory at the London School of Hygiene and Tropical Medicine following a systematic evaluation, including:

1. The test has been evaluated for its specificity and validated against the other available field method the GPHF-MiniLab®. This includes testing of the following:
    a. All major antimalarials currently used on the market
    b. A wide selection of active principles from the WHO list of essential medicines
    c. A wide range of excipients used in the pharmaceutical formulation of tablets

2. Application of the test to a representative range of samples (> 9000) from the field.

3. Confirming the results against high performance liquid chromatography with photo-diode array detection (HPLC-PDA) as the gold standard method.

As a result of this validation it has been found that the ADT detects only artemisinin derivatives with the exception of artemisinin itself.

ACTs (fixed dose combination) that can be tested

Artemether/lumefantrine

Artesunate/amodiaquine

Artesunate/mefloquine

Dihydroartemisinin-piperaquine

Procedure

Principle

The artemisinin derivatives are extracted with methanol and determined by the colour reaction test with reference to authentic standard (if available).

List of equipment

TLC aluminium sheets silica gel 60 F_{254}
Pestle (or other tool to pulverise tablet)
Sonicate and/or centrifuge
10ml vials
Pipettes & pipette tips (measure 5 µl)
Eppendorf tubes
Pencil
Ruler or Stencil to draw 1x1cm squares or 1cm diameter circles
Reference standard (if available)

List of reagents

Methanol
2M Sulphuric Acid2, 4 dinitrophenylhydrazine (DNP)
4-Benzoylamino-2, 5-dimethoxybenzenediazonium chloride hemi (zinc chloride) salt (Fast Blue Salt – FBS).

Test Procedure

Both components of the ADT should be carried out on each sample i.e. testing with DNP and FBS. Results from each individual assay should corroborate the result of the other (see figure 1). If either assay fails to produce the expected colour, the test would need to be repeated. A further discordant result would require the sample to be sent for definitive analysis by HPLC.

Note: The procedures below assume that a reference standard is available. If this is not the case any steps referring to standards can be omitted.

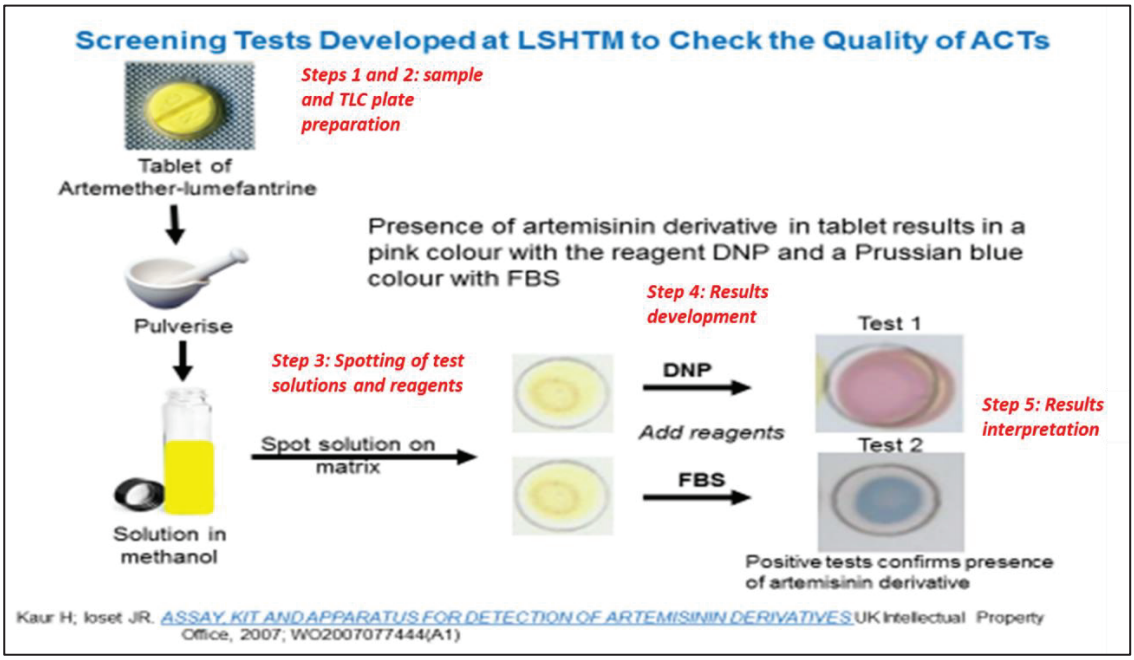


Figure 1: ADT test developed at LSHTM to check the quality of artemisinin based medicines. The text in red shows the major steps for carrying out the test: steps 1 and 2 - preparation of the sample and TLC plate; step 3 – spotting of solution on matrix on TLC plate; step 4 – development of the results; step 5 - interpretation of resulting colours.

