Bridging the Interagency Silos

Taking a political economy perspective to tackle substandard and falsified medicines in Indonesia

Amalia Hasnida

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Het overbruggen van de silo's tussen agentschappen
Een politiek-economisch perspectief om ondermaatse
en vervalste medicijnen in Indonesië aan te pakken

Thesis

to obtain the degree of Doctor from the
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by

Siti Amalia Hasnida
born in Jakarta, Indonesia.

Erasmus University Rotterdam

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Co-promotor	Dr. M.O. Kok

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Abbreviations and acronyms

AMR	Antimicrobial resistance
APIs	Active pharmaceutical ingredients
BPOM	*Badan Pengawas Obat dan Makanan*
DEG	Diethylene glycol
DHOs	District health offices
EG	Ethylene glycol
GDP	Gross domestic products
HICs	High-income countries
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
INN	International non-proprietary rights
IPR	Intellectual property rights
JKN	*Jaminan Kesehatan Nasional*
LMICs	Low-and-middle income countries
MoH	Ministry of Health
NMRA	National Medicines Regulatory Authority
OOP	Out-of-pocket payment
OOS	Out-of-specification
PHCs	Primary health centres
PHOs	Provincial health offices
PMS	Post-market surveillance
SFM	Substandard and falsified medicines
SSFFC	Substandard/spurious/falsely-labelled/falsified/counterfeit
STARmeds	Systematic Tracking of At-Risk Medicines
UHC	Universal health coverage
USP	United States of Pharmacopeia
WHO	World Health Organization
WHO GSMS	WHO Global Monitoring and Surveillance Systems

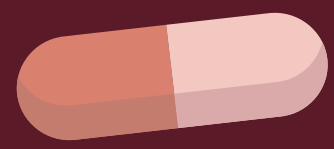
“It is not the mountain we conquer, but ourselves

-Edmund Hilary

Chapter 1.

Introducing a political economy perspective to tackle substandard and falsified medicines

The English language in this chapter has been edited using Grammarly, an artificial intelligence software



Opening quotes

Researcher :

"In the end, what did you decide about medicines with damaged packaging?"

District health authority official:

"Unfortunately, we still gave them to patients because we had no other choice with this shortage. The choice is between the patient receiving medicines that might still work or none at all. And the latter option would be a worse choice (for service delivery)."

(Interview at a medicine dispensing facility in Eastern Indonesia)

"…If you want to talk about (medicine) quality, you are talking to the wrong party."

(Pharmacist and Ministry of Health official)

Prologue

Medicines are one of the building blocks of health systems that contribute to the quality of care (Lat et al., 2024). Patients consume medicine hoping to cure or prevent a disease or manage to live with one. However, in some ill-fated cases, these medicines do not work properly because they are of poor-quality. The consequences can be dire as these poor-quality medicines will worsen the disease, might kill patients, waste financial and other resources, and undermine trust in the health system (Newton et al., 2010). In 2019, the United Nations General Assembly declared a link between the quality of medicines and universal health coverage (UHC), a global priority agenda, emphasizing "the need for access to safe, quality, efficacious, and affordable medicines and vaccines, without incurring financial hardship for all people "(General Assembly of the United Nations, 2019). However, achieving Universal Health Coverage (UHC) remains challenging, given the poor-quality of medicines in any health system (Lee et al., 2025).

Poor-quality medicines are caused by complex risk factors (World Health Organization, 2017b), most framed by technical and regulatory approaches or domains. In 1999, the World Health Organization (WHO) published a report highlighting causes, risk factors, and recommendations around pharmaceutical regulation and technical capacity, law enforcement and governance, and access to medicines (WHO, 1999). Almost two decades later, in 2017, another report was published, but still contained a similar risk factors analysis and recommendations, although its information was based on incident reports collected by the WHO Global Monitoring and Surveillance System (WHO GSMS), presumably the most comprehensive platform for recording poor-quality incidents globally (World Health Organization, 2017b). More recently, in 2024, the WHO published an updated report, stating that the underlying causes of poor-quality medicines "remain significantly unaltered" as the previous reports (World Health Organization, 2024a). Meanwhile, global incidents related to poor-quality medicines continue to increase, affecting both low- and middle-income countries (LMICs) and high-income countries (HICs). In the latter section of this chapter, I will explain further about the political economy perspective I use in this thesis and what it entails.

Access to medicines remains a substantial factor in exposing patients to poor-quality medicines (R. Ravinetto et al., 2024). In particular, gaining access to quality-assured medicines is challenging (Gray & Suleman, 2025; Oldfield et al., 2025), especially in LMICs striving to achieve UHC. Approximately one-third of the world's population still lacks access to these products. Furthermore, the first opening quote illustrates the dilemma in practice between providing quality-assured medicines and not providing medicines at all when shortages occur. Thus, there is an intricate link between quality and other issues in pharmaceutical policy, such as availability (Nungo et al., 2024) and affordability (World Health Organization, 2017b), suggesting that these issues are not mutually exclusive or, in other words, they do not stand alone. A comprehensive understanding of the socioeconomic dimensions, including the political and economic

factors of poor-quality medicines and how they relate to other areas of pharmaceutical policies, such as access to medicines or availability, is necessary to combat this problem effectively.

From a policy perspective, medicine quality is generally seen as a technical and regulatory matter that falls under the authority of the national medicine regulator. This agency is responsible for conducting post-market surveillance, an activity that ensures the quality of medicines in the market. This involves sampling medicines from dispensing points and testing their quality in the laboratory. Post-market surveillance can be a resource-intensive and expensive activity that many regulators in LMICs struggle to implement effectively (United States Pharmacopeial Convention, Babigumira, et al., 2018; United States Pharmacopeial Convention, Nkansah, et al., 2018). Meanwhile, other actors or institutions in the health sector or elsewhere may be seen to play a role in overcoming this problem (Bigdeli et al., 2013). This multi-actor constellation gives rise to shifting responsibility between actors and often leads to "siloisation". As in the second opening quote, discussing medicine quality with a pharmacist at the Ministry of Health may be inappropriate due to differences in institutional roles and responsibilities.

Interagency silos can undermine governance and policy responses to tackle poor-quality medicines. I use the term interagency to encompass different sections or departments within the same organization *or* between different organizations. These silos can be defined as different areas of pharmaceutical policy, such as availability, pricing, or affordability, as well as irrational or inadequate use of medicines. Each area has interrelationships between the technical and regulatory domains, as well as the political, social, economic, and ethical domains. Overall, I describe the interagency silos as a state where different agencies work independently according to their duties and functions in their respective policy field or areas but without effective alignment, coordination, and collaboration with each other to synchronize agenda setting and policy responses comprehensively. In this thesis, I will also use specific terms related to medicines and other components, as listed in Textbox 1.

Globally, poor-quality medicines remain a complex challenge; yet, policy responses are primarily informed by technical and regulatory approaches, with less prominent contributions from other domains. In this thesis, I argue that poor-quality medicines can benefit from alternative political and socioeconomic lenses to understand the problem, bridge the interagency silos, and propose different approaches to policy responses. In particular, my thesis aims to explore insights into broadening the frame and problem definition of poor-quality medicines, later called substandard and falsified medicines (SFM), by taking a political economy perspective and operationalizing it to tackle the issue. Using a political economy perspective, I (1) open the scope of the problem definition and broaden the existing framing, which is mainly technical and regulatory, to understand the mechanisms that drive the production and trade of SFM. For example, understanding the interplay of incentives of different actors, the interrelatedness between different policies in the health sector and beyond, and the

roles and responsibilities of multiple actors and the changes around them as the SFM problem is redefined and broadened using a political economy perspective. Another focus of this thesis is (2) to understand the work that can be done to operationalize the political economy perspective and combine it with technical and regulatory approaches to strengthen post-market surveillance activities. In this regard, I study the roles of researchers as policy entrepreneurs in broadening the frame and problem definition of SFM in the policy process by exploiting opportunities, opening policy windows, and shaping agenda settings. Taking the role of a policy entrepreneur myself, I also operationalize risk factors based on the political economy perspective into risk indicators to indicate or flag products at the highest risk of being SFM, test the risk indicators for substandard products, and test the assumed relationship between medicine price and quality. Lastly, taking the perspective of an external observer, I also study stakeholder engagement in a research collaboration on SFM.

In this introductory chapter, I will first provide an overview of the definitions, current challenges, and complexities of **substandard and falsified medicines (SFM)** globally, focusing on systemic or non-technical challenges such as market and institutional dynamics, as well as data sharing. Then, I will outline the theoretical lens of **framing, problem identification, and agenda setting**, including an overview of the literature about the importance of framing SFM in policy. Next, I will outline the **perspective of political economy** and the market risk-based framework from which this thesis is derived. In the next section, I will provide contextual information about the **case study in Indonesia**, including specific challenges related to SFM in this setting. Following this, I will describe the **analytical focus** of this thesis, my **research journey** of different projects which constructed this thesis, and the **outline of the chapters**.

Textbox of medicine terms

Textbox 1. Medicine terms

This thesis focuses on medicines or pharmaceuticals. WHO broadly describes "medical products" as medicines, vaccines, and in vitro diagnostic and medical devices (World Health Organization, 2017b). I included an analysis of falsified vaccines primarily in Chapter 2, but subsequent analysis focuses on medicines. When referring to the industry, I use the term "pharmaceuticals" because it "refers to the act of making and selling medicines" (Xu, 2022). In some cases, when I refer to previous surveys or research, I will use "medical products" where appropriate to the available evidence.

Throughout this thesis, I will use different terms to categorize types of medicines as follows (Kaplan et al., 2013):

- Originator products: A product first authorized in a country for marketing (usually as a patented product) based on the documentation of its efficacy, safety, and quality following the requirements at the time of authorization.
- Unbranded generic products or generics: Non-originator products sold under an international non-proprietary name (INN) (i.e., the generic name of the ingredient molecule(s)) rather than a brand name.
- Branded generic products: Non-originator products. They can be either novel dosage forms of off-patent products produced by a manufacturer who is not the originator of the molecule or a molecule copy of an off-patent product with a trade name produced by a manufacturer who is not the originator.

In addition to finished products such as medicines, in this thesis, I sometimes also discuss the components of medicines below (Kumar et al., 2022):

- Active pharmaceutical ingredients (APIs): Chemical-based compounds that are chemically and biologically active for the medicines to work in the body system. For example, amoxicillin, amlodipine, etc.
- Excipients: Chemically inactive compounds that help the delivery of APIs in the body system and provide volume, sweetness, or color. For example, lactose or mineral oil in the pill.

The complexities around substandard and falsified medicines

In this section, I will explain the complexities of SFM, which encompass both technical and socioeconomic domains. I will also describe the technical measures to ensure the quality of medicines on the market, namely, post-market surveillance. When discussing the challenges in addressing SFM, I will focus on governance aspects to build a case for why adding a political economy perspective as a frame for existing technical measures is potentially useful as an alternative policy solution.

A long way to define the problem

Defining and framing SFM is a socially constructed process (M. C. M. Lamy, 2017, p. 20; Xu, 2022), primarily shaped by technical and regulatory domains. Different actors, including global health institutions, the pharmaceutical industry, and pharmaceutical experts, have shaped and transformed the debates. In 1992, the World Health Organization (WHO) and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) organized a workshop in which the first definition of "counterfeit" medicines was suggested, which combined the commercial aspects of intellectual property rights (IPR) and quality assurance of medicines from a public health perspective ('t Hoen & Pascual, 2015). Multinational pharmaceutical manufacturers were proponents of framing the issue of counterfeit medicines from a commercial and IPR infringement perspective. At the same time, global health actors were strong advocates for the public health perspective. Consequently, these different views created fundamental tensions between the actors.

The term "substandard" first appeared in policy discourse two decades later. In 2012, WHO included all definitions of poor-quality medicines and introduced the acronym SSFFC, which stands for Substandard/Spurious/Falsely-Labelled/Falsified/Counterfeit (WHO, 2012). Several scholars have argued that this term indicates a shift towards framing the issue as a public health problem (Gostin et al., 2013). However, this new acronym also caused a stir in practice because each category of poor-quality medicines requires different policy solutions (M. C. M. Lamy, 2017). Moreover, this new term still overlapped with intellectual property issues. The lack of agreement in terminology also complicated efforts to harmonize language between actors and to compare findings from different surveys (Ozawa et al., 2020; Rasheed et al., 2023; World Health Organization, 2017b).

To drive more concerted efforts in tackling the problem, WHO once again published an official definition of SFM in 2017, ignoring the IPR issue and emphasizing only the public health perspective (Rasheed et al., 2023; World Health Organization, 2017b; Xu, 2022). The following terms in Table 1 are the current official definition of SFM, which I will also refer to throughout the chapters in this thesis.

Table 1. Definitions of poor-quality medicines (World Health Organization, 2017b)

Poor-quality medicines	Definitions
Substandard	Products are authorized medical products that fail to meet either their quality standards or their specifications, or both.
Falsified	Products are deliberately/ fraudulently misrepresented with regard to their "identity, composition, or source."
Illegal	Medical products have not undergone evaluation and/or approval by the National Regulatory Authority (NRA) for the market in which they are marketed/distributed or used.

From this historical perspective, the current framing of SFM in public health relies heavily on regulatory and technical frameworks. The WHO published two reports nearly two decades apart that contained similar causes, risk factors and recommendations despite different periods and increases in reported incidences on their Global Surveillance and Monitoring System or GSMS (WHO, 1999; World Health Organization, 2017b). They highlighted three main contributory factors: (1) constrained access to affordable, safe, and quality products, (2) weak technical capacity, and (3) poor governance. In 2024, the WHO published a new report stating the same causes of SFM as seven years ago (World Health Organization, 2024a). However, this time, the WHO foregrounds several risk factors or facilitators of SFM, most of which still came from a technical and regulatory perspective, as shown in Table 2. Meanwhile, little attention was paid to the underlying political and economic factors that contribute to the drivers of SFM production and trade. Overlooking political and economic factors may limit alternative policy solutions to tackle complex SFM problems, and this consideration has motivated a group of interdisciplinary researchers, including myself, to investigate further (Pisani et al., 2019). In this thesis, I will use a political economy perspective to broaden the problem definition and explore the socioeconomic dimensions. However, I will first explain the magnitude of the SFM problem and its impact to illustrate the severity of the problem globally.

