Health and Economic Burden of Substandard and Falsified Medicines

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Abstract

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One in 10 medical products in low- and middle-income countries (LMICs) are reportedly substandard or falsified (SF). Poor quality medicines burden health systems and individuals by diverting resources to harmful or ineffective products, prolonging illnesses and increasing risks of complications and mortality. While several models have been developed to estimate the health and economic impact of SF medicines, they have been applied solely to specific medicines (i.e., antimalarials and antibiotics) in a small number of settings. In order to address this gap and advance the field, this dissertation aimed to develop tools to help countries assess their health and economic burden from SF medicines more broadly. First, we developed a conceptual framework as a guide for the estimation of the health and economic burden of SF medicines by identifying high priority medicines and evaluating data availability, gaps and modeling approaches. Second, we developed an adaptable model as a tool that can be used to estimate the health and economic burden of any medicine in any country. Third, we applied it oxytocin in Kenya as a case study. Finally, we developed a comprehensive disease-specific model for oxytocin that captures all relevant aspects of disease progression and specifications to generate more accurate estimates and to compare its findings to those generated by an adaptable model. The adaptable model estimated that among 1.2 million pregnant patients delivering in healthcare facilities in Kenya yearly, the

burden of SF oxytocin (assuming a prevalence of 7%) is estimated be responsible for 2,493 additional cases of postpartum bleeding, 25 hysterectomies, 26 deaths and over 420 years of life lost. The economic burden was estimated to be approximately $1,240,000 from a societal perspective, reflecting approximately $300,000 due to early death and lost productivity and approximately $940,000 in direct medical costs annually. For the same population, the oxytocin-specific model estimated that 7% SF oxytocin is responsible for 2,067 additional cases of postpartum bleeding, 15 hysterectomies, 32 deaths, over 600 years of life lost, 560 QALYs lost and 2,187 DALYs accrued every year. The economic burden was estimated to be approximately $1,970,000 from a societal perspective, reflecting approximately $740,000 due to early death and lost productivity and approximately $1,220,000 in direct medical costs. The magnitude of the burden generated by the oxytocin-specific model was comparable to the adaptable model. but the results yielded were more accurate. These findings demonstrate that SF oxytocin is an urgent issue to be addressed and Kenya and that the adaptable model can be leveraged by relevant stakeholders as a tool to generate high-level estimates on the health and economic burden of any medicine in their country. The significance of this study lies in its ability to provide policymakers in Kenya with crucial information that will assist them in making informed decisions about the issue of SF oxytocin and in its potential to provide other key stakeholders tools to generate locally specific and policy-relevant evidence on the burden of other SF medicines.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Chapter 1. INTRODUCTION

Access to quality-assured medical products is a critical component of achieving improved health outcomes and achieving health-related Sustainable Development Goals. Poor quality medicines, vaccines, biologics and diagnostics may be ineffective, wasteful, and/or even harmful. Yet, one third of the global population is unable to obtain quality-assured medicines in a reasonable time frame.[1] This may be due to several factors, including inadequate healthcare infrastructure, limited resources, and regulatory barriers.[1]

The World Health Organization (WHO) reported in 2017 that, on average, one in 10 medical products circulating in low- and middle-income countries (LMICs) is substandard or falsified (SF). The most recent estimated expenditure on acquiring SF medical products of LMICs as of 2017 is in the order of US$ 30.5 billion annually.[2] The WHO study acknowledged that, due to limitations in data availability and the non-representative nature of the samples collected, the true health and economic burden of poor-quality medicines in LMICs is unknown and likely much higher in some settings.

Substandard medicines are defined as "authorized medical products that fail to meet their quality standards, specifications, or both".[3] For example, substandard medicines may contain less or more active pharmaceutical ingredients (API) than specified on the package, which may be due to issues in the manufacturing process.[4] Degraded medicines are also substandard medicines and may result from the exposure of quality-assured medicines to excessive light, heat, and/or humidity.[5] Falsified medicines are medical products that "deliberately and fraudulently misrepresent their identity, compositions, or source".[3]

Systematic reviews have established that SF medicines pose a health and economic burden in LMICs.[2,6] The use of SF medicines contributes to prolonged illnesses and risk of treatment failure resulting in an increase in morbidity, mortality and prevalence of disease.[2,7] SF antimicrobials put entire communities at risk of developing drug resistance and threatening global treatment effectiveness. Moreover, the circulation of SF medicines undermines public confidence in the healthcare system and in the legitimacy of healthcare professionals.[2,7–11] The erosion of trust in the healthcare system and healthcare professionals can further encourage inappropriate self-medication and informal care-seeking over time.[12]

Unfortunately, there is a scarcity of reliable data on the public health and socioeconomic burden of SF medicines.[2] A stronger evidence base is needed to help prevent, identify and respond to SF medicines and the public health threat they may pose. A WHO proposal for a study on the public health and socioeconomic impact of SF medical products stated that *"The lack of understanding of the public health and economic costs [of SF medical products] has frustrated efforts at making the argument that investments in strengthening regulatory systems are a good buy and has prevented countries from understanding and acting on the problem in their own settings."*[13]

Globalized production and distribution systems are becoming more complex but are not accompanied by strengthening and harmonization of regulatory systems globally, particularly in LMICs.[14] As of 2021, it is estimated that 80% of APIs and 40% of finished pharmaceutical products are imported for domestic use in the United States.[15] Hence, the issue of SF medical products continues to grow in importance and the global pharmaceutical market is now characterized by multiple standards of quality.[16] Strengthening regulatory systems is a public health good as it ensures access to safe, quality-assured, and affordable medical products. Yet, only 30% of national regulatory authorities (NRAs), according to the WHO, have the capacity to perform all core regulatory functions for medicines and can efficiently and effectively regulate medical products in their countries.[17] That limits their capacity to assess and approve health products and hampers efforts to ensure the quality, safety and efficacy of medical products.[17] Thanks to the development of the WHO Global Benchmarking Tool (GBT), the first globally accepted tool that enables an objective assessment and strengthening of NRAs, countries now have a tool that allows them to identify gaps and establish institutional development plans with realistic standards and well-defined interventions to rigorously strengthen their system.[18] The availability of this globally recognized GBT for regulatory systems emphasizes the need for increased national-level commitments to strengthening NRAs; a better understanding of in-country SF health outcomes and economic costs would support countries in making these commitments. For example, locally-specific evidence on the burden of SF medicines can inform the GBT's market surveillance and control module activities including the prevention and detection of and response to SF medicine and the market surveillance program for monitoring the quality of medical products throughout the supply chain.[18]

However, to date, there is no methodological framework to assist countries in estimating the health and economic burden of SF medical products. Greater development and use of models could inform LMIC governments and other stakeholders on the threats and burden of use of SF medicines to their countries. That can bolster arguments in favor of additional investments by governments and other stakeholders, such as donor organizations towards regulatory system strengthening to combat SF medicines and to achieve maximum population health impact.[19,20]

Overall goal and specific objectives

The overall goal of this dissertation is to create tools to generate evidence on the health and socioeconomic burden of SF medicines. In my first aim, a conceptual framework and adaptable model were developed as a tool intended to be used in situations where time and resources are limited for estimating the health and economic burden of any SF medical product. In my second aim, this framework and adaptable model were operationalized in the form of a case study where the health and economic burden of SF oxytocin were estimated in Kenya. In my third aim, a full disease model for oxytocin was developed to provide a more detailed understanding on the burden of the SF oxytocin and to compare its findings to those obtained using the adaptable model.

Chapter 2. Conceptual framework for estimating the health and economic burden of substandard and falsified medicines

2.1 INTRODUCTION

Substandard and falsified (SF) medicines pose a significant global health threat for many reasons. First, they can contain incorrect or inadequate quantities of active pharmaceutical ingredients (API), which can result in treatment failure, prolonged illness, increased risks of harm, illness and even mortality to patients who consume them.[2,7] Second, SF antimicrobials can contribute to the development of drug-resistant strains of pathogens, making it difficult to treat common conditions.[2,9,10,21,22] Third, the availability of SF medicines undermines public confidence in healthcare systems, potentially leading to decreased adherence to recommended treatments, increased tendency for individuals to seek informal care and resort to self-medication over time and ultimately, decreased health outcomes.[12]

In addition to the humanistic impact, the proliferation of SF medicines can also have a substantial economic burden on healthcare systems and patients due to increased healthcare costs and loss of productivity. According to a report by the World Health Organization (WHO), the economic costs of acquiring SF medicines only was estimated in 2017 to be approximately $30 billion annually.[2] Determining the exact global prevalence of SF medicines proves challenging due to the scarcity of reliable data, as well as the substantial variations observed across regions, countries, and different types of medicines. Antimalarials and anti-tuberculosis drugs appear to be particularly affected by this issue. A 2018 meta-analysis reported that SF medicines can represent up to 13.6% (95% CI: 11.0-16.3) of essential medicines in LMICs.[6] The WHO has emphasized the urgent need to improve the monitoring, reporting and regulatory measures to combat the phenomenon of SF medicines and to ensure the quality, safety and efficacy of medical treatments worldwide.[2]

The globalized production and distribution of medicines has increased access to affordable treatments worldwide, but it has also resulted in the rapid spread of SF medicines in the supply chain before it is possible to detect them and intervene in a timely manner.[23] This globalization has not been accompanied by strengthening and harmonization regulatory systems globally. The spread of SF medicines highlights the importance of regulatory oversight and the need for increased collaboration among international agencies to ensure the safety and efficacy of medicines globally.[14]

In high-income countries, national regulatory authorities (NRAs) have developed stringent criteria and regulations to ensure medications are safe, effective, and of high quality. However, in LMICs, the ability of NRAs is constrained by a shortage of human and financial resources within the health sector, leading to a sub-optimally regulated environment where SF medicines production can go undetected or unaddressed.[14] The issue of SF medical products continues to grow in importance and the global pharmaceutical market is now characterized by multiple standards of quality which can lead to differences in the safety and efficacy of medicines available in different countries.[16]

Some medication regulations are standardized, transferable and can apply to most countries, such as the International Conference on Harmonization (ICH) guidelines.[24] But the extent to which these regulations are implemented and enforced can vary widely between countries. Some regulations may be more applicable to countries with strong regulatory and monitoring systems in place, while others may be more flexible to accommodate the different levels or regulatory capacity in different countries.[25]

With competing and conflicting health priorities and limited resources, allocating sufficient resources to build and strengthen pharmaceutical quality assurance is essential but remains a challenge for LMICs. Many countries lack the capacity to carry out all key medicines' regulatory functions.[18] This situation calls for prioritization of resources, which can be done using the concept of a risk-based approach (RBA).[26] RBA is a strategy that aims to identify and manage potential risks to patient safety and healthcare outcomes by directing resources to the areas of highest risk.

If product quality risks are identified, an RBA could prioritize them based on their risks and assign appropriate resources to mitigate or prevent them.[27] This approach is designed to inform the proportional allocation of regulatory resources and optimize the impact of investments by ensuring regulatory activities are targeting high-risk issues.[28] It is important for LMIC governments and other stakeholders to understand and mitigate their country-specific threats and burden of SF medicines to their countries. By addressing immediate challenges in a targeted and strategic manner, countries can build momentum and create a foundation for longer-term regulatory strengthening efforts, which can help sustainably improve healthcare quality and patient safety over time. Lack thereof may lead to inadequate attention, funding and actions to address this health problem.

The development of a conceptual framework is an essential aspect of research. I It can serve as a guide to standardize the estimation of the health and economic burden of SF medicines. The need for such a framework is particularly high in countries where SF medicines are prevalent so it can guide the generation of estimates of the burden of SF medicines and identify key data gaps for SF medicines. This chapter focuses on the development and presentation of the conceptual framework for the estimation of the health and economic burden of any SF medicine in any country.

2.2 MATERIALS AND METHODS

A conceptual framework was developed to describe the process, the considerations and decisions of the scope, data and modeling approach to generate country-specific SF burden estimates. The research question was defined as follows: *"How can we estimate the health and economic burden of SF medicines for priority diseases in LMICs?"*

This research question includes two key components: The first component of the conceptual framework is the concept of priority setting and identifying priority diseases and/or medicines in a given LMIC. The second component of the conceptual framework is determining the "how", i.e., the different modeling approaches that can be utilized to estimate the burden of SF medicines. To address the research question, the development of a conceptual framework was divided into four steps: (1) targeted literature review; (2) content analysis to identify other frameworks, key concepts and variables relevant to the research question; (3) conceptualization and (4) expert review to validate the conceptual framework.[29]

Targeted literature reviews were performed in January 2021 in PubMed, Embase and Google to identify published and grey literature to address the different components of the research question, i.e., priority setting and estimating the health and economic burden of SF medicines. The search terms used for the priority setting component of the research question were: (priority) and (setting) and (framework) or (evaluation). The search terms used for the approaches to estimate the health and economic burden of SF medicines were: (substandard) and (falsified) and (medicines) and (model) or (framework) or (approach). A targeted literature review, also known as a focused literature review, is a structured review based on a clearly formulated question and narrowed towards finding the key evidence needed to answer the research question. While less comprehensive and less reproducible than a systematic literature review or a scoping review, this approach is faster and is performed by a single reviewer.[30,31] Due to the pace and nature of the project work, a targeted review was chosen over a systematic review as it still enables one to adequately answer the research question and fits the timeline better. Different combinations of search terms were used.

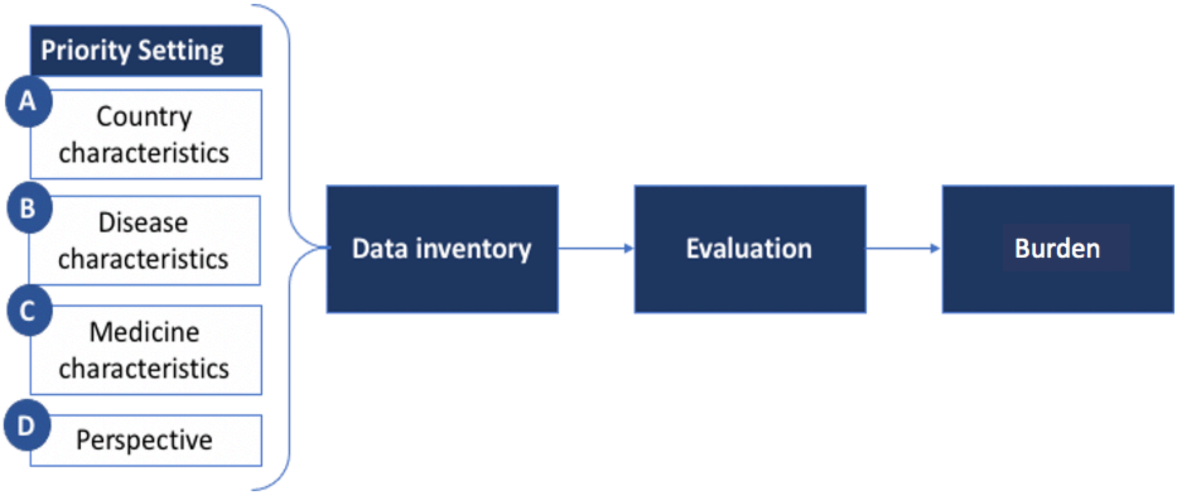
We isolated the important variables for the conceptual framework relevant to priority setting and existing approaches to estimate the impact of SF medicines described in the literature. The latter included model characterization and data needs. Then, we assessed how these variables were related to each other and used the findings to generate the conceptual framework that addresses the research question.

An interdisciplinary expert advisory board was convened. The members of the advisory board were selected using purposive sampling with the assistance of U.S. Pharmacopeia (USP).[32] The advisory board included Promoting the Quality of Medicines Plus program (PQM+) partners who are subject matter experts in the field of SF medicines, global health and health economics from the University of North Carolina Chapel Hill (UNC), Harvard University, USAID, and USP. The conceptual framework was presented to elicit review and collect feedback from members of the advisory board to refine and validate the framework.[33]

2.3 RESULTS

Previous conceptual frameworks describing priority setting, risk-based approaches in healthcare and a review of the literature of the approaches and models that investigated SF medicines were identified and different components and core variables from these articles were used to build this conceptual framework.[28,34–36] A high-level summary of the conceptual framework to estimate the health and economic burden of SF medicines is shown in Figure 2.1. The framework is intended to be a guide consisting of four core elements: (1) Priority Setting, (2) Data inventory, (3) Evaluation, and (4) Burden. The conceptual framework describes the process and the considerations for prioritizing medicines and disease areas impacted by the issue of SF medicines, identifying and evaluating available data, selecting a modeling approach to generate country-specific estimates for the burden of SF medicines and presenting key outcomes.