Preparation of FBS

To prepare the FBS dissolve 1mg of FBS powder in 950 µl of 2M Sulphuric acid and 50µl of methanol. Shake well to dissolve all the powder. The resulting solution can now be used as a reagent for testing the AD samples. DNP is commercially available in liquid form and is ready to use.

Preparation of sample (step 1)

If available an ultrasonic bath and/or centrifuge should be used. This section describes what to do with or without this equipment. Samples are pulverised with a pestle, emptied into a 10 ml vial, methanol (10 ml) added and solubilisation achieved by placing the mixture in an ultrasonic bath for 30s. Alternatively manual shaking can be used. If a tablet cannot be pulverised it will need to be left in the sonicate for up to 10 minutes. If fragments still remain (and they cannot be broken down manually) the mixture should be centrifuged. If breaking down manually care should be taken not to break the glass vial. Draw up 1ml of the mixture and transfer to an Eppendorf tube for centrifugation. If centrifuge is not available the mixture is left on the bench until sedimentation occurs (a clear top layer is formed). The time taken for sedimentation to occur will be variable depending on the specific drug sample. Once centrifugation takes place the mixture is ready to test.

Always label the sample (whether in original vial or Eppendorf tube) with a suitable code for the sample e.g. AL20 for artemether/lumefantrine 20mg/120mg.

Once a sample has been prepared it must be tested on the same day. Leaving samples for extended periods of time can cause degradation and lead to erroneous results being obtained.

To minimise the risk of contamination, clean out any remaining residue from the pestle using water and dry thoroughly (this is applicable to any other apparatus used) before preparing the next sample.

Preparation of TLC plate (step 2)

Prior to performing the test the TLC plate must be prepared as a matrix as in figure 1. This step can be undertaken at any time before or whilst preparing the sample. Using a pencil (and if available a stencil) draw square or circular shapes roughly $1cm^2$ or 1cm in diameter. For each drug a minimum of 6 squares should be drawn, 3 in each row (or a total 4 squares with 2 squares in each row if no reference available).

The first row is for DNP and the second for FBS, and should be labelled accordingly . The first column of squares or circles should be marked blank (BL). The second column should be marked as reference (Ref). The third column should be marked as 'tablet', however given that an individual plate will be used for several drugs it is advisable for the operator to use a familiar code for the drug as they would do when carrying out analysis with other similar tests and write this on the plate itself. The example in figure 2 is AL 20, AL 40 and AL 80, which represent artemether-lumefantrine 20mg/120mg, 40mg/240mg and 80mg/480mg respectively.

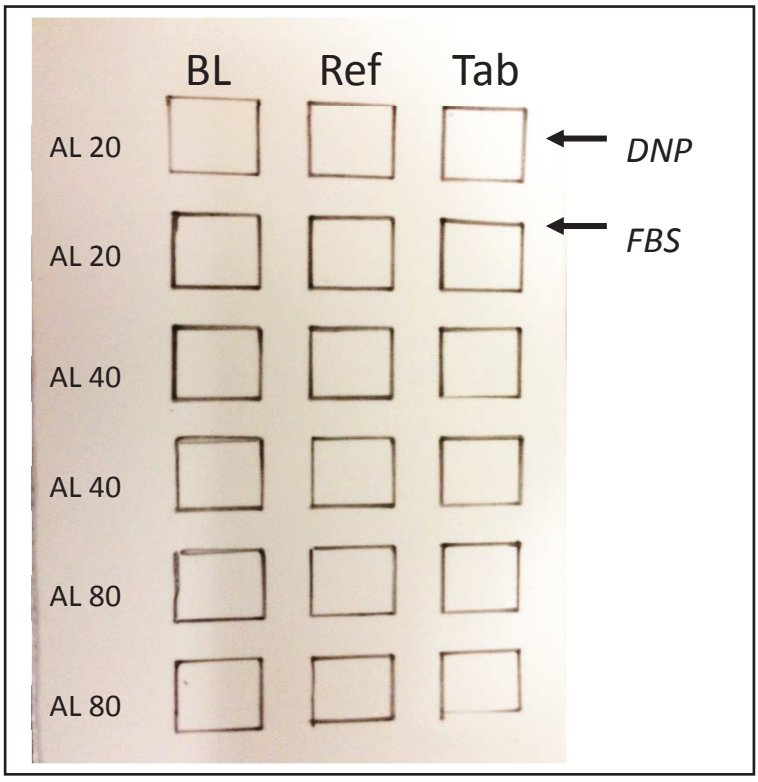


Figure 2: Matrix drawn on TLC plate

Spotting (step 3)

Regardless of the steps followed in preparing the sample once the supernatant has appeared and all insoluble fragments or particles have settled the sample is ready to test. Draw up the mixture using the pipette. Be careful to only draw up the supernatant (liquid at the top of the mixture). Make sure none of the sediment is drawn into the pipette. To minimise the risk of

contamination, use a different pipette tip once for each new sample (old pipette tips should be discarded).

