PQM Promoting the Quality of Medicines

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Integrating Medicines Quality Assurance into Universal Health Coverage Programming

A path to increasing efficiency, access, and coverage

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About PQM

The Promoting the Quality of Medicines (PQM) program is a cooperative agreement between the U.S. Agency for International Development (USAID) and the U.S. Pharmacopeial Convention (USP). The PQM program provides technical assistance to strengthen medicines regulatory authorities and quality assurance systems and supports manufacturing of quality-assured priority essential medicines for malaria, HIV/AIDS, tuberculosis, neglected tropical diseases, and maternal and child health.

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Abbreviations

ACT	artemisinin-based combination therapy
DALY	disability-adjusted life year
DRC	Democratic Republic of the Congo
GDP	gross domestic product
GMP	good manufacturing practices
LMIC	low- and middle-income country
MRA	medicine regulatory authority
SAFARI	Substandard and Falsified Antimalarial Research Impact (model)
SF	substandard and falsified
UHC	universal health coverage
UNICEF	United Nations Children's Fund
USAID	U.S. Agency for International Development
WHO	World Health Organization

Introduction

The goal of universal health coverage (UHC) is to ensure that all people obtain the health services they need without suffering financial hardship when paying for them [1]. The World Health Organization (WHO) reports that more than 50 percent of the world's population does not yet have full coverage of essential health services, with 12 percent of the population spending large amounts of their household income on health [2]. Sustainable Development Goal 3.8 supports UHC by aiming to achieve "access to safe, effective, quality and affordable essential medicines and vaccines for all" [3]. A well-functioning UHC system would ensure access to essential services, including safe, effective, affordable, quality-assured essential medicines.

The use of poor-quality medicines can prolong disease and harm patients. Consuming medicines containing insufficient amounts of active ingredients leads to longer and more severe illness, resulting in higher fatalities, greater opportunity for the spread of disease, and growth of drug resistance [4]. These health effects are accompanied by economic consequences such as additional healthcare costs, lost income, and lost productivity. Patients in low- and middle-income countries (LMICs) are especially at risk of health and economic harm from poor-quality medicines, as these countries have relatively weaker capacity to assure the quality of medicines in their markets. Medicine quality plays an important role in UHC, as quality health services cannot be delivered without quality-assured medicines. It has also been recognized that, for investments in health insurance schemes to be effective, they require allocations to build the capacity of supply chain managers and regulatory authorities [5, 6]. Improvements in health outcomes, reduced waste from the purchase and use of poor-quality medical products, and increased health system efficiency may all yield returns on investments in medicines quality assurance as part of health insurance schemes.

WHO estimates that 1 in 10 medical products circulating in LMICs are substandard or falsified [7]. WHO defines substandard medicines as "authorized medical products that fail to meet their quality standards, specifications, or both" [8]. Medical products that "deliberately and fraudulently misrepresent their identity, composition, or source" are classified as falsified [8]. A recent meta-analysis found that 13.6 percent (95% CI, 11.0%-16.3%) of essential medicines in LMICs are substandard or falsified, while the regional prevalence in Africa and Asia was 18.7 percent (95% CI, 12.9%-24.5%) and 13.7 percent (95% CI, 8.2%-19.1%), respectively [9]. Other recent literature reviews reported comparable ranges [7, 10]. The highest prevalence of poor-quality medicines was found in antimalarials (19.1%) and antibiotics (12.4%) [9].

Ensuring medicine quality is paramount in providing safe and effective healthcare and reducing overall healthcare costs, but the process of quality assurance presents challenges in the LMIC context. The pharmaceutical system operates within a complex health system, where pharmaceutical good governance is a necessary component of health systems strengthening to support UHC in LMICs [11]. Medicines are a leading source of health system inefficiency due to the pervasiveness of inappropriate use, variable quality of medicines on the market, and consumer preference for high-priced brand name medicines over generics despite their bioequivalence [12]. In addition, the availability

of unregistered medicines presents alternatives for patients to access and use medicines that are neither supported by health systems nor covered by health insurance plans. Creating good governance structures that can link the different components of the health system together is important in reducing inefficiencies, enhancing transparency, and maintaining quality standards throughout the pharmaceutical system. Moreover, improving financing schemes and strengthening governance of medicine procurement systems is essential to increasing financial protection and access to health services, which are core tenets of UHC [11, 13]. Increased healthcare utilization alone will not result in better health outcomes if the quality of health services is low [14]. Similarly, the full benefits of expanded coverage may not be realized without also ensuring the quality of medicines [15].

Financing and procurement of medicines play an important role in UHC schemes [11]. Financing schemes have the opportunity to shape patient demand for quality-assured medicines by implementing standard treatment guidelines and incentivizing certain prescribing behaviors of physicians [5]. Globally, a quarter of all health expenditure is spent on medicines [16]. *The Lancet*'s Commission on Essential Medicines Policies estimated that between $13 and $25 per capita (US$77.4 to $151.9 billion) is required to finance a basic package of essential medicines in all LMICs [16]. However, the majority of low-income countries and over a quarter of middle-income countries spend less than this benchmark [16]. Moreover, medicines are often paid out of pocket in many countries, putting individuals and households at risk of catastrophic healthcare costs [17-19]. UHC can improve population health by providing quality health services and quality-assured medicines while preventing catastrophic medical expenditures for the world's poorest communities.

Although there is growing evidence of the problem, the importance and challenge of ensuring medicine quality is rarely discussed in UHC planning, despite its inherent importance to achieving UHC goals. This report demonstrates the benefit of ensuring medicine quality in UHC, examines the association between UHC and medicine quality in the context of essential medicines in LMICs, assesses the health and economic impact of poor-quality antimalarials in a case study, and provides recommendations to integrate medicines quality assurance into UHC programming.