Table 2. Factors increasing the likelihood of SFM, potential risks, and limit effective responses (World Health Organization, 2024a)

1.	Weak regulatory systems
2.	Inadequate legal frameworks for market control
3.	Ineffective coordination among national regulatory authorities, law enforcement and customs agencies
4.	Little public awareness of the risks
5.	Limited use of technology for product authentication or tracking
6.	Rapidly evolving scientific and medical developments

Incidence, incidents, and impact

SFM is a global health policy issue, given the magnitude of its incidents, incidence, and impact. Current studies focusing on low and middle-income countries (LMICs) reported comparable numbers and sizes of the problems. A review published by WHO in 2017 based on more than 48,000 medicine samples collected from 88 countries reported a sample failure rate of 10.5% (World Health Organization, 2017b), indicating the problem is often underreported and likely to continue to proliferate (World Health Organization, 2024a). From 2017 to 2021, with an annual increase rate of 36.3%, the WHO recorded 877 incidents, providing information on over 1600 confirmed or suspected SF products (ibid.). Additionally, available evidence from several reviews highlights that the therapeutic areas where poor-quality products are most frequently identified are antimalarials (from 11.8%-19.1%) and antibiotics (from 7.2%-12.4%) (Ozawa et al., 2018; World Health Organization, 2017b, 2024a). These two classes are generally used to treat infectious diseases common in LMICs.

The complexity of SFM is also demonstrated by the scattered and fragmented nature of the problem in terms of region, product type and sources. The problem is often framed as a concern in LMICs (Ofori-Parku, n.d.). According to a study, Africa has the highest prevalence of SF medical products (18.7%), followed by Asia (13.7%) (Wada et al., 2022). However, SFM has also been found outside LMICs; for example, human carcinogen nitrosamines were detected in Europe and the United States (Charoo et al., 2019; World Health Organization, 2019). SF products have been found in active pharmaceutical ingredients (APIs), excipients, and branded and unbranded generic medicines (Newton et al., 2019). Global pharmaceutical manufacturers and exporters, such as those in China and India, have been implicated as major sources of SFM (Attaran et al., 2012; Office on Drugs and Crime, 2010; Xu, 2022). The recent COVID-19 pandemic has also exacerbated the problem of SFM (World Health Organization, 2024a); for example, a

report found that incidents of SF medical products increased by nearly 47% from 2020 to 2021 (Bhatt, 2023).

The incidence of SFM has many implications. In the clinical domain, studies have reported that SFM can cause adverse health impacts and treatment failures, affecting the development of antimicrobial resistance (Kelesidis & Falagas, 2015; Pyzik & Abubakar, 2022; Renschler et al., 2015; World Health Organization, 2017a, 2024a). Also, major incidents have been reported; between 2022 and 2023, the public was shocked by at least 300 deaths of children in three countries, mainly under the age of 5 years, after consuming cough syrups that were contaminated with diethylene glycol (DEG) and ethylene glycol (EG) (Lateef et al., 2023).

In the socioeconomic domain, SFM reduces public trust in the health system and increases the burden on staff to manage the medical consequences of mortality and morbidity (Mengesha et al., 2024; Newton et al., 2010; Pyzik & Abubakar, 2022). In addition, SFM distorts medicine prices, creates incentives for theft, fraud, or corruption, and undermines confidence in the market itself, as well as the integrity of authorities and professionals working within the system (Mengesha et al., 2024). In some cases, SFM incidents also led to organizational changes in medicine regulatory governance (Amindoni, 2016; Rashid, 2015).

Assuring the quality of medicines on the market

This thesis focuses on the quality of medicines circulating on the market, both those available in distribution channels and those already distributed to patients from health facilities. The primary measure for ensuring the quality of these medicines comes from the technical and regulatory domains. In this section, I will focus on the actor responsible in the technical domain: medicine regulators. In the latter part, I will describe the technical activities conducted by medicine regulators to ensure the quality of medicines on the market, namely, post-market surveillance. My research will focus on integrating socioeconomic dimensions using a political economy perspective into post-market surveillance activities.

Regulatory environment

National medicine regulators are the agencies responsible for authorizing and monitoring the quality, safety, and efficacy of medicines and medical products in their health systems (United States Pharmacopeial Convention, 2021). Despite their critical role, the capacity of medicine regulators to carry out these activities varies widely between countries. WHO estimates that only 28% of its Member States have "a stable, well-functioning, integrated regulatory system" (World Health Organization, 2024a), which implies that the capacity of medicine regulators to regulate medical products effectively and efficiently in their countries is still limited (Twesigye et al., 2021). Many countries struggle with competing priorities, chronic underfunding, limited human resources, inadequate equipment and systems to support surveillance activities and a lack of necessary legal mandate (Duga et al., 2024; Fimbo et al., 2024; Twesigye et al.,

2021; United States Pharmacopeial Convention, 2021).

Several technical initiatives seek to strengthen the capacity of medicine regulators. For example, WHO GSMS provides technical support to national medicine regulators to report SFM incidents and issue medical product alerts to Member States (World Health Organization, 2024a, 2025b). Additionally, WHO also provides the Global Benchmarking Tool to evaluate the overall regulatory framework and functions, including post-market surveillance, which categorizes regulators into four Maturity Levels, with level 3 representing the minimum target for a well-functioning system and level 4 being the "Regulatory system operating at an advanced level of performance and continuous improvement"(Pan American Health Organization (PAHO), n.d.; World Health Organization, 2024b). WHO also published its strategic recommendations for Member States to address SFM, which include prevention, detection, and response mechanisms (World Health Organization, 2022, 2024a). Apart from response, which includes coordination and collaboration across sectors, *prevention* and *detection* mainly consist of technical measures.

Medicine regulators are mandated to ensure the quality of medicines on the market; however, several institutional and governance barriers impede their authority. First, these agencies tend to take centre stage during highly visible public health crises. Meanwhile, the benefits of their work, in the absence of a crisis, are "diffused, difficult to attribute, and hidden from the public" (Twesigye et al., 2021). Second, in contrast to their roles in coordinating medicine quality, safety, and efficacy issues, lower political rankings have weakened their policy coordination and political mobility authority (Xu, 2022).

Post-market surveillance

Post-market surveillance aims to ensure that the quality of medicines, after registration and market authorization, is maintained until the product reaches patients (Aroca & Guzmán, 2017; FDA, 2014; United States Pharmacopeial Convention, 2021). Post-market surveillance is critical in preventing, detecting, and responding to SFM (World Health Organization, 2024a). The broader technical scope includes various surveillance activities such as "maintenance of product authorization and/or registration of variations or renewals; regular inspections of manufacturers, wholesalers, distributors, and retailers; quality control testing; pharmacovigilance; promotion control; public reporting of poor-quality products; handling of market complaints; and removal and disposal of non-compliant products" (USP Promoting the Quality of Medicines, 2018). In this thesis, the scope of post-market surveillance is on product sampling from facilities where patients can access medicines, such as pharmacies or drug stores, and quality testing in the laboratory.

Post-market surveillance is a challenging and expensive activity due to the massive pharmaceutical market, complex pharmaceutical supply chain and globalization of trade, the large variety of medical products in the market (United States Pharmacopeial Convention, 2021; United States Pharmacopeial Convention, Babigumira, et al., 2018;

United States Pharmacopeial Convention, Nkansah, et al., 2018), and expensive reference standards for laboratory testing (Valente de Almeida et al., 2024). In governance, uneven enforcement between central and peripheral regulatory offices nationwide exacerbates the challenges (M. C. M. Lamy, 2017). This gap is due to ineffective decentralization of regulatory functions and inefficient delegation of inspection responsibilities to provincial branches. Therefore, technical agencies support country efforts, such as the United States Pharmacopoeia's "Promoting Quality of Medicines Program in LMICs" or the USP PQM program (USP Promoting the Quality of Medicines, 2018). This program widely supports risk-based sampling and testing as a potential solution to SFM problems in LMICs (United States Pharmacopeial Convention, 2021; United States Pharmacopeial Convention, Babigumira, et al., 2018; United States Pharmacopeial Convention, Nkansah, et al., 2018).

To make the best possible use of limited resources and to increase the likelihood of detecting poor-quality products, the WHO and others promote risk-based sampling. This is especially relevant in settings where resources are scarce and/or the prevalence of poor-quality products is low. Some researchers have attempted to develop or advance risk-based sampling by considering multiple risk factors (Aroca & Guzmán, 2017; FDA, 2014; United States Pharmacopeial Convention, 2021). However, evidence from these studies suggests that existing risk-based sampling strategies do not clearly distinguish between the risk to products and public health risks. Therefore, in this thesis, I will focus on product risk by operationalizing the political economy perspective into risk indicators to flag which products are at risk of being substandard. Based on the available resources for this research, I decided to focus on the risk of substandard quality associated with the selected study medicine, amoxicillin, which is more likely to face issues of substandard quality rather than falsification.

Challenges in governing substandard and falsified medicines

In addition to the technical challenges, SFM also has complex political and socioeconomic dimensions related to the characteristics of this issue and other attributes. In this section, I will outline the governance-focused challenges to understand interagency silos in policy responses. I will first elaborate on the massive pharmaceutical market organization, then explain why SFM is a politically sensitive and neglected issue, and, finally, discuss the challenges around the availability, sharing, and transparency of fragmented data.

The massive and intricate pharmaceutical markets

The pharmaceutical supply chain is an intricate network of public, private, or informal supply chains, each of which poses different risks to quality (Satheesh et al., 2025; United States Pharmacopeial Convention, Nkansah, et al., 2018). Informal markets, also known as unlicensed outlets, are seen as a threat to society, especially in LMICs, where access to affordable, quality-assured medicines through licensed channels is constrained (Evans et al., 2012; Jean-Baptiste et al., 2020; Mengesha et al., 2024; Okereke et al., 2021; Zabala et al., 2022). Another type of unlicensed retail outlet increasingly proliferating

worldwide is illicit websites or unregulated e-pharmacies (Satheesh et al., 2025; World Health Organization, 2024a). Previous studies have identified substandard and falsified products in formal and informal markets (Gabel, Lächele, et al., 2024; World Health Organization, 2024a).

Regarding product types, many products circulating in a given market consist of prescription-only and over-the-counter medicines, which are either manufactured domestically or imported from other countries (Bizimana et al., 2021; Gabel, Difäm-EPN Minilab Network, et al., 2024; Gabel et al., 2023; Koech et al., 2020). Products can also experience diversion, meaning that they can be illicitly diverted from licensed to unlicensed channels (Rx-360 Supply Chain Security, 2013; Scholten, 2017; United Nations Office on Drugs and Crime, 2022). Countries can also have vast geographical areas with extreme temperatures that pose degradation risks when distributing products to remote locations (Kayumba et al., 2004; Toroitich et al., 2024; Twagirumukiza et al., 2009; United States Pharmacopeial Convention, Nkansah, et al., 2018). As a result, all of the factors mentioned above complicate the task of medicine regulators in selecting which medicines and areas to sample.

In addition, regulators need to interact or collaborate with various actors who are involved in the manufacturing, distributing, and selling or dispensing medicines along the supply chain, such as the pharmaceutical industry, distributors, wholesalers, pharmacists, warehouse officials, drug store owners, procurement agencies and others. Unfortunately, it can be challenging for regulators and procurement agencies to cooperate in LMICs, as the latter tend to focus on price above all else (Orubu et al., 2020), creating silos that disconnect them from regulatory decisions such as marketing authorization approvals and product recalls (Boche et al., 2022; Campos & Pradhan, n.d.; Kohler et al., 2025).

A politically charged and neglected issue

SFM is a politically sensitive issue for various actors, especially national governments (Xu, 2022). Each actor has their interests and concerns regarding the topic's sensitivity. For example, governments may have vested interests in manufacturing and distributing medicines, leading to a lack of political will to recognize the problem or refusal to address the topic and implement the policy (M. C. M. Lamy, 2017; Xu, 2022). Additionally, governments have incentives to avoid bad publicity by refusing to announce and report SFM incidents in their markets (Xu, 2022). Meanwhile, regulators in neighbouring countries can also be reluctant to share information about falsified medicines in the border regions, as this may lead to accusations of blame against one country or another (M. C. M. Lamy, 2017). The political sensitivity surrounding SFM thus complicates law enforcement and long-term efforts to tackle the problem.

In addition to its sensitivity, SFM is considered a neglected public health issue. One argument is that unless the impact of SFM is very massive and profound, such as the recent fatal cases of contaminated cough syrup in several countries, the problem is usually largely invisible and difficult to detect compared to other public health crises, such as

HIV/AIDS, tuberculosis, or the COVID-19 pandemic (World Health Organization, n.d.-b). Furthermore, the discussion of SFM is highly specialized, isolating it from the social, economic, and political contexts in which the problem arises (Mengesha et al., 2024). As a result, despite the significant impact of SFM on health systems, attention and infrastructure for the quality of essential medical products are still lacking (Kingori et al., 2023).

Fragmented data availability, sharing, and transparency

One factor that contributes to SFM being a neglected issue is the limited availability of data (Jere et al., 2024). As mentioned above, the nature of SFM problems is illicit and invisible, while research on SFM is sparse. Quantitative prevalence data on the magnitude and distribution of SFM is a vital data source supporting effective and timely evidence-based regulatory respons (M. C. M. Lamy, 2017; Rasheed et al., 2023; Xu, 2022).

If data are available, the standards are often questioned for generalizability (Opuni et al., 2024). SFM prevalence studies tend to report all samples that fail a quality test without distinguishing between different pharmacopoeias, the definitions used, the tests performed, and the extent to which the failed samples deviate from quality specifications (Ozawa et al., 2022). Furthermore, published studies report small sample sizes, unrepresentative study designs, and a variety of medicines included (Pisani et al., 2024).

Data sharing and transparency are another dimension of the challenge. Data on SFM are fragmented within and outside the health system (Xu, 2022) or between countries (Duga et al., 2024), and the willingness to share knowledge and information transparently between actors appears to be low (M. C. M. Lamy, 2017; Wilder et al., 2025; World Health Organization, 2024a). Governments and pharmaceutical companies are reluctant to share SFM data to avoid bad publicity that would deter patients from using quality-assured products (Cockburn et al., 2005). Meanwhile, only a few national medicine regulators regulate the publication of data on SFM reports (Newton et al., 2019). For example, during the recent cough syrup incidents, Indian authorities, as a manufacturing country, were criticised for being slow in sharing information with the WHO, raising serious concerns from the global community (Lateef et al., 2023). Consequently, the lack of data sharing and transparency can hinder alignment between actors and affect timely decision-making and effective interventions (World Health Organization, 2024a).