Previous experimentation with test parameters has suggested that the amount of mixture and reagent added can influence the depth of the colours produced. Therefore, to ensure standardised results it is recommended that the exact amount of sample mixture and reagent must be spotted and the sample mixture must be homogenous throughout.

Step 1: Spotting of sample/reference mixture

Note: In the steps below, It is recommended to spot 2 x 5µl as opposed to 1 x 10µl to ensure that the sample/reagents are enclosed within the square/circle. Spot 1 x 5µl to the square then spot another 1 x 5µl on top of it.

Using the pipette:

- To each blank square/circle; spot 2 x 5µl of methanol. Replace pipette tip
- To each reference square/circle; 2 x 5µl of the reference mixture. Replace pipette tip
- To each sample square/circle; 2 x 5µl of the sample mixture. Replace pipette tip.

Step 2: Spotting of reagents

It is not necessary to allow the sample/reference mixture spots to dry. Step 2 can commence immediately after Step 1. Using a different pipette for DNP and FBS reagents:

- In the first row to each square/circle; spot 5µl of DNP. Replace pipette tip.
- In the second row to each blank square/circle; spot 5µl of FBS.

Repeat Steps 1 and 2 as necessary for each drug sample being analysed.

Processing multiple samples (batch processing)

Both the 'preparation of the sample' and 'spotting' steps can be conducted with multiple samples at the same time.

When preparing samples, to save time it is advisable to produce a number of samples concurrently which can then be placed in the sonicate together.

When spotting the samples, several mixtures can be spotted onto the same TLC plate. Ensure the steps in 'Preparation of TLC plate' have been followed and the matrix is large enough to accommodate multiple samples, and is clearly labelled with an appropriate code for each different drug sample. Spot each sample mixture onto the same TLC plate one after another; ensuring that pipette tips are changed and discarded after each different drug sample is spotted.

Once spotting of all sample mixtures is complete the DNP and FBS can be spotted to all the squares/circles in the appropriately labelled rows as a single step. Ensure that after DNP has been spotted that the pipette tip is replaced prior to spotting with FBS. In addition, if labelled

prior to use, the pipette tips used for spotting the methanol “blanks”, FBS and DNP can be reused. Discard these pipettes at the end of the day.

Development (step 4)

The TLC plate should be kept out of direct sunlight. The plate should not be read before 40 minutes have elapsed. Although the minimum time taken for the colour with DNP to appear is 20 minutes and the minimum time taken for the colour to appear with FBS is 40 minutes. The colours produced are stable for a maximum of 2 weeks. To appreciate the true depth of colour the plate can be re-read after 24 hours.

Observation

DNP will produce a pink colour and the FBS a blue colour if the active ingredient (AD) is present (see figure 1 above).

Results

If both pink and blue colours appear with DNP and FBS respectively this indicates the ART is present in an ACT (see figure 3, showing colour reactions with different artemisinin-based drugs).

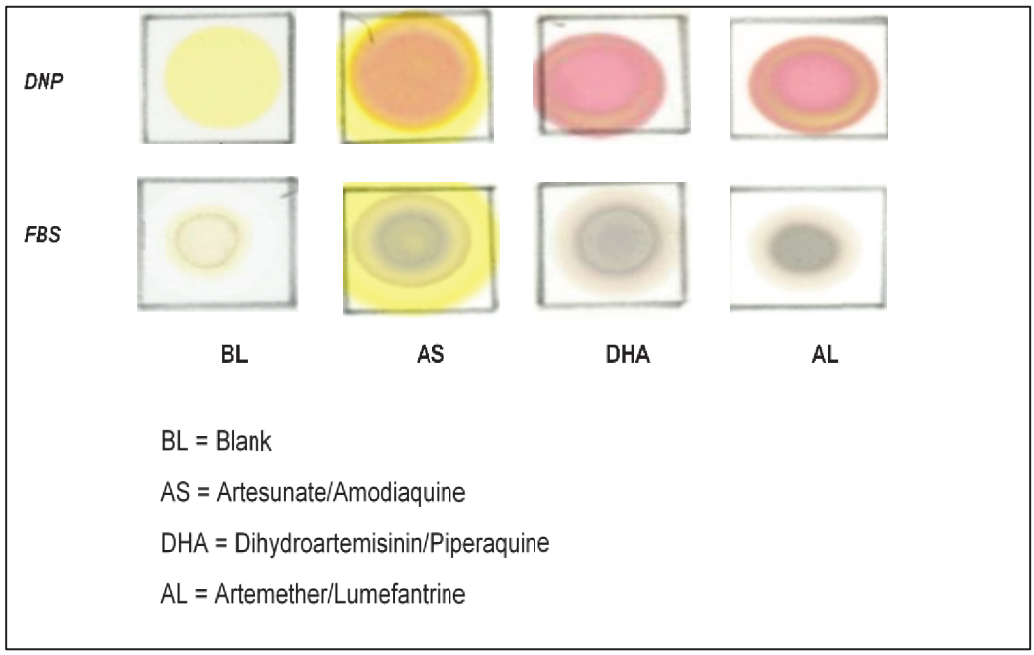


Figure 3: Colours produced following testing of artemisinin derivatives

Results Interpretation and actions taken (step 5)

The interpretation of test results is subjective. Figure 4 shows the range of colours produced by samples of artemether/lumafantrine (AL) 20mg/120mg. In this example the AL samples producing image C would be regarded as good quality. However the samples producing images A and B would be regarded as poor quality (A represents a sample that contains no active ingredient (ART) at all).