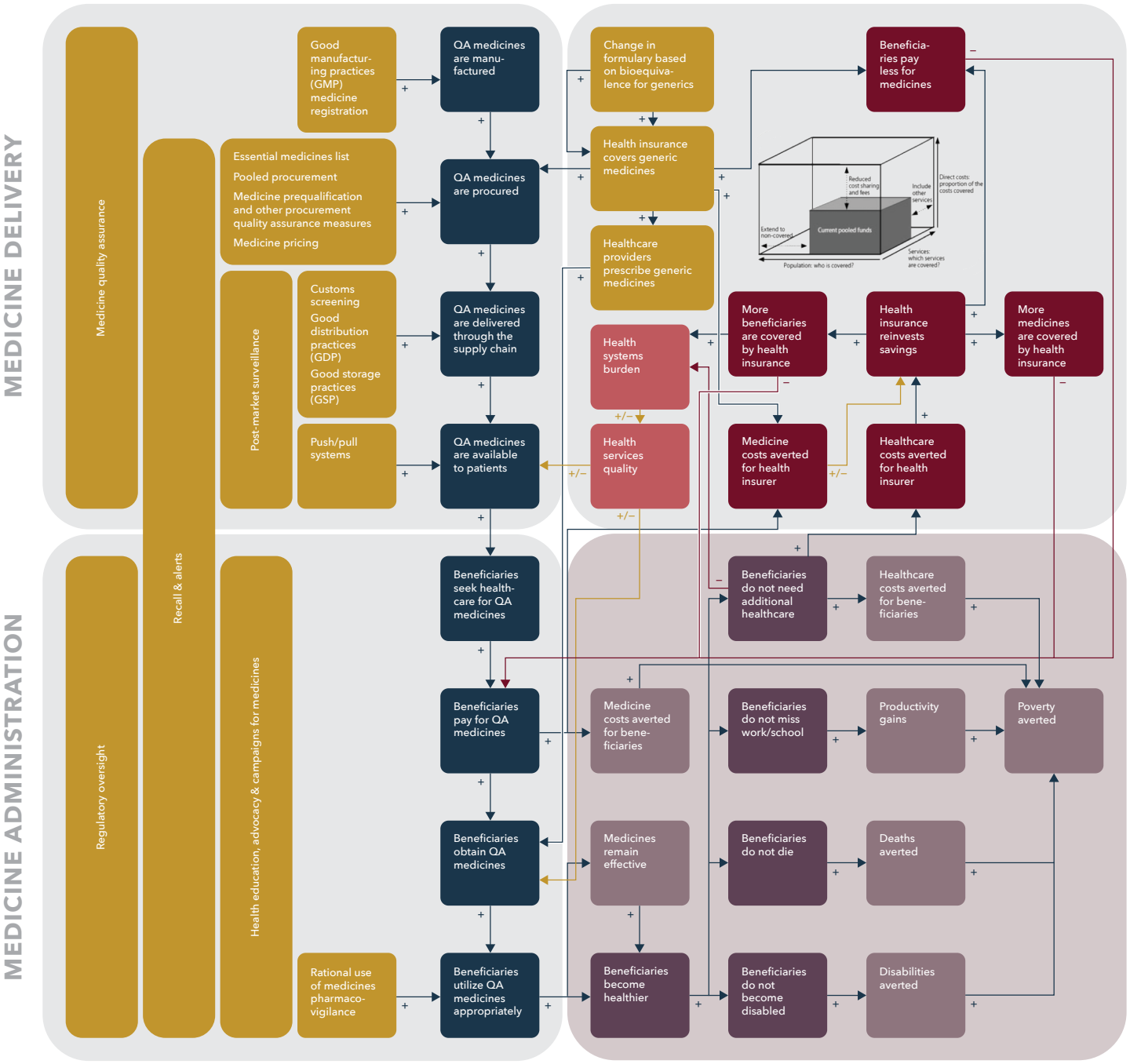
Medicines in UHC: Ensuring supply and use of quality-assured medicines

Systems map linking medicine quality with UHC

Systems maps have increasingly been used in health to help understand indirect effects in complex systems [20, 21]. With more detail displaying associations among variables than in a conceptual framework, systems maps can show how different parts of the system fit together and interact, which makes them a useful tool for understanding linkages that are less frequently explored. Taking a systems perspective is particularly useful for medicine quality due to the variety of processes and stakeholders involved in medical product quality assurance, from medicine manufacturing, purchasing, and supply chain delivery, to utilization. As medicine quality is not commonly emphasized in UHC planning and policies, we use the systems approach to connect the two. This research mapped the series of stages where processes are necessary for ensuring that quality-assured medicines reach patients, illustrating the flow from medicine manufacturing to utilization. We illustrate the linkages among health system and health insurance processes, and the resulting benefits to patients. The systems map also highlights the three dimensions of UHC, demonstrating how medicine manufacturing, distribution, and use relate to UHC [12]. Finally, we depict interventions that illustrate some of the key levers required to ensure quality-assured products in UHC.

Boys smiling near Dhaka, Bangladesh. Photo credit: Emdadul Bitu/USP.

Figure 1. Systems map linking medicine quality with UHC



LEGEND

QA – quality-assured

(+) increasing effect

(–) decreasing effect

(+/–) increasing or decreasing effect

Medicine quality interventions

Medicine supply chain

Universal Health Coverage mechanisms

Health system mechanisms

Beneficiary mechanisms

Benefits to beneficiaries

Figure 1 presents the systems map of associations among medicine quality and essential components of UHC. We first mapped the medicine supply chain (blue boxes), demonstrating the movement of medicines from manufacturing, procurement, and through the supply chain to reach health facilities, after which beneficiaries can obtain and utilize medicines. When beneficiaries utilize quality-assured medicines rather than no medicines or poor-quality medicines, beneficiaries can be healthier with a shorter duration of illness and milder symptoms, thus needing no additional healthcare and having the possibility to return to work (dark purple boxes) [4, 22-24]. With quality-assured medicines, beneficiaries can be cured of illness, averting disability and death [22-24]. Conversely, using a substandard medicine with inadequate active pharmaceutical ingredient could add days to recovery time or be completely ineffective, requiring a patient to seek additional care or suffer longer without proper treatment, increasing the severity of disease [22-24].

These beneficiary mechanisms result in further benefits (light purple boxes). When beneficiaries receive quality treatments without needing to seek additional care, there is a decrease in the risk of economic hardship due to reduced expenses for medicines and healthcare [5]. Beneficiaries also have more opportunity to be productive in society. In addition, appropriate use of quality-assured medicines contributes to maintaining medicine efficacy by delaying the development of antimicrobial resistance [4, 25]. Ensuring medicine quality thus contributes to the overall goal of UHC: to ensure healthcare access without suffering financial hardship.

Averting the need for additional healthcare services when beneficiaries become healthier with quality-assured medicines can trigger a number of health system mechanisms (pink boxes): when beneficiaries require less healthcare, the health system is less burdened and the quality of health service provision could improve [26]. Healthier beneficiaries utilizing quality-assured medicines can also trigger UHC mechanisms (dark red boxes): as beneficiaries require less care, health costs for health insurers decrease, and savings could be reinvested back into the system [27]. Health insurers can reinvest savings into three dimensions of UHC (illustrated by the cube in Figure 1) by covering more medicines and services, covering more beneficiaries, or covering more costs incurred by individuals through reducing cost-sharing for medicines and health services [12].

Regulatory oversight and quality assurance mechanisms throughout the supply chain make up the backbone of the system that ensures patients have access to and use quality-assured medicines. Along with other key interventions (yellow rectangles), these mechanisms are categorized as affecting medicine delivery, administration, or UHC. These interventions include best practices (e.g., good manufacturing, distribution, and storage practices), policies (e.g., for medicine registration, prequalification requirements, procurement), regulations (e.g., post-marketing surveillance, including customs screening and inspections), and education (e.g., health education on medicines, advocacy campaigns) [28-30]. Within UHC, we include the role of formulary management, where bioequivalence studies can trigger changes in formularies [31, 32]. This can subsequently impact insurance coverage for generic medicines, positively affecting prescribing practices and costs to health insurers and beneficiaries [33-36]. Getting quality-assured generic medicines on the preferred list of formularies is an example of a medicine quality assurance intervention that can save costs to health insurers and affect UHC [35, 36].