In this thesis, in addition to collecting primary data, I will also use secondary routine data from various sources and organizations to operationalize the problem definition of SFM using a political economy perspective into risk indicators.

The governance challenges mentioned above have created and exacerbated interagency silos in tackling SFM. With these circumstances in mind, the next section will elaborate on broadening the existing frame of SFM as an alternative perspective.

Broadening the frame of substandard and falsified medicines

In this sub-section, I will outline the theoretical lens of this thesis, focusing on the role of researchers as policy entrepreneurs in broadening the frame and problem definition of SFM by exploiting opportunities or opening policy windows and shaping agenda settings. In the first part, I will outline the existing framings of SFM as presented in the literature. Then, in the second part, I will explain the concepts of framing, problem identification, and agenda setting. Finally, I will explain policy entrepreneurship, particularly the role of academic researchers, policy windows, and some research gaps in the literature.

Framing substandard and falsified medicines from multiple perspectives

As mentioned earlier, international organizations, such as the WHO, frame SFM as a technical issue, which is reflected in many national regulatory frameworks (Department for Business, Energy & Industrial Strategy, 2016; FDA Center for Drug Evaluation and Research, 2021; Keputusan Menteri Kesehatan Republik Indonesia 189/MENKES/SK/III/2006 2006 tentang Kebijakan Obat Nasional, 2006; Tanzania Medicines & Medical Devices Authority, 2019; Zaken, 2015). There are also broader framings in the literature, but very few scholars have studied this subject (Borup & Traulsen, 2016; M. C. M. Lamy, 2017; M. Lamy & Liverani, 2015; Xu, 2022). For example, in her in-depth investigation regarding SFM framing in China, Xu (2022) argues that three core frames have been shaping the country's policy responses: economism, health and well-being, and security. The economism frame views the SFM issue in China as rooted in the country's economic policies that reframed medicines from common goods into commercial commodities. Therefore, the policy response was to increase the production of medicines, with less priority given to the quality of medicines. The medicine regulators notably accepted the health and well-being frames following serious SFM or food safety incidents. While economism, health, and well-being still play important roles, the security frame has become the meta-frame that helps elevate SFM issues higher on the political agenda and has emerged as a potential bridge for coordinated policy responses among actors. In general, the security frame can provide a sense of threat, risk, and feelings of fear and uncertainty, thereby creating a sense of urgency for policymakers to act (Xu, 2022).

Cross-border security is also a prominent frame in governing SFM at the regional level. Lamy (2017) researched three countries in the Greater Mekong Region in Southeast Asia – Thailand, Cambodia, and Laos – and identified six frames: security, health system, medical, economic, regulatory, and political. The economic frame covers aspects such as the affordability of medicines, economic development and poverty, regional investment and inequity, and domestic industry. Meanwhile, the political frame includes transparency and corruption, political will and accountability, and governance. However, when described as a shared responsibility to protect the well-being of populations across borders, SFM is elevated to the political agenda and engages policy actors in discussions on improving coordination and promoting policy coherence across the three countries

(M. C. M. Lamy, 2017).

Both scholars mentioned above underline the existing SFM framings from political and economic perspectives. Based on her findings on the political frame, Lamy (2017) stated that SFM issues are context-bound and related to political interests (M. C. M. Lamy, 2017). Meanwhile, Xu (2022) explained that the economism frame suggests policy responses result from the interaction of economic ideas with political intentions, social ideas, and context (Xu, 2022). In this thesis, I will build on these broader framings to introduce my frame by focusing on the political economy perspective. However, I will first explain why framing and problem definition matter for policy responses to SFM.

Framing and problem identification

Framing determines how actors perceive and experience reality (Goffman, 1959). Framing is a collective phenomenon that influences how individuals and groups select and organize information and allows actors to agree on interpretations of facts and reach a consensus. In other words, (policy) actors construct specific meanings regarding a particular framing of an issue (Schön & Rein, 1994). The frame also has a diagnostic-prescriptive function, making it a normative power (Behr et al., 2015; Schön & Rein, 1994). For example, Behr et al. (2015) analyzed how patient safety was framed over the years; they found three dominant frames, explaining patient safety as an instance of medical error, as a matter of organizational responsibility and as a matter of good governance within the healthcare system (Behr et al., 2015). Each framing led to different types of research on safety issues as well as different attributions of blame and follow-up policies.

Frames are interrelated and coexist, but they can also initiate conflicts due to the absence of a common frame, mutually accepted structures and shared values among actors (Schön & Rein, 1994). For example, in healthcare governance during the COVID-19 pandemic in the Netherlands, tension arose between the top-down logic of care coordination and the traditionally dominant market-based logic, as well as consensus-based decision-making (de Graaff et al., 2023). Framing is, moreover, a dynamic practice that changes over time and can, therefore, lead to reframing (Behr et al., 2015; de Graaff et al., 2023). We also saw this with the definition of SFM in the early historical background section, where SFM gradually became uncoupled from intellectual property and commercial issues.

In reframing, a crisis can play an important role. In the above-mentioned patient safety case by Behr et al. (2015), the subsequent case investigation around the death of a baby in a hospital was reframed from a medical error to a matter of good governance within the healthcare system due to public outcry and legal challenges (Behr et al., 2015). Thus, reframing has broad implications for what is identified as the object (or problem definition), the legitimate solutions, the actors involved, the assignment of responsibility, and to whom conclusions and recommendations are made (Behr et al., 2015; de Graaff et al., 2023). To illustrate, framing SFM using a critical context neglects the area of

the availability of affordable quality-assured medicines, which is considered the best approach to combat the supply of illegal medicines ('t Hoen & Pascual, 2015; Xu, 2022).

Redefining an issue involves replacing one issue with another; a more specific issue is usually redefined as a general issue (Cobb et al., 1976). A broader expansion process will likely include several redefinitions of the issues as more groups of actors become involved. Meanwhile, some actors will actively resist the problem redefinition, especially if the status quo benefits them and the problem is defined away from their interests. In this thesis, I will also study the roles and responsibilities of multiple actors and the changes around them when SFM problem redefinitions are (re)framed using a political economy perspective. For example, before taking an explicit public health lens, the term "counterfeit", which has an emphasis on commercial connotation, was suggested to be reframed into "fraudulent" as the latter emphasizes a more criminal perspective, placing the patients as the real victims, rather than the pharmaceutical manufacturers (Bandiera & Marmo, 2017).

While essential for policy response, clear framing is sometimes lacking. For instance, efforts to address the SFM problem in Ethiopia have been hampered by the lack of a clear framing of the issue and consensus on how it should be understood (Mengesha et al., 2024). Medicine regulation and control highlight the issue of a wide variety of SFM from diverse sources in the pharmaceutical market in Southern Ethiopia. The emergence of this complex supply chain is due to barriers to accessing essential medicines on demand. The authors further suggested that without understanding the determinants and alignment between actors regarding the problems in practice or whether there are any problems at all, interventions in the form of tighter regulation are unlikely to solve the problem.

Agenda settings

As stipulated earlier, SFM is not a common policy priority despite its increasing incidences and serious consequences for public health (M. C. M. Lamy, 2017). Many governments, especially in LMICs, are grappling with multiple health sector challenges, such as health financing, inequitable access to medicines and health facilities, and workforce shortages. Therefore, the quality of medicines may rank lower in terms of priority. As previously mentioned, the political sensitivity surrounding SFM also undermines efforts to prioritize this issue in the policy arena. If a complex issue such as SFM is not prioritized, it is unlikely that action will be taken to resolve it. This raises several questions about how to gain more attention from policymakers for an issue that is not usually a policy priority, such as SFM. In this thesis, I propose an alternative approach, namely, broadening the problem definition by adopting a broader framing.

The way and form in which policy problems are understood and framed shape the importance assumed on the policy agenda and assert influence on policy responses or how policymakers address them (Buse et al., 2012; Xu, 2022). Positioning a particular issue on the policy agenda is crucial because more problems are being discussed publicly

than the government has the time and resources to address (Buse et al., 2012). This is particularly relevant for politically charged and neglected issues such as SFM, as using different frames can significantly impact priority setting and policy responses (Pisani et al., 2019; R. M. Ravinetto et al., 2012; Xu, 2022). Some plausible policy responses include aligning different perceptions, changing regulatory frameworks, gaining political influence, legitimizing particular policy actions, and prioritizing or deprioritizing the importance of issues on the policy agenda (Shiffman & Smith, 2007; Xu, 2022). In a case study on the Falsified Medicines Directives in Europe, policymakers rejected early proposals from private sector stakeholders to increase regulatory requirements when they were framed as policies to benefit business. However, they felt obligated to accept the proposals when the aim was to protect public health from harm (Borup & Traulsen, 2016)

Agenda or priority setting is the process of translating the demands of various groups into items that require serious attention from public officials. Previous scholars explained that the public agenda consists of "issues which have achieved a high level of public interest and visibility". In contrast, a formal agenda is "the list of items which decision-makers have formally accepted for serious considerations" (Cobb et al., 1976). Framing SFM in priority setting is crucial for defining the problem, which is instrumental in getting the problem on the agenda, formulating policy solutions, and identifying responsible actors (M. C. M. Lamy, 2017). For example, suppose SFM is viewed as merely a technical or regulatory issue. In that case, particular agencies, such as the medicine regulators, are considered the problem owners and, therefore, fully responsible for addressing it.

Policy agendas can shift during crises, where policymakers' failure to act during such times can worsen the situation (Buse et al., 2012). At the same time, however, agendas can change due to subtle changes in "politics-as-usual", where many different reforms may compete for policymakers' attention, including changes driven by particular actors such as policy entrepreneurs.

Policy entrepreneurs and policy windows

Given the limited attention and resources of the government, (policy) actors compete and clash to persuade governments not only to place particular issues on the agenda but also in how they want those issues presented and addressed (Buse et al., 2012). Objective conditions, such as changing disease patterns, are unlikely to directly shape the policy agenda. Instead, multiple actors with different interests and perspectives, both inside and outside formal decision-making structures, can propose potential strategies, interventions, and solutions, which await selection in what is called policy windows (Kingdon, 2014, p. 20). Policy windows can be elusive, short-lived, and often rare and fleeting opportunities to reform (Béland, 2016; Kingdon, 2014).

Policy entrepreneurs are "advocates for [policy] proposals or the prominence of an idea", exploiting ephemeral policy windows (Béland, 2016; Kingdon, 2014). A policy entrepreneur can be any actor with definitional power, including experts, academics,

political parties, industry, patients, and international organizations. To open policy windows, propose potential solutions to policy problems or alternatives, and increase the likelihood that policy agendas are realized, they can deploy their status, reputation or resources to identify problems, develop policies, and bring together networks or mediate between interest groups. In the case of medicine quality, these would include the pharmaceutical industry, healthcare professionals, patient groups, governments, and researchers. For instance, supply chain actors in Europe actively framed falsified medicines as a problem that required a legislative solution to benefit their business interests (Borup & Traulsen, 2016).

In particular, researchers are among the actors and policy entrepreneurs who engage in reframing issues. Since framing is a dynamic practice, it can also change in response to various drivers. The change of frames can occur during the crisis, for example, when a policy window opens, but also due to subtle changes attributed to the role of policy entrepreneurs or new actors. Researchers can play roles in ideational processes that are always in flux (Carstensen, 2011), emphasizing the role of ideas in constructing and classifying policy problems. Framing a situation in a particular way reduces ambiguity and complexity and, in turn, highlights or ignores certain aspects through a coherent narrative (de Graaff et al., 2023; Schön & Rein, 1994). For example, as I will explain later in this thesis, researchers can take advantage of the policy windows by proposing risk indicators developed from a political economy perspective to detect more products at risk of being substandard.

The evidence above suggests the importance of framing and problem definitions of SFM in priority setting. However, there is a dearth of evidence on scientists' active participation as policy entrepreneurs in broadening the frame and reshaping the problem definition during interactions with policymakers. Thus, it raises the question of what insights are obtained from researchers' efforts in broadening problem framing. In this thesis, I am specifically interested in the role of scientists in broadening the frame issues related to SFM. Therefore, I do not specifically investigate the frames used in my study's context but focus on the researchers' role in intentionally shaping (policy) actors' understandings and perceptions of a particular framing, which I will explain in the next section.

Taking a political economy perspective to broaden the framing

In this thesis, I will use a particular frame derived from political economy. Political economy studies the relationship between individuals and society, as well as between markets and the state. Another description of political economy is "the study of how a country – the public's household – is managed or governed – taking into account both political and economic factors" (Vesth & Balaam, 2024). The approach acknowledges the

crucial roles of actors but aims "to understand the forces that empower or disempower competing groups in the political process" (Stuckler et al., 2010). Furthermore, Rosa and colleagues (2025) argued that the need to use a political economy framework and economic instruments in public health is due to susceptibility and sudden social changes, such as drastic resource cuts and challenges to financing schemes for universal health systems (Rosa et al., 2025).

The impetus for shifting to the political economy perspective on SFM in this thesis, as explained earlier, stems from the inquiry that while previous approaches recognized immediate drivers of poor-quality medicines, they did not sufficiently consider specific political and economic factors (Pisani et al., 2019). The assumption is that these factors shape the markets for SFM and may undermine policy responses aimed at addressing the problem. Previous research described existing political and economic frames of SFM used by multiple actors (M. C. M. Lamy, 2017; Xu, 2022). However, little is known about using political economy as a broader perspective to tackle SFM. Therefore, in this thesis, I will consider several contextual aspects in broadening the frames of SFM, including political promises, economic logic, and sociocultural influences. A further explanation of what is included in the scope of a study when using the political economy perspective on SFM will follow in a later sub-section. First, I will state why this particular framing is needed to address this complex problem.

Why use political economy?

For several reasons, a political economy perspective is useful for viewing the SFM problem. First, it relates to the complexity of the system and the relevant actors involved outside the regulatory domain. In her in-depth case study of multiple SFM framings, Lamy (2017) suggested considering political economy to fully capture the complexity of the problem in context after studying the policy responses shaped by different actors (M. C. M. Lamy, 2017). The pharmaceutical supply system is intricate and consists of varying market elements and forces, such as economic and trade goals (Bigdeli et al., 2013), as well as a variety of stakeholders with overlapping roles and limited coordination. Despite the diversity of actors, SFM caused by a poorly regulated environment results in fear and uncertainty for actors at all levels of the health system, hindering their ability to make informed decisions in protecting public health (Kingori et al., 2023). Meanwhile, each stakeholder has economic and political interests, moral imperatives, a distribution of responsibilities, and social obligations that interact in complex ways, driving the existence of SFM products. The political economy perspective, therefore, can broaden the scope of actors involved in tackling SFM beyond the medicine regulators.