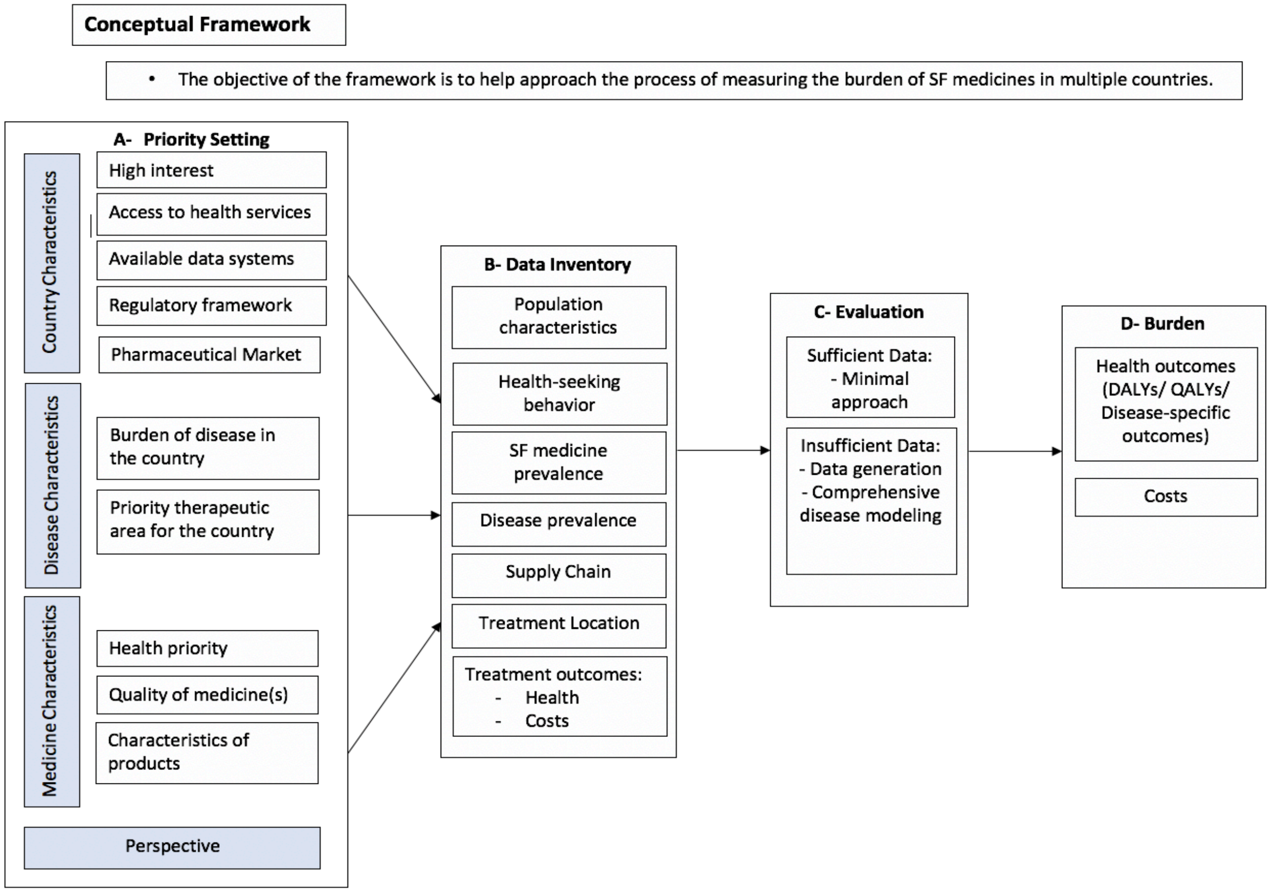
Figure 2.1 Summary Framework for the estimation of the health and economic impact of SF medicines



Priority setting is the process and strategy of making a decision about which country, disease(s) and medicine(s) to prioritize. Priority setting consists of examining (A) country characteristics, (B) disease characteristics and (C) medicine characteristics and selecting (D) the perspective of the analysis.

In a particular application, one might select the disease with the greatest burden, or the medicine with the greatest perceived SF problem or the most potential benefit from reducing SF prevalence. Once these four attributes are examined and the priority medicine and setting are determined, data needs are identified, and a data inventory can be performed. The data inventory is a complete described record of the inputs, datasets and metadata available, their contents, source, and other useful information.[7] Once the data inventory is completed, the evaluation step allows to assess whether there is sufficient data or insufficient data, which can inform the modeling approach that is feasible. The final step in the framework is the assessment of the key outcomes for the health and economic burden of the use of SF medicines. The detailed framework, including subcategories and attributes is shown in Figure 2.2.

Figure 2.2 conceptual framework to estimate the health and economic burden of SF medicines



1- Priority Setting

Health systems in resource-constrained settings often face a wide range of challenges, including inadequate funding and limited access to quality medical products. These challenges can make it difficult to provide quality health services to those who need them and can result in a high burden of disease and mortality. By prioritizing and contextualizing decision making, health systems can ensure that resources are allocated in a way that meets the health needs with the highest priority. The following characteristics were based on the risk-based resource allocation framework for pharmaceutical quality assurance.[28]

A- Country characteristics

The country characteristics included are high interest, access to health services, regulatory framework, and pharmaceutical market. High interest as a country characteristic is defined as the expressed interest, need and/or willingness of a given country to estimate the health and economic burden of SF medicines. Access to health services has four dimensions: availability of health services, geographic accessibility, affordability and acceptability.[8,9] Locations where health services and medicines are sought should be identified to understand the availability, i.e., stockouts, and affordability of medicine and assess whether that contributes to the SF burden, i.e., large use of informal market drug shops as opposed to pharmacies. If medicines are readily available and affordable in the country, it may suggest that the quality of these medicines is generally acceptable and that there is a well-functioning market for medicines, with sufficient competition to keep prices low. In such a market, it may be less likely for SF medicines to proliferate. However, if medicines are not widely available, people may resort to purchasing medicines from unregulated sources, increasing the risk of SF medicines. Additionally, if medicines are prohibitively expensive, people may also be more likely to seek out cheaper, unregulated sources of medicine, increasing the risk of SF medicines.

Regulatory framework is another country characteristic that shows whether a country has a well-trained and resourced NRA with adequate regulatory capacity to ensure that the manufacture, distribution, surveillance, and use of medicines are regulated effectively.[10] A functional NRA is better equipped to undertake rigorous scientific assessments of medicines and detect and prevent the entry of SF medicines into the market and provide access to safe, effective medicines of good quality, meeting current international regulatory standards. On the contrary, a weak regulatory environment can suggest that it may be easier for SF medicines to enter and remain on the market.

Understanding the regulatory framework for countries is important and the maturity level as evaluated by the Global Benchmarking Tool (GBT) can be used to assess the regulatory capacity of NRAs for medicines.[18] The maturity level is evaluated based on nine core regulatory functions: national regulatory system and functions, registration and marketing authorization, vigilance, market surveillance and control, licensing establishments, regulatory inspection, laboratory testing, clinical trial oversight, and NRA lot release.

Country characteristic is the knowledge of the pharmaceutical market as it includes the supply side and the demand side. The supply side involves manufacturers, importers, wholesalers, distributors, and dispensers from various sectors (e.g., public, private, donors, nongovernmental organizations, informal markets). In addition to licensed manufacturers, there may be actors operating outside of the regulatory framework that may not be subject to the same standards and regulations as licensed actors. These include illicit industries, repackaging groups and itinerant drug sellers.[28] The attributes on the supply side of the pharmaceutical market can provide insights to define risk and assess priority. As for the demand side, it refers to the willingness of individuals, healthcare providers, and governments to purchase and use pharmaceutical products. Demand is driven by various factors, including healthcare needs, burden of disease, and actual healthcare utilization. Understanding these factors is critical for making decisions about priority setting in healthcare.

B- Disease characteristics

Identifying priority therapeutic areas can be done, in part, by considering information on the burden of disease in a country which describes loss of health and death due to diseases, injuries and risk factors. Such information is needed to assess the comparative importance of diseases, injuries and risk factors in causing premature death, loss of health and disability in different populations.

The burden of a particular disease or condition can be estimated by using different health metrics including cause-specific mortality rate, disease incidence or prevalence, disability-adjusted life years (DALYs). According to the WHO definition, one DALY "represents the loss of the equivalent of one year of full health". A DALY for a disease or for a specific health condition combines the number of years of life lost as a result of a premature death due to the disease, i.e., years of life lost (YLL) and the number of years of life a person lives with a disability caused by the disease or specific health condition, i.e., years of life lived with disability (YLD). [37] Besides DALY, other measures can be used, including quality-adjusted life years (QALY) which is a function of length of life and quality of life.[13] Countries may use these data along with information about policies and costs to determine how to set their health agenda.

C- Medicine characteristics

Depending on the country selected, the choice of medicines evaluated by the model should have the potential to result to poor health outcomes and higher economic costs if poor quality. Medicine(s) of interest should also be medicines that are likely to have SF versions on the market and/or are not provided by quality-assured manufacturers. Key medicine characteristics include manufacturing practices, quality control processes, storage and packaging, which are factors that can contribute to substandard quality or falsified drugs. Data can be obtained from previous or recent reports that suggest issues with the quality, safety and efficacy of the products or complaints from heath care providers and/or patients. Quality testing during procurement or from sampling within the supply chain is a key source of data.

D- Perspective

Several guidelines for economic evaluation highlight the importance of clearly specifying the perspective for whom the analysis is being undertaken.[38,39] Different stakeholders are interested in health care costs and outcomes that are relevant to their specific interests. Cost components included in the analysis may have a significant impact on policy and resource allocation decisions. An economic evaluation can be conducted from the perspective of a patient, a specific payer (public or private), the entire healthcare sector, or all of society depending on the purpose of the analysis. The analytic perspective selected is important to determine prior to data inventory as it determines which costs and health outcomes to include and influences the study results.[39,40] Table 2.1 describes different perspectives, their definitions and potential data needs for the model.

Table 2.1 Definitions and data needs of different healthcare and health economics perspectives

Perspective	Definition	Data needs
Societal	The societal perspective can be defined by the inclusion of all relevant costs, regardless of who pays. It is differentiated from other perspectives by inclusion of time costs, the use of opportunity costs, and the use of community preferences.[41]	Direct medical costs[1] Direct non-medical costs[2] Indirect costs[3] Intangible costs[4]
Healthcare sector	The health care sector perspective includes formal health care sector, i.e., medical, costs borne by third-party payers or paid for out-of-pocket (OOP) by patients. This includes "current and future health costs, related and unrelated to the condition under consideration".[38]	Direct medical costs Direct non-medical costs
Payer/ Insurer	The payer's perspective includes the costs that would be incurred or saved by a payer/ insurance company	Direct medical costs
Patient	The patient's perspective includes the expenses that patients pay for medical products or health care services not covered by their health insurance.[42]	Direct medical costs Direct non-medical costs Indirect costs Intangible costs

2- **Data inventory**

The second component of the conceptual framework is data inventory. Once priority setting is completed and the country and medicine are selected, a data inventory is required to evaluate data

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[1] Direct medical costs include costs such as clinical services, hospitalization and medications

[2] Direct non-medical costs include costs such as transportation or childcare expenses incurred due to an illness or disability.

[3] Indirect costs include time lost from work/ productivity loss

[4] Intangible costs such as pain and suffering. Although these are often difficult to measure, they represent a cost to the patient and a cost to society, often in terms of quality of life.

availability and to inform the modeling approach. Potential data inputs to be evaluated examples and potential data sources are described in Table 2.2. These are based on the findings of a review of existing models and approaches that estimated the health and economic impact of SF medicines.[34] Data needs include epidemiological and demographic parameters on eligible population, disease incidence, SF medicine prevalence, health-seeking behavior and treatment locations, e.g., public and private sector, health outcomes, i.e., medicine efficacy, medication procurement costs and disease management costs data at different health facility levels.

Table 2.2 Potential data inputs and possible data sources to be evaluated during data inventory

Data Inputs	**Examples**	**Possible Data Sources**
Demographic and epidemiological data	Population eligible Life expectancy Proportion of public and private sector	Country profiles Ministry of health annual reports Published peer-reviewed data and grey literature Regulatory Agencies' and in-country or regional pharmacovigilance data, e.g., post marketing surveillance data (PMS) Primary data collection Pharmaceutical market reports Publicly available data Global Burden of Disease
Health-seeking behavior	Percentage of patients receiving care and treatment locations	
SF medicine prevalence	Prevalence of SF medicines depending on percentage of active pharmaceutical ingredient (API)	
Disease prevalence	Incidence and number of cases of a given condition or illness	
Health outcomes	Treatment efficacy when given treatment, disease outcome without treatment, deaths, mild and severe cases, case fatality rate	
Treatment costs	Drug procurement costs, disease management costs	

3- Evaluation

An evaluation of the data availability and quality is conducted to inform the modeling approach and data is either considered sufficient or insufficient. If data on outcomes of interest are available, data are considered sufficient and a minimal modeling approach can be conducted in certain circumstances to develop a generalizable model to estimate the health and economic burden of SF medicines. Minimal modeling approaches are defined as those that seek to simplify the process by focusing on the most essential aspects. The goal is to create a model that captures the most important parameters while minimizing complexity and computational parameters are feasible in certain circumstances.[19] Minimal modeling in the context of SF medicines would focus on key model outcomes without incorporating the disease progression and treatment process. If data, time and resources are available, comprehensive disease modeling or full disease modeling can be considered. Full disease modeling is defined as the full characterization of the disease or treatment using a decision model or other simulation models of relevant health states. This type of modeling requires additional data on disease progression and treatment protocols as well as corresponding health outcomes and costs. While it entails a complex and time-consuming modeling exercise, it provides more precise and robust estimates. If key data availability is insufficient, data generation through primary or secondary data collection may be needed.

4- Burden

The metrics for burden are the potential health and economic outcomes associated with the use of SF medicines.

Health outcomes

Health outcomes can be estimated by using general commonly accepted metrics such as DALYs or QALYs or disease-specific outcomes. The advantage of these general metrics is that they allow comparison of interventions across different therapeutic areas in the health sector. Other primary health outcomes can include years of life lost (YLLs) and number of deaths. Depending on the medicine of interest selected during priority setting, additional disease-specific outcomes can also be included subject to audience interest and data availability, e.g., incremental cases of disease-specific outcome.

Costs

The economic burden includes the total costs incurred due to the use of SF medicines. Depending on the perspective selected for the analysis, the economic burden can encompass different costs and provide a unique understanding of the burden of SF medicines. Direct medical costs refer to the expenses incurred in the treatment and management of a condition, including medications, physician visits, health worker's time, hospitalizations and laboratory tests. Direct non-medical costs comprise expenses related to transportation and upkeep associated with medical appointments; indirect costs include costs associated with productivity losses due to short-term illness, convalescence, disability or death, such as missed days at work, reduced work capacity, early retirement or premature death. By taking into account different perspectives and types of costs, policymakers, healthcare providers, and patients can better understand the full economic burden of SF medicines and make informed decisions about prevention and resource allocation.

2.4 DISCUSSION

This conceptual framework was developed to standardize the estimation of the health and economic burden of SF medicines. It is designed to be broad and comprehensive and when operationalized, the framework can demonstrate its utility as a country-level tool that can assist key stakeholders in LMICs to estimate the health and economic burden of SF medicines.