UHC indicators: Is there an association with poor-quality medicines?

To further investigate the potential association between UHC and medicine quality, we analyzed existing data on the prevalence of poor-quality medicines and a variety of UHC indicators. Two indicators were used to determine progress toward UHC: an indicator on essential services coverage [37], and an indicator on the proportion of the population with large household expenditures on health as a share of household expenditures [37-39]. Countries need to commit to enacting proper legislation and providing support to develop robust regulatory authorities responsible for the implementation and maintenance of a system to assure medicine quality. To explore the association of poor-quality medicines with a government's ability to regulate and its commitment to policies, we employed two indicators on government effectiveness and regulatory quality from the World Bank [40]. We also retrieved UNICEF's under-5 mortality rates for each country [41]. We examined how these indicators were associated with estimated substandard and falsified (SF) medicine prevalence for each country using data across 63 LMICs previously gathered from a systematic literature review and meta-analysis [7]. SF prevalence was estimated based on the number of samples that failed chemical testing over the total number of samples tested and reported within each country. We examined the association between country-specific SF prevalence and the proportion of essential services covered, government effectiveness, regulatory quality, and under-5 mortality using simple linear regression models. We analyzed how large health expenditures may be related to SF prevalence while controlling for gross domestic product (GDP) per capita [42].

We assessed the association between the prevalence of SF medicines and UHC indicators in 63 LMICs (Table 1). Across these countries, coverage of essential services by health insurance schemes was found to be slightly negatively associated with prevalence of SF medicines (p value 0.054; Figure 2A). This illustrates that countries with higher coverage of essential services by health insurance were likely to have a lower prevalence of poor-quality medicines. This may indicate that countries with stronger capacity to provide greater health insurance coverage are also able to better regulate the medicine supply chain. It could also indicate that coverage of more services can bring patients into the formal healthcare system, where they can access medicines secured through streamlined, well-regulated processes, mitigating the need to seek potentially compromised medicines from the informal system. UHC financing schemes can also provide incentives for providers to prescribe and dispense specific medicines procured through a system that ensures medicine quality; thus, as coverage of services and populations increases, this system may be reinforced through increased demand for quality-assured medicines.

Table 1. Summary of linear models of associations with prevalence of SF essential medicines

Variable*	Coefficient	Standard error	p value
Proportion of essential services covered† (N = 63)	−0.0023	0.001	0.054
Proportion of households with health expenditures at 10% or more of household expenditure*†	−0.0022	0.002	0.335
GDP per capita (N = 51)§	2.081e-05	5.21e-06	<0.001
Indicator for government effectiveness‡ (N = 63)	−0.0609	0.030	0.048
Indicator for regulatory quality‡ (N = 63)	−0.0762	0.037	0.046
Under-5 mortality rate (N = 63)	0.0011	0.001	0.056

SF: substandard and falsified, GDP: gross domestic product

** Data from the most recent year were used for each country by indicator: coverage of essential services: 2015; large household expenditure: 1998–2015; government effectiveness: 2017; regulatory quality: 2017; under-5 mortality rate: 2017.*

† Data were retrieved from the Global Health Observatory repository.

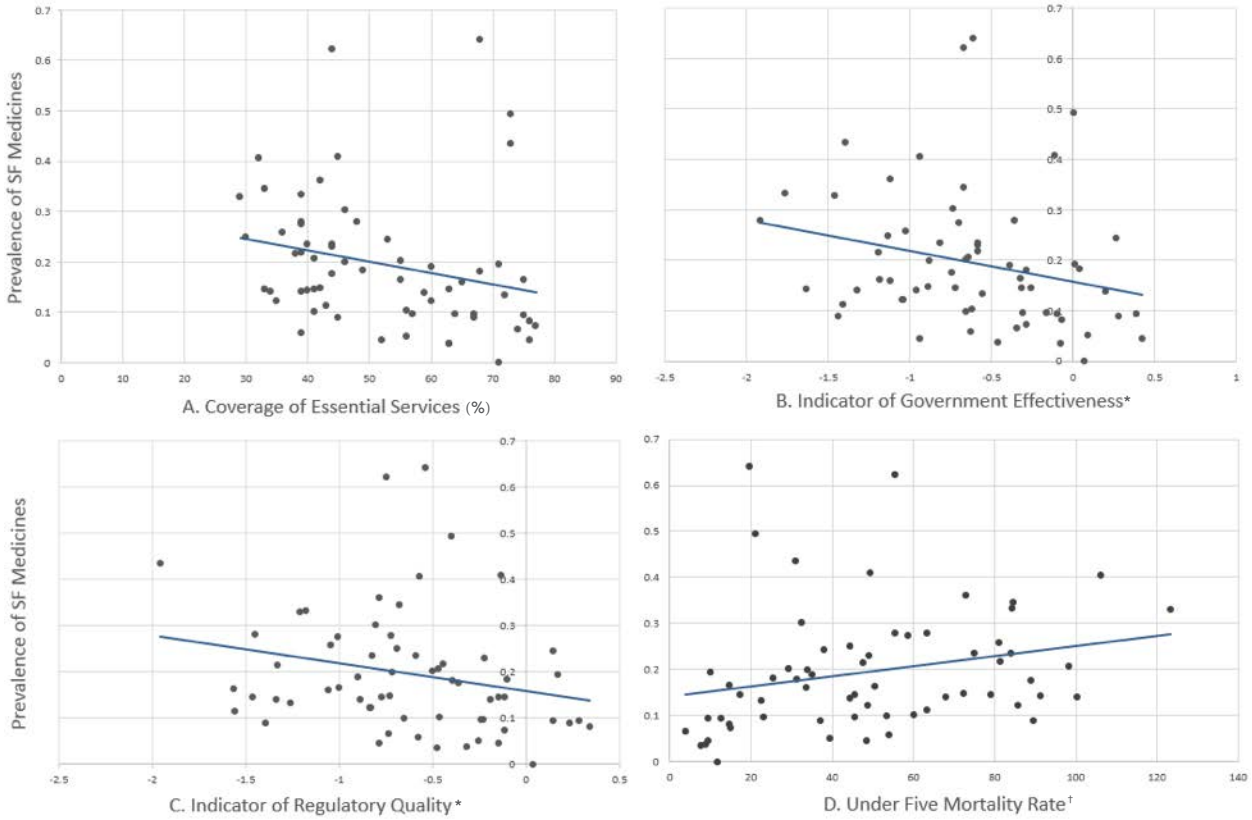
‡ Data were retrieved from the World Bank Governance Indicators, measured on a linear scale between −2.5 and +2.5.