Second, addressing SFM as an inherently political issue using only a technical approach is considered insufficient (Xu, 2022). Viewing the SFM problem as merely a technical and access issue has resulted in the same policy recommendations for almost two decades (Pisani et al., 2019). Medicine regulators alone are seen as ill-equipped to address the SFM problems (M. C. M. Lamy, 2017), and no single entity can fully mitigate the risks they pose (World Health Organization, 2024a). Therefore, other scholars have called for

addressing both technical and non-technical elements that involve various stakeholders (Opuni et al., 2024). In addition, other studies have argued that stricter regulations on SFM will not be sufficient to address the problem if health systems cannot prevent shortages and ensure access to affordable, quality-assured products (Mengesha et al., 2024; Rasheed et al., 2023; Van Gurp et al., 2024). Thus, a political economy perspective can offer an alternative lens beyond considering SFM merely a technical issue.

Third, given the scale and complexity of SFM, multisectoral collaboration is considered a panacea (Gabel, Lächele, et al., 2024; Rasheed et al., 2023), but little is known about its implementation. Multiple actors on the supply side (e.g., manufacturers, distributors, pharmacies) and demand side of the health system (e.g., patients, healthcare providers), as well as regulatory and law enforcement agencies (e.g., police, judiciary, customs), are often encouraged to collaborate (World Health Organization, 2024a; Xu, 2022). A stronger call for interdisciplinary collaboration and research to address SFM emerged at the first International Conference on Medicine Quality and Public Health in 2018 (Newton et al., 2019). By elucidating various interests, incentives, and roles and responsibilities of multiple actors, including researchers, political economy can illuminate collaborative processes and interactions among them to tackle SFM.

What is entailed when using political economy in the study of SFM?

In this thesis, using a political economy perspective to tackle SFM entails the study of the following scopes. First, I am interested in the relationships between SFM issues and other agenda-setting policy priorities, such as UHC (Wodnik et al., 2024), national prosperity or economic well-being (e.g., domestic jobs and taxation), and sociocultural influences (e.g., religious affairs and policies) (Pisani et al., 2019). In particular, I focus on the mechanisms by which political promises and economic logic at the national level are translated into policies that shape the market and how these policies interact and create market dynamics and incentives that drive SFM production and trade. Second, my research examines the roles and responsibilities of various actors within and outside the healthcare sector, including the relationships and interactions between researchers as policy entrepreneurs and other stakeholders such as policymakers. Finally, I also examine the work researchers can do to address SFM by contributing to efforts to strengthen post-market surveillance. As I will explain in Chapters 3 and 5, I operationalize the SFM risk factors from a political economy perspective by combining them with technical domains, such as regulatory inspection results or market authorization databases, into a conceptual model of objective indicators for risk-based sampling. Additionally, I will trial the risk indicators to flag products at the highest risk of being substandard and test the relationship between price and quality of medicines.

As mentioned previously, the quality of medicine is entangled with other areas in pharmaceutical policy. My research uses a political economy perspective to articulate the interrelationships between quality and the following areas. The first area is the price or affordability of medicines, particularly in light of cost containment policies to support the national priority agendas mentioned above. The subsequent area is the availability

of medicines, especially considering the estimated volume of substandard medicines circulating in the market. The last area is the patient preferences for specific products or brands and the practice of purchasing antibiotics without prescriptions, the latter of which falls under the irrational or inadequate use of medicines (Ahmed et al., 2025). In the following sub-section, I will elaborate on the main assumptions derived from using a political economy perspective in this thesis: the relationship between medicine price and quality.

Assuming the relationship between the medicine price and quality

One dominant notion related to the political economy perspective and how pharmaceutical markets function is the notion of prices and the affordability of medicines. While medicine prices are often linked to accessibility and availability issues (Oldfield et al., 2025), drawing on insights from economic theories, scholars have also attempted to conceptualize the relationship between price and quality (Bate et al., 2011, 2015; Gabel, Difäm-EPN Minilab Network, et al., 2024). To combat SFM, scholars argue that "price and quality are fundamentally linked" (Bate et al., 2011). Thus, poor-quality medicines cannot be isolated from their affordability or price, and some researchers have argued that policies aimed at lowering medicine prices may distort the pricing mechanism for sorting out quality-assured products (Bate et al., 2011, 2015). Other authors suggested that to strengthen the regulatory systems, it is essential "to allow for a fair and competitive market, removing low-priced, substandard products from the market" (Twesigye et al., 2021).

Despite the above argument, the literature shows mixed evidence (Bate et al., 2011, 2015; Gabel, Difäm-EPN Minilab Network, et al., 2024; Rahman et al., 2021; Schiavetti et al., 2018). One study found that falsified products tend to be sold at lower prices than generics circulated in the same city. Substandard medicines are priced 10% lower on average than the same generics (Bate et al., 2015). Others reported that SF products tend to be priced lower than quality-assured products through licensed and unlicensed channels after being stolen or diverted or manufactured at a lesser cost (Chaudhry & Stumpf, 2013; Outterson & Smith, 2006). Another study, however, stated that "the signalling effect is not clear as the theory suggests: high price does not always guarantee high quality"(Bate et al., 2011). A similar conclusion was drawn in a recent study, where the authors argued that "adequate quality assurance does not necessarily imply an increase in medicine prices" (Gabel, Difäm-EPN Minilab Network, et al., 2024).

The relationship between medicine prices and quality will be a prominent theme throughout this thesis. Additionally, I will test this assumption in one of the chapters when operationalizing the problem definition of SFM using a political economy perspective.

Ensuring the quality of medicines in a country of 17,000 islands

This thesis consists of several case studies conducted in Indonesia. In this section, I will describe contextual information about the country, including the pharmaceutical market and regulatory environment, as well as specific governance challenges, including interagency silos in tackling SFM. In this thesis, I will focus on the private market in the country.

Country context & health system governance

Few countries are as diverse as Indonesia. As the largest archipelagic country in the world, Indonesia comprises over 17,000 islands, of which 7,000 are inhabited (see Figure 2). Home to over 280 million people (Statistics Indonesia, 2024), the population is not evenly distributed across the country. Almost half of the population resides in Java, the most populous island in the country (Fanda, Probandari, Yuniar, et al., 2024).

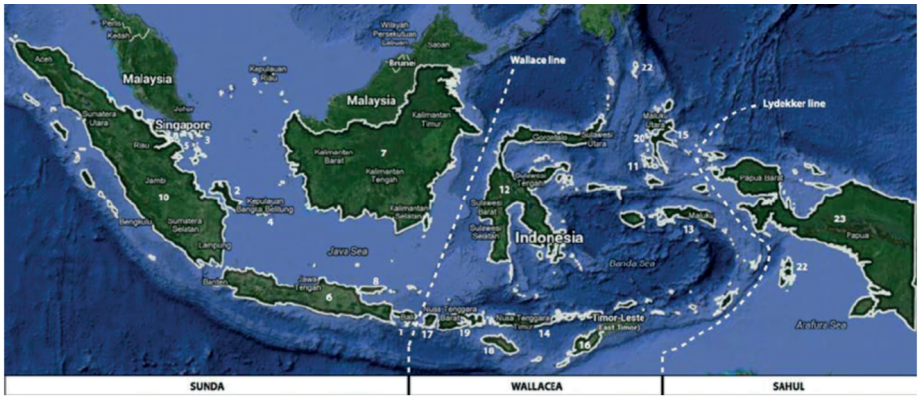


Figure 2. Map of Indonesia (Hubert et al., 2015)

Indonesia's health system is largely decentralized, with responsibility for health service provision divided between the national and sub-national levels (WHO Indonesia, 2023). Some tasks and functions are coordinated vertically from the national or central government. This first layer of government, represented by the Ministry of Health (MoH), provides overall guidance, such as the National Medicine Policy, and, among other functions, coordinates vertical disease programmes, including vaccination, and sets the national policy on health financing, including medicine pricing and national insurance premiums. The second layer is the sub-national government, which consists of provincial health offices (PHO) and district health offices (DHO) under the Ministry of Home Affairs. These offices coordinate health services within the provincial regions (PHO) and manage services, including primary health centres (PHCs). The relationship between the MoH, PHOs, and DHOs is not hierarchical, adding to the complexity of health service governance, including adopting national policy (Fanda, Probandari, Kok, et al., 2024).

Recent developments in Indonesia's health sector show promising figures regarding the national government's commitment and capacity to improve access to healthcare (WHO Indonesia, 2023). As an upper-middle-income country, Indonesia has gradually increased health expenditure as a percentage of gross domestic product (GDP), rising from 1.85% in 2000 to nearly 2.2% in 2021. Indonesia launched the ambitious national health insurance scheme (Indonesian: *Jaminan Kesehatan Nasional/JKN*) in 2014 to provide access to healthcare services without financial hardship (Pisani et al., 2016). A decade later, the scheme had enrolled more than 248 million Indonesians, accounting for over 90% of the total population (Dewan Jaminan Sosial Nasional Indonesia, 2024), and aligned with the country's ambition to achieve near-universal coverage by 2024 (Yoo et al., 2024).

Despite the progress mentioned above, Indonesia continues to grapple with multiple challenges in its health system. The country faces a double burden of communicable (e.g., tuberculosis, malaria, and HIV/AIDS) and non-communicable diseases (e.g., cardiovascular, diabetes) (Mboi et al., 2022). More recently, the COVID-19 pandemic further exposed vulnerabilities in the health system and vaccination coverage (WHO Indonesia, 2023). Other ongoing challenges include inequalities in insurance coverage, the financial sustainability of the national health insurance system (Agustina et al., 2018), fragmented governance structures, imbalanced funding allocation, inadequate facilities, a health workforce shortage, and a shortage of pharmacists (Meilianti et al., 2025). To address these issues, the MoH launched a comprehensive health system reform focusing on preventive and promotive initiatives, health security, resource needs, and the health workforce (Ministry of Health of Indonesia, 2025).

Among the challenges mentioned above, this thesis particularly highlights the issue of affordability, namely out-of-pocket (OOP) payments and the availability of medicines. Although JKN has generally protected Indonesians against catastrophic healthcare costs, there is also an increasing trend of OOP among insured and urban populations (Yoo et al., 2024). Patients in the JKN schemes are supposed to receive medicines listed in the National Formulary free of charge. However, reality speaks otherwise. The percentage of OOP in health expenditure is relatively high at 31.8%, with a significant proportion on medicines (Ramadaniati et al., 2024; World Health Organization, n.d.-a). Further, despite seemingly high insurance coverage, disparities in political commitment and the capacity of sub-national governments (Fanda, Probandari, Kok, et al., 2024) to provide resources for health services and infrastructure have led to inequities in access to healthcare facilities (Pratiwi et al., 2021), low usage of health services in remote areas (Yoo et al., 2024), and significant regional disparities in medicine availability in the public sector, including essential medicines (Fanda, Probandari, Yuniar, et al., 2024). Given the challenges of availability in public facilities and persistent OOP expenditure, this thesis, especially in Chapters 4 and 5, focuses on the private market as a popular source from which patients purchase medicines. The following sub-section will outline the private pharmaceutical market and regulatory environment.

Pharmaceutical market & regulatory environment

Indonesia has a competitive and large domestic pharmaceutical industry characterized by many medical products in circulation and an extensive supply chain and distribution network. As of March 2025, approximately 220 registered pharmaceutical manufacturers (88% of which are domestic companies) (Pharmaboardroom, 2017) and around 19,000 pharmaceuticals and vaccines are in circulation (National Medicines Regulatory Authority of Indonesia, 2025). Most manufacturers are located in Java, making it challenging to distribute quality-assured products nationwide. Despite recent government efforts to increase domestic raw materials production, the country still largely relies on imported APIs from China or India (Ministry of Health of Indonesia, 2023).

Particular products, such as antibiotics, come in a wide variety of brands, formulations, and prices, leading to intense competition among pharmaceutical manufacturers to ensure the absorption of these products (Alfajri & Diveranta, 2024). WHO projects that, by 2030, Indonesia will become one of the five countries with the highest increase in antimicrobial consumption (WHO Indonesia, 2025). Pharmaceutical products are distributed to approximately 40,000 licensed and 95,000 unlicensed channels nationwide in the private market. The latter channel is only permitted to dispense over-the-counter medicines. The medicine regulator reported that in 2023, approximately 71% of pharmaceutical service facilities dispensed antibiotics without medical prescriptions (Muhamad & Difa, 2024), raising serious concerns about the irrational or inadequate use of medicines and antimicrobial resistance (AMR).

Responsibility for tackling SFM in the health system primarily lies with the National Medicines Regulatory Authority or NMRA (Indonesian: *Badan Pengawas Obat dan Makanan*/BPOM). The NMRA generally ensures the safety, quality, efficacy, and proper labelling of pharmaceuticals, food, traditional medicines, cosmetics, and other health-related products in Indonesia (WHO Indonesia, 2023). Historically, the agency was a directorate general of the MoH. However, since the late 1980s, it has become an independent authority coordinating closely with the MoH, but it is not directly accountable to the ministry, but to the president. Meanwhile, a directorate general of pharmaceuticals and medical devices at the MoH regulates supply, availability, and affordability in the public sector and the licensing of pharmaceutical manufacturers and outlets. However, the MoH has relatively minor official responsibilities for SFM or the quality of medicine. Therefore, as shown in one of the opening quotes, one MoH official firmly stated that discussing medicine quality with their agency was inappropriate.

The Indonesian NMRA is equipped with the technical capacity to protect the public from SFM and continues strengthening its capacity. Each year, the agency conducts extensive and proactive post-market surveillance. For example, in 2021, the NMRA tested 10,980 medicines collected through randomized sampling in the regulated supply chain (Direktorat KMEI, BPOM, 2023; Pisani et al., 2024). Based on the WHO Global

Benchmarking Tool, Indonesia has reached maturity level 3 for vaccine production (World Health Organization, 2025a). Regarding technical domains, there is variation in the capacity of control laboratories located across 36 sites nationwide, which may hinder the effort to detect and combat SFM (Slamet, 2019; USP Promoting the Quality of Medicines, 2018).