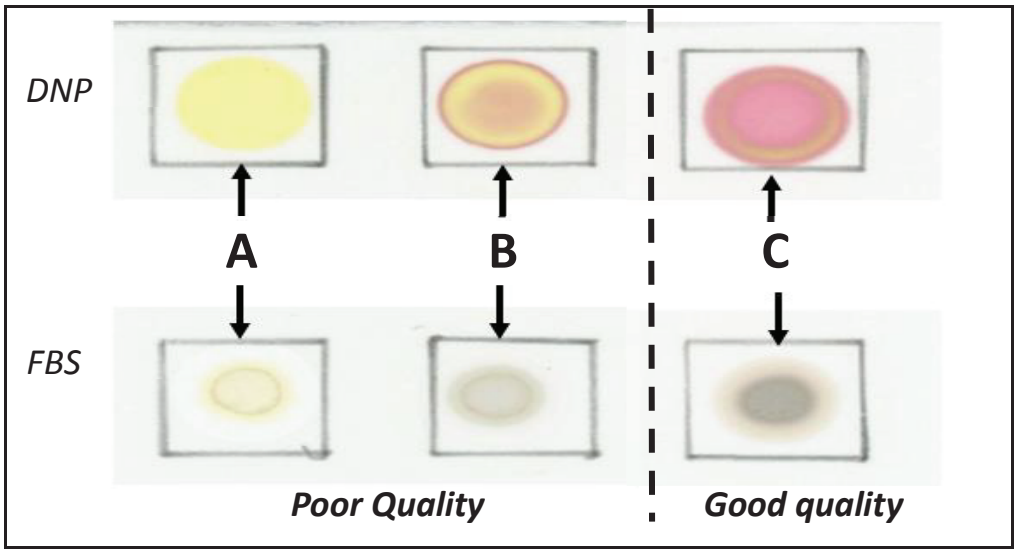


Figure 4: A, B and C are samples of artemether in solution of artemether/lumefantrine 20mg/120mg

Should the colour (blue or pink) not be observed with one reagent yet the other reagent did result in a colour reaction (i.e. the DNP and FBS results are inconsistent), then the test should be repeated. If when repeated, the results obtained remain inconsistent, the sample should be referred for definitive analysis by HPLC.

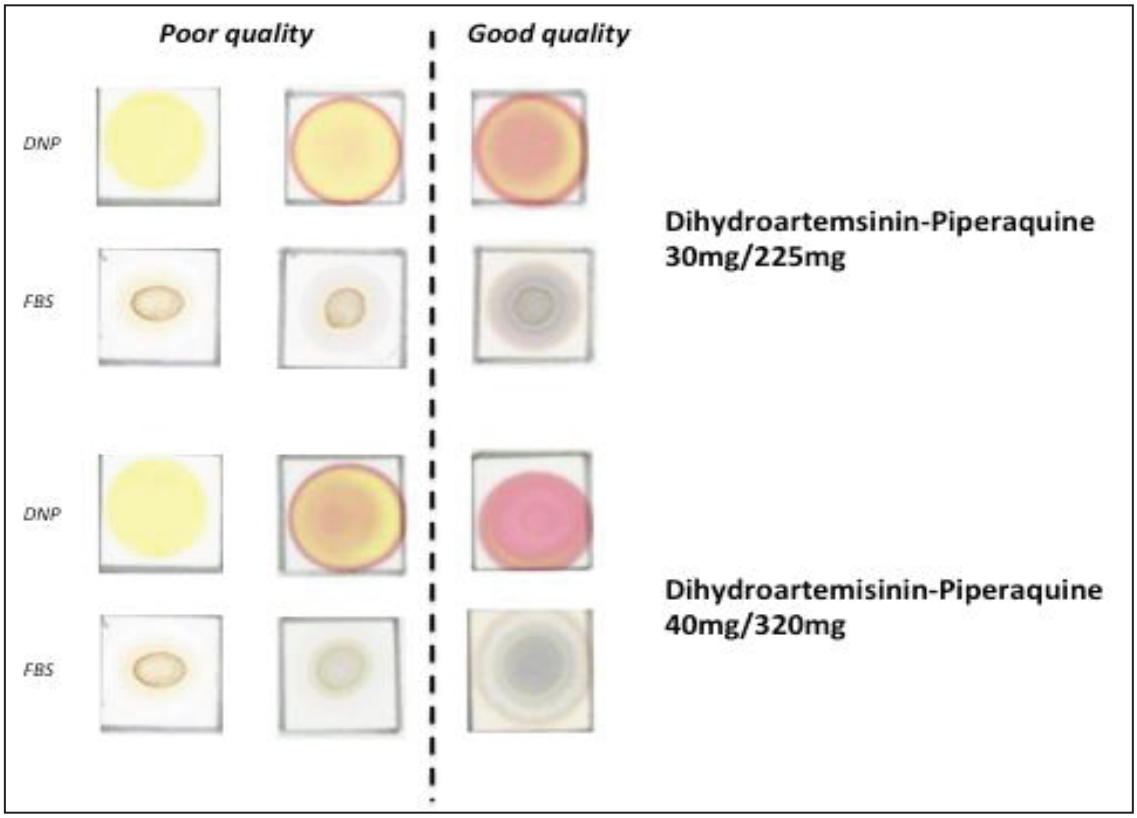
Once results have been categorised and it has been determined whether the medicine is of good (acceptable) quality or poor quality, action must be taken. **All poor quality samples need to be sent for further testing** at a national medicine quality control laboratory for analysis by HPLC. Whilst **it is not necessary to further samples deemed to be of good (acceptable) quality** most medicine quality surveillance systems recommend that around 5% of these samples are tested further by laboratory methods.