The first step of this framework is priority setting, which is often a missing step in connecting research with policy and practice needs.[35] Although there is no unanimous consensus on the definition of research priority setting, most definitions suggest it entails a range of processes and activities that include identifying, prioritizing and agreeing on research areas or questions that are important to relevant stakeholders.[40,] Priority setting in the context of SF medicines assists policy makers in effectively choosing to evaluate or address SF medicines that have the greatest potential health and economic burden. That is essential to maximize the impact of investments, especially in low-resource settings.[43] Overlooking priority setting in healthcare research can have important implications. First, it can lead to a failure to address the most pressing, high-risk issues. This consequently can lead to allocation of resources to interventions that are less impactful or less urgent which leads to missed opportunities to make a significant impact on health and economic outcomes. Second, overlooking priority setting can result in a lack of stakeholder engagement and buy-in from policymakers, regulators, healthcare providers, or patients. This can limit the effectiveness of interventions that could potentially address the SF medicines issue. On the contrary, when the framework is operationalized, priority setting allows flexibility to integrate and address the needs of in-country stakeholders and to identify components that may be of greater importance to the setting. This flexibility enhances the potential utility and applicability of the complete framework.[43]

Once a priority medicine is selected, data inputs are identified based on variables used in previous models and any existing data on the health and economic burden of SF medicines. Once data availability and data gaps are evaluated, a modeling approach is chosen. The health and economic burden of SF medicines can be generated using an adaptable minimal model or a more complex comprehensive disease model. Depending on the modeling approach, additional data may be needed to sufficiently populate the model.

Minimal modeling offers an advantage over comprehensive disease modeling when high-level, rapid estimates of the SF burden are needed and when building a full disease model is not feasible due to the lack of time and/or resources. While a minimal modeling approach was used by Meltzer et al. for value of information (VOI) studies to simplify complex models by reducing the number of variables and assumptions, the same concept can be applied to the modeling of the estimation of the burden of SF medicines.[45] In their study, and despite the simplifications, they were able to demonstrate the value of genetic testing in breast cancer patients. Further research was needed to validate the assumptions made in their model and to refine the estimates of treatment effectiveness and costs, but minimal modeling approach still provided them with reliable evidence.[45] It is important to note that while minimal modeling approaches present a reduced need for complex and time-consuming modeling, they do require good quality data for individual inputs to generate reliable results.

Several data sources can be used to estimate disease-specific or general health outcomes, depending on the SF medicine of interest and the specific outcomes being measures. Some examples include clinical trials data on disease progression, survival, quality of life and patient outcomes. Other sources are electronic health records, disease registries for specific diseases, patient-reported outcomes, etc.

The model, whether it is using a minimal or a full disease modeling approach, is intended to generate results and to help relevant stakeholders understand the burden of SF medicines. Findings may support the use of RBA to explore root causes, prioritize interventions and commit to address the specific issues underlying the quality problems of that medicine type (or medicines in general) in their country. RBAs have been adopted by mature regulatory authorities such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for key regulatory functions, including inspection of manufacturing facilities and product sampling for quality testing. [46] The first and last steps of the conceptual framework, i.e., priority setting and burden estimation, can inform and support RBAs so that priority attention and improvement efforts are focused on the highest-risk products, geographies and actors. Put another way, using this framework to identify the products with the highest burden, estimating that burden and an RBA can yield the most health and economic impact per investment dollar.[28]

Developing this conceptual framework was an important first step to help organize and guide the development of a model to estimate the health and economic burden of SF medicines. However, there are several limitations to consider. First, we performed targeted literature reviews to address the separate components of the research question that included priority setting and "how" to estimate the burden. Targeted literature reviews are not as comprehensive and reproducible as a scoping or systematic literature review. Hence, the conceptual framework may not capture all of the important variables or relationships in the field and the process may not be replicable. However, to address this limitation, we relied on previous published frameworks for priority setting and a comprehensive literature review that synthesized all of the existing models and approaches to estimate the health and economic impact of medicines. The work was also presented to and validated by an advisory board of subject matter experts.

Another limitation is that this framework was developed to be a generalizable tool that can be adapted and used for any SF medicine. However, it is important to note that there may be specific case studies or contexts where the framework may require adaptation for effective application. Further research is needed to validate its applicability in different settings for different medicines. From an applied perspective, it may also be challenging to follow the framework sequentially as an idea of the modeling approach may be needed in certain situations to inform data requirements.

While it is recommended to apply this framework sequentially for optimal results, it is important to remain flexible in its use, as certain steps or processes may need to be modified or used in a different order depending on the specific case or context.

2.5 CONCLUSION

The development of a conceptual framework for estimating the health and economic burden of SF medicines represents an innovative approach to tackling a complex and pressing global health challenge. By providing a framework for estimating the burden of SF medicines, this framework has the potential to inform evidence-based policymaking and resource allocation decisions. This conceptual framework can serve as a tool that allows a reproducible and feasible process for researchers, practitioners and stakeholders working to combat SF medicines. Overall, the development of this conceptual framework represents as a first step in a project that seeks to develop tools that can help stakeholders generate country-specific estimates on the magnitude of burden resulting from use of SF medicines, which is a critical step towards addressing their impact.

Chapter 3. Development of an Adaptable Model to Estimate the Health and Economic Burden of Substandard and Falsified Medicines: Oxytocin Case Study

3.1 INTRODUCTION

Substandard and falsified (SF) medicines threaten health and undermine progress towards meeting the Sustainable Development Goals (SDGs).[2] The World Health Organization (WHO) defines substandard medicines as authorized products that fail to meet their quality standards or specifications or both and falsified medicines as products that deliberately or fraudulently misrepresent their identity, composition or source.[47] SF medicines can lack necessary quantities of active pharmaceutical ingredients (API) reducing the clinical effect and resulting in prolonged illness and the need for further treatment.[2,7,8,47,48] Furthermore, SF medicines can cause severe adverse reactions and avertable disease outcomes including death and suffering.[2,7,8,47,48]

A 2017 report by the WHO on SF medical products noted that there is limited accurate and reliable information characterizing the public health and economic impact of SF medicines.[2]Of the 100 published studies on the prevalence of SF medicines included in the WHO report, only one was a systematic attempt to estimate the association between poor-quality drugs and mortality, in that case, antimalarials and under-five year old deaths.[49] As a result, conclusions are difficult to draw about the overall health and economic burden of SF medical products.[2] A stronger evidence base is needed to estimate the health and economic burden of SF medical products to better prevent, detect and respond to their threat.

Impact models have been developed to estimate the health and economic impact of SF medicines, but they have been applied solely to examine the impact of poor-quality antimalarials and antibiotics. Additionally, the scope of these models has been limited to certain countries, i.e., Kenya, Benin, Democratic Republic of Congo (DRC), Uganda, Nigeria, Zambia, and Laos, or regions, i.e., sub-Saharan Africa or industrialized countries compared to developing countries.[2,50–52] It remains challenging for governments of low- and middle-income countries (LMIC) not included in these studies and for other stakeholders to utilize these models' findings to understand and mitigate their country-specific threats and burden from SF medicines. This limitation may lead to inadequate attention and funding for this health problem at country and global levels.

An adaptable model that can be applied by any country and used for any medicine or clinical indication would allow a reproducible and feasible process to generate estimates of the burden of SF medicines within and across countries and identify key data gaps. This approach can address the inefficiency of building full disease models for each SF medicine of interest. An adaptable model also provides stakeholders with locally specific and policy-relevant information on the magnitude of burden resulting from the use of SF medicines. The development of such a model may be particularly useful for countries where the prevalence of SF medicines is high, and resources are limited for undertaking primary research studies on the impact of SF medicines.

In this study, we developed an adaptable model that can be used to generate country-specific estimates of the health and economic burden of any SF medicine. This paper describes the methodology of the model and findings for a case study applied to SF oxytocin for active management of the third stage of labor among pregnant women in Kenya.

3.2 MATERIALS AND METHODS

Model Structure

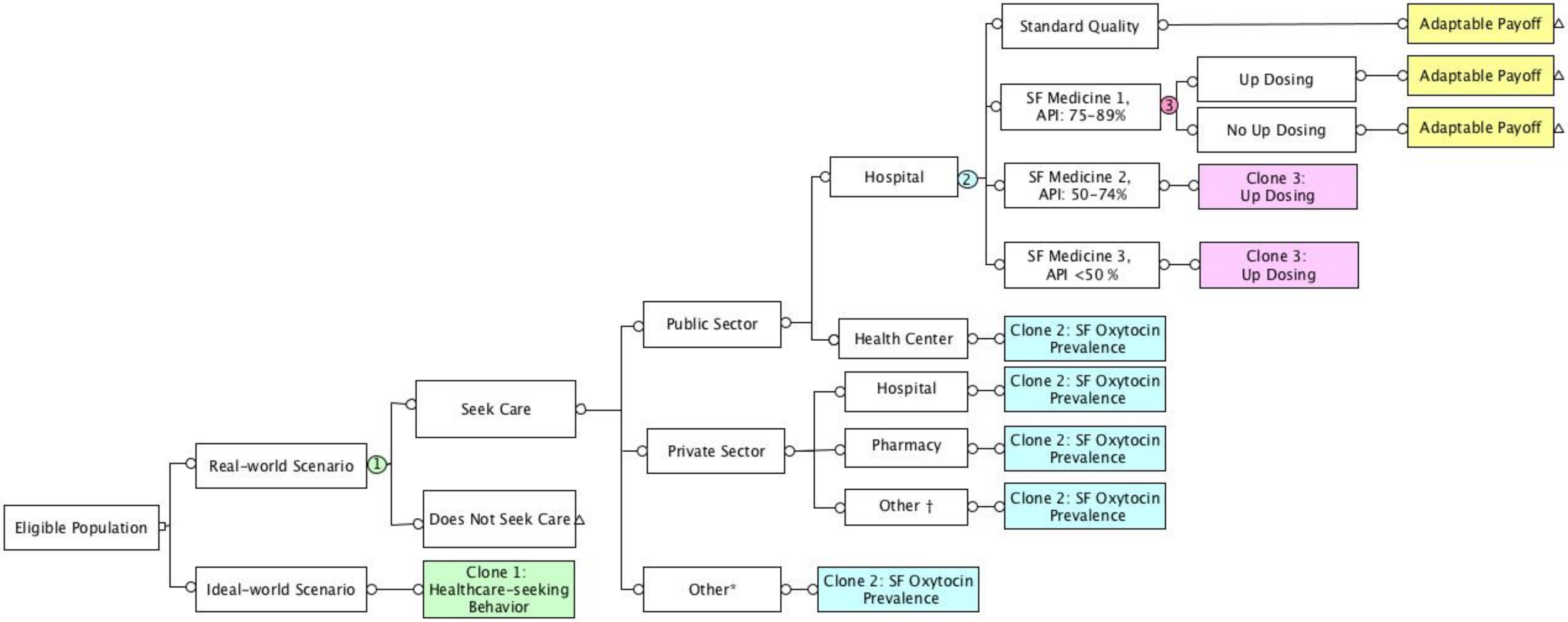
Our model development leveraged a review of published literature, which identified seven existing models and approaches to estimating the health and economic burden of SF medicines.[34]

The characteristics of these existing models, such as the modeling approach, model structure, data inputs and outputs, were utilized to inform a parsimonious set of key inputs to include in the model and their potential data sources. We then developed a decision tree model that estimates the health and economic burden of SF medicines from a healthcare sector and societal perspective using Microsoft Excel. A decision tree model was selected because it is a systematic, quantitative approach that allows users to represent alternative options, evaluate the alternatives in terms of costs and outcomes of interest, and quantify the uncertainty in the strategies or scenarios being compared. Additionally, a decision tree can accommodate any medicine and it is sufficiently simple to use and be managed by key stakeholders.[53] In order to estimate the incremental health outcomes and costs of SF medicines, our model compares two mutually exclusive scenarios:

- A real-world scenario that reflects the estimated prevalence of specified SF medicines in a given setting.
- A hypothetical, ideal or standard quality scenario, in which no SF medicines are present, i.e., the prevalence of SF medicines = 0.

A schematic representation of the model structure and set of inputs are presented in Figure 3.1.

Figure 3.1 Decision tree model structure to estimate the health and economic burden of SF medicines



* Other refers to other health sectors in a given coountry that can be cutomized or disregarded by the user.

† Other refers to health facilities other than hospitals and pharmacies in a given country, that can be customized or disregarded by the user.

Δ Adaptable Payoff can be customized depending on the medicine, outcomes of interest and available literature

The decision tree (Figure 3.1) starts with the eligible population, i.e., the number of people within a defined population (e.g., country) with the disease or health condition of interest. For each scenario, eligible patients can either seek care or not (i.e., healthcare seeking behavior). If they seek care, they can receive care at a public location (i.e., public hospital or health center), private location (i.e., hospital, health center, pharmacy, clinic) or other location. "Other locations" were included in the model to allow the user to customize and incorporate different healthcare system sectors and facilities and services that may vary in different countries.

For each health care location, the medicine(s) that the patient receives may be of standard quality, or a substandard and/or falsified level of quality. The prevalence of SF medicines is incorporated into the decision tree (Figure 3.1) as the distribution of four different levels of quality of medicines based on the percentage of active pharmaceutical ingredient (API), i.e., the ingredient that produces the intended health effect, in the medicine. The four quality levels used in the model are:

- Standard quality: 90 -110% of the API as defined by the United States Pharmacopeia (USP)[54]
- Substandard quality and falsified 1 (SF1): 75 - 89% of the API required by the USP standard[54]
- Substandard quality and falsified 2 (SF2): 50 - 74% of the API required by the USP standard[2]
- Substandard quality and falsified 3 (SF3): < 50% of the API required by the USP standard[2]

These ranges were based on the malaria model developed by Bath et al. as reported in the 2017 report by the WHO, and slightly adjusted to accommodate the USP definition of standard quality medicines (i.e., SF1 in this model has an API between 75%-89% instead of 75-84% included in the model by Bath et al as reported in the 2017 report by the WHO).[2]

In some settings, the dose of an SF oxytocin may be increased beyond the allowable prescription dose ("up-dosing"). Up-dosing is reported to be a common practice with oxytocin in LMICs and is defined as a healthcare provider administering more than the dose initially prescribed when medicines are believed to be substandard to maintain treatment efficacy.[55] This practice is incorporated into the decision tree as up-dosing or no up-dosing. Finally, at the end of the model, the end nodes represented by triangles in Figure 3.1 are the health and economic payoffs or outcomes. These payoffs are adaptable and can be customized depending on the medicine and key outcomes of interest.

For our case study, the eligible population is the number of pregnant patients annually in Kenya. Care locations included in the model were selected based on expert opinion for types of public and private institutions where pregnant patients typically seek care and may receive SF medical products. Payoffs for oxytocin included in this case study were selected based on the literature and expert opinion.

Assumptions

We make assumptions shown in Table 3.1 based on the Bath et al. model as reported in the 2017 report by the WHO regarding the relationship between the API percentage and medicine efficacy.[2] For each outcome, data on treatment efficacy with and without treatment are needed to estimate the effect of SF medicines. The payoffs are then multiplied by the branch probability and aggregated to provide the expected outcome for each comparator.

Table 3.1 Key assumptions on the relationship between percentage of required API, reduction in efficacy and medicine efficacy

Medicine quality rating	% of required API	Reduction in efficacy	Medicine efficacy
Standard	90 – 110% [54]	0%	100%
Substandard level 1	75 – 89% [54]	30% [2]	70%
Substandard level 2	50 – 74%[2]	60% [2]	40%
Substandard level 3	< 50% [2]	100% [2]	0%

Additional model assumptions that help assess the effect of SF medicines, reduce complexity, or reduce data requirements are the following:

- If a patient receives their medicine at a given facility, the model assumes that the patient continues to do so and does not change location.
- Patients have adequate adherence to their medical treatment.
- Treatment efficacy based on medicine quality does not vary by treatment location.
- Because the purchaser and/or administrator is unaware of drug quality, the cost of SF, standard, and adulterated drugs is the same per given location.
- According to stakeholders from Kenya, by giving the additional doses, in practice, healthcare providers reach the efficacy they expect with a single dose. So we assume that if providers increase the number of doses, treatment efficacy is considered maintained, but costs of medication are increased.

- It is assumed that stock availability does not differ between the real-world scenario and the ideal-quality scenario.