Interagency silos in protecting the Indonesian public from SFM

Tackling SFM in Indonesia is further complicated by several governance challenges and interagency silos. First, the regulatory data is conservatively kept confidential, and there is a lack of access to key data for external organizations or parties (USP Promoting the Quality of Medicines, 2018). Furthermore, there is minimal dissemination of regulatory inspection results or sharing of data for joint decision-making with other organizations responsible for pharmaceutical policy, such as the MoH. In a feasibility study on using mobile phone applications to report SFM incidents, several medicine regulators expressed concerns about reporting risks, losing public trust in their organizations and healthcare providers (Wagnild et al., 2023).

The second challenge is a communication gap between agencies (USP Promoting the Quality of Medicines, 2018). For example, bureaucratic challenges between the MoH and medicine regulators have made it difficult to deliver the right information to the right stakeholders at the right time. Furthermore, poor interagency communication occurs horizontally (at the central government level between the medicine regulators, MoH, technical agencies or donors) and vertically (to the provincial and district health offices).

The third challenge is the significant gap between regulation and enforcement in practice (Pisani et al., 2022) and between national policies and local practices at the district level (Fanda, Probandari, Kok, et al., 2024). For example, the district health office may decide to forgo sanctions against midwives who sell prescription-only medicines in remote areas lacking licensed pharmaceutical outlets (Pisani et al., 2022). Given Indonesia's highly diverse conditions, discrepancies in local government capacity, and limited access to medicines in some areas (Fanda, Probandari, Yuniar, et al., 2024), dispensing medicines by unlicensed medical professionals such as midwives is often a pragmatic response to balance the needs of multiple constituents (Pisani et al., 2022).

Overall, the above challenges have fragmented the fight against SFM. I assume that the political economy perspective may help bridge the gap between these silos and offer an alternative framing and problem definition that enables collaboration, joint action, and more effective policy solutions. While the examples above focus on specific actors or organizations, such as the medicine regulators and the MoH, this thesis will cover dynamics among other actors, such as academic researchers, health service providers, and the private sector.

Analytical focus and research questions

SFM is a multifaceted and complex global problem. For years, the above reasons have contributed to a status quo in addressing SFM problems. In addition, the perception of the same problem determinants has led to the formulation of similar solutions. Meanwhile, new incidents continue to emerge, endangering public health.

In this thesis, I will broaden the frame and problem definition of SFM by taking a political economy perspective. Furthermore, I construct a conceptual bridge between the technical, socioeconomic and political domains of SFM to articulate the problem more concretely and, ultimately, make it more actionable in practice. Using a participatory approach, I conduct a mixed-methods study in Indonesia.

Many policy-oriented research aims to create impact, but research impact can be openly defined in many ways. What I specifically aim to contribute through this thesis is to bridge the interagency silos (Indonesian term: *ego sektoral)* between various actors and organizations that work directly or indirectly to protect public health from SFM.

In this thesis, I will use the term interagency to encompass different sections, departments, and directorates within the same organization *or* between different organizations. I describe the silos as different areas in pharmaceutical policies, such as availability, pricing or affordability, and or inadequate use of medicines. Each area has an interrelationship between technical and regulatory domains, as well as political, social, economic, and ethical domains.

I recognize that SFM has technical determinants, but I assume that other factors may also contribute to the risk to public health. Thus, we can explore alternative solutions by considering the political and socioeconomic dimensions. I assume that (re)defining the problem of SFM by broadening its frame using a political economy perspective can foreground several neglected areas and better articulate the roles and responsibilities of other actors and organizations to formulate more effective policy responses.

My aim in this thesis is to explore insights into broadening the frame and problem definition of SFM by taking a political economy perspective and operationalizing it to contribute to policy agenda setting. The **main question underlying this research** is what can we learn from a political economy approach and how can it shape the efforts in tackling SFM. In answering the main question, I was guided by the following **sub-research questions**:

1. What is the problem definition of SFM from a political economy perspective?
2. How can the SFM problem definition and related assumptions from a political economy perspective be operationalized and tested?
3. What are the findings from operationalizing and testing the SFM problem definition and assumptions from a political economy perspective?

4. How does intersectoral stakeholder engagement contribute to broadening the frame and problem definition of SFM and its operationalization in a research collaboration?

Research journey

I wrote this thesis based on three interdisciplinary research projects spanning different periods, which I collaborated on with various partners and was funded by three international study sponsors. Although the objectives of the three projects can appear very different, the political economy perspective on the drivers of SFM underlies them all and, therefore, serves as the common thread. In the following chapters, I will provide a detailed account of the methods employed in these projects; here, I offer a more general introduction.

I began my research trajectory on medicine quality in late 2017 by joining a multidisciplinary group of researchers with backgrounds in epidemiology, public administration, criminology, and regulatory science. Funded by The Wellcome Trust, we conducted qualitative case studies of political and economic drivers of SFM in four middle-income countries: China, Indonesia, Romania, and Turkey. In this project, I collaborated with Migunani Research Institute, a research institute based in Yogyakarta, Indonesia.

Following this, I continued working to operationalize the key concepts of the market risk-based framework into risk categories and to develop a risk-flagging approach. I received a Fellowship in Quality of Medical Products, funded by the United States Pharmacopoeial Convention (USP) Quality Institute, which began in mid-2019. I will refer to this project hereafter as the risk-flagging study. I collaborated with several pharmacists, chemists, and public health specialists at Pancasila University and the USP Promoting Quality Medicines team in Jakarta. This project also marked the period where I started to systematically observe and take detailed notes of interactions with different actors within and outside the health system.

In late 2020, I led the policy learning research team as part of the *Systematic Tracking of At-Risk Medicines* (STARmeds) project, collaborating with Imperial College London and Pancasila University and funded by the UK National Institute for Health and Care Research. Our team studied stakeholder engagements in research on developing a method for estimating the prevalence of SFM. While the policy learning study itself was not directly informed by the risk-based framework, it largely shaped the work performed by other partners in the STARmeds consortium. This project allowed me to study how the framework was operationalized and how stakeholder engagement influences the research process, including establishing a research-policy partnership and the uptake of the study results.

Organization of this thesis

This thesis is structured as follows. Following this introduction, in the **second chapter**, I explore the problem definition of SFM using the political economy perspective or, in other words, the political and economic factors that drive various actors to produce, distribute, and consume SFM in Indonesia. To collect the empirical data, I conducted in-depth interviews. Then, in the **third chapter**, I conceptualize several objective indicators based on political economy or market dynamic factors to indicate products that are at risk of being substandard or falsified. I collected and reviewed secondary regulatory, procurement, and pharmaceutical market data to conceptualize the indicators. Next, in the **fourth chapter**, I describe the quality assessment of amoxicillin, considering sampling locations, types of outlets, market volume, and the relationship between price and quality. I conducted a cross-sectional survey to collect the samples, and a third-party laboratory in Jakarta performed the quality testing analysis. Following this, in the **fifth chapter**, I build a risk-flagging model or approach to indicate products at the highest risk of being substandard in the market. I operationalized the political and economic risk factors into several objective indicators based on several datasets collected in Chapter 3 and tested the risk-flagging approach. In the **sixth chapter**, I attempt to understand how stakeholder engagement in a research collaboration about medicine quality evolved, influenced the actors and research, and the potential uptake of the results. I combined various qualitative methods, including in-depth interviews, participant observations, and document analysis, in a longitudinal study conducted as part of a three-year research project. Finally, in the **seventh chapter**, I conclude and discuss my main findings, formulate implications for research and policy, share my reflections as a researcher, and finally, add my final notes on this thesis.

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Chapter 2.

Broadening the problem definition of substandard and falsified medicines using a political economy perspective

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Abstract

Introduction

Indonesia, the world's fourth most populous nation, is close to achieving universal health coverage (UHC). A widely-publicised falsified vaccine case in 2016, coupled with a significant financial deficit in the national insurance system, has contributed to concern that the rapid scale-up of UHC might undermine medicine quality. We investigated the political and economic factors that drive production and trade of poor-quality medicines in Indonesia.

Methods

We reviewed academic publications, government regulations, technical agency documents, and news reports to develop a semi-structured questionnaire. We interviewed healthcare providers, policy-makers, medicine regulators, pharmaceutical manufacturers, patients and academics (N=31). We included those with in-depth knowledge about the falsified vaccine case or the pharmaceutical business, medicine regulation, prescribing practice, and the implementation of UHC. We coded data using Nvivo software and analysed by constant comparative method.

Results

The scale-up of UHC has cut revenues for physicians and pharmaceutical manufacturers. In the vaccine case, free, quality-assured vaccines were available but some physicians, seeking extra revenue, promoted expensive alternatives. Taking advantage of poor governance in private hospitals, they purchased cut-price "vaccines" from freelance salespeople.

A single-winner public procurement system which does not explicitly consider quality has slashed the price paid for covered medicines. Trade, industrial and religious policies simultaneously increased production costs, pressuring profit margins for manufacturers and distributors. They reacted by cutting costs (potentially threatening quality) or by market withdrawal (leading to shortages which provide a market for falsifiers). Shortages and physician-promoted irrational demand push patients to buy medicines in unregulated channels, increasing exposure to falsified medicines.

Conclusion

Market factors, including political pressure to reduce medicine prices and healthcare provider incentives, can drive markets for substandard and falsified medicines. To protect progress towards UHC, policy-makers must consider the potential impact on medicine quality when formulating rules governing health financing, procurement, taxation and industry.

Introduction

For several decades, the global health community has worked to increase access to medicines, with efforts centred on affordability, especially in low- and middle-income countries (LMICs). Recent reports indicate that many of the medicines circulating in LMICs are substandard or falsified (Ozawa et al., 2018; World Health Organization, 2017a) . These medicines often harm patients; they also waste money, contribute to antimicrobial resistance, and undermine confidence in health systems (Buckley & Gostin, 2013; Pisani, 2015).

In 2017, the World Health Organization (WHO) analysed the first 1500 cases reported to the WHO Global Surveillance and Monitoring System for substandard and falsified medical products. WHO suggested that substandard and falsified medicines exist where constrained access to affordable, safe, and effective medical products intersect with limited technical capacity to ensure good manufacturing practice, and/or corruption and poor governance in health and judicial systems (World Health Organization, 2017c). The analysis did not differentiate between drivers of substandard medicines (which are made by registered manufacturers, but which do not meet quality standards set out in their marketing authorisations, because they are poorly made or have degraded) and drivers of falsified medicines (which are illegally made, or repackaged so that they misrepresent the product's contents, identity or source).

In every country, access to medicine, technical capacity and governance are substantially shaped by wider political and economic factors. However, the relationship between those contextual factors and medicine quality outcomes is not well understood. A clearer understanding of this relationship may help identify policies that create vulnerabilities, and suggest actions to reduce the risk that patients are exposed to substandard or falsified medicines.

In order to contribute to this understanding, we investigated the political and economic factors that drive production and trade of poor-quality medicines in four middle-income countries (Pisani et al., 2019). Here we report in detail on a case study in Indonesia. Indonesia, the world's fourth most populous country, was chosen for two reasons. Firstly, it embarked in 2014 on an ambitious programme to achieve universal health coverage (UHC) by providing national health insurance coverage to its 280 million citizens by 2019 through a programme known as *Jaminan Kesehatan Nasional,* or JKN (Agustina et al., 2018; Prabhakaran et al., 2019; World Bank, 2018). Health financing and pharmaceutical procurement were extensively reformed, with potential consequences for medicine quality.

Secondly, Indonesia in 2016 experienced a widely-publicised case of vaccine falsification, which resulted in approximately 1,500 children being injected with fake products (*Putusan nomor 1508/Pid.Sus/2016/PN Bks*, 2016; The Jakarta Post, 2017). We reasoned

that a careful examination of this case would provide a clear "micro-level" entry point for investigation of the more "macro-level" political and economic factors shaping medicine quality during the period of rapid scale-up of UHC.

Methods

Study set-up & participants

For this in-depth case study, we combined document analysis and interviews with purposively selected key participants. We analysed peer-reviewed publications, news reports, government regulations and presentations, court records, and technical reports from development institutions. To maximise the potential utility of the study, we solicited input around policy interests and ethics from the National Medicines Regulatory Authority (NMRA) at the study planning stage.

Full details of our methods reported following COREQ criteria, together with topic guides and coding tree, can be found at https://doi.org/10.7910/DVN/CVPSBB. We purposively selected heterogenous key participants with in-depth knowledge of the 2016 falsified vaccine case or of: the pharmaceutical business in Indonesia; prescribing practices; the medicine regulatory environment; pharmaceutical quality assurance; the implementation of JKN at the national or sub-national level.

Data collection

Using a topic list, the lead researcher (AH) and/or EP conducted interviews in person or by phone from December 2017 to May 2018. We provided the participants with detailed information about the study purpose and confidentiality procedures before the interview and obtained written or recorded consent from all participants. Interviews were conducted in Indonesian or English and lasted between 45 and 90 minutes. Nine participants declined recording, but gave written consent for note-taking.

Data analysis

Data were transcribed and coded using NVivo 12 software (*NVivo*, 2018) by the first author (AH); another team member (EP) coded a subset of in interviews in parallel – differences in coding were discussed until a shared understanding was reached. Using constant comparative method of analysis (Pope et al., 2000), we combined themes from the coded interviews and document analysis to develop a rich and coherent narrative of the vaccine and JKN case. Following a grounded theory approach, we then identified and described the political and economic drivers of poor-quality medicine (Glaser et al., 1968).

We presented preliminary results at feedback meetings with the medicine regulator, development agencies, and an informal study advisory group. We incorporated their feedback to enrich our analysis and policy recommendations.

Ethical approval

Ethical clearance was obtained from the Daily Board, Medical Ethics Committee at Erasmus University, Rotterdam (MEC-2018-016). Indonesian health research guidelines do not require ethics approval for studies of this type (National Institute of Health Research and Development, n.d.). We discussed the study protocol with the NMRA before data collection began, and communicated our preliminary results during minuted meetings with them in May and August 2018.

Patient and public involvement

We sought the views of patients, and parents of vaccinated children, as participants during the study, but they were not specifically involved in the design, conduct, reporting, or dissemination of what is largely a policy-focused investigation.

Results

Characteristics of study participants

We interviewed thirty-one (N=31) key participants from different professional backgrounds, detailed in table 1.

Table 1. Study participants, by professional role

Roles / professions	Number of participants
Healthcare providers	8
National government / Ministry of Health	3
Sub-national government	1
Medicine regulator	2
Technical agencies	2
Manufacturers/pharma industry group	4
Distributors	2
National insurer	1
Academic	2
Patient, media, civil society	6

We report first on the details of the vaccine case, then on the broader landscape affected by the scale-up of national health insurance.