§ We regressed the prevalence of SF essential medicines on the proportion of households with health expenditures at 10% or more of household expenditure, controlling for GDP per capita.

A negative association was also found between SF prevalence and both indicators for government effectiveness and regulatory quality. Higher prevalence of SF medicines was associated with lower governmental effectiveness (*p* value 0.048; Figure 2B) and lower regulatory quality (*p* value 0.046; Figure 2C). As was highlighted in the systems map, strong regulatory oversight is key to ensuring medicine quality, but it is only one part in a system that also relies on commitment from government stakeholders to be successful.

As one would expect solely based on medicine efficacy, SF prevalence was shown to have a slightly positive association with under-5 mortality (*p* value 0.056; Figure 2D).

Figure 2. Associations between country prevalence of SF medicines, UHC indicators, and under-5 mortality



** Regulatory quality and government effectiveness are measured on a linear scale between −2.5 and +2.5.*

† Measured in deaths per 1000 live births.

No significant association was found between large health expenditures and SF prevalence (*p* value 0.335) after controlling for GDP per capita. This lack of observable association does not indicate that poor-quality medicines do not result in larger household expenditures; it only suggests that it may not be the main driver of enhanced healthcare expenditure, where other factors (e.g., poverty, types of prevalent illnesses, and levels of health insurance) are at play. Furthermore, data on catastrophic health spending were not available for all countries, resulting in a lower number of observations for this analysis compared to others (51 compared to 63 countries).

Health and economic impact of poor-quality medicines: What does it mean for UHC implementation and sustainability?

Consumption of poor-quality medicines has harmful health effects that lead to social and economic losses for patients [4, 7]. Prolonged illness can lead to lost income and savings, due to the need for additional health services. One of the goals of UHC is to protect patients from financial hardship that results from paying for medical care out of pocket. By incorporating medicine quality assurance in UHC planning, UHC financing schemes can protect populations from the cost of additional care incurred by utilization of poor-quality medicines. Impact models are used to estimate the scale of the health and economic effects of poor-quality medicines by combining data on prevalence of specific SF drugs and estimates of their effects, such as lower efficacy or higher case-fatality rates, on patients. The results presented in the models below demonstrate the health and economic costs to the patient and the health system of having poor-quality medicines on the market, and the extent of savings that could be achieved under UHC by implementing interventions that would prevent the presence of SF medicines in the market.

Malaria is associated with high levels of morbidity and mortality in LMICs, and medicines to treat malaria (antimalarials) are, within the therapies surveyed, among the most common medications found to be of poor quality [9]. UHC planning in malaria-endemic countries would naturally entail making decisions about which malaria medications and services to make available and which populations will receive these benefits. To illustrate the potential health and economic impacts that can result from ensuring quality antimalarials, we analyzed the current landscape of the impact of SF antimalarials in a case study. Four countries were included in our analysis: Democratic Republic of the Congo (DRC), Nigeria, Uganda, and Zambia [22-24]. Estimates of country-specific impact were obtained from the Substandard and Falsified Antimalarial Research Impact (SAFARI) model, an agent-based model that simulates malaria disease progression, care seeking, and outcomes for children under age 5 [22-24].

Substandard and Falsified Antimalarial Research Impact (SAFARI) model

The SAFARI model was adapted and run separately for each country using country-specific demographic and epidemiological inputs. Methods for the development of the SAFARI model and individual country data are described in detail in other publications [22-24]. Agents sought malaria treatment and received either quality-assured or poor-quality antimalarials. Poor-quality antimalarials reduced medication efficacy and increased the likelihood of children progressing to severe malaria.

We demonstrate the potential savings in a system that assures the quality of antimalarials, which could be estimated by fewer deaths, fewer hospitalizations, lower costs of care, and gains in productivity (Table 2). The economic impact of SF antimalarials was further assessed at an individual level to demonstrate the cost of poor-quality medicines per malaria case and the cost attributable to SF medicines for each additional malaria death, hospitalization, and disability-adjusted life year (DALY).

To contextualize the impact of improving medicine quality, we compared it to other options that governments might consider in addressing malaria outcomes. We simulated two additional interventions: a scenario in which there were no stockouts of antimalarials, and one in which only first-line artemisinin-based combination therapies (ACTs) were taken. Low-quality anti-infectives can induce further costs to health systems and society by contributing to the development of antimicrobial resistance. We simulated the impact of widespread ACT resistance in a scenario where the effectiveness of ACTs was reduced, impacting the duration and severity of malarial illness.

Table 2 summarizes the results of the SAFARI model, showing the monetary and health savings that could result if all available antimalarials were of high quality. The overall prevalence of SF antimalarials in the four countries ranged from 10.3 percent in Zambia to 23 percent in Uganda. By improving the quality of antimalarials, we simulated fewer deaths annually: 12,300 averted in Nigeria, 1,121 in Uganda, 192 in Zambia, and 1,273 and 9,100 in the Kinshasa and Katanga regions of the DRC. This means that ensuring antimalarial quality can result in 33 fewer deaths per day in Nigeria and 4 fewer deaths per week in Zambia. The main driver for the large difference in absolute impact of antimalarial quality among the countries considered here is the variation in the burden of malaria in each country. For example, Nigeria has the highest burden of malaria cases of any single country in the world and has a much larger population, which drives the amount of medicines consumed in the model, resulting in large absolute differences in the impact of SF medicines [43].

The SAFARI model results suggest that each country would experience substantial savings by improving the quality of antimalarials for children. Total annual savings were simulated at $892 million in Nigeria, $130 million in Katanga, $31 million in Uganda, $21 million in Kinshasa, and $12.3 million in Zambia. Savings in direct costs incurred by public facilities and by patients were estimated to contribute between 3.3 percent and 23.8 percent of total savings ($660,000 to $30 million) across countries. We estimated that annual productivity losses attributable to SF antimalarials ranged from $7 million (Zambia) to $862 million (Nigeria). These savings were largely composed of the potential economic productivity that a child would contribute over a lifetime by averting death or disability due to poor-quality antimalarials.

Based on these estimates, SF antimalarials contributed between $6 per malaria case in Zambia and $86 per malaria case in the Katanga region in the DRC. Each additional death due to poor-quality antimalarials cost between $14,286 per death due to SF antimalarials in Katanga and $72,499 per death due to SF antimalarials in Nigeria. Each additional pediatric malaria-related hospitalization attributable to SF medicines cost between $584 per hospitalization in Kinshasa and $26,779 per hospitalization in Nigeria.