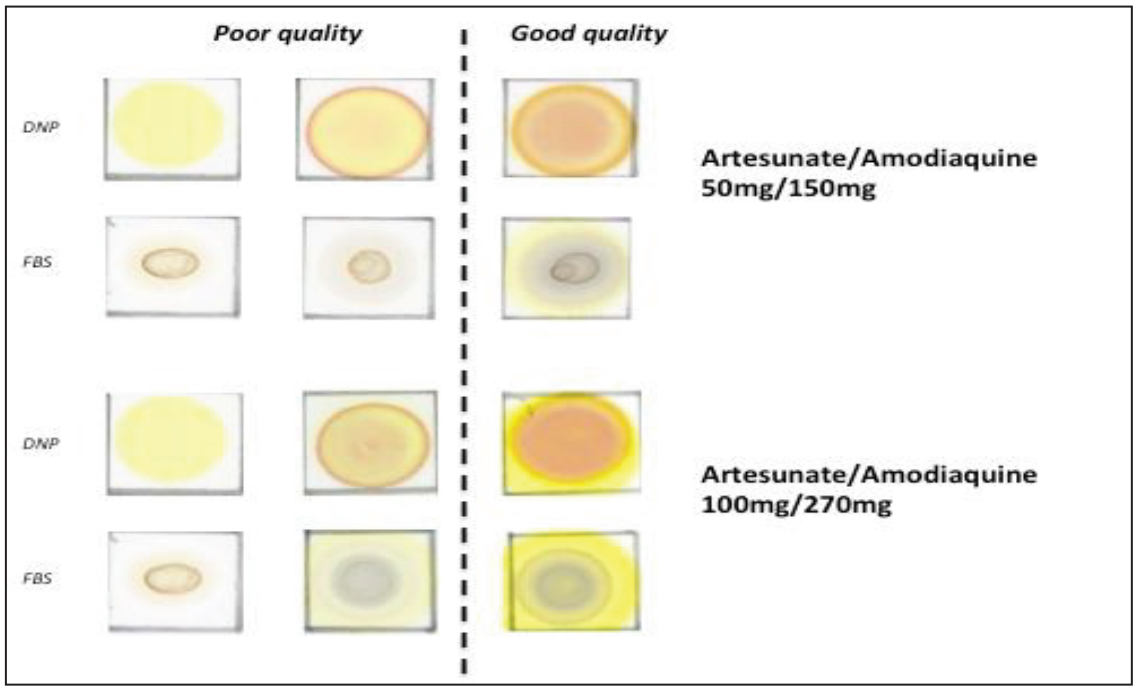
Colour Chart

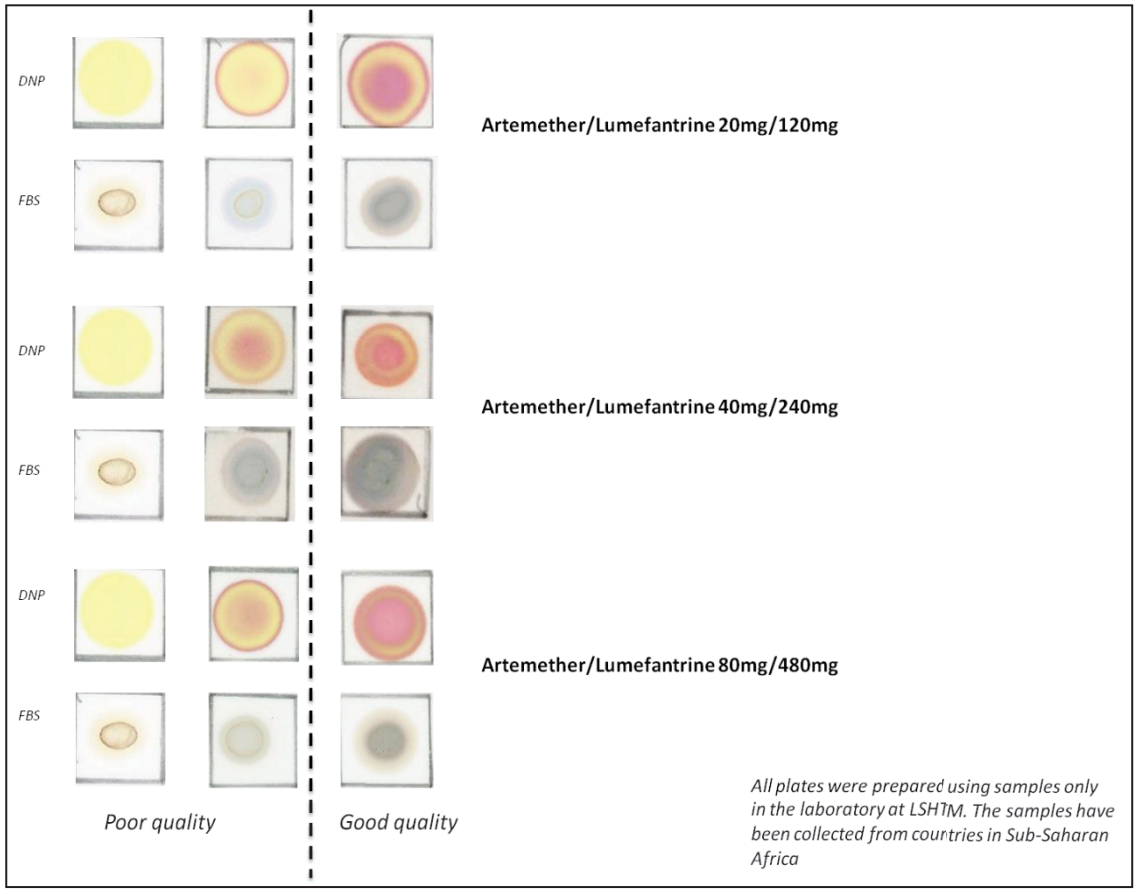
The colour chart below represents images produced following testing of samples of various ADs. The chart should be used to cross check the identity of a sample. For example, if a sample according to labelling on packaging states it is artemether/lumefantrine 20mg/120mg the image produced by the sample using the ADT test should correspond in colour (including depth) to the image listed as good quality for artemether/lumefantrine 20mg/120mg on the colour chart.

In terms of the quality of the medicine - any samples that produce images that are comparable to the poor quality images of ADs in the colour chart would need to be sent for further testing by HPLC. Samples that produce images that correspond to good (acceptable) quality images of ADs in the colour chart do not need to be sent for further testing.

The images in the colour chart were produced using samples of medicines that are commonly available in sub-Saharan Africa. The interpretation of the colour chart maybe regarded as subjective. Colours obtained with samples may appear slightly different to the corresponding images on the colour chart. However, as a general rule if a deep pink or blue colour is observed an AD is present and the sample is of good (acceptable) quality.




Poor quality
Good quality
DNP
FBS
DNP
FBS
Artesunate/Amodiaquine
50mg/150mg
Artesunate/Amodiaquine
100mg/270mg


DNP
FBS
DNP
FBS
DNP
FBS
Artemether/Lumefantrine 20mg/120mg
Artemether/Lumefantrine 40mg/240mg