The falsified vaccine case: incentives at the micro level

In June 2016, Indonesian police announced that they had arrested seven people suspected of making and selling fake vaccines. Shortly thereafter, the NMRA issued a statement saying that falsified vaccines have been found in 37 private sector health facilities across

nine provinces of Indonesia (National Medicines Regulatory Authority of Indonesia, 2016b). Police investigations later determined that falsifiers had refilled used imported vaccine vials, collected by an organised network of hospital cleaners (*Putusan nomor 1508/Pid.Sus/2016/PN Bks*, 2016).

The Indonesian Ministry of Health (MOH) runs a well-functioning immunisation programme. Free vaccinations are provided in the public health system, and community health workers actively encourage participation. A domestic manufacturer makes all of the mandatory childhood vaccines; all are quality-assured through WHO prequalification (National Medicines Regulatory Authority of Indonesia, 2016c). At the time of the falsified vaccine case in 2016, there was no reported shortage of quality-assured domestically produced vaccine in the public system (Ministry of Health of Indonesia, 2016).

Private healthcare providers may also charge parents to immunise their children using non-programme vaccines. These tend to be imported products. Market data from 2016 record 10 branded or generic vaccines sold by the single domestic producer of vaccines, and 37 imported vaccines. Among paediatric vaccines, list prices for domestic products ranged between US$ 0.2/dose for polio to US$ 10/dose for a pentavalent vaccine. For imported vaccines, they range from to US$ 4/dose for a Hepatitis B vaccine to US$ 48/dose for a hexavalent product (IQVIA, 2019).

In a press conference, the NMRA said it suspected falsification of 12 vaccines registered to the domestic manufacturer and two multinational manufacturers. However, an official statement from the regulator later confirmed that all domestically produced vaccines were safe (Manafe, 2016; National Medicines Regulatory Authority of Indonesia, 2016c).

Disruptions in manufacturing at the two named multinational manufacturers from late 2015 to early 2016 caused a shortage of several imported vaccines for children (*Putusan nomor 1508/Pid.Sus/2016/PN Bks*, 2016). Yet demand for these products persisted. One participant, an academic who studies medicine regulation, underlined the cultural tendency of Indonesian patients to follow advice from physicians without asking for more information; physicians in the private sector actively promoted imported vaccines as having fewer side-effects than domestic equivalents. This, and the high price charged, contribute to patient perceptions that imported vaccines are better than alternatives available at no cost under government programmes.

> *"In my opinion, if a vaccine is more expensive then it's automatically better quality, and that's that."*
>
> - Mother of an infant

The profit motive

The introduction of national health insurance in 2014 capped the amount paid to health facilities for insured patients across a wide range of services. This reduced income in

particular for private hospitals and physicians, which had previously commonly set tariffs as high as the market would bear (Britton et al., 2018; Prabhakaran et al., 2019; Wasir et al., 2019; Yuniarti et al., 2019). Some made up for lost income by promoting demand for medicines and procedures not covered by the scheme.

> *Q: If I can get something for IDR [Indonesian Rupiah] 300 rupiah, why would I pay 48,000?*
>
> *A: The consumer, they don't have the right to choose. Because everything is decided by the physician… And in this country, physicians offer medicines … mostly on a conflict of interest. The more they prescribe, the more they get the opportunity to travel, attend conferences, etc."*
>
> -Pharmacologist

Regulation of procurement in the private sector is sometimes lax (Undang-undang Republik Indonesia nomor 36 tahun 2009 tentang kesehatan, 2009). Participants explained that some physicians in private hospitals bypassed hospital procurement to source their own medicines, then charged above list prices. A consumer advocate said parents reported paying for vaccines directly to the physician's bank account instead of paying the hospital.

When shortages of imported vaccines occurred in late 2015, facilities found it harder to procure the products from appointed distributors. Shortly thereafter, freelance sales agents supplied by falsifiers began approaching surgeries in private hospitals directly, offering imported vaccines at low prices. Since some physicians were buying on their own account, cheaper vaccines translated into larger profits.

> *"Those physicians should have been suspicious from the start because of the cheaper prices [of falsified vaccines] …but instead they just praised the Lord for this, and thought of the profits."*
>
> -Former medicine regulator

These private sales channels result in a lack of accountability on the part of hospitals.

> *"One of the directors [in hospital X] said that the physicians purchased the vaccines without the hospital's knowledge …from March to June 2016... Meaning, for 3 months, the hospitals did not know that there were any purchases of vaccines [outside their authorised system]. Every [falsified] vaccine purchase was the sole responsibility of the respective physician."*
>
> -Civil society activist advocating falsified vaccine case

Unclear oversight, limited punishment

Participants explained that at the time of the falsified vaccine case, regulatory oversight

of the medicines supply chain was unclear, hampering detection and effective investigation. The regulator was responsible for the quality of products made by legitimate manufacturers, but had limited power to investigate falsified products, which were a matter for the police. Regulators could not easily access health facilities for post-market surveillance, since these were under the authority of the MOH (Peraturan Menteri Kesehatan Republik Indonesia nomor 30 tahun 2014 tentang standar pelayanan kefarmasian di puskesmas, 2014; Peraturan Menteri Kesehatan Republik Indonesia nomor 35 tahun 2014 tentang standar pelayanan kefarmasian di apotek, 2014; Peraturan Menteri Kesehatan Republik Indonesia nomor 58 tahun 2014 tentang standar pelayanan kefarmasian di rumah sakit, 2014).

> *"Regulation-wise, at that time, we were not allowed to inspect pharmaceutical services in hospitals. The parliament pushed us to do more to investigate [the falsified vaccines]. But … we could not get into those hospitals' systems."*
>
> -Former medicine regulator

Criminals were not dissuaded by the penalties for medicine falsification. The health law of 2009 sets the maximum penalty at IDR 1.5 billion (currently US$ 101,000) (Undang-undang Republik Indonesia nomor 36 tahun 2009 tentang kesehatan, 2009). However, in 2013 falsifiers of an imported vaccine were fined just IDR 1 million (US$ 96) (National Medicines Regulatory Authority of Indonesia, 2016a). This compares with profits of up to IDR 25 million a week made by individual members of the vaccine falsification ring in 2016, according to court documents and police investigators.

The 2016 scandal was the result of irrational demand from patients, fuelled by profit-maximising physicians who took advantage of poor governance in the private health sector to buy vaccines from unregistered suppliers. Gaps in regulatory structures and historically low penalties allowed criminals to exploit these weaknesses. The case was a watershed, resulting in fines of up to IDR 1 billion (US$ 75,000) and prison sentences of 6-10 years for 11 people. (For documentation of all of the court proceedings (in Indonesian), see: https://doi.org/10.7910/DVN/CVPSBB).

While regulatory structures have since been greatly strengthened, many other factors that threaten medicine quality persist. We therefore turned our attention to the wider health system, as it strives to deliver UHC.

The broader health system: incentives at the macro level

In 2014, Indonesia's newly-elected president promised to provide national health insurance coverage to all citizens by 2019 (Pisani et al., 2016). The system provided for full coverage and free medication for almost all conditions, for a monthly contribution ranging from IDR 25,500 to 80,000 per person (US$ 2.15 – 6.74) (Prabhakaran et al., 2019). Contributions for the poor are paid by the state. The system was in deficit from its first year, despite new procurement regulations designed to control medicine costs (Agustina et al., 2018; BPJS Kesehatan, 2018).

Falling revenues for pharmaceutical manufacturers and distributors

The new procurement system consolidated the market for all JKN patients, allowing manufacturers to bid to supply medicines for one year (two years since 2018). The MOH forecasts demand and sets a ceiling price, and manufacturers bid (or, for innovator medicines, negotiate) to supply specific provinces. Figure 1 shows the simplified version of medicine flow within public procurement system in JKN (Anggriani et al., 2020; Britton et al., 2018; Peraturan Menteri Kesehatan Republik Indonesia nomor 28 tahun 2014 tentang pedoman pelaksanaan program Jaminan Kesehatan Nasional, 2014, p. 28; Peraturan Menteri Kesehatan Republik Indonesia nomor 63 tahun 2014 tentang pengadaan obat berdasarkan katalog elektronik (E-catalogue), 2014, p. 63; Peraturan Presiden Republik Indonesia nomor 16 tahun 2018 tentang pengadaan barang/jasa pemerintah, 2018; Wasir et al., 2019). For all but a handful of medicines, there is only one winner per medicine per province, although companies commonly win contracts for several provinces, or the whole country. Bidders must hold a valid market authorisation, and must undertake to supply up to the volume forecast. With those conditions met, contracts are awarded on price alone.

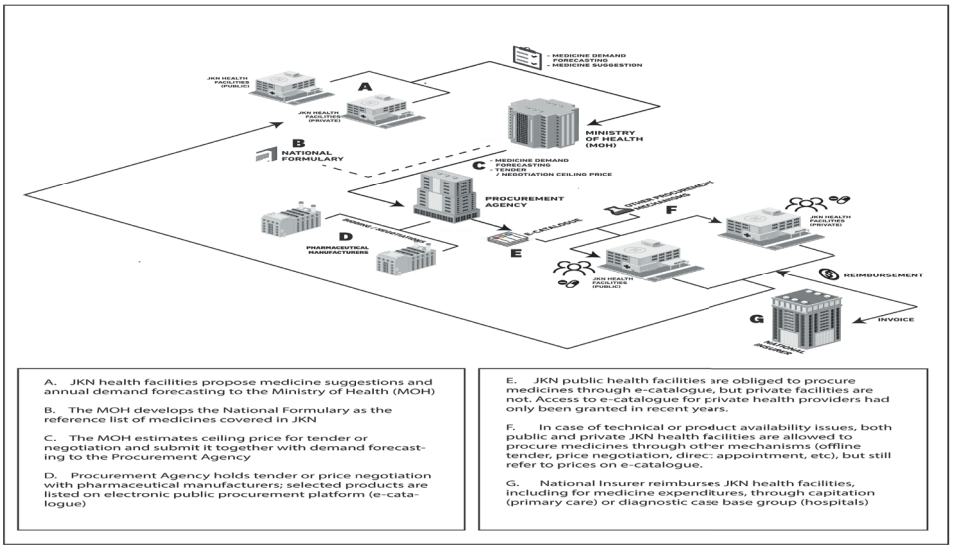

Figure 1. Summary steps in the procurement of medicines in the JKN system.

The Indonesian pharmaceutical market is dominated by domestic manufacturers (88% of 206 registered companies) (Pharmaboardroom, 2017). The expansion of JKN has increased the use of health care, escalating the overall volume of medicines sold. However, prices have plummeted, so in value terms the picture is less clear (Britton et al., 2018; Pharmaboardroom, 2017; Pramisti, 2017). By 2016, prices had fallen for almost 80% of 539 medicines publicly procured under JKN, many steeply (Anggriani et al., 2020). For example, amlodipine prices were slashed by 80% by 2018; simvastatin

fell by 60% (Sosialine, 2018). In 2020, the public procurement price for amoxicillin 250mg caplets, at IDR 195, was 55% less than New Zealand's, the regional benchmark for competitive public pricing among countries with UHC (Morgan et al., 2017; New Zealand Pharmaceutical Management Agency, 2020).

> *"In 2014, the MOH predicted that with JKN the pharma market would grow by 40%, but in fact growth in value terms actually dropped, to the mid-single digits. Volume is increasing, but market value not so much."*
>
> -Pharmaceutical industry representative

While pharmaceutical companies must promise to deliver the contracted volumes, the government does not undertake to buy those volumes. According to a former government official, the MOH does not use volume data from the procurement agency or claims data from the insurer in demand forecasting, instead compiling data only from health facility reports. Actual procurement often differs substantially from forecasts (Anggriani et al., 2020). In 2017 the government bought 30% of the forecast amount of paracetamol, while for iron folate, purchases exceeded forecasts by over a quarter (Sosialine, 2018).

Manufacturers complain that inaccurate demand planning leaves them with unwanted stock, eating in to revenues. Some bidders now take their commitment to meet forecast volumes less seriously than in early years.

> *"We refer to the [government] demand planning… …but I also look at the market research data. To forecast production, you can't look just at the demand planning. If it's right, great. But if it is not? Where are you going to sell all those drugs?"*
>
> -Pharmaceutical manufacturer

Delayed reimbursement from the national insurer to hospitals cascades through late payment to distributors, further constraining manufacturers' cash-flow (Tang, 2019). In August 2018, the domestic pharmaceutical manufacturers' association sent a complaint letter to the Minister of Health demanding an immediate settlement from the insurer to hospitals, and later to distributors and manufacturers (GP Farmasi, personal communication, 13 August 2018). The association reported IDR 3.5 trillion (US$ 246 million) worth of debts outstanding for over one year to local pharmaceutical manufacturers. An average 24-month lag in repayment of Value Added Tax aggravates the cash flow (GP Farmasi, personal communication, 13 August 2018; Tirtokoesnadi, 2020).

Rising costs

While prices fell, several policies from outside the health sector potentially increased production costs for the pharmaceutical industry. Wanting to boost the national economy, the government established local content requirements for publicly procured goods including pharmaceuticals (Ministry of Industry of Indonesia, 2018; Peraturan Presiden Republik Indonesia nomor 16 tahun 2018 tentang pengadaan barang/jasa pemerintah, 2018). Since Indonesian manufacturers import 95% of their active pharmaceutical

ingredient (API), this caused consternation (Britton et al., 2018; Pharmaboardroom, 2017). The implementing regulations for pharmaceutical companies, eventually published in 2020, in fact, provides considerable leeway in the way "domestic content" is calculated (Peraturan Menteri Perindustrian Republik Indonesia nomor 16 tahun 2020 tentang ketentuan dan tata cara penghitungan nilai Tingkat Komponen Dalam Negeri produk farmasi, 2020). In interviews, however, both pharmaceutical executives and a former medicine regulator said that meeting the requirements would increase costs.

In addition, the Indonesian parliament enacted a populist-driven Halal Product Law that requires all medicines to be halal certified by 2019 (Pharmaboardroom, 2017; Undang-undang Republik Indonesia nomor 33 tahun 2014 tentang jaminan produk halal, 2014). Participants found this similarly worrying. While manufacturers with existing halal certification will benefit in the short run, those without could incur significant costs if the law is enforced (Britton et al., 2018).