Table 2. SAFARI model results for the annual impact of SF antimalarials in four countries*

Country	GDP/ capita (2017 USD)	Overall SF Prevalence	Fewer Deaths	Fewer Hospitalizations	Fewer DALYs	Savings in Direct Costs†	Savings in Productivity	Total Savings from Improving Antimalarial Quality	Cost of SF per Case of Malaria	Cost per Death due to SF	Cost per Hospita-lization due to SF	Cost per DALY averted due to SF
Kinshasa (DRC)	$463	14.4%	−1,273	−35,800	–	−$4,968,700	−$15,980,000	−$20,900,000	$51	$16,413	$584	–
Katanga (DRC)	$463	14.4%	−9,100	−127,600	–	−$19,099,000	−$111,000,000	−$130,000,000	$86	$14,286	$1,019	–
Nigeria	$1,968	14.1%	−12,300	−33,300	−318,538	−$29,845,700	−$861,890,700	−$891,736,200	$37	$72,499	$26,779	$2,799
Uganda	$606	23.0%	−1,121	−13,919	−106,684	−$5,150,938	−$25,858,522	−$31,009,460	$9	$27,668	$2,228	$291
Zambia	$1,513	10.3%	−192	−912	−4,900	−$660,462	−$7,062,475	−$7,722,937	$6	$40,130	$8,471	$1,576

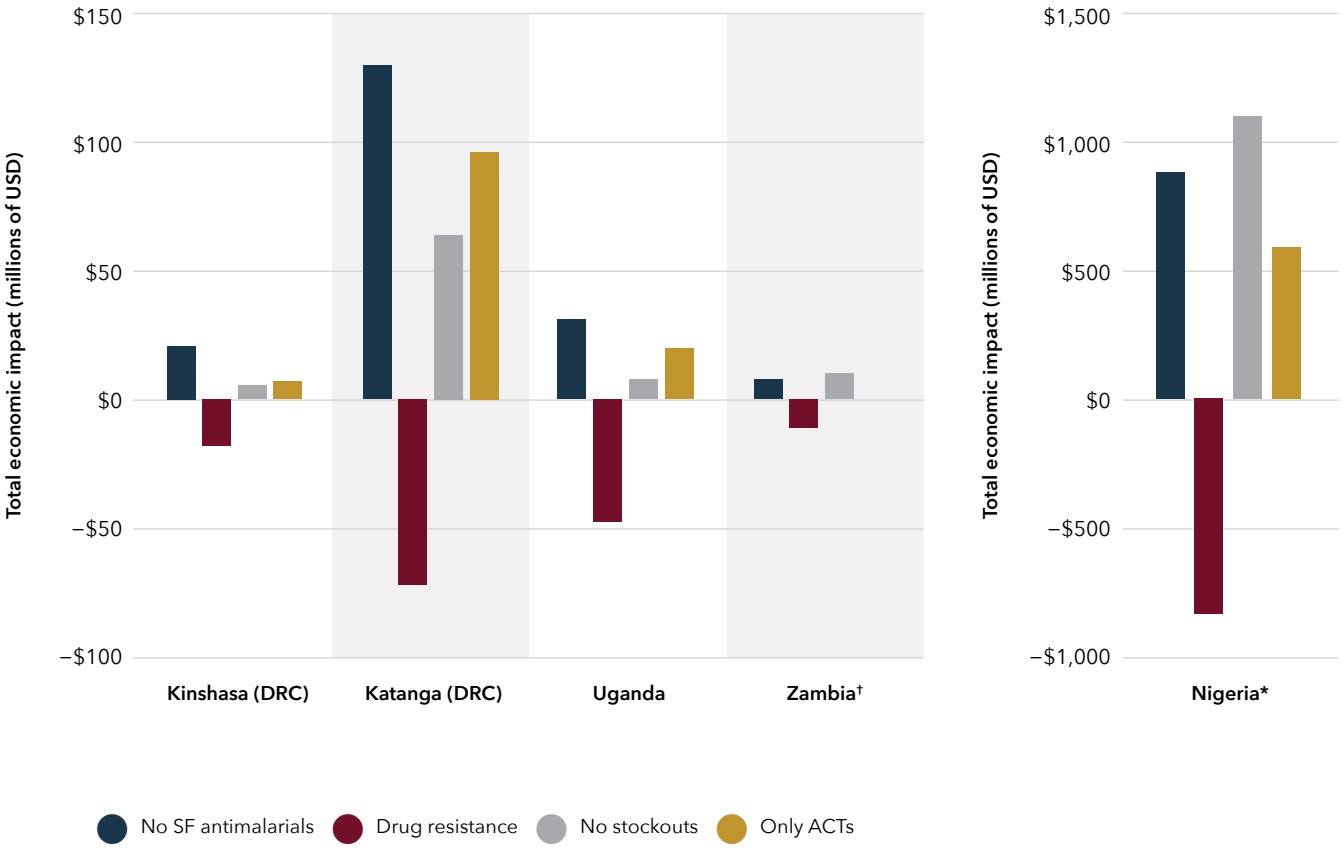
DRC: Democratic Republic of the Congo, GDP: gross domestic product, SF: substandard and falsified, DALYs: disability adjusted life years.

** Table results were calculated by comparing baseline results for the health and economic burden of malaria to a scenario in which only quality-assured antimalarials were available.*

† Costs for Zambia are in 2018 USD, all other countries' costs are in 2017 USD. Lifetime costs were discounted at 3 percent.

Figure 3 compares the potential impact of three simulated interventions (no SF antimalarials, no stockouts, and replacement of all antimalarials with ACTs) and one negative scenario (emergence of antimalarial resistance) in each country. Among the different investments that governments could make toward malaria reduction, providing quality-assured antimalarials was found to be the most impactful course in DRC, Uganda, and Zambia, while in Nigeria it was second to preventing stock-outs. In addition, the negative impact of antimalarial resistance, a potential consequence of recurrent use of poor-quality medicines, could be substantial, annually costing countries nearly $11 million in Zambia to $839 million in Nigeria.

Figure 3. Total economic impact of simulated scenarios



**Nigeria is depicted separately due to scale.*

† The only ACTs scenario for Zambia is slightly negative and does not appear in the figure due to scale. Costs for Zambia are presented in 2018 USD, all other countries are in 2017 USD.

SF impact in LMICs from 2017 WHO models

Two recent impact models have provided global and regional estimates of the health effects and economic impacts of SF medicines. The exact effect of poor-quality medicines on a patient varies depending on the type of medicine and the ineffectiveness of SF medicines, which can be modeled through different assumptions. A model for the impact of SF antimicrobials on childhood pneumonia assumed that poor-quality medications had between a 2- and 4-fold increase in case-fatality rate for the patients who received them [7]. Using the WHO estimate that 1 in 10 medications in LMICs are SF, it was estimated that annually between 72,430 and 169,271 excess deaths are attributable to poor-quality antibiotics used to treat childhood pneumonia [7].