Model Inputs

Model inputs are divided into five sections: health-seeking behavior, epidemiological parameters, medicine quality, health outcomes and costs. The main data inputs used in this case study and uncertainty ranges are shown in Table 3.2. All model inputs were either extracted from available literature or secondary data provided by a technical working group (TWG) from Kenya.[5]

Table 3.2 Main data parameters, base case value, range and source for the Kenya SF oxytocin case study

Parameter	**Base Case**	**Range**	**Source**
Health-seeking behavior			
Eligible population (pregnant women in Kenya annually)	1,599,306	(1,507,450, 1,723,692)	56
Percentage of population who seek care (percentage of health facility deliveries)	75%	(67, 79)	56
Percentage of population who receive care in the public sector (percentage of deliveries in the public sector)	71%	(69, 74)	56
Percentage of population who receive care in the private sector (percentage of deliveries in the private sector)	17%	(15, 18)	56
Percentage of population who receive care in other sectors, if applicable (percentage of deliveries in the faith-based sector)	13%	(11, 14)	56
Proportion of Hospitals in Public Sector	40%	N/A	57
Proportion of Public Health Centers in Public Sector	60%	N/A	57
Proportion of Hospitals in Private Sector	46%	N/A	57
Proportion of Private Pharmacies in Private Sector	21%	N/A	57
Proportion of "other locations" in Private Sector, if applicable (Proportion of doctors'/clinical officers' clinics)	33%	N/A	57
Percentage of healthcare providers who up dose when using SF medicines	41%	(0, 50)	58

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[5] The technical working group (TWG) was formed by subject matter experts in medicine quality, policy and maternal health from different entities: academia, pharmacy and poison board, ministry of health,

Number of doses to compensate for SF1 medicines [6]	2	(0, 2)	58
Number of doses to compensate for SF2 medicines [7]	3	(0, 3)	58
Number of doses to compensate for SF3 medicines [8]	4	(0,4)	58
Epidemiological Parameters			
Mother's mean childbearing age	28.6	(14, 50)	59,60
Expectation of life at age 25-29	47.47	(30.44, 56.83)	61
Employment Rate	49.9%	(29.4, 61.6)	62
Prevalence of standard quality medicines	93%	(86, 100)	63
Prevalence of SF1 medicines [6]	7%	(0,14)	63
Prevalence of SF2 medicines [7]	0%	N/A	63
Prevalence of SF3 medicines [8]	0%	N/A	63
Health Outcomes			
Probability of disease- specific outcome 1 (mild PPH) with oxytocin	0.12	(0.092, 0.255)	64,65
Probability of disease- specific outcome 1 (mild PPH) without oxytocin	0.239	(0.123, 0.464)	66
Probability of disease- specific outcome 2 (hysterectomy) with oxytocin	0.0013	(0.001, 0.0032)	64,67
Probability of disease- specific outcome 2 (hysterectomy) without oxytocin	0.0028	(0.0024, 0.0032)	68
Probability of disease- specific outcome 3 (severe PPH) with oxytocin	0.014	(0.006, 0.08)	64
Probability of disease- specific outcome 3 (severe PPH) without oxytocin	0.043	(0.018, 0.09)	69
Mortality Risk due to PPH	0.054	(0.021, 0.13)	70,71
Mortality risk due to hysterectomy	0.00292	(0.0006, 0.00378)	72
Number of days missed at work due to mild PPH	2.98	(2.94, 3.08)	73
Number of days missed at work due to hysterectomy	7.8	(0.4, 28)	74,75
Number of days missed at work due to severe PPH	3.67	(3.56, 3.78)	73
Costs			
National average Drug Cost per Dose	$0.39	(0.03-1.35)	64,76,77
National average Unit Cost of Mild PPH Management	$77.61	(50-500)	58,64
National average Unit Cost of Hysterectomy Management	$663	(500-1,663.25)	58,78,79
National average Unit Cost of severe PPH Management	$1343	(77.61-1,611)	64,80
Productivity loss due to days of missed work (per day)	$5.5 [9]	(2.39, 7)	58,81
GDP Per capita	$1,838.21		81
Drug Cost per Dose at public hospitals	$0.03	(0.02, 0.03)	58,76
Drug Cost per Dose at Public Health Centers	$0.03	(0.03, 0.04)	58,76
Drug Cost per Dose at Private hospitals	$1.35	(1.08, 1.62)	58,76

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[6] Substandard and falsified medicines 1 with 75 - 89% of the API required by the USP standard

[7] Substandard and falsified medicines 2 with 50 - 74% of the API required by the USP standard

[8] Substandard and falsified medicines 3 with less than 50% of the API required by the USP standard

[9] GDP per capita divided by 365 days [87]

Drug Cost per Dose at Private pharmacies	$1.25	(1, 1.5)	[8,35]
Drug Cost per Dose at "other locations" in Private Sector, if applicable (Doctors'and Clinical Officers' clinics)	$1.25	(1, 1.5)	[8,35]
Drug Cost per Dose at other sectors, if applicable (faith-based Locations)	$0.672	(0.16-0.672)	[76]
Mild PPH management at public hospitals	$77.61	(50-500)	[64]
Mild PPH management at Public Health Centers	$77.61	(50-500)	Assumption based on [64]
Mild PPH management at Private hospitals	$400	(320,480)[10]	[58]
Mild PPH management at "other locations" in Private Sector, if applicable (Doctors'and Clinical Officers' clinics)	$400	(320,480)	Assumption based on [18]
Mild PPH management at other sectors, if applicable (faith-based Locations)	$238.8 [11]	(77.61, 400)[12]	Assumption
Average Unit Cost of Hysterectomy Management at Public Hospitals	$662	(64, 2,074)	[64,79]
Average Unit Cost of Hysterectomy Management at Public Health Centers	$662 [13]	(64, 2,074)	[64]
Average Unit Cost of Hysterectomy Management at Private Hospitals	$2,074	(1,659, 2,489)	[58]
Average Unit Cost of Hysterectomy Management at Private Pharmacies	N/A		
Average Unit Cost of Hysterectomy Management at "other locations" in Private Sector, if applicable (Doctors'and Clinical Officers' clinics)	$2,074	(1,659, 2,489)	[58]
Average Unit Cost of Hysterectomy Management at other sectors, if applicable (faith-based Locations)	$1,368	(1,094, 1,642)	Assumption
Average Unit Cost of Severe PPH Management at Public Hospitals	$1,343	(77.61-1,611)	[64,80]
Average Unit Cost of Severe PPH Management at Public Health Centers	$1,343	(77.61-1,611)	Assumption
Average Unit Cost of Severe PPH Management at Private Hospitals	$2,686	(77.61-3,223)	Assumption based on [58,64,80]
Average Unit Cost of Severe PPH Management at "other locations" in Private Sector, if applicable (Doctors' and Clinical Officers' clinics)	$2,686	(77.61-3,223)	Assumption based on [58,64,80]

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[10] Range was defined as +/- 20% due to lack of evidence

[11] Using an average between public and private locations as faith-based locations are typically more expensive than public hospitals and cheaper than private hospitals

[12] We defined the range as the costs of public hospitals and private hospitals

[13] No hysterectomies are performed at public health centers, we assume these are redirected to public hospitals

Average Unit Cost of Severe PPH Management at other sectors, if applicable (faith-based Locations)	\$2,014	(77.61-2,417)	Assumption based on [58,64,80]

Model Outcomes

The primary outputs of the model are estimates of the health burden, i.e., health outcomes, and healthcare sector and societal costs in the presence and absence of SF medicines.

a. Health outcomes

Two types of health outcomes can be used for this model: general health outcomes and disease-specific health outcomes. General health outcomes are comparable across different diseases/health conditions and health interventions. They are DALYs, QALYs, years of life lost (YLL) and death. Disease-specific outcomes are specific to the disease or health condition being treated by the medicine of interest. In this case study, due to the lack of data availability on DALYs and QALYs with and without the use of oxytocin, these outcomes were not included. However, YLLs and deaths were estimated. For disease-specific outcomes, mild postpartum hemorrhage (PPH), severe PPH and hysterectomies were identified as key health outcomes.

The incremental number of deaths was calculated as the total number of deaths due to PPH, i.e., obtained by multiplying the incremental number of PPH by the mortality risk due to PPH, and the total number of deaths due to hysterectomies, i.e., obtained by multiplying the incremental number of hysterectomies by the mortality risk of hysterectomies. To calculate years of life lost, the incremental number of deaths was multiplied by the remaining life-span at mean age of childbearing (25-29 years in Kenya).[61] A half-cycle adjustment was applied with an assumption that all deaths occurred in the middle of the year.

b. Economic outcomes

To estimate the economic burden of SF medicines, unit average costs are assigned to different health outcomes. Once the incremental health outcomes due to use of SF medicines are estimated, they are multiplied by the average management cost of the outcome. Productivity losses were estimated using the human capital approach based on gross domestic product (GDP) per capita, sex-specific employment rate, and duration of lost productivity, i.e., missed days at work.[52]

Lifetime productivity losses were estimated based on lost economic productivity between mean age of death and life expectancy, taking into account sex-specific employment rate between 15 and 64 years old. Depending on the parameters included, the model can estimate economic outcomes from a healthcare sector perspective and societal perspective.

In this case study, oxytocin, unit average costs were assigned to different oxytocin-specific health outcomes. The incremental cases of mild PPH, severe PPH and hysterectomies were multiplied by the management cost of these outcome, taking into account different costs at different treatment locations. Lifetime productivity losses were estimated based on lost economic productivity between mean age of childbearing, i.e., 28.6 years in Kenya and life expectancy, taking into account sex-specific employment rate between 15 and 64 years old. A 3% discount rate was used for the analysis. Costs were estimated from a healthcare sector perspective and societal perspective and converted from Kenyan Shillings (KES) to US dollars (USD) using the average annual exchange rate for 2021 (1 USD = 122.935 KES) and were rounded to the nearest thousands.[82]

Uncertainty Analysis

A one-way sensitivity analysis (OWSA) was used to assess parameter uncertainty and to estimate the impact of a change in given inputs on the model's output results. The results provide useful information regarding which variables are most influential and how they impact health outcomes and costs.

Internal and external validation

Model validation was performed to evaluate whether the model is a proper representation of the health and economic burden of SF medicines and whether the results of the analysis can serve as a basis for decision making.[83] The research question, the model structure and the potential data sources were reviewed and validated by an interdisciplinary expert advisory board. The members of the advisory board were selected using purposive sampling and included subject matter experts in the field of SF medicines, global health, medicines regulation and health economics.[32] Two subject matter experts in model developments verified the mathematical calculations, code and formulas. The model was also pressure tested by entering different values, entering extreme values, running multiple scenarios, and zeroing out inputs. A research team of health economists and modelers at University of North Carolina Chapel Hill (UNC) performed an external verification for the model by checking the model inputs and formulas to ensure they are correct, checking for coding errors, and ensuring the Excel-based model cells are linked in appropriate ways.

3.3 RESULTS

Base Case Results for Application of Model to Case Study in Kenya

This case study presents the model results for oxytocin in Kenya for an annual cohort of approximately 1.2 million pregnant women delivering in healthcare facilities, assuming a 7% prevalence of SF medicines 1 (API between 75-90%) compared to an ideal scenario of standard quality oxytocin. The model estimates that every year there are 2,005 additional cases of mild PPH, 488 cases of severe PPH, 25 cases of hysterectomies, 26 deaths and 420 of life years lost due to SF oxytocin.

In addition to the health burden, the economic burden of SF oxytocin due to the additional morbidity and mortality caused by SF oxytocin is estimated at a total of $1,239,121 from a societal perspective, including $937,050 in direct costs from the healthcare sector perspective. Productivity losses as a result of SF oxytocin were estimated as $302,071 a year including $21,729 due to missed days of work and $280,342 due to premature death.

The annual health and economic burden of SF oxytocin in Kenya are presented in Table 3.3.

Table 3.3 The annual health and economic burden of SF oxytocin in Kenya generated by the adaptable model in 2021 USD

	Real-world Scenario (SF presence)	Ideal Scenario (No SF present)	Burden due to SF oxytocin
Cases of mild PPH	146,391	144,386	2,005
Cases of severe PPH	17,334	16,845	488
Cases of hysterectomy	1,589	1,564	25
Incremental deaths	940	914	26
Life years lost	14,924	14,504	420
Cost of drugs	$260,890	$253,034	$8,856
Cost of mild PPH (from a healthcare sector perspective)	$18,270,229	$18,020,050	$250,178
Productivity loss due to missed days at work due to mild PPH	$1,190,317	$1,174,017	$16,300
Cost of severe PPH (from a healthcare sector perspective)	$23,279,013	$22,622,948	$656,065
Productivity loss due to missed days at work due to severe PPH	$173,575	$168,683	$4,892
Cost of hysterectomies (from a healthcare sector perspective)	$1,380,771	$1,358,820	$21,950
Productivity loss due to missed days at work due to hysterectomies	$33,828	$33,290	$538
Total costs (from a health care sector perspective)	$43,191,903	$42,254,852	$937,050
Productivity loss due to missed days at work (total)	$1,397,720	$1,375,990	$21,730
Productivity loss due to premature death	$9,967,880	$9,687,540	$280,340
Total productivity loss	$11,365,600	$11,063,530	$302,070
Total societal cost	$54,557,500	$53,318,380	$1,239,120

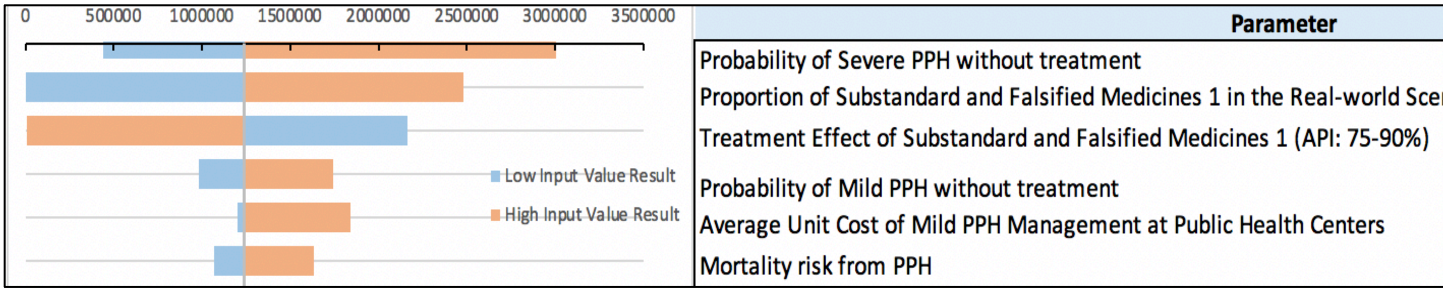
One-way sensitivity analysis

The probability of severe PPH without treatment had the largest effect on economic outcomes and incremental cases of severe PPH. With a probability ranging from 0.018 to 0.097, incremental cost estimates varied between $442,897 and $ 3,003,463 and the number of incremental cases of severe PPH varied between 75 and 5,929.

The probability of mild PPH without treatment had the biggest impact on the estimated number of incremental cases of mild PPH (50-5,795 cases), and the proportion of SF1 medicines had the biggest impact on the estimated number of incremental hysterectomies (0-51 hysterectomies). For life-years lost and deaths, the most influential parameter was the probability of severe PPH without treatment. For an uncertainty range of 0.018 to 0.097, the number of deaths varied between 4 and 76 and the number of life-years lost varied between 65 and 1,205.

Figure 3.2 presents the Tornado diagram of univariate sensitivity analysis of the main parameters that had the largest effects on incremental costs.

Figure 3.2 Tornado diagram of univariate sensitivity analysis on incremental costs using the adaptable model



3.4 DISCUSSION

This paper presents the development of and methodology for an adaptable model that can be used to generate evidence about and quantify the health and economic burden of SF medicines. The results of this case study illustrate the application of the model to estimate the effects of the presence of an assumed 7% SF oxytocin on maternal outcomes, including PPH, hysterectomies, and mortality, and to potentially avertable costs for the healthcare sector and society in Kenya.