Artemether/Lumefantrine 80mg/480mg
Poor quality
Good quality
All plates were prepared using samples only in the laboratory at LSHTM. The samples have been collected from countries in Sub-Saharan Africa

Bench Aid

ADT Testing Procedure (bench aid)

Test preparation

Note: The procedures below assume that a reference standard is available. If this is not the case any steps referring to standards can be omitted.

Sample Preparation

1. Pulverise samples with a pestle (if available), empty into a vial and dissolve resulting powder in 10 ml of methanol. Place mixture in ultrasonic bath for 30s. *(If pestle is unavailable shake manually and place mixture in sonicate for up to 5 minutes).*

2. If fragments of tablet remain after step 1 attempt to break the tablet down manually, do this carefully so the vial does not break. Alternatively draw 1ml of the mixture, transfer to Eppendorf tube and centrifuge *(If a centrifuge is not available the mixture is left on the bench until a clear top layer appears (sedimentation), the time taken for this is variable depending on the specific drug sample).*

3. Always label the sample (whether in original vial or Eppendorf tube) with a suitable code for the drug e.g AL 20 for artemether/lumefantrine 20mg/120mg

4. The sample mixture is now ready to be tested. All prepared samples must be used on the same day.

5. Clean out pestle using water and dry ensuring all residue is removed prior to pulverisation of next sample. This applies to any apparatus that may be reused.