Another analysis estimated the regional impact of SF antimalarials in sub-Saharan Africa, indicating that among cases that sought care, between 3.8 percent and 8.9 percent of deaths from malaria in the region were due to poor-quality antimalarials [7]. Depending on the malaria case estimates used, they found the total annual economic impact to be from $12.1 million up to $44.7 million (2017 USD). These added direct costs were incurred due to additional treatments caused by lowered efficacy of antimalarials.

These models demonstrate the extent of extra costs that are incurred due to the use of poor-quality medicines. The economic costs are borne by both patients who pay out of pocket for further care and health systems that provide additional care. The health impact demonstrated by these models can have even broader socioeconomic effects, as poor-quality medicines lead to lost productivity, increase risk of poverty, and disproportionately affect lower-income and rural patients [7, 44].

A health worker sees a mother and child outside Dhaka, Bangladesh. Photo credit: Emdadul Bitu/USP.

Quality assurance and universal health coverage

Quality assurance and regulatory functions across the supply chain

The medicine supply chain spans manufacturing, procurement, distribution, and storage; the last two occur at various stages, depending on the complexity of product distribution. Quality assurance of medicines requires measures along each stage of the supply chain to ensure that quality-assured medicines are procured and guarantee that quality is preserved until their delivery to patients and consumers [45, 46]. Quality of medicines is maintained along the supply chain primarily by regulatory functions of medicine regulatory authorities (MRAs). MRA functions include registration and market authorization of medicines, licensing of facilities, enforcement of standards and regulations through inspections, and post-marketing surveillance and pharmacovigilance [28, 29].

To ensure the quality of medicines in manufacturing, manufacturers follow good manufacturing practices (GMP) established either by WHO or national MRAs [30, 47, 48]. MRAs verify manufacturers' compliance with GMP before registering medicines and also enforce compliance through manufacturing facility inspections [48]. Similarly, during production, it is critical to ensure that manufacturers are compliant with GMP. To ensure such compliance, products may be prequalified if they are (1) included in the list of WHO-prequalified products [49], (2) have undergone the U.S. Food and Drug Administration's tentative approval process [50], (3) were recommended for use by the Expert Review Panel [51], or (4) have been registered by a WHO-Listed Authority [52]. Beyond procurement, stakeholders involved in the distribution and storage of medicines must adhere to good storage practice and good distribution practice standards, such as those established by WHO [53, 54], to ensure that medicine quality is maintained in the supply chain until they reach patients or final customers. MRAs are responsible for enforcing good storage practices and good distribution practices through customs screening of medicines and other inspection activities across the supply chain [48].

Impact of quality assurance and regulatory functions on UHC

In addition to ensuring the quality of medicines, quality assurance and regulatory measures performed across the supply chain can create cost savings in the health system, which in turn can improve UHC. For example, as part of their regulatory functions, MRAs oversee and require bioequivalence studies to ascertain the therapeutic equivalence between innovator and generic medicines [31, 32]. Data from these studies can inform inclusion of less expensive, quality-assured generics on the national formulary, allowing health payers to cover generic medicines and health providers to prescribe generic medicines. The lower costs of generic medicines can increase available pooled funds, which can be used to lower costs for patients, expand coverage of health services, or cover more people under UHC schemes.

Discussion and recommendations

Impact of medicine quality for UHC

Poor-quality medicines result in negative health, socioeconomic, and economic impact across the population. Poor-quality medicines contribute to increased mortality and morbidity, and decreased effectiveness of medicines necessitates prolonged and repeated treatments. Poor treatment outcomes caused by poor-quality medicines result in economic losses, wasted resources on ineffective treatments, and increased out-of-pocket health expenditures. In the long term, the health system cost burden of poor-quality medicines may contribute to making UHC schemes unsustainable, through increased avoidable expenditures and poor outcomes. Additional medicine and healthcare costs averted by utilizing quality-assured medicines can stretch pooled health system funds, which can then be reinvested into covering more services or more people under UHC, while also lowering out-of-pocket expenditures. Averting the negative effects of poor-quality medicines through quality assurance and strong regulatory functions will enable countries to scale the implementation of UHC.

Recommendations

Quality assurance of medicines in the context of UHC is dependent on strong regulatory systems overseen by MRAs. The complexity of medicine supply chains, limited resources, and capacity challenges contribute to weak regulatory systems, making quality assurance of medicines in UHC schemes a challenge [55-57]. Therefore, interventions to build capacity and strengthen regulatory systems are essential to sustainable implementation of UHC, underpinned by quality-assured medicines [58]. To mitigate the effects of limited resources for regulatory system capacity-building, data-driven and risk-based approaches can be adopted to ensure effective quality assurance and UHC implementation, despite weak regulatory systems.

Data-driven regulatory approaches emphasize decision-making based on data generated from quality assurance measures across the supply chain, and inform interventions to ensure quality of medicines. For example, data from the national quality control laboratory can inform decisions to issue recalls and alerts for poor-quality medicines. Similarly, data on bioequivalence of generics can inform decisions on registration and procurement of generic medicines. MRAs in weak regulatory systems can also leverage collaborations and exchange data to inform medicine quality assurance with other stronger regulatory authorities, as part of regulatory harmonization and reliance initiatives. Risk-based regulatory approaches focus resources on medicines that are at greatest risk of becoming of poor quality or have the potential to pose the greatest effects as a result of poor quality [59, 60]. For example, MRAs could focus quality assurance efforts on medicines that are covered under UHC schemes, such as those included on the Essential Medicines List or in the national formulary.

Research studies are needed in settings with weak regulatory systems that are implementing UHC schemes to inform data-driven and risk-based regulatory approaches. These studies are needed to determine which medicines, geographic areas, and supply chains need to be prioritized with limited regulatory resources [59]. Evidence is also needed on the benefits and costs of interventions to ensure medicine quality and to assess how these interventions support UHC schemes.

In summary, medicine quality plays an important role in UHC, and discussion to ensure the quality of medicines is essential for UHC planning.

Workers from a quality control laboratory in Indonesia receive hands-on training. Photo credit: USP.

References

[1]. World Health Organization. *What is health financing for universal coverage?* 2019 [cited 2019 February 1]; Available from: https://www.who.int/health_financing/universal_coverage_definition/en/.

[2]. World Health Organization. *Universal Health Coverage (UHC).* 2019 [cited 2019 May 5]; Available from: https://www.who.int/en/news-room/fact-sheets/detail/universal-health-coverage-(uhc).

[3]. World Health Organization. *Sustainable development goals (SDGs): Goal 3. Target 3.8.* 2019 [cited 2019 February 1]; Available from: http://iris.wpro.who.int/handle/10665.1/12880.

[4]. Bassat, Q., M. Tanner, P.J. Guerin, K. Stricker, and K. Hamed., *Combating poor-quality anti-malarial medicines: a call to action.* Malaria journal, 2016. **15**: p. 302-302.