Comparing the base case results to annual incidence of maternal outcomes in Kenya, our model estimates that, with 8.4 maternal deaths per 100,000 live births, poor quality oxytocin contributes to nearly 1.7% of total annual maternal deaths estimated at 488 maternal deaths per 100,000 live births.[84] The presence of SF oxytocin in Kenya presents a challenge in meeting the SDG of reducing the global mortality ratio to less than 70 per 100,000 live births by 2030.[85]

Out of $1.2 million in economic burden from a societal perspective, approximately 23% of the total economic burden was due to productivity loss due to premature death. An evident result of premature mortality is a decrease of potential labor supply. A study conducted in Europe estimated the value of market production lost due to early deaths and found that premature death cases are not only a significant public health burden, but they also result in explicit loss for the economy.[86] The findings of this study by Łyszczarz et al. describe the magnitude of the economic burden attributable to early deaths which provides data that can be used in prioritizing public policy choices aimed at improving health and sustaining economic viability, thereby supporting advancement toward SDGs.

This adaptable model allowed us to generate rapid country-specific results for a high priority medicine in Kenya. Disease-specific models such as the substandard and falsified antimalarial research impact model (SAFARI) can generate more accurate results than an adaptable model as they take into account disease progression, demographics, behaviors and follow patients over time.[87] However, the process of developing a new model for each disease is not efficient for the primary objective of using one adaptable model for any medicine or indication in a timely manner. This adaptable model is efficient in generating high-level estimates of the SF burden of multiple diseases. The adaptable model also minimizes the analytic burden due to the reduced number of inputs needed to generate results compared to an agent-based model.

This model's main assumption is the relationship between the level of API and efficacy reduction. This definition was based on previous efforts to estimate the impact of SF medicines.[2] The levels of API to define the three SF medicines categories are slightly different than the ones used in the Bath et al. model as reported in the 2017 report by the WHO to accommodate USP's definition of standard quality medicines.[2]

The Bath et al. model, as reported in the 2017 report by the WHO, SF1 categorization contains 75-85% of API (vs. 75-90% in this model). That means that the 85-90% range adjustment that was considered standard quality in their model is considered substandard in this model. As our model is using the same assumption for treatment efficacy reduction but broadening the range of API for the definition, caution should be taken in the interpretation of the results as they may be overestimating the burden of SF medicines.

A limitation of this case study is that the estimates of reduction in efficacy are assumptions based on the malaria model developed by Bath et al. as reported in the 2017 report by the WHO and the SAFARI model; generally, there is limited data to parameterize these variables. If model assumptions are not true, the model may inaccurately reflect reality and may result in inaccurate predictions. This relationship between percentage of API and efficacy reduction can be medicine-specific and may not be generalizable across different medicines. In an effort to make the model adaptable, the assumptions about different levels of API and efficacy reductions are customizable. Model users are encouraged to seek evidence on this relationship for the medicine of interest and include uncertainty ranges in sensitivity analyses.

In this model, it is assumed that SF medicines contain sub-therapeutic concentrations of API or have no API at all. However, SF medicines can also contain improper ingredients.[88] Hence, a proportion of SF medicines may also be adulterated (i.e., include ingredients that may have harmful effects) and lead to increased health and economic burden. While data about adulterated medicines and the effects on health outcomes were unavailable for this case study, the model can estimate the health and economic burden of the harmful effects arising from medicine adulteration in case it becomes available. Additionally, samples with API more than 110% were not included in the SF categories. Some medicine quality studies found that there were two types of moderate medicine quality deviations: batches with lower and batches with higher than the acceptable content of APIs.[89] Antibiotics with higher API contents were the most observed medications in those studies. This may limit the use of the model with SF medicines and/or antimicrobials with API>110%. Finally, the model is dependent on available data, specifically for health outcomes with and without treatment. If these data aren't available, results cannot be generated but key data gaps can be identified.

Models are inherently limited by the quality and availability of the data used to derive model parameters and their ability to account for heterogeneity.[90] However, our model attempts to mitigate these limitations by using the most up-to-date and recognized definitions for classifying medicine quality. We also include an uncertainty analysis using data ranges to cover probable high and low estimates for variables to assess how outcomes vary under different assumptions.[91]

3.5 CONCLUSIONS

After years of global cooperation and initiatives designed to facilitate greater access to quality medicines, SF medicines remain a major threat to global health for LMICs. To ensure that progress continues, it is essential to provide local estimates of burden in order to address the factors that are contributing to the prevalence of SF medicines. This adaptable model is presented as a tool that can assess and illustrate the magnitude of the health and economic impact of SF medicines in different countries through a case study of oxytocin in Kenya. The model results should inform key stakeholders to recognize the burden of SF oxytocin and identify interventions to improve the quality of medical products. [20] As the world seeks to achieve the SDGs by 2030, reducing the prevalence of SF medicines will be essential to provide access to good-quality health services for all.

Chapter 4. Using comprehensive disease modeling to assess the burden of substandard and falsified oxytocin in Kenya

4.1 INTRODUCTION

Maternal mortality is a major global health concern, especially in low- and middle-income countries (LMICs).[92] Although global maternal mortality declined by 38% between 2000 and 2017, it still remains alarmingly high. Each year, nearly 295,000 women die during and following pregnancy and childbirth with 94% of these deaths occurring in LMICs.[92] In Kenya, the death rate for pregnancy-related causes is 355 per 100,000 live births.[84] This equals approximately 5,000 girls and women dying annually of pregnancy and childbirth complications, most of which could be prevented.[93]

Postpartum hemorrhage (PPH), defined as a blood loss of 500mL or more following childbirth, is a leading direct cause of maternal mortality globally, accounting for 27.1% of all maternal deaths.[94] Over 14 million women experience PPH every year causing 70,000 maternal deaths due to bleeding complications related to pregnancy and childbirth.[95] Women who survive PPH are at subsequent risk for severe maternal morbidities including organ dysfunctions and long-term disabilities.[96,97] When PPH occurs, early identification and management of bleeding using evidence-based guidelines can prevent most PPH-related severe complications and deaths.[98] According to guidelines, the use of uterotonics is key for both the prevention and management of PPH. Specifically, oxytocin is recommended by the World Health Organization (WHO) as the drug of choice for preventing and treating PPH.[99] Oxytocin is included in the WHO Essential Medicines list and in the United Nations Commission on Life-Saving commodities for Women and Children list.[99–101]

While oxytocin is widely accessible, there are concerns about its quality in LMICs.[100,102,103] A systematic review of the literature reported a median prevalence of 45.6% (range 0-80%) of substandard and falsified (SF) oxytocin in LMICs mainly due to inadequate levels of active pharmaceutical ingredients (API) among tested samples.[103] One study conducted in Ghana reported that 74% of oxytocin purchased at private pharmacies did not meet manufacturer specifications for percentage of API.[104] Due to lack of sufficient reporting on medication quality, inconsistencies in study sampling methods and variability in product testing, the estimates of SF oxytocin prevalence have limitations and are likely "just a small fraction of the total problem".[7]

Research groups have estimated the health and economic impact of selected SF medicines especially antimalarials and antibiotics. However, the burden of SF oxytocin remains an understudied problem.[34,87] A novel adaptable SF medicines model was developed as a tool to address this information gap.[105] This adaptable model can generate evidence on the health and economic burden of any SF medicine in any setting.[105] The model was applied to a case study for SF oxytocin in Kenya to generate estimates for the health and economic burden of SF oxytocin. Because it is using a simplified adaptable framework, this model captures the essential features of healthcare seeking behavior and SF medicines prevalence and is flexible enough to incorporate different payoffs for different medicines. However, the generalizable framework may not fully capture the complexity and heterogeneity of specific disease progressions and does not capture the varying disease severity and response to treatment at different stages. On the other hand, a comprehensive disease model addresses these gaps by capturing all relevant aspects of a disease. By incorporating information about how the disease progresses and its treatment pathway, a comprehensive disease model can better simulate the course of the disease and yield a more accurate representation of the impact of SF medicines on patient outcomes and costs.[106]

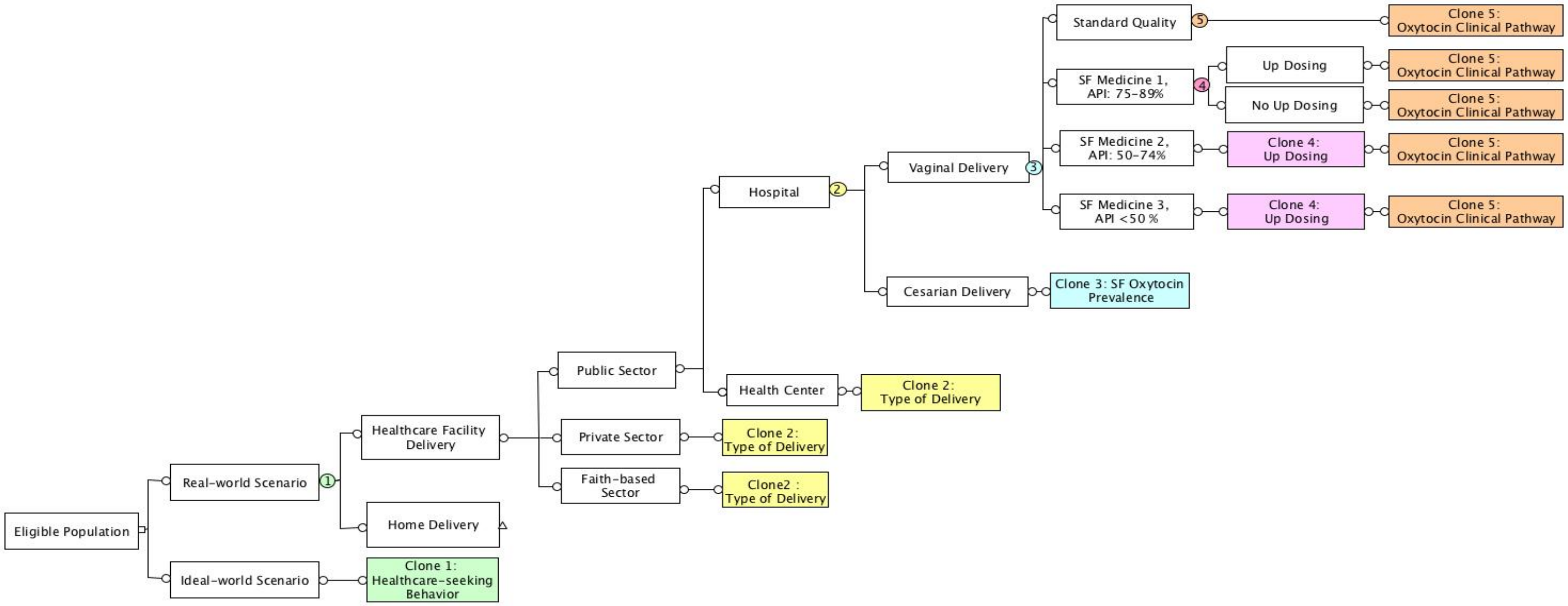
In recognition of the need to combat the threat of SF medicines and to improve the quality of PPH care, we developed a comprehensive disease model to generate country-specific evidence on the health and economic burden of SF oxytocin used for the prevention and treatment of PPH among pregnant women from the first stage of labor until discharge or maternal death. This paper describes the methodology of the model and findings for Kenya.

4.2 MATERIALS AND METHODS

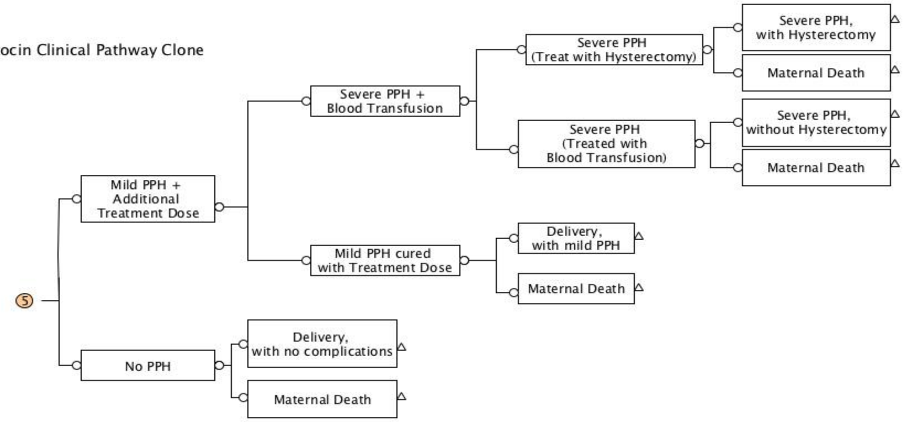
Model Structure

A decision tree model was developed based on previous SF burden models, economic evaluations of uterotonics in the prevention and treatment of PPH, and a review of clinical practice guidelines.[2,105,107–111] The model estimates the health and economic burden of SF oxytocin from a healthcare sector and societal perspective over a lifetime horizon using Microsoft Excel software (Microsoft Corp., Redmond, WA, USA). To estimate the incremental health outcomes and costs of SF oxytocin, our model compares two mutually exclusive scenarios: a real-world scenario based on the estimated prevalence of SF oxytocin and an ideal-world scenario where the prevalence of SF oxytocin is zero. Figure 4.1 shows the schematic representation of the model structure and model inputs.

Figure 4.1 Decision tree model to estimate the health and economic burden of SF oxytocin



Clone 5: Oxytocin Clinical Pathway Clone



A cohort of pregnant women of mean childbearing age, i.e., 28 years old, entering the first stage of labor at a healthcare facility enters the model and delivers at a private, public or faith-based healthcare.[60] The cohort of women is divided into two groups: vaginal deliveries and cesarean deliveries. In the model, each group receives a prophylactic dose of oxytocin as recommended by the WHO for PPH prevention.[99]

Model Inputs

There are four quality categories of oxytocin based on the percentage of the active pharmaceutical ingredient (API):

- Standard quality: 90 -110% of the API as defined by the United States Pharmacopeia (USP) [54]
- Substandard quality and falsified level 1 (SF1): 75 – 89% of the API required by the USP standard [54]
- Substandard quality and falsified level 2 (SF2): 50 – 74% of the API required by the USP standard [2]
- Substandard quality and falsified level 3 (SF3): < 50% of the API required by the USP standard [2]

A proportion of providers are expected to increase the dose (up dose) of presumed SF1, SF2 or SF3 drugs based on a study that found that 41% of the healthcare providers at a healthcare facility in Nigeria doubled the WHO-recommended dose and 10% used two to six vials instead of one to achieve the desired outcome when medicines where thought to be of SF quality.[55]

After the initial prophylactic dose, a woman can either have an adequate response to the treatment and is discharged or she can experience mild PPH (blood loss <500mL) [99,112] and is given another dose of oxytocin as a first line of PPH treatment following WHO and UK guidelines.[65,113,114]

After a treatment dose of oxytocin, bleeding either stops and the woman is discharged, or the woman does not respond to the treatment and severe PPH persists, in which case, she typically receives intrauterine balloon tamponade, exploration of uterine cavity, uterine compression sutures and a blood transfusion.[58,115] After treatment for persistent severe PPH, the bleeding stops and the woman is discharged; or the treatment fails and a hysterectomy is performed.[115] After the hysterectomy, the two outcomes modeled are either maternal survival with secondary infertility or maternal death.

Each branch in the pathway is associated with costs and health outcomes, which are accumulated over the time horizon of the model, i.e., lifetime, and are discounted at 3%. Incremental cases of mild PPH, severe PPH, hysterectomies and deaths were obtained by multiplying branch probabilities for each health outcome for the real-world scenario and for the ideal-world scenario and the difference was calculated.