> *"The Minister of Health told parliament – and she's quite right- should this [Halal Law] be enacted, medicine prices will rise. … It is difficult to find halal-certified APIs. Medicine prices could rise by one and a half to two times.… It is possible that [exporters] will boycott us. Europe has said should this regulation be enforced, they will withdraw themselves from the Indonesian market."*
>
> -Former medicine regulator

Net effect 1: pressure on profit margins erodes quality

Table 2 summarizes the main factors decreasing revenues and increasing production costs in the Indonesian pharmaceutical market.

Table 2. Factors pressuring profit margins

Factors that decrease revenue	Factors that increase costs
• Downward price pressures on medicine • Inability to secure sales due to inaccurate demand planning on public procurement channel • Constrained cash-flow	• Local content policy – including for active pharmaceutical ingredients (APIs) • Mandatory halal certifications for medicines • Local currency (IDR) devaluation

Participants said that pharmaceutical companies respond to the erosion of profit margins in several ways that may compromise medicine quality. The most dangerous is cutting production costs, especially those related to raw materials and packaging.

> *Q: Is there an effect, where, because of the low offering prices, the components of medicines are compromised?*

A: Yes, definitely. Starting with the raw materials. That's the first thing, manufacturers are going to look for the very cheapest API, they're going to look for a cheaper supplier. Next is the way they make the medicines available. For example, they might have started with blister packs, but they'll change those to strips, something cheaper. Basically, they're looking for ways to make more profit.

-Pharmaceutical manufacturer

The risk for quality is observed by healthcare providers:

"Sometimes we receive medicines [for JKN patients] with poor packaging. Look at this strip packaging: it's supposed to be sealed. But some medicines come with an already opened strip… so air gets in…. Medicine like this is not fit for consumption"

-Apothecary assistant at primary care services

To cut costs, some market authorisation holders outsource production to smaller companies. This is legal, as long as it is stated on the market authorisation, and the contractor is certified for Good Manufacturing Practice (GMP) (Peraturan Kepala Badan Pengawas Obat dan Makanan Republik Indonesia nomor 24 tahun 2017 tentang kriteria dan tata laksana registrasi obat, 2017). However, this is not always the case. One former regulator said that some smaller manufacturers continued to operate even after the withdrawal of their GMP certificates.

"How come these factories were still running? …It turns out they got production orders from bigger manufacturers…The dangerous thing was these bigger manufacturers did not use their own APIs, they just ordered [finished products] directly from the smaller one…So, it was like ordering food in a restaurant. The bigger manufacturers only see the end product. They did not want to know what kind of APIs were used."

-Former medicine regulator

Participants said distributors also cut costs in response to tight distribution margins, causing localised shortages and increasing the risk of degradation e.g. reducing investment in temperature-monitored storage for injections.

Net effect 2: Flight from the market creates shortages, with attendant risks for quality

When ceiling prices (calculated by the MOH using an unpublished formula) fall below a threshold covering the cost of quality-assured production, distribution and fair profit, some companies anticipate reduced profit margins and refrain from bidding in public auctions, according to an industry executive. In 2018, auctions failed nationally for 253/1001 products, though 133 of these were later successfully rebid. A further 155 auctions failed for at least some provinces (National Public Procurement Agency of Indonesia & Jasa Pemerintah, 2019). At least one multinational manufacturer of quality-assured generic medicines has ceased its commercial operations in Indonesia, and many domestic companies report struggling (Britton et al., 2018; GP Farmasi, personal communication, 13 August 2018; Sandoz, 2017).

Reimbursement for JKN patients is mostly fixed by capitation or diagnostic group, and must include the cost of medicine whether or not it is available through the public procurement platform (Britton et al., 2018). Failed auctions thus leave health facilities to procure low-cost alternatives through other mechanisms (Anggriani et al., 2020). Some suggest quality may suffer.

> *"If JKN medicines are out-of-stock, [our hospital procurement staff] must search for the same medicines from different manufacturers… and they look for the cheapest medicines. We receive other products from other manufacturers…… Previous products were packaged in a blister, a better packaging, but those new ones have strip packaging, which has lower quality."*
>
> -Apothecary assistant at hospital

Participants also reported cases in which the search for cheaper medicines disincentivised due diligence, increasing opportunities for dumping of degraded, expired or repackaged products.

Shortage of publicly-procured medicines facilitates the already common practice of encouraging patients to pay for medicines out of pocket (Yuniarti et al., 2019). This sometimes drives patients to shop in more affordable but unregulated outlets, increasing the risk of exposure to falsified medicines.

> *"The physician told us to look for the medicines outside the hospital since they have an insulin shortage. We received the [diabetes] medicines from the hospital after an inpatient care. But, for outpatient treatment, they asked us to buy the medicines outside the hospital… ...So, many patients try to look for insulin in the [informal] medicine market.*
>
> -Chronic disease patient

Localised shortages are common even when auctions have not failed. The procurement system groups provinces into six regional blocks meant to reflect cost of distribution, allowing for a fixed increment for each block. The highest (applying to the remotest areas) is set at 20% above the lowest, regardless of product value. For low-value items, this small increment does not cover the cost of distribution across the 17,508-island nation, discouraging distributors from shipping to remote areas.

> *"As a brand owner, I make a marketing forecast. ... What is most important is that we still make a profit. Since I know the Cost of Goods Sold will be higher because the distribution chain to [the easternmost province] Papua is longer with higher costs, our margins will be reduced. So, I allocate more drugs to nearby areas, which are more reachable."*
>
> -Pharmaceutical manufacturer

Table 3 summarizes profit protection by manufacturers, distributors and healthcare providers in JKN and the risks for medicine quality.

Table 3. Profit protection by actors and risks for medicine quality

Actors	Profit protection	Risks for medicine quality
Manufacturers or distributors	Cut production costs: Use cheaper active pharmaceutical ingredients (APIs)	Substandard products at point of manufacture
	Cut production costs: Use cheaper packaging materials	Downgraded packaging, prone to degradation
	Cut production costs: Unregistered contract manufacturing to smaller factories without valid Good Manufacturing Certificate (GMP)	Substandard products at point of manufacture
	Cut distribution costs: Limit supply to remote areas	Localized shortage, creating market opportunity for falsification
	Cut distribution costs: Reduce investment in temperature-monitored storage for injections	Downgraded storage, prone to product degradation
	Withdraw from market (including non-participation in public procurement)	Shortage, creating market opportunity for falsification
Healthcare providers	Prescribe premium & uncovered medicines	Irrational unmet demand of certain products or brands, creating market opportunity for falsification
	Select cheapest possible products especially during JKN medicines stockouts	Downgraded packaging, prone to degradation
	Limit medicine dispensed to patients	Push patients to unregulated supply chain, more vulnerable to poor-quality products especially falsified ones

Regulatory oversight

Indonesia's NMRA, which also regulates food and cosmetics, runs quality control laboratories in 33 of Indonesia's 34 provinces, employs over 3,700 staff, and in 2018 had a budget of more than IDR 2.17 trillion (currently around US$ 148 million) (National Medicines Regulatory Authority of Indonesia, 2019). The agency issues market authorisations, works with the MOH to certify and licence pharmaceutical manufacturers, and conducts regular inspections of factories, issuing sanctions as necessary. It also performs annual post-market surveillance based on public health risk. Until the vaccine case, the NMRA 's ability to prevent, detect and respond to threats of falsification were constrained by complex governance arrangements which, for example, restricted oversight of hospitals and public health facilities (Peraturan Menteri Kesehatan Republik Indonesia nomor 30 tahun 2014 tentang standar pelayanan kefarmasian di puskesmas, 2014; Peraturan Menteri Kesehatan Republik Indonesia nomor 35 tahun 2014 tentang standar pelayanan kefarmasian di apotek, 2014; Peraturan Menteri Kesehatan Republik Indonesia nomor 58 tahun 2014 tentang standar pelayanan kefarmasian di rumah sakit, 2014). After that case, structures were changed and new regulations issued, and progress has been made in streamlining procedures for post-market surveillance (Peraturan Menteri Kesehatan Republik Indonesia nomor 72 tahun 2016 tentang standar pelayanan kefarmasian di rumah sakit, 2016, p. 72; Peraturan Menteri Kesehatan Republik Indonesia nomor 73 tahun 2016 tentang standar pelayanan kefarmasian di apotek, 2016, p. 73; Peraturan Menteri Kesehatan Republik Indonesia nomor 74 Tahun 2016 tentang standar pelayanan kefarmasian di puskesmas, 2016, p. 74; Peraturan Menteri Kesehatan Republik Indonesia nomor 75 tahun 2016 tentang penyelenggaraan uji mutu obat pada instalasi farmasi pemerintah, 2016, p. 75).

The work of the regulators is not, however, taken fully into consideration by other agencies, especially those involved with procurement. With the exception of a valid market authorisation, which is issued for five years, quality assurance is not explicitly considered in public procurement criteria (Peraturan Presiden Republik Indonesia nomor 16 tahun 2018 tentang pengadaan barang/jasa pemerintah, 2018). While the regulator specifically includes JKN medicines in its post-market surveillance, the national procurement agency does not, in following rounds of procurement, take into account regulatory infractions such as testing failures during post-market surveillance, or documented violations of good manufacturing practice.

To ensure continuity of supply, winners of public procurement tenders face penalties ranging from warning letters to disqualification from future tenders if they do not fulfil their contractual obligations (Peraturan Lembaga Kebijakan Pengadaan Barang/Jasa Pemerintah nomor 11 tahun 2018 tentang katalog elektronik, 2018). Implementation of the measures is, however, unclear (Britton et al., 2018), and sanctions for failure to deliver to remote areas are rare.

Discussion

This study is the first to investigate political and economic drivers of poor-quality medicines in Indonesia. We looked in detail at a specific case of falsification, as well as at the broader landscape of risk in the context of the rapid scale-up of public health insurance. Our results confirm a previous global analysis by WHO, which indicates that limited access to affordable, quality-assured medicines, limited technical capacity for production, and poor governance contribute to the risk that substandard and falsified medicines will reach patients (World Health Organization, 2017c).

Our study also identified drivers of falsified and substandard medicine that are not clearly articulated in the WHO's analysis. These relate principally to markets, and other incentive structures that drive the behaviour of companies, institutions and individuals involved in the production, supply and consumption of medicines.

In the vaccine falsification case, free, quality-assured vaccines were universally available. There was no "unmet need" for imported vaccines. There was, however, unmet *demand*, created largely by some physicians who profit by promoting expensive brands. This reinforced patient perceptions that equate branding and expense with quality – something that researchers have identified as creating irrational demand for costlier medicines in other markets, including China (Reynolds & McKee, 2011; Yang et al., 2016). Recently, a registered distributor in Indonesia took advantage of this dynamic, repackaging JKN generics as fake branded products (Halim, 2019). Previous research in Indonesia has identified this profit-maximising as driven in part by the reduction in physicians' earnings that accompanied the scale-up of national health insurance (Wasir et al., 2019).

Some physicians were also willing to buy "premium" products from freelance salespeople at a discount. While there was indeed a shortage of imported products on the national market, these healthcare providers stepped out of the regulated supply chain largely to increase their profits. As predicted in WHO's framework, this unethical behaviour provided an entry point for falsified medicines. Poor governance within hospitals and institutional curbs on regulatory oversight allowed falsification to go virtually unchallenged for several years. To tackle policy issues around unmet demand and incentives, we recommend further studies to investigate the externalised impacts of physician and hospital compensation on patient well-being, including exposure to poor-quality medicines.

One other major finding significantly expands the WHO framework: profit protection by pharmaceutical companies and distributors can incentivize the production of substandard medicines, as well as creating shortages which may be filled by falsifiers. Companies acted to protect profits largely in response to new procurement rules introduced to reduce medicine prices in the public sector, helping the government to

deliver on its political promise to achieve universal health coverage. We found that prices that manufacturers view as excessively low incentivised cost-cutting activities, compromising quality assurance and good distribution practice; this corroborates findings recently reported by Wasir and colleagues (Wasir et al., 2019).

We also found that companies will simply pull out of auctions, market sectors or entire markets that they judge to be unprofitable, triggering shortages. Constrained access to affordable medicines is widely recognised as creating opportunities for falsifiers. However, shortages are most often attributed to spikes in demand caused by disease outbreaks, combined with regulatory and logistic hurdles, shortage of raw material and poor inventory management (Fox et al., 2009; World Health Organization, 2017c; Yang et al., 2016). The solutions proposed often include technical measures such as establishing an information system facilitating stock monitoring and communication between diverse actors (Wagner et al., 2014; Yang et al., 2016). While we agree that improved demand forecasting would reduce shortages, we underline the important role that corporate incentives play as a driver of shortages. A similar study in in Romania found that rapid changes in procurement and pricing policy led to the withdrawal of around 2,000 of 6,200 registered products (Pisani et al., 2019). Multinational producers are particularly likely to withdraw or withhold products because their calculus includes the possible reduction of profits in higher-margin markets, through parallel exports or price benchmarking (Pisani, 2019).

The imperative to reduce medicine prices in Indonesia, the world's fourth most populous nation, became a focus of political attention, growing along with JKN's well-publicised deficit (National Parliament of Republic of Indonesia, 2017). Similar dynamics are observed in a number of middle- and lower-income countries as they try to increase public health provision (Lu et al., 2011; Nguyen et al., 2015; Sun et al., 2008; Wirtz et al., 2017; Yang et al., 2016). We find that if these efforts eliminate what companies consider a reasonable profit, medicine quality is likely to suffer.

More transparency from pharmaceutical companies about actual manufacturing, development or marketing costs, and from governments and insurers about prices paid for medicines, would greatly facilitate more productive discussion about what constitutes a fair profit (Colbert et al., 2020; Moon et al., 2020; World Health Organization, 2017b, 2019). It is clear, however, that price calculations must include the cost of complying with good manufacturing and distribution practice, and other aspects of quality assurance. In Indonesia, we strongly encourage the adoption of explicit quality assurance criteria in the procurement of medicines (a possibility that is currently under discussion) (Inotai et al., 2018).