TLC plate preparation (see diagram below)

This stage can be undertaken at any time before or during the sample preparation.

6. Using a pencil and stencil draw square or circular shapes roughly $1cm^2$ or 1cm in diameter.

7. For each drug 6 squares should be drawn, 3 in each row. The first row is for 2, 4 dinitrophenylhydrazine (DNP) and the second row is for Fast Blue Salt (FBS). Label each row.

8. Label the first column of squares/circles as blank (BL), the second column as reference (Ref) and the third column of squares/circles as ‘tablet.’

9. Label each row of three squares with an appropriate code for the drug e.g AL 20 (artemether/lumefantrine, 20mg/120mg)

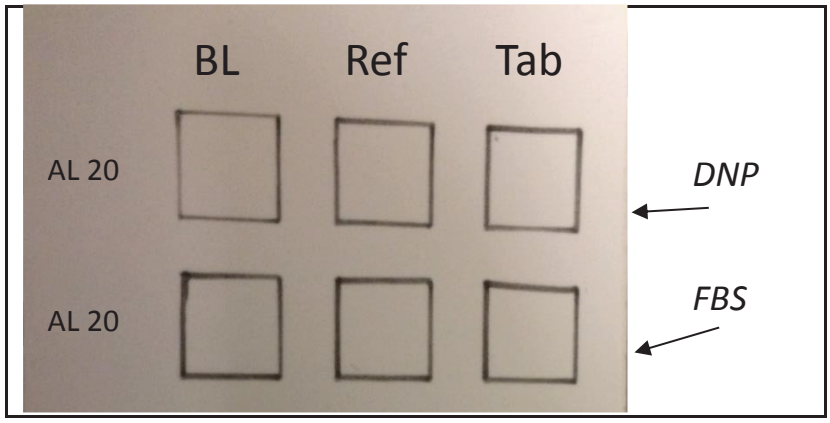


Figure 1: Matrix drawn on TLC plate

Testing steps

Note: In all relevant steps below it is recommended to spot 2 x 5µl as opposed to 1x 10µl to ensure that the sample/reagents are enclosed within the square/circle. Spot 1 x 5µl to the square then spot another 1 x 5µl on top of it.

1. Using a pipette, spot 2 x 5µl of methanol on the 'blank' (BL) square. Replace pipette tip.

2. Spot exactly 2 x 5µl of reference mixtures to the (Ref) squares. Replace pipette tip.

3. Spot exactly 2 x 5µl of sample mixture to the respective squares. Only draw up the supernatant (liquid at the top of the mixture), and make sure none of the sediment is drawn into the pipette. To minimise the risk of contamination, replace pipette tip before each new sample.

4. In the first row to each square/circle spot 5µl of DNP. Replace pipette tip.

5. In the second row to each blank square/circle spot 5µl of FBS.

6. Repeat Steps 1-6 as necessary for each drug sample being analysed.

Results Interpretation and actions taken (see diagram below)

1. Keep the TLC plate out of direct sunlight.

2. Read the plate after 40 minutes have elapsed.The colours produced are stable for a maximum of 2 weeks. To appreciate the true depth of colour the plate can be re-read after 24 hours.

3. DNP will produce a pink colour and the FBS a blue colour if the active ingredient (AD) is present. The image below illustrates the type of colour reaction observed at differing levels of active pharmaceutical ingredient (API).

4. If a sample produces an image such as C then the sample is regarded as of acceptable pharmacopeial quality (good quality) and does not need further testing.

5. If a sample produces an image such as those as A and B in the diagram below then the drug is regarded as poor quality. All samples regarded as poor quality should be sent for further testing by HPLC.

6. If either of the pink or blue colours are not observed, the result is inconsistent and the ADT test should be repeated.