The decision tree incorporates the following health states:

1- Delivery, with no complications
2- Delivery, with mild PPH
3- Severe PPH without hysterectomy
4- Severe PPH with hysterectomy
5- Maternal death

Each of these health states was associated with a utility and a disability weight. Utility weights were obtained from a cost-effectiveness study comparing oxytocin and carbetocin where EQ-5D-5L was used to collect primary data on vaginal and cesarian deliveries with and without PPH that was then converted to utility scores.[116] Utility weights for hysterectomy and secondary infertility were obtained from cost-effectiveness studies examining the treatment of heavy menstrual bleeding and menorrhagia.[117,118] Based on the Briones et al. economic evaluation for PPH prophylaxis, we assumed that delivery with no complications, delivery with mild PPH and severe PPH without hysterectomy and severe PPH with hysterectomy lasted 6 weeks.[116] After the six weeks, we assumed that the utility weight retuned to 1, i.e., “perfect health”, for all the aforementioned health states, except for severe PPH with hysterectomies, where the utility weight for secondary infertility was assigned for the remaining of the woman’s lifetime.[118]

We estimated YLLs associated with each health state and then QALYs and DALYs were calculated by multiplying the number of years that the women were expected to be alive (converted from the six-week cycle length used in the analysis) by utility scores and disability weights, respectively.

Six categories of model inputs were included: health-seeking behavior, epidemiological parameters, medicine quality, treatment efficacy, outcome measures and costs. Health-seeking behavior inputs consist of the percentage of women who have a healthcare facility delivery in the private, public or faith-based sector. Epidemiological parameters include the annual number of pregnant women delivering in healthcare facilities, percentage of hospitals and health centers and/or clinics in the public and private sector, probability of hysterectomy if severe PPH occurs, probability of PPH-related mortality and probability of dying by age (using life tables). Medicine quality inputs include the percentage of standard quality medicines and percentage of SF medicines depending on their levels of API. Treatment efficacy included oxytocin treatment effects, probabilities of mild and severe PPH with and without oxytocin, and outcomes measures included health state utilities and disability weights.

We obtained these inputs from peer-reviewed literature, public institutions, recent Kenya Demographics and Health Surveys data (DHS) and secondary data collection from in-country stakeholders in Kenya.[84] The secondary data was obtained through Kenyan subject matter experts in the field of medicine quality and maternal health. The 7% data input for prevalence of SF medicines specifically was the best available estimate provided by them; however, it is based on a small sample size for the entire country, which makes the input highly uncertain.

For cost inputs, using healthcare sector and societal perspectives, direct and indirect costs were considered in the analysis. The direct medical costs included were the costs of medical and surgical interventions, staff labor during intervention, drug costs, blood transfusions and hospital stay.[64] Medical and surgical interventions were calculated based on the cost of disposable apparel, disposable consumables, instruments and their sterilization fees, cleaning, laboratory tests, and use of operating theaters. Staff labor was calculated based on the monthly salary or hours worked by all personnel required for a procedure per month multiplied by the hours devoted to intervention. Drug cots included the total price of the full tray of drugs available for the intervention, including oxytocin, additional uterotonics and concomitant medicines.[64] Depending on the severity of the hemorrhage, interventions included were: cervix and high vaginal tear suturing, intrauterine balloon or condom tamponade, exploration of uterine cavity, uterine compression sutures, uterine or hypogastric ligation, hysterectomy, manual or surgical correction of uterine inversion, manual removal of placenta and bimanual compression. Direct medical costs were either derived from the literature or secondary data collection from a Kenyan technical working group. Indirect costs consisted of productivity losses incurred by patients due to days missed at work or premature maternal death. Productivity losses were estimated using the human capital approach based on gross domestic product (GDP) per capita, duration of lost productivity, and rate of employment. Productivity losses due to premature death were also estimated using the human capital approach, life of years lost and employment rate.[119] All monetary units were converted from Kenyan Shillings

(KES) to US dollars (USD) using the average annual exchange rate for 2021 (1 USD = 122.935 KES) and were rounded to the nearest thousands.[82]

Base case inputs were identified as the “most likely” estimates for each data input. For each parameter, we also identified an uncertainty range to capture potential variation from base case values. Uncertainty ranges were either formal estimates of variance when available (e.g., 95% confidence intervals), an evidence-based assumption or a ±10% variation from the base case.

All model inputs, low and high range estimates and distributions are shown in Table 4.1.

Table 4.1 Model inputs: base-case values, uncertainty ranges, distributional forms and sources

Parameters	Base-case Value	Uncertainty range (low, high)	Distribution	Sources
Population and health-seeking behavior in Kenya				
Eligible population: Number of pregnant people at third stage of labor	1,599,306 [14]	(1,507,450, 1,723,692)[15]	Normal	[56]
Percentage of healthcare facility delivery	75%	(67, 79)[15]	Beta	[56]
Percentage of home delivery	25%	(21, 33)[15]	Beta	[56]
Percentage of pregnant people who deliver in the public sector	70%	(69, 74)[15]	Beta	[56]
Percentage of pregnant people who deliver in the private sector, i.e., private hospital	17%	(15, 18)[15]	Beta	[56]
Percentage of pregnant people who deliver in "Other" sector, if any	13%	(11, 14)[15]	Beta	[56]
Proportion of Hospitals in Public Sector	40%	(36,44)[16]	Beta	[57]
Proportion of Public Health Centers in Public Sector	60%	(54,66)[16]	Beta	[57]
Percentage of people who have vaginal delivery	83.6%	(81, 97.9)[15]	Beta	[56]
Percentage of people who have cesarian delivery	16.4%	(2.1, 19) [15]	Beta	[56]
Percentage of healthcare providers who up dose oxytocin	51%	(45.9, 56.1) [15]	Beta	[55]
Number of doses used to compensate for SF oxytocin during updosing approach				
SF medicines with 75-89% API	2	(1, 3)[15]	Normal	[55]
SF medicines with 50-74% API	3	(1, 5)[15]	Normal	[55]
SF medicines with less than 50% API	6	(1, 6)[15]	Normal	[55]
Medicine Quality (National Average) [17]				
Prevalence of standard quality medicines (API 90% - 110%)	93%	(86, 100)[15]	Beta	[63]
Prevalence of SF1 medicines (API ≥75 - <90%)	7%	(0, 14)[15]	Beta	[63]
Prevalence of SF2 medicines (API ≥50- <75%)	0%	N/A	Beta	[63]
Prevalence of SF3 medicines (API <50%)	0%	N/A	Beta	[63]
Model assumption: SF medicine efficacy reduction				
Efficacy reduction (75–90% API)	30%	(15, 45)[15]	Beta	[2]
Efficacy reduction (50–74% API)	60%	(45, 75)[15]	Beta	[2]
Efficacy reduction (<50%API)	100%	N/A	Beta	[2]
Health outcomes				

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[14] Average of total number of pregnancies in 2019, 2020 and 2021 used as the base case input

[15] Evidence-based assumption (data from other years or sources)

[16] ±10% assumption

[17] Location-specific SF prevalence weren't available, so we applied a national average as reported by PMS data

Vaginal delivery: Probability parameters				
Probability of mild PPH occurrence / needing additional uterotonics with oxytocin	0.122	(0.089, 0.172) [18]	Beta	[66]
Probability of mild PPH occurrence/ needing additional uterotonics without oxytocin	0.239	(0.174, 0.337)[18]	Beta	[66]
Probability of severe PPH occurrence / needing transfusion with oxytocin	0.029	(0.02, 0.041)[18]	Beta	[66]
Probability of severe PPH occurrence /needing transfusion without oxytocin	0.048	(0.033,0.069)[18]	Beta	[66]
Probability of hysterectomy if severe PPH	0.016	(0.144, 0.0176)[16]	Beta	[120]
Probability of maternal death if hysterectomy	0.00292	(0.0006, 0.00378)[18]	Beta	[121]
Cesarian delivery				
Probability of mild PPH occurrence with oxytocin	0.442	(0.247, 0.791) [18]	Beta	[122]
Probability of mild PPH occurrence without treatment	0.7	(0.39, 0.8)[15]	Beta	[123]
Probability of severe PPH occurrence / needing additional uterotonics with oxytocin	0.374	(0.272, 0.524)[18]	Beta	[122]
Probability of severe PPH occurrence / needing additional uterotonics without oxytocin	0.598	(0.4352, 0.8384)[18]	Beta	[123]
Probability of hysterectomy if severe PPH	0.027	(0.0243, 0.0297)[16]	Beta	[124]
Probability of maternal deaths if severe PPH/hysterectomy	0.054	(0.021, 0.13)[15]	Beta	[70,125]
Vaginal and Cesarian deliveries				
Numbers of days missed at work due to mild PPH	2.98	(2.94, 3.08)[15]	Normal	[73]
Number of days missed at work due to severe PPH	3.67	(3.56, 3.78)[15]	Normal	[73]
Numbers of days missed at work due to hysterectomy	7.8	(0.4, 28)[15]	Normal	[74,75]
Quality of life parameters				
Utility weight in vaginal delivery, no complication (6 weeks)	0.85	0.01[19]	Beta	[116]
Utility weight, mild PPH episode (7 days)	0.59	(0.53, 0.93)	Beta	[126]
Utility weight, severe PPH episode (21 days)	0.47	(0.42, 0.93)		[126]
Utility weight in cesarian delivery, no complications (6 weeks)	0.83	(0.8, 0.85)	Beta	[126]
Utility weight hysterectomy, short term (21 days)	0.42	(0.4,0.7)	Beta	[126]

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[18] 95% confidence interval

[19] Standard error

Utility weight hysterectomy, long term	0.88	(0.75,0.95)	Beta	[118]
Disability weight in vaginal delivery, no complication	0.002	(0.001, 0.003)[18]	Gamma	[126]
Disability weight for maternal hemorrhage (less than 1L blood loss)	0.114	(0.078, 0.159)[18]	Gamma	[127]
Disability weight for maternal hemorrhage (Greater than 1L blood loss)	0.324	(0.220, 0.442)[18]	Gamma	[127]
Disability weight hysterectomy	0.274	(0.2466, 0.3014)[16]	Gamma	[126]
Disability weight in cesarian delivery, no complication	0.004	(0.0036, 0.044)[16]	Gamma	[126]
Disability weight of secondary infertility after hysterectomy (Proxy weight of infertility due to puerperal sepsis)	0.005	(0.002, 0.011)[18]	Gamma	[127]
Population characteristics				
Mother's mean childbearing age	28.6	(14, 50)[20]	Normal	[59,60]
Employment Rate	49.9%	(29.4, 61.6)	Beta	[62]
Costs ($)				
Cost of oxytocin per treatment ($), national average	0.39	(0.03-1.35)[15]	Gamma	[64,76,77]
Cost of oxytocin per treatment ($), public sector	0.029	(0.0232, 0.0348)[15]	Gamma	[77]
Cost of oxytocin per treatment ($), private sector	1.354	(1.0832,1.6248) [15]	Gamma	[77]
Cost of oxytocin per treatment ($), faith-based sector	0.672	(0.16-1.354)[15]	Gamma	[76]
Cost of additional oxytocin and mild PPH management (Public sector)	77.61	(50-500)[15]	Gamma	[58,64]
Cost of additional oxytocin and mild PPH management (Private sector)	400	(320, 480)[21]	Gamma	[58,64]
Cost of additional oxytocin and mild PPH management (Faith-based sector)	238.8	(77.61, 400)[15]	Gamma	[58,64]
Cost of Cost of severe PPH management (public)	1,343	(77.61-1,611)[15]	Gamma	[58,64]
Cost of Cost of severe PPH management (private)	2,686	(77.61-3,223)[15]	Gamma	[58,64]
Cost of Cost of severe PPH management (faith based)	2,014	(77.61-2,417)[15]	Gamma	[58,64,80]
Cost of hysterectomy (public)	662	(640, 2,074)[15]	Gamma	[64,79]
Cost of hysterectomy (private)	2,074	(1,659, 2,489[15]	Gamma	[58]
Cost of hysterectomy (faith based)	1,368	(1,094, 1,642)[15]	Gamma	[64,80]
Discount rate	3%	(0, 5)[22]		[38]

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[20] Wide range that reflects all plausible values

[21] ± 20%

[22] Assumption

Model Outcomes

The primary outputs of the model are estimates of the health and economic burden based on the increased morbidity and mortality due to SF oxytocin.

a. *Health outcomes*

Health outcomes estimated by the model are incremental cases of mild PPH, severe PPH, hysterectomies, deaths, years of life lost (YLLs), additional DALYs incurred and QALYs lost due to the presence of SF oxytocin.

Economic outcomes

Economic outcomes in the model are estimated from a healthcare sector and societal perspective and included total costs for the real-world scenario with presence of SF oxytocin, total costs for the ideal-world scenario without SF oxytocin and incremental costs due to the presence of SF oxytocin.

Assumptions

The main assumption in this model is the relationship between the API percentage and medicine efficacy, based on a burden model developed by Bath et al as reported in the 2017 report by the WHO.[2] This assumption states that standard quality medicines have 100% medicine efficacy. Medicines in the SF level 1 category with API between 75 and 89%, have a 30% efficacy reduction. Medicines in the SF 2 category with API between 50 and 74%, have a 60% efficacy reduction and medicines in the SF 3 category with API less than 50%, have 100% efficacy reduction, i.e., equivalent to not receiving treatment.

Sensitivity analyses

To quantify the impact of parametric uncertainty on model results, a one-way sensitivity analysis (OWSA) and a probabilistic sensitivity analysis (PSA) were performed. For each outcome, an OWSA assessed the influence of uncertainty in individual model parameters on model results. This was achieved by varying each fixed parameter around the maximum and minimum of its uncertainty interval and plotting the model results in a Tornado diagram.

The PSA was conducted to evaluate the range of plausible outcomes given joint uncertainty in all inputs. We used Monte Carlo simulations with 10,000 iterations, where inputs were randomly and simultaneously generated within a specific distribution.[128] Epidemiological inputs were assumed to be normally distributed. Probabilities and percentages were assumed to have a beta distribution for binomial data inputs or a Dirichlet distribution for multinomial data inputs. Cost inputs were assumed to have a gamma distribution.

Model Validation

A model validation was performed to evaluate how well the model represents the health and economic burden of SF oxytocin and whether the results of the analysis can serve as a basis for decision making.[83] First, we verified that the model was parsimonious and sufficient to answer the research question by incorporating the main assumptions about SF medicines and the current care of disease progression and treatment strategies.[129] Because there are no other model that examined SF oxytocin specifically, this was performed by comparing our model characteristics and structure to existing models and approaches that estimated the impact of SF medicines and economic evaluations of different uterotonics for the prophylaxis and treatment of PPH during third stage of labor.

We assessed internal validity and consistency by checking that the mathematical equations, calculations and code were accurate and consistent with the specifications of the model. We performed external validation and consistency, whereby we compared the model outputs for the real-world scenario with current in-country maternal outcomes to ensure that the model adequately reflects the current situation in Kenya. This was performed by comparing the existing estimates of number of PPH episodes, hysterectomies and PPH-related deaths in Kenya as a benchmark for our model predictions.

Three technical working group meetings were held with key stakeholders from Kenya between January and December 2021 to gather subject matter experts' opinion on data inputs for the model and assumptions. All data inputs and uncertainty ranges were reviewed and discussed by local experts and policymakers from public health and public policy agencies and universities to reach consensus on the most locally representative and recent data to be used in the model.

4.3 RESULTS

Deterministic base case results

The health and economic outcomes for the real-world and ideal-world scenario for SF oxytocin burden are presented in Tables 4.2 and 4.3. For an annual cohort of pregnant women and assuming a prevalence of 7% SF oxytocin, the model estimates that the presence of SF oxytocin in Kenya is associated with 1,484 additional cases of mild PPH, 583 additional cases of severe PPH, 15 hysterectomies, 32 deaths, 2,187 DALYs incurred, 560 QALYs lost, and 594 years of life lost per year compared to the ideal-world scenario without SF oxytocin.

In addition to the health burden, these health outcomes contributed to a total estimated economic burden of $1,970,013 USD in Kenya from a societal perspective over a lifetime horizon. Approximately 37% of the economic burden ($738,049) was due to productivity losses. These productivity losses included $12,069 due to missed days at work as a result of care seeking and convalescence, and $725,979 economic losses due to premature death. The remaining 63% of the economic burden ($1,219,895) was due to direct medical costs from a healthcare sector perspective. The direct medical costs included drug costs ($11,645), mild PPH management costs ($227,675), severe PPH management costs ($965,396) and hysterectomy management costs ($15,540).