[5]. World Health Organization. *Medicines in health systems: advancing access, affordability and appropriate use.* 2014 [cited 2019 June 1]; Available from: https://www.who.int/alliance-hpsr/resources/publications/9789241507622/en/.

[6]. Health Action International. *No Universal Health Coverage without Universal Medicines Coverage*. 2019 [cited 2019 August 27]; Available from: https://haiweb.org/universal-health-coverage/?pdf=18602.

[7]. World Health Organization. *A study on the public health and socioeconomic impact of substandard and falsified medical products.* 2017 [cited 2019 June 1]; Licence: CC BY-NC-SA 3.0 IGO]. Available from: https://www.who.int/medicines/regulation/ssffc/publications/se-study-sf/en/.

[8]. World Health Organization, *Seventieth World Health Assembly Update. 29 May.* 2017, World Health Organization: Geneva, Switzerland.

[9]. Ozawa, S., D.R. Evans, S. Bessias, D.G. Haynie, T.T. Yemeke, S.K. Laing, et al., *Prevalence and Estimated Economic Burden of Substandard and Falsified Medicines in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis.* JAMA Netw Open, 2018. **1**(4): p. e181662.

[10]. Koczwara, A. and J. Dressman, *Poor-Quality and Counterfeit Drugs: A Systematic Assessment of Prevalence and Risks Based on Data Published From 2007 to 2016.* J Pharm Sci, 2017. **106**(10): p. 2921-2929.

[11]. Kohler, J.C., T.K. Mackey, and N. Ovtcharenko, *Why the MDGs need good governance in pharmaceutical systems to promote global health.* BMC Public Health, 2014. **14**: p. 63.

[12]. World Health Organization. *World health report: health systems financing - the path to universal coverage*. 2010 [cited 2019 May 5]; Available from: https://www.who.int/whr/2010/en/.

[13]. World Health Organization. *Delivering Quality-Assured Medical Products for All 2019-2023 – WHO's Five-Year Plan to Help Build Effective and Efficient Regulatory Systems*. 2019 [cited 2019 June 1]; Available from: https://www.who.int/medicines/news/2019/WHO_ActionPlan.pdf?ua=1.

[14]. Kruk, M.E., A.D. Gage, N.T. Joseph, G. Danaei, S. Garcia-Saiso, and J.A. Salomon, *Mortality due to low-quality health systems in the universal health coverage era: a systematic analysis of amenable deaths in 137 countries*. The Lancet, 2018. **392**(10160): p. 2203-2212.

[15]. Wagner, A.K., J.D. Quick, and D. Ross-Degnan, *Quality use of medicines within universal health coverage: challenges and opportunities*. BMC Health Serv Res, 2014. **14**: p. 357.

[16]. Wirtz, V.J., H.V. Hogerzeil, A.L. Gray, M. Bigdeli, C.P. de Joncheere, M.A. Ewen, et al., *Essential medicines for universal health coverage*. Lancet, 2017. **389**(10067): p. 403-476.

[17]. Bigdeli, M., R. Laing, G. Tomson, and Z.U. Babar, *Medicines and universal health coverage: challenges and opportunities*. J Pharm Policy Pract, 2015. **8**(1): p. 8.

[18]. Huang, Y., Y. Jiang, L. Zhang, W. Mao, J.F.M van Boven, M.J. Postma, et al., *Availability, use, and affordability of medicines in urban China under universal health coverage: an empirical study in Hangzhou and Baoji*. BMC Health Serv Res, 2018. **18**(1): p. 218.

[19]. Onarheim, K.H., M.M. Sisay, M. Gizaw, K.M. Moland, O.F. Norheim, and I. Miljeteig, *Selling my sheep to pay for medicines - household priorities and coping strategies in a setting without universal health coverage*. BMC Health Serv Res, 2018. **18**(1): p. 153.

[20]. Lee, B.Y., S.M. Bartsch, Y. Mui, L.A. Haidari, M.L. Spiker, and J. Gittelsohn, *A systems approach to obesity*. Nutr Rev, 2017. **75**(suppl 1): p. 94-106.

[21]. Ozawa, S., L. Paina, and M. Qiu, *Exploring pathways for building trust in vaccination and strengthening health system resilience*. BMC Health Serv Res, 2016. **16**(Suppl 7): p. 639.

[22]. Ozawa, S., D. Haynie, S. Bessias, S. Laing, E.L. Ngamasana, T.T. Yemeke, et al., *Modeling the Economic Impact of Substandard and Falsified Antimalarials in the Democratic Republic of the Congo*. Am J Trop Med Hyg, 2019. **100**(5): p. 1149-1157.

[23]. Ozawa, S., D.R. Evans, C.R. Higgins, S.K. Laing, and P. Awor, *Development of an agent-based model to assess the impact of substandard and falsified anti-malarials: Uganda case study*. Malar J, 2019. **18**(1): p. 5.

[24]. Beargie, S.M., C.R. Higgins, D.R. Evans, S.K. Laing, D. Erim, S. Ozawa, *The economic impact of substandard and falsified antimalarial medications in Nigeria*. PLoS One, 2019. **14**(8): p. e0217910.

[25]. Nwokike, J., A. Clark, and P.P. Nguyen, *Medicines quality assurance to fight antimicrobial resistance.* Bull World Health Organ, 2018. **96**(2): p. 135-137.

[26]. World Health Organization, Organisation for Economic Co-operation and Development, and The World Bank, *Delivering quality health services: a global imperative for universal health coverage.* 2018 [cited 2019 5 September]; Available from: https://www.who.int/servicedeliverysafety/quality-report/en/.

[27]. Homer, J., B. Milstein, G.B. Hirsch, and E.S. Fisher, *Combined Regional Investments Could Substantially Enhance Health System Performance And Be Financially Affordable.* Health Affairs, 2016. **35**(8): p. 1435-1443.

[28]. Kaddu, G., E. D'Amore, A. Clark, and P. Nkansah. *Strengthening Regulatory Systems To Improve Medical Product Quality in Low- and Middle-Income Countries.* 2018 [cited 2019 June 1]; Available from: https://www.usp-pqm.org/sites/default/files/pqms/article/strengtheningregulatorysystemsforqa_sept2018.pdf.

[29]. World Health Organization. *Regulatory system strengthening.* 2019 [cited 2019 27 June]; Available from: https://www.who.int/medicines/regulation/rss/en/.

[30]. World Health Organization. *Good Manufacturing Practices.* 2019 [cited 2019 26 June]; Available from: https://www.who.int/biologicals/vaccines/good_manufacturing_practice/en/.

[31]. Kaplan, W.A., J. Cardenas, C. Mansilla, T. Tobar, and W.J. Wirtz, *The implementation of the bioequivalence certification policy in Chile: An analysis of market authorization data.* PloS one, 2019. **14**(5): p. e0217334-e0217334.