7. If the results obtained on repeat testing are also inconsistent, the sample should be referred for analysis by HPLC.

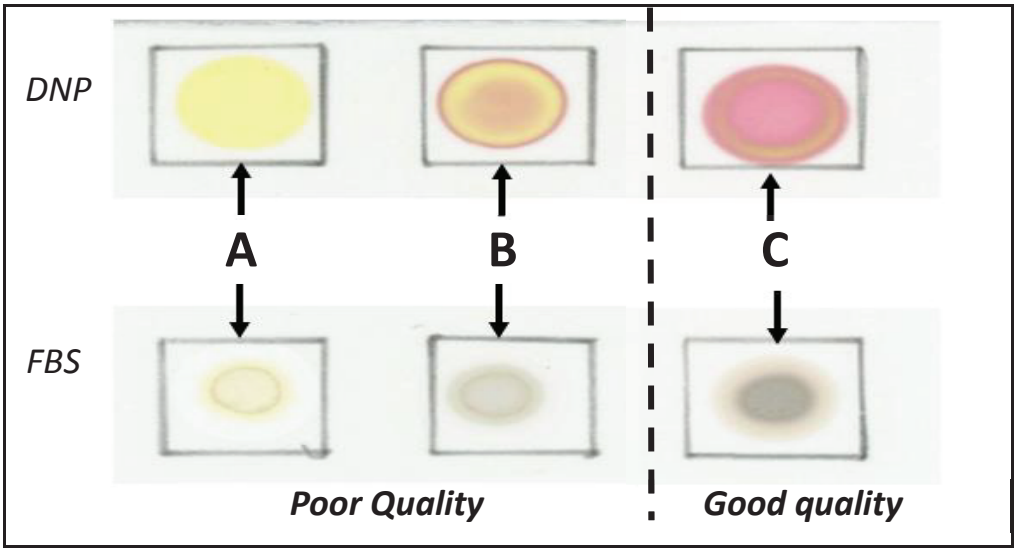


Figure 2: A, B and C are samples of artemether in solution of artemether/lumafantrine 20mg/120mg

References

1. World Malaria Report, Summary. World Health Organisation 2010. http://www.who.int/malaria/world_malaria_report_2010/worldmalariareport2010.pdf. [cited 16th June 2014]
2. Rozendaal J. Fake antimalaria drugs in Cambodia. *Lancet (London, England)*. 2001;357(9259):890.
3. Dondorp AM, Newton PN, Mayxay M, Van Damme W, Smithuis FM, Yeung S, et al. Fake antimalarials in Southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials. *Trop Med Int Health*. 2004;9(12):1241-6.
4. Newton PN, Fernandez FM, Plancon A, Mildenhall DC, Green MD, Ziyong L, et al. A collaborative epidemiological investigation into the criminal fake artesunate trade in South East Asia. *PLoS medicine*. 2008;5(2):209--19.
5. Sengaloundeth S, Green MD, Fernandez FM, Manolin O, Phommavong K, Insixiengmay V, et al. A stratified random survey of the proportion of poor quality oral artesunate sold at medicine outlets in the Lao PDR - implications for therapeutic failure and drug resistance. *Malaria journal*. 2009;8:172.
6. Bate R, Hess K. Anti-malarial drug quality in Lagos and Accra - a comparison of various quality assessments. *Malaria journal*. 2010;9:157.
7. Klein EY, Lewis IA, Jung C, Llinas M, Levin SA. Relationship between treatment-seeking behaviour and artemisinin drug quality in Ghana. *Malaria journal*. 2012;11:110.
8. Ofori-Kwakye K. Quality of Artesunate Tablets Sold in Pharmacies in Kumasi, Ghana. *Tropical Journal of Pharmaceutical Research*. 2008;7 (4):1179-84.
9. Osei-Safo D. Validation and Application of Quality Assurance Methods Developed for Artemisinin-based Antimalarial Drugs to Asses the Quality of a Selection of Such Drugs Distributed in Accra, Ghana. *African Journal of Pharmaceutical Sciences and Pharmacy*. 2010:1-25.
10. Chaccour CJ, Kaur H, Mabey D, Del Pozo JL. Travel and fake artesunate: a risky business. *Lancet (London, England)*. 2012;380(9847):1120.
11. Newton PN, Green MD, Mildenhall DC, Plancon A, Nettey H, Nyadong L, et al. Poor quality vital anti-malarials in Africa - an urgent neglected public health priority. *Malaria journal*. 2011;10:352.
12. Survey of the Quality of Selected Antimalarial Medicines Circulating in Madagascar, Senegal, and Uganda. United States Pharmacopeia United States Pharmacopeia U; 2009 November 2009. Report No. http://apps.who.int/medicinedocs/documents/s17069e/s17069e.pdf. [cited 26th February 2017]
13. Survey of the Quality of Selected Antimalarial Medicines Circulating in Six Countries of Sub-Saharan Africa. Geneva: World Health Organization 2011. http://www.who.int/medicines/publications/WHO_QAMSA_report.pdf. [cited 20th February 2017]
14. Green MD, Nettey H, Villalva Rojas O, Pamanivong C, Khounsaknalath L, Grande Ortiz M, et al. Use of refractometry and colorimetry as field methods to rapidly assess antimalarial drug quality. *J Pharm Biomed Anal*. 2007;43(1):105-10.
15. GPHF Minilab. Frankfurt, Germany: Global Pharma Health Fund 2012. www.gphf.org. [cited 25th April 2017]
16. Risha PG, Msuya Z, Clark M, Johnson K, Ndomondo-Sigonda M, Layloff T. The use of Minilabs to improve the testing capacity of regulatory authorities in resource limited settings: Tanzanian experience. *Health Policy*. 2008;87(2):217-22.
17. Ioset JR, Kaur H. Simple field assays to check quality of current artemisinin-based antimalarial combination formulations. *PLoS One*. 2009;4(9):e7270.