Table 4.2 Results describing the health burden of SF oxytocin in Kenya for an annual cohort of pregnant women

	YLLs (discounted)	**QALYs (discounted)**	**DALYs (discounted)**	**Deaths** [23]	**Mild PPH** [23]	**Severe PPH** [23]	**Hysterectomies** [23]
Presence of SF	22,601,637	18,983,693	134,577	1,931	174,703	35,714	950
No SF	22,602,231	18,984,253	132,390	1,900	173,219	35,132	935
Increment	(594)	(560)	2,187	32	1,484	583	15

Table 4.3 Results describing the economic burden of SF oxytocin in Kenya for an annual cohort of pregnant women

	Type of costs	**Cost of drugs** [24]	**Mild PPH** [24]	**Severe PPH** [24]	**Hysterectomy** [24]	**Premature deaths (discounted)**	**Total Direc Medical Cost**
Presence of SF	**Direct Medical Costs**	$ 417,380	$ 26,794,430	$ 59,168,490	$ 944,167	N/A	$ 87,324,468
	Productivity Loss	N/A	$ 321,596	$ 396,060	$ 22,391	$ 44,495,750	N/A
	Total	$ 417,380	$ 27,116,027	$ 59,564,550	$ 966,559	$ 44,495,750	$ 87,324,468
No SF	**Direct Medical Costs**	$ 405,736	$ 26,566,755	$ 58,203,094	$ 928,987		$ 86, 104,573
	Productivity Loss	N/A	$ 316,349	$ 389,598	$ 22,032	$ 43,769,771	N/A
	Total	$ 405,736	$ 26,883,105	$ 58,592,692	$ 951,019	$ 43,769,771	$ 86, 104,573
Incremental	**Direct Medical Costs**	$ 11,645	$ 227,675	$ 965,396	$ 15,180	N/A	$1,219,895
	Productivity Loss	N/A	$ 5,247	$ 6,462	$ 360	$ 725,979	N/A
	Total	$ 11,645	$ 232,922	$ 971,858	$ 15,540	$ 725,979	$1,219,895

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[23] These health outcomes are not discounted due to the events occurring within the 6-week timeframe following delivery

[24] These costs are not discounted due to the events occurring within the 6-week timeframe following delivery

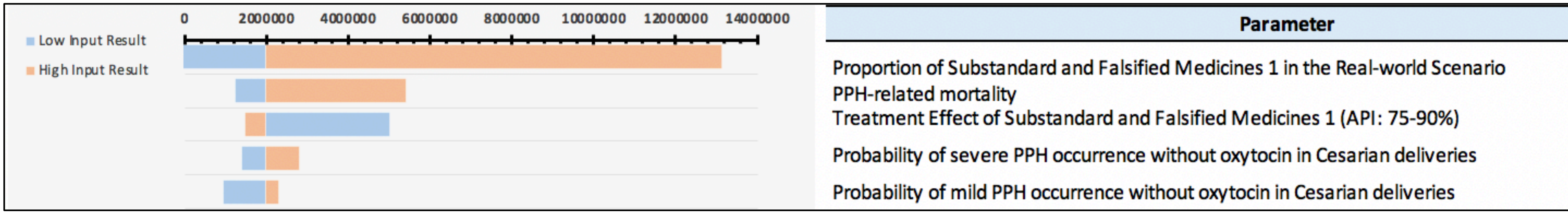
[25] These costs include discounted premature deaths costs occurring over a lifetime horizon and non-discounted costs occurring within the 6-week timeframe following delivery

Sensitivity Analysis

One-way sensitivity analysis

The impact of a one-way sensitivity analysis on incremental societal costs are presented in a tornado diagram (Figure 4.2). The analysis found that the most sensitive variables were the assumed proportion of SF 1 in the real-world scenario followed by the probability of mild PPH occurrence with oxytocin. Other individual tornado diagrams for mild PPH cases, severe PPH cases, hysterectomies, deaths, years of life lost, DALYs incurred, and QALYs lost can be found in Appendix A.

Figure 4.2 Tornado Diagram for the total costs due to SF oxytocin using oxytocin-specific model

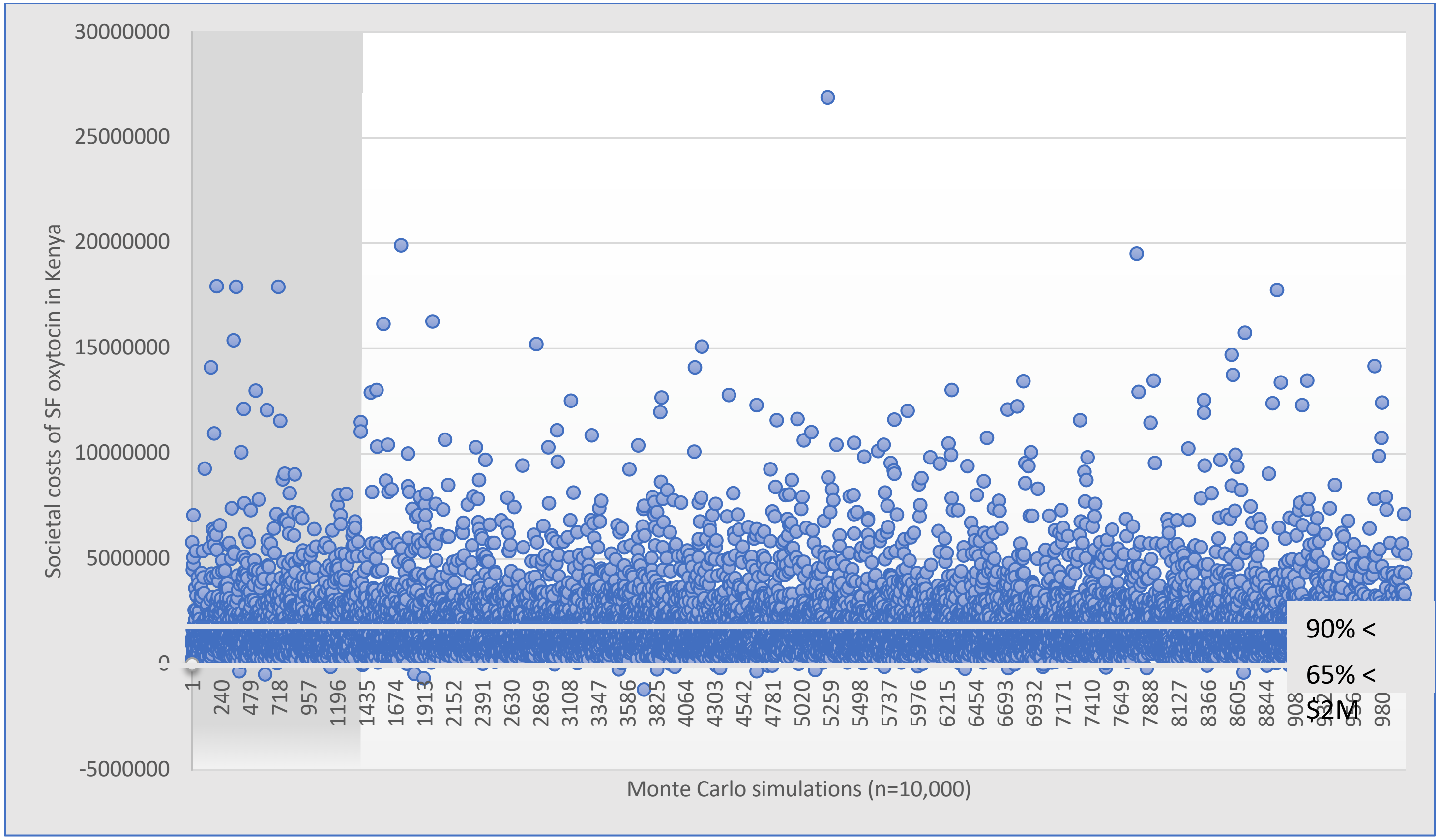


In the event of higher prevalence of SF oxytocin with API between 75% and 89% (SF1), significant increases in morbidity and costs would occur. With 14% prevalence of SF1 medicine, SF oxytocin can be associated with up to an additional 15,094 cases of mild PPH, 3,625 cases of severe PPH, 96 cases of hysterectomies and 196 deaths compared to base case results where we assumed 7% prevalence. The economic burden can also vary between $0 and $ 13,133,145 USD from a societal perspective.

Probabilistic sensitivity analysis

Results from the PSA show that, across all simulations, SF oxytocin was found to be associated with a mean societal cost of $1,957,944. The results of 10,000 runs are plotted in Figure 4.3 for societal costs and show that 65% of the simulations were found to be less than $2M and 90% less than $4M. SF oxytocin resulted in a mean increase of 1,485 mild PPH cases, 583 severe PPH cases, 15 hysterectomies and 31 deaths. The average probabilistic results are presented in Table 4.4. Scatterplots illustrating the Monte Carlo simulations for health outcomes are available in Appendix A.

Figure 4.3 Monte Carlo simulations describing the societal costs of SF oxytocin based on the simultaneous variation of model inputs


30000000
25000000
20000000
15000000
10000000
5000000
0
-5000000
Societal costs of SF oxytocin in Kenya
1
240
479
718
957
1196
1435
1674
1913
2152
2391
2630
2869
3108
3347
3586
3825
4064
4303
4542
4781
5020
5259
5498
5737
5976
6215
6454
6693
6932
7171
7410
7649
7888
8127
8366
8605
8844
908
980
Monte Carlo simulations (n=10,000)
90% <
65% <
$2M

4.4 DISCUSSION

This decision tree model estimated the health and economic burden of SF oxytocin in Kenya from the healthcare sector and societal perspectives. The model follows a cohort of pregnant women of mean childbearing age in a real-world scenario where SF oxytocin is compared to an ideal-world scenario without SF oxytocin. In both scenarios, the model incorporates women's care-seeking behaviors, their mode of delivery, the progression from first to third stage of labor and its management, the treatment outcomes, and associated costs.

Our findings indicate that every year, the presence of 7% SF oxytocin with API between 75% and 89% in Kenya contributes to the burden of PPH, the leading cause of maternal mortality in the country, with a total of 583 episodes of severe bleeding due to SF oxytocin under base case assumptions. A recent study using the Kenyan Confidential Enquiry into Maternal Deaths (CEMD), a database that includes all maternal deaths reported through the District Health Information system (DHIS2), recently estimated that between 2014 and 2017, 728 deaths of a total of 2,292 maternal deaths were due to PPH, or an average of 182 PPH-related death, annually.[130] Data frames and time periods are different, so any comparisons should be cautious, but contrasting these findings with our model estimates of 32 deaths due to PPH per year indicates that SF oxytocin may be contributing significantly to annual PPH-related maternal mortality in Kenya.[130] That is important as the 7% prevalence of SF is highly uncertain and may not be representative of exposures across the country. This input was based on the Kenyan technical group's expertise and not empirical studies. The samples collected for medicine quality assessments by the Kenyan Pharmacy and Poison Board are typically small (n=100s) for the entire country and across many different pharmaceutical categories.

Because our findings are based on the assumed prevalence of 7% SF oxytocin, it is important to interpret the findings of this study cautiously. Uncertainty was incorporated in the OWSA with a low value of 0% and a high value of 14%, and SF oxytocin prevalence was found to have the most effect on the health and economic burden of SF oxytocin which varies drastically if the prevalence was significantly higher or lower.

The economic burden of SF oxytocin is also substantial as our model estimates that almost USD $2 million are expended on direct and indirect costs every year due to SF medications. In our analysis, the management costs of severe PPH comprise the majority of the economic burden is, followed by productivity losses due to premature deaths. Despite the common practice of updosing in Kenya, our model estimated that drug costs constituted only 0.5% of the total cost of PPH management. These findings align with a study conducted in the United Kingdom that found that drug costs also only accounted for 0.5% of the total cost of PPH management, suggesting that the bulk of direct costs is allocated to medical procedures and to staff labor necessary to stop severe PPH.[131]

Our model builds upon previous efforts by Bath et al. as reported in the 2017 report by the WHO and Ozawa et al. that estimated the health and economic burden of antimalarials and antibiotics.[2,52] For example, the efficacy reduction assumption utilized in these models are comparable to the assumptions we use. However, there are several limitations in our model. Our model uses decision tree modeling and cannot account for national, regional and patient-specific variations, i.e., heterogeneity within the cohort of pregnant women. However, we can change the mean age and the number of pregnancies of a cohort. Several studies found that hypertension, prolonged labor, advanced maternal age, multiple pregnancies were among the most common risk factors for PPH.[71,132,133] Because the same population is entering the model in two different scenarios, i.e., real-world and ideal-world scenario, the distribution of risk factors for PPH among women is similar; therefore, these factors are not accounted for in the model.

Lastly, the quality of the data inputs inherently limits the findings of our model. We performed an extensive literature search to ensure the most recent and highest quality peer-reviewed data were used. We also held three meetings with subject matter experts from Kenya to validate all data inputs and their ranges to ensure local relevance and performed a OWSA and a PSA with wide ranges to address uncertainty.

Our oxytocin-specific model can be used in Kenya and other countries where maternal mortality is high to provide country-specific estimates of avertable health outcomes and costs due to SF oxytocin or to evaluate the impact of interventions combatting SF oxytocin. The findings can be leveraged by policy makers to respond with an evidence-based strategy to combat SF oxytocin at the country level.

4.5 CONCLUSIONS

The Kenyan government's efforts over the last decade to invest in maternal health led to a 30-percent decline from 488 deaths per 100,000 live births in 2010 to 342 deaths per 100,000 live births in 2017 but the maternal mortality ratio still remains high compared to the Sustainable Development Goal to reduce the global maternal mortality ratio to less than 70 per 100,000 live births, with no country having a maternal mortality ratio exceeding twice the global average.[92,134,135] The majority of maternal deaths are due to PPH and can be prevented if access to high quality care and oxytocics during and after childbirth is available. Our study demonstrates that SF oxytocin contributes significantly to the health and economic burden of maternal morbidity and mortality and emphasizes the importance of reducing the health and economic burden of SF oxytocin through providing access to better quality medications.

Chapter 5. SUMMARY CHAPTER

Substandard and falsified (SF) medical products are an important yet understudied global health issue. SF medicines burden health systems by diverting resources to harmful or ineffective products, prolonging illnesses and heightening risks of treatment failure that can result in increased illness and mortality and decreased confidence in the healthcare system. Despite years of global cooperation and initiatives designed to facilitate greater access to quality medicines, one third of the global population is still unable to obtain quality-assured medicines in a timely manner.

Several models have been developed to estimate the health and economic impact of poor-quality medicines, but they have focused on specific medicines, i.e., antimalarials and antibiotics, in certain settings. To date, only one study attempted to systematically estimate health impacts of poor-quality medicines, albeit it was limited to malaria. Failing to comprehensively quantify the burden of poor-quality medicines leads to inaccurate assessment of the scope of the issue and inadequate attention to address it. To help governments understand their country-specific health burden and costs for SF medicines, we developed tools to help relevant stakeholders estimate the health and economic impact of any poor-quality medicine.

We developed a conceptual framework and an adaptable model that allow a reproducible process to identify high-priority medicines and evaluate data availability and gaps on their quality and associated health outcomes and costs and generate estimates of the burden of SF medicines from a healthcare sector and a societal perspective. A review of specific causes of maternal deaths in Kenya showed that postpartum hemorrhage (PPH) is an issue that needs to be addressed and that over 80% of maternal deaths are attributed to poor quality of care. For this reason, we applied this adaptable model to oxytocin, a high-priority medicine for prevention and treatment of PPH in Kenya. The adaptable model we developed can be utilized to estimate the health and economic burden of other medicines used in other settings. This approach of using an adaptable tool addresses the inefficiency of building distinct models for each medicine and disease area while providing stakeholders with locally specific and policy-relevant information on the magnitude of burden resulting from the use of poor-quality medicines.

This adaptable model estimated that for 1.2 million pregnant patients delivering in healthcare facilities in Kenya yearly, poor quality oxytocin was associated with approximately 2,500 additional cases of postpartum hemorrhages (PPH), 25 hysterectomies, 26 deaths and over 420 years of life lost. That cost $1.2M for society: $300,000 due to early death and lost productivity and $900,000 in direct medical costs.