[32]. Nation, R.L. and L.N. Sansom, *Bioequivalence requirements for generic products.* Pharmacology & Therapeutics, 1994. **62**(1): p. 41-55.

[33]. Cameron, A., A.K. Mantel-Teeuwisse, H.G. Leufkens, and R.O. Laing, *Switching from originator brand medicines to generic equivalents in selected developing countries: how much could be saved?* Value Health, 2012. **15**(5): p. 664-73.

[34]. Sarpatwari, A., N.K. Choudhry, J. Avorn, and A.S. Kesselheim, *Paying Physicians to Prescribe Generic Drugs and Follow-On Biologics in the United States*. PLoS Medicine, 2015. **12**(3): p. e1001802.

[35]. Conrad, R., W. Liu, Z. Tillman, A. So, A. Schick, C. Nardenelli, et al., *Estimating Cost Savings From Generic Drug Approvals In 2017.* 2017 [cited 2019 September 5]; Available from: https://www.fda.gov/media/113500/download.

[36]. Hassali, M.A., A.A. Alrasheedy, A. McLachlan, T.A. Nguyen, S.K. Al-Tamimi, M.I. Ibrahim, et al., *The experiences of implementing generic medicine policy in eight countries: A review and recommendations for a successful promotion of generic medicine use.* Saudi Pharmaceutical Journal, 2014. **22**(6): p. 491-503.

[37]. World Health Organization, *UHC service coverage* 2015, World Health Organization: Geneva, Switzerland.

[38]. UHC 2030. *UHC indicators for SDG monitoring framework agreed*. 2017 [cited 2019 March 1]; Available from: https://www.uhc2030.org/news-events/uhc2030-news/uhc-indicators-for-sdg-monitoring-framework-agreed-398330/.

[39]. World Health Organization, *Population with household expenditures on health greater than 10% of total household expenditure or income*. 2015, World Health Organization: Geneva, Switzerland.

[40]. World Bank, *World Governance Indicators*. 2018, The World Bank: Washington, DC.

[41]. UNICEF. *Child Mortality Estimates*. 2019 January 15, 2019 [cited 2019 January 15]; Available from: https://data.unicef.org/topic/child-survival/under-five-mortality/.

[42]. World Bank, *GDP per capita (current US$)*. 2017, The World Bank: Washington, DC.

[43]. World Health Organization. *World Malaria Report 2018*. 2018 [cited 2019 June 1]; Available from: https://www.who.int/malaria/publications/world-malaria-report-2018/en/.

[44]. Evans, D.R., C.R. Higgins, S.K. Laing, P. Awor, and S. Ozawa, *Poor-quality antimalarials further health inequalities in Uganda*. Health Policy and Planning, 2019.

[45]. World Health Organization. *A model quality assurance system for procurement agencies*. 2007 [cited 2019 June 1]; Available from: https://www.who.int/medicines/publications/ModelQualityAssurance.pdf.

[46]. Seiter, A. and R. Lakshminarayanan. *Pharmaceuticals: quality assurance in the distribution chain* HNP brief 2005 [cited 2019 May 5]; Available from: http://documents.worldbank.org/curated/en/199821468013806092/Pharmaceuticals-quality-assurance-in-the-distribution-chain.

[47]. World Health Organization. *WHO good manufacturing practices for biological products*. 2015 [cited 2019 June 1]; Available from: https://www.who.int/biologicals/areas/vaccines/Annex_2_WHO_Good_manufacturing_practices_for_biological_products.pdf.

[48]. Gouveia, B.G., P. Rijo, T.S. Goncalo, and C.P. Reis, *Good manufacturing practices for medicinal products for human use*. Journal of pharmacy & bioallied sciences, 2015. **7**(2): p. 87-96.

[49]. World Health Organization. *Prequalification of medicines by WHO*. 2013 [cited 2019 26 June]; Available from: https://www.who.int/news-room/fact-sheets/detail/prequalification-of-medicines-by-who.

[50]. Chahal, H.S., J.S. Murray, M. Shimer, P. Capella, R. Presto, M.L. Valdez, et al., *The US Food and Drug Administration's tentative approval process and the global fight against HIV.* Journal of the International AIDS Society, 2017. **20**(4): p. e25019.

[51]. The Global Fund. *Sourcing & Management of Health Products*. 2019 [cited 2019 25 July]; Available from: https://www.theglobalfund.org/en/sourcing-management/quality-assurance/expert-review-panel.

[52]. Ward, M. *WHO-listed Authorities (WLA): promoting timely access and reliance*. 2018; Available from: https://extranet.who.int/prequal/sites/default/files/documents/1_Ward-Day3-2018.pdf.

[53]. World Health Organization. *Guide to good storage practices for pharmaceuticals*. WHO Technical Report Series 2003 [cited 2019 May 5]; No. 908:[Available from: https://www.who.int/medicines/areas/quality_safety/quality_assurance/GuideGoodStoragePracticesTRS908Annex9.pdf?ua=1.

[54]. World Health Organization. *WHO good distribution practices for pharmaceutical products*. WHO Technical Report Series No. 957, Annex 5 2010 [cited 2019 May 5]; Available from: https://www.who.int/medicines/areas/quality_safety/quality_assurance/GoodDistributionPracticesTRS957Annex5.pdf.

[55]. Moran, M., N. Strub-Wourgaft, J. Guzman, P. Boulet, L. Wu, and B. Pecoul, *Registering New Drugs for Low-Income Countries: The African Challenge*. PLoS Medicine, 2011. **8**(2): p. e1000411.

[56]. Pezzola, A. and C.M. Sweet, *Global pharmaceutical regulation: the challenge of integration for developing states*. Globalization and Health, 2016. **12**(1): p. 85.

[57]. Lim, J.C.W., *Strengthening Health Products Regulatory Systems to Enhance Access to Quality Health Products in the Asia-Pacific*. Ther Innov Regul Sci, 2018. **52**(6): p. 751-754.

[58]. Roth, L., D. Bempong, J.B. Babigumira, S. Banoo, E. Cooke, D. Jeffreys, et al., *Expanding global access to essential medicines: investment priorities for sustainably strengthening medical product regulatory systems*. Globalization and health, 2018. **14**(1): p. 102-102.

[59]. Babigumira J.B., A. Stergachis, T. Kanyok, L. Evans, M. Hajjou, P. Nkansah, et al., *A Framework for Risk-Based Resource Allocation for Pharmaceutical Quality Assurance for Medicines Regulatory Authorities in Low- and Middle-Income Countries*. 2018 [cited 2019 June 1]; Available from: https://www.usp-pqm.org/sites/default/files/pqms/article/risk-based_resource_allocation_framework_june2018.pdf.

[60]. Hammett, R. and L. Hunt, *The Australian Medicines Regulatory System: A Risk-Based Approach to Regulation*. Drug Information Journal, 2009. **43**(1): p. 17-20.