Lastly, we developed an oxytocin-specific model that incorporates delivery mode, disease progression and treatment guidelines and their associated health outcomes to generate more accurate results and compare its findings to the findings of an adaptable model to help better interpret the results generated by the adaptable model.

When comparing the health and economic burden of SF oxytocin generated by the two models, we found that the magnitude of health outcomes and costs was fairly comparable despite the differences in specific outcomes. The comprehensive disease model found that for a cohort of 1.2 million pregnant patients delivering in healthcare facilities, every year, SF oxytocin was associated with approximately 2,000 cases of PPH, 15 hysterectomies, 32 deaths and 600 years of life lost.

Additionally, we were able to estimate DALYs and QALYs and found that SF oxytocin was associated with almost 2,200 DALYs incurred and 560 QALYs lost over a lifetime horizon. In addition to the health burden, the oxytocin-specific model estimated that the total economic burden of almost $2M USD in Kenya from a societal perspective (compared to $1.2M estimated by the adaptable model).

The differences in health outcomes and costs between the adaptable model and comprehensive disease model can be explained by the difference in the methodology used in both models. First, the oxytocin-specific model stratifies the population by their mode of delivery allowing it to integrate the probabilities for health outcomes and utilities for vaginal and cesarian deliveries separately. For example, the oxytocin-specific model reflects that 16% of women underwent cesarian deliveries and had a higher risk of PPH and hemorrhage-related morbidity, compared to vaginal deliveries.[136,137]

The probability of mild PPH is 3.6 times higher and the probability of severe PPH 12 times higher in cesarian deliveries than vaginal deliveries.[122] In the adaptable model, the probabilities of mild and severe PPH incidence with and without oxytocin used were from data collected for vaginal deliveries as these represent the majority of pregnancies.[65] Second, this oxytocin-specific model incorporates the natural progression of the disease from first to third stage labor based on clinical practice guidelines and the WHO guidelines and recommendations for PPH prevention and management.[2,105,107–111] This approach ensures that the burden of each health outcome and its associated costs such as mild and severe PPH is differentiated and cannot be duplicated. This approach also allowed us to construct QALYs and DALYs instead of relying on data from previous studies that estimated QALYs and DALYs with and without treatment that was not available for oxytocin.

Whether one model is more useful than the other depends on the research question we are trying to address. Overall, the value of the adaptable model lies in its capacity to be used for any medicine, which makes it particularly useful in resource-limited settings to provide high-level country-specific estimates for the health and economic burden of any poor quality of medicines. On the other hand, the value of using the oxytocin-specific model lies in its ability to generate more accurate estimates for oxytocin, when compared to current estimates of maternal morbidity and mortality in Kenya If the research question is to estimate the health and economic burden of oxytocin, the oxytocin-specific model would be preferred. If the research question is to estimate the health and economic burden of another medicine and a disease-specific model doesn't yet exist, the adaptable model would better address it. The findings of my dissertation demonstrate that the adaptable model can serve as a tool to be leveraged by relevant stakeholders to generate evidence on the health and economic burden of any medicine in their country. Evidence from an adaptable model needs to be interpreted cautiously but can help prioritize resource allocation when developing effective policies and strategies to strengthen regulatory systems to reduce the prevalence of poor-quality medicines and to achieve maximum population health impact. As the world seeks to achieve the sustainable development goals by 2030, reducing the prevalence of poor-quality medicines will be essential to provide access to quality health services for all.

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Based+Resource+Allocation+for+Pharmaceutical+Quality+Assurance+for+Medicines+Regulatory+Authorities+in+Low-+and+Middle-Income+Countries.+USP%3A+Rockville%2C+MD.+Submitted+to+USAID.+June+2018.&aqs=chrome..69i57j69i60.1228j0j7&sourceid=chrome&ie=UTF-8. Accessed January 15, 2021.

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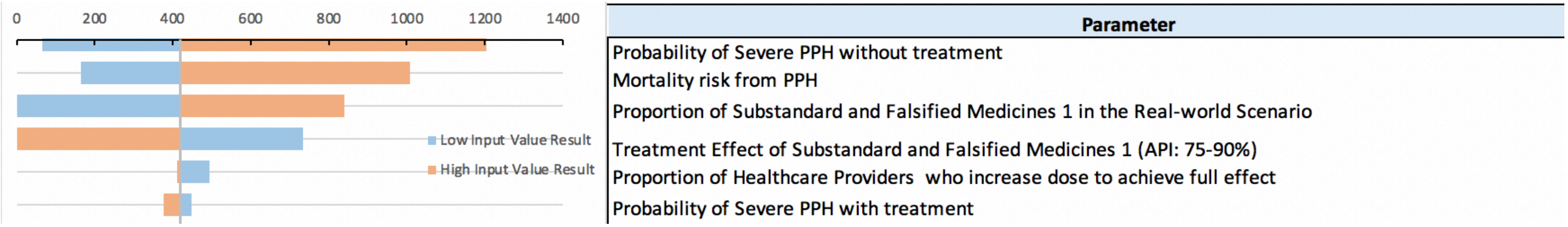
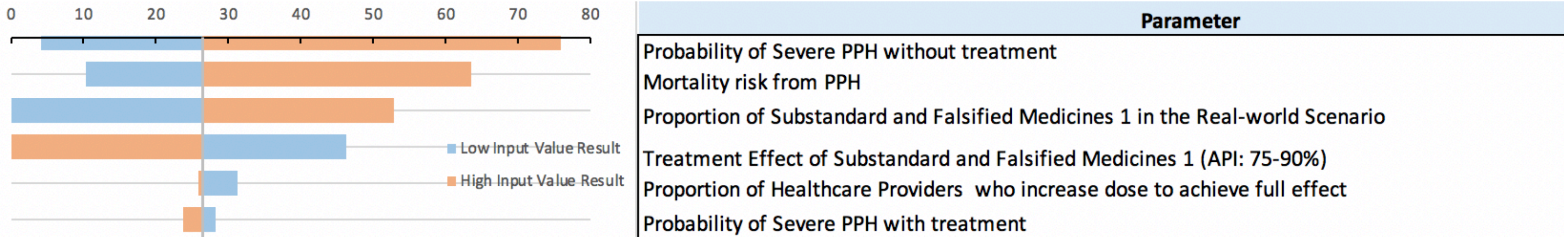
Appendix

Figure 1. A-D Tornado diagrams generated by the adaptable model to assess the impact of parameter uncertainty on model's results

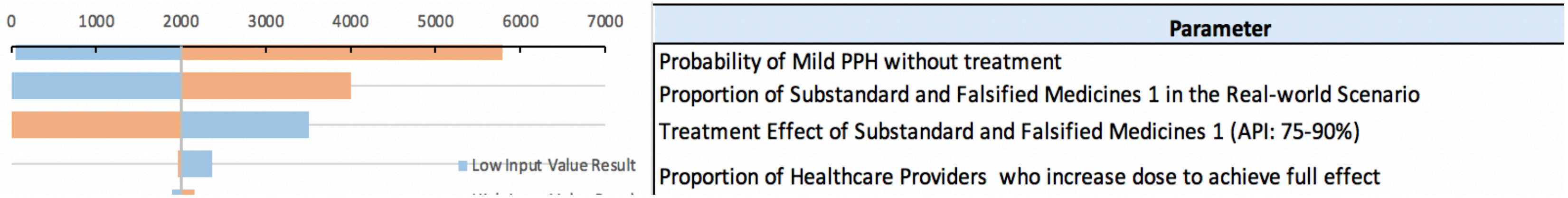
1.A. Incremental YLLs



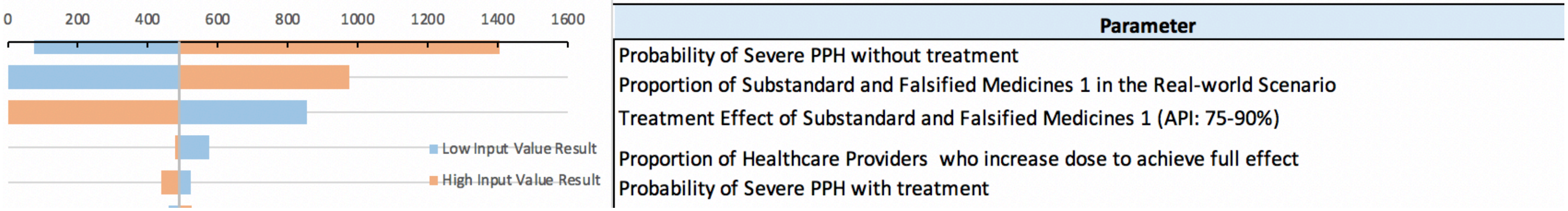
1.B. Incremental Deaths



1.C. Incremental mild PPH

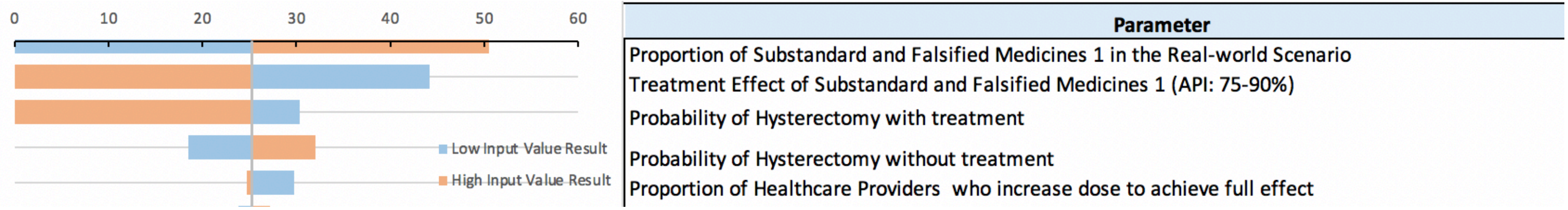


1.D. Incremental severe PPH



Parameter
Probability of Severe PPH without treatment
Proportion of Substandard and Falsified Medicines 1 in the Real-world Scenario
Treatment Effect of Substandard and Falsified Medicines 1 (API: 75-90%)
Proportion of Healthcare Providers who increase dose to achieve full effect
Probability of Severe PPH with treatment

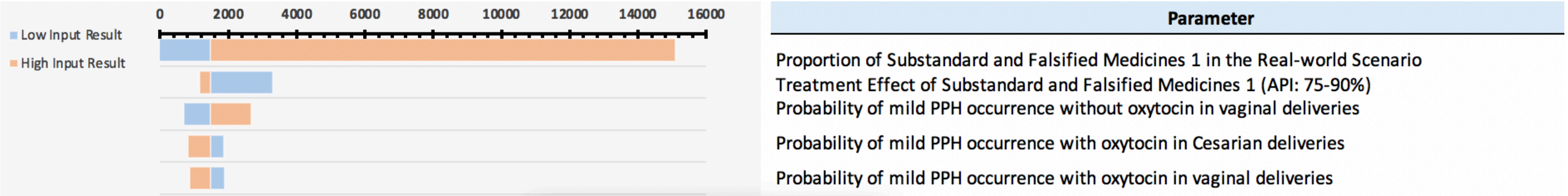
1.E. Incremental Hysterectomies



Parameter
Proportion of Substandard and Falsified Medicines 1 in the Real-world Scenario
Treatment Effect of Substandard and Falsified Medicines 1 (API: 75-90%)
Probability of Hysterectomy with treatment
Probability of Hysterectomy without treatment
Proportion of Healthcare Providers who increase dose to achieve full effect

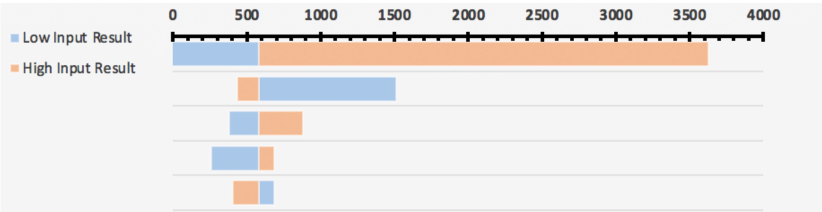
Figure 2.A-G. Tornado diagrams generated by the oxytocin-specific model to assess the impact of parameter uncertainty on model's results

2.A. Incremental mild PPH



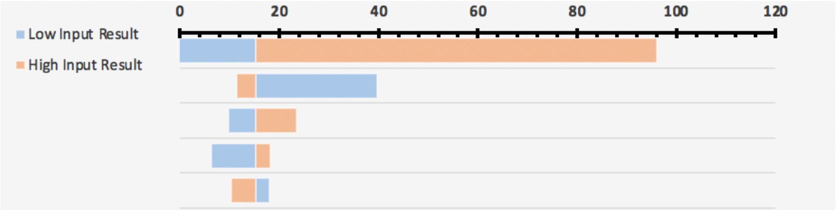
Parameter
Proportion of Substandard and Falsified Medicines 1 in the Real-world Scenario
Treatment Effect of Substandard and Falsified Medicines 1 (API: 75-90%)
Probability of mild PPH occurrence without oxytocin in vaginal deliveries
Probability of mild PPH occurrence with oxytocin in Cesarian deliveries
Probability of mild PPH occurrence with oxytocin in vaginal deliveries

2.B. Incremental severe PPH



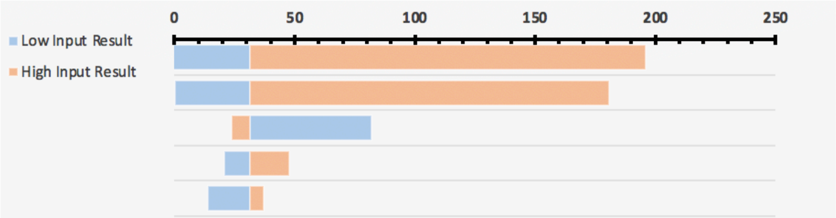
Parameter
Proportion of Substandard and Falsified Medicines 1 in the Real-world Scenario
Treatment Effect of Substandard and Falsified Medicines 1 (API: 75-90%)
Probability of severe PPH occurrence without oxytocin in Cesarian deliveries
Probability of mild PPH occurrence without oxytocin in Cesarian deliveries
Probability of mild PPH occurrence with oxytocin in Cesarian deliveries

2.C. Incremental Hysterectomies



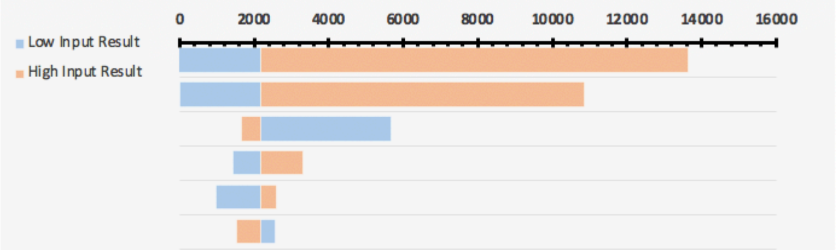
Parameter
Proportion of Substandard and Falsified Medicines 1 in the Real-world Scenario
Treatment Effect of Substandard and Falsified Medicines 1 (API: 75-90%)
Probability of severe PPH occurrence without oxytocin in Cesarian deliveries
Probability of mild PPH occurrence without oxytocin in Cesarian deliveries
Probability of mild PPH occurrence with oxytocin in Cesarian deliveries

2.D. Incremental Deaths



Parameter
Proportion of Substandard and Falsified Medicines 1 in the Real-world Scenario
PPH-related mortality
Treatment Effect of Substandard and Falsified Medicines 1 (API: 75-90%)
Probability of severe PPH occurrence without oxytocin in Cesarian deliveries
Probability of mild PPH occurrence without oxytocin in Cesarian deliveries

2.E. Incremental DALYs



Parameter
Proportion of Substandard and Falsified Medicines 1 in the Real-world Scenario
PPH-related mortality
Treatment Effect of Substandard and Falsified Medicines 1 (API: 75-90%)
Probability of severe PPH occurrence without oxytocin in Cesarian deliveries
Probability of mild PPH occurrence without oxytocin in Cesarian deliveries
Probability of mild PPH occurrence with oxytocin in Cesarian deliveries

Figure 3. Monte Carlo simulations for the health burden of SF oxytocin generated by the oxytocin-specific model