Many studies of poor-quality medicines in LMICs conclude with a call to strengthen the national medicine regulator (Orubu et al., 2020; Preston et al., 2012; World Health Organization, 2010). While the NMRA encounters gaps in infrastructure and technical capacity across different provinces in Indonesia, the agency has been greatly

strengthened since the vaccine case (Peraturan Presiden Republik Indonesia nomor 80 tahun 2017 tentang Badan Pengawas Obat dan Makanan, 2017; Slamet, 2019). Our study highlights the role of market factors, industrial policy and other politically-driven policies in increasing the risk of substandard production, degradation and falsification of medicines. In Indonesia, as in most other countries where the same factors are likely to be at play, the medicine regulator has no authority in these areas. While acting as a keystone for the enforcement of quality assurance, medicine regulators must thus coordinate closely with other institutions to reduce the incentives that drive falsification and substandard production (Newton et al., 2019). Political commitment to achieving UHC may provide the power to convene actors across sectors, and to balance competing objectives by taking a system-wide perspective (Bigdeli et al., 2015; Wagner et al., 2014). We believe that medicine quality is a joint responsibility, which requires a strong coordination and clear division of roles and tasks between different institutions.

Our qualitative study allowed for the detailed investigation of factors shaping the behaviours of medicine producers, distributors, providers, consumers and regulators. Interviews, conducted at both national and sub-national levels, were limited in number, and a few participants were rather normative. However, we were able to triangulate information between participants, including about unethical practices and the limitations of governance structures. This may have been because we took the much-publicised case of vaccine falsification as a starting point. Large variation of study participants with quite small numbers on each group curtailed a consensus within each group, but we identified a general thematic saturation between different groups. We received feedback from the national regulator and others during our analysis, enriching our understanding, and were also able to validate some statements (for example about pricing and shortages) with quantitative data. Health service provision in Indonesia is highly decentralised, so some of the findings relating to patient-level risk may not be representative. However, the national insurance system, including its reimbursement and procurement mechanisms, are centralised, meaning that there will be less variation in their effects nationwide.

Conclusion

Our study shows that in Indonesia, market factors, including political pressure to reduce medicine prices to help achieve UHC and healthcare provider incentives, can be influential determinants of medicine quality. The risk of substandard production and degradation rises when revenues earned by legitimate manufacturers do not adequately cover the cost of quality-assured production and fair profit. The risk of falsification rises as shortages become more common following market withdrawal; they are greatly increased by profit-maximising healthcare providers who promote irrational demand and neglect due diligence. Taking these factors into account when formulating policies around medicine procurement, reimbursement, taxation, and industry would

complement existing product regulation measures, help further secure access to quality-assured medicines for Indonesian patients as the country works towards achieving UHC.

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Chapter 3.

Conceptualizing risk indicators of substandard and falsified medicines for case-finding and sentinel surveillance strategies

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Abstract

The World Health Organization and others warn that substandard and falsified medicines harm health and waste money, especially in low and middle income countries. However, no country has measured the market-wide extent of the problem, and no standardized methods exist to estimate prevalence of either substandard or falsified medicines. This is in part because the task seems overwhelming; medicine markets are huge and diverse, and testing medicines is expensive. Many countries do operate some form of post-market surveillance of medicines, but their methods and goals differ. There is currently no clear guidance on which surveillance method is most appropriate to meet specific public health goal.

In this viewpoint, we discuss the utility of both case finding and sentinel surveillance for substandard and falsified medicines, linking each to specific public health goals. We posit that choosing the system most appropriate to the goal, as well as implementing it with a clear understanding of the factors driving the production and sale of substandard and falsified medicines, will allow for surveillance resources to be concentrated most efficiently.

We adapted principles used for disease outbreak response to suggest a case-finding system that uses secondary data to flag poor quality medicines, proposing risk-based indicators that differ for substandard and falsified medicines. This system potentially offers a cost-effective way of identifying "cases" for market withdrawal, enhanced oversight, and another immediate response. We further proposed a risk-based sentinel surveillance system that concentrates resources on measuring the prevalence of substandard and falsified medicines in the risk clusters where they are most likely to be found. The sentinel surveillance system provides base data for a transparent, spreadsheet-based model for estimating the national prevalence of substandard and falsified medicines. The methods we proposed are based on ongoing work in Indonesia, a large and diverse middle-income country currently aiming to achieve Universal Health Coverage. Both the case-finding and sentinel surveillance are designed to be adaptable to other resource-constrained settings.

Introduction

In late 2017, World Health Organisation's (WHO's) press department issued a press release with the bold headline: "*1 in 10 medical products in developing countries is substandard or falsified*" (World Health Organization, 2017d). More recently, with governments scrambling to secure supplies of diagnostics, medicines and vaccines to cope with the COVID-19 epidemic, WHO and others have issued new warnings that the world may face an increased threat from poor quality medicines (Newton et al., 2020; Willmer, 2020; World Health Organization, 2020b, 2020c). These include substandard medicines, which are made by registered pharmaceutical companies in regulated factories but which don't meet the quality standards set out in their market authorisation paperwork, either because they were poorly made or have degraded since manufacture. This increased the threat of poor-quality medicines also includes falsified medicines which are made, repackaged or sold by criminals, who seek deliberately to misrepresent the identity, composition, or source of the product (World Health Organization, 2017b).

Poor quality medicines can use up family and national budgets without curing patients; indeed, they sometimes poison or kill people instead of curing them. Underdosing infectious pathogens also allows drug-resistant infections to spread. If these "medicines" are indeed common, they may thus substantially undermine physical and financial health (Buckley & Gostin, 2013; World Health Organization, 2017c). Thus, if these "medicines" are indeed common, they may substantially undermine physical and financial health. Estimates based on available data for particularly well-studied molecules provide an order of magnitude: poor-quality antimalarials were estimated to cost US $130 million per year in a single region of the Democratic Republic of Congo, US $141.5 million in Zambia, and US $830 million across Nigeria. In the latter country, substandard antimalarials are estimated to contribute to 12,300 deaths per year (Beargie et al., 2019; Jackson et al., 2020; Ozawa et al., 2019). A 2015 study reported that, in 39 sub-Saharan African countries, there were 122,350 deaths attributable to poor-quality antimalarials among children under 5 years of age. However, the authors noted that "there is considerable uncertainty surrounding our results because of gaps in data on case fatality rates and prevalence of poor-quality antimalarials" (Renschler et al., 2015). Similarly, the meta-analysis of studies that gave rise to WHO's press release, which said that 10% of medical products in developing countries are substandard or falsified, is careful to note the many limitations of that estimate. This meta-analysis was based on studies of uneven sizes and methods, conducted largely in low-income countries with limited domestic pharmaceutical industries, and heavily skewed toward antimalarials and a few other medicines that most interest global health agencies. Even within that constrained pool and looking only at studies that included sample sizes of 50 or more, reported prevalence of substandard or falsified medicines ranged from 0% to 91% (World Health Organization, 2017a). Reviews have reported similar data constraints and findings (Johnston & Holt, 2014; McManus & Naughton, 2020; Nayyar et al., 2019; Ozawa et al., 2018; Rojas-Cortés, n.d.). For example, Ozawa and colleagues (Ozawa et al., 2018) found that studies reported a prevalence of substandard or falsified medicines

between 0.8% and 89% in Africa and a prevalence of between 0.7% and 50% in Asia.

WHO actively maintains a case-reporting system for substandard and falsified medical products including medicines, contraceptives, vaccines and point of sale diagnostics. For brevity, we use the term medicine throughout this paper to cover all these medical products. Regular training provided to individuals designated as in-country focal points increases the use of the system, but, similar to all case reporting systems, it provides no information on denominators (the number of products inspected or tested), so interpretation of trends and comparison between countries is difficult.

It may be that the problem of medicine quality is understated because of a vicious cycle of limited systematic measurement, leading to limited visibility and limited awareness of the problem that in turn restricts resources available for systematic measurement? Alternatively, the problem may be that WHO and researchers cherry-picking data to overstate the problem, perhaps for reasons of self-interest, as (Hodges & Garnett, 2020) suggest.

We do not know which of these dynamics holds true. There is, to our knowledge, no clear understanding of the prevalence of substandard or falsified medicines in any single country, let alone across all the "developing countries", as suggested by the press release's headline. No country has yet made systematic estimates of the prevalence of substandard or falsified medicines across all therapeutic categories in its medicine market, and no standardized methods for calculating such estimation exist.

In this viewpoint, we aimed to briefly review different approaches to surveillance and estimation in public health, discuss their relevance in the context of medicine quality, and lay out ideas for 2 potentially cost-minimising methods that may improve our ability to measure or reduce the prevalence of poor quality medicines, especially, in low and middle income settings.

Approaches to surveillance

Overview of surveillance system

We follow WHO, United States Centers for Disease Control and Prevention, the World Bank and others in defining public health surveillance as the ongoing and systematic collection and use of data to inform policy; plan and evaluate interventions; and improve health outcomes (B. C. K. Choi, 2012; Garcia-Abreu et al., 2002). Surveillance systems monitor the prevalence of infectious and noncommunicable diseases; of disability; and, increasingly, of the behavioral, social, corporate, and environmental causes of ill-health. In addition, surveillance systems have, in recent decades, expanded to include the systematic monitoring of health system factors such as service use, prescription practices, or access to medicine.

Surveillance can take many forms, each serving a slightly different purpose within the catch-all definition of "improving health outcomes." However, most can be categorized into either "passive" or "active" surveillance. Passive surveillance involves reporting events such as disease diagnoses as they arise. An early example of passive sentinel surveillance in the United States was the weekly reporting of diseases by designated physicians, which began in Massachusetts in 1874 (B. C. Choi & Pak, 2001). The informatics era has greatly expanded the potential for secondary data to be used to inform public health decision-making. Examples include the use of both retail data of over-the-counter medicine sales and data from internet searches to flag potential disease outbreaks and the use of medical-claims data to track trends in noncommunicable diseases (Kirian & Weintraub, 2010; Simonsen et al., 2016). Active surveillance tends to be more resource intensive, usually involving purposive data collection—often the collection and screening of blood or other biological samples or, more recently, medical imaging.

Active surveillance systems systematically collect and test samples for the purpose of tracking ill-health or health-related risks. Some active surveillance, such as active sentinel surveillance, test a cross-section of a defined population to establish disease prevalence. Others, such as case finding, specifically, target individuals at highest risk of needing services. These 2 types of active surveillance have different purposes. Sentinel surveillance, similar to many other surveillance systems, such as those that track noncommunicable diseases, determinants of health, and health system factors, provides data intended to guide medium- or longer-term health program planning. Case-finding systems, frequently used in infectious disease outbreaks but also used for early detection of treatable noncommunicable conditions, provide data intended to inform immediate therapeutic or preventative action. These different goals, upon which this paper focuses in the context of medicine quality, affect the design and use of surveillance systems and data, as show in Table 1.

Purpose	Outbreak Response	Health Programme Planning
System design:	**Case finding:** identifies infected individuals	**Sentinel surveillance:** track prevalence over time
Resulting action:	Isolate, treat	Adjust policies and programmes
Key characteristic:	Specific: pinpoints individuals for rapid follow-up	Comparable: standardised methods allowing comparison over time
Cannot be used to:	Estimate prevalence; track trends over time	Respond at individual level

Table 1. Major types of surveillance systems in public health

Case finding

The control of outbreaks and epidemics of infectious disease requires that chains of transmission be broken. In these circumstances, surveillance systems try to identify infected individuals, isolating and/or treating them to interrupt transmission. We term these systems "case finding". They are relatively rare but have seen a resurgence during the COVID-19 epidemic.

Sentinel surveillance

Sentinel surveillance systems are more common. Designed to track trends in infection over time, they use standardised methods to measure the prevalence of a disease within a defined population, comparing the result with prevalence measured in the same way in earlier years or in different locations. Sentinel surveillance is used to estimate burden of disease, to target prevention and treatment interventions, and to monitor the impact of these interventions.

While passive surveillance can achieve these goals, it is of limited use for tracking rare diseases, which are easily missed by these systems (Nsubuga et al., 2006). While epidemiological orthodoxy holds that regular screening of randomly-selected samples provides the best approximation of disease trends across a population as a whole, this is also impractical for rare conditions, since it requires very large samples.

The HIV epidemic entrenched the idea of sentinel surveillance in populations defined not by geography but by risk of exposure to the virus. This allowed health authorities to focus surveillance resources in sub-populations where the majority of cases of the largely invisible disease were to be found while still producing comparable data and tracking trends over time. In many countries, those groups included injecting drug users; gay men; sex workers of all genders; and their most frequent clients.

Figure 1 illustrates randomised and risk-based approaches to HIV sentinel surveillance. For the same limited resources (in this simplification, 5 tests), random sampling, on

the left, yields just 1 positive test, while sentinel surveillance, on the right, yields 3. Combined with robust estimates of the size of those sub-populations, this approach will provide a more accurate estimate of prevalence of infection nationally; the data produced will more accurately reflect the effect of targeted risk-reduction interventions, and these benefits will be achieved at a lower cost compared with random sampling.

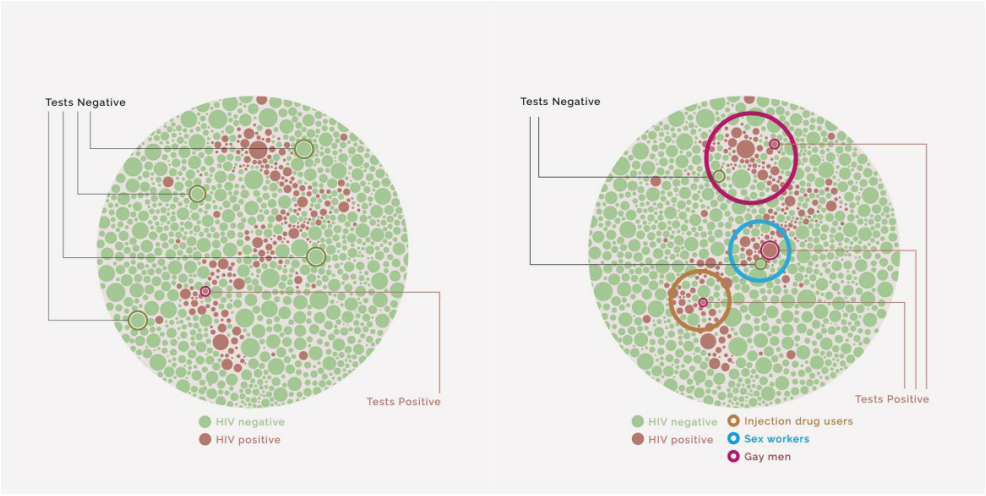

Figure 1. Illustrative difference between random and risk-based surveillance for HIV

The HIV example is of considerable relevance when thinking about surveillance of substandard and falsified medicines, because both involve something that is largely invisible until actively tested and clusters around known risk factors. A similar model for medicine quality is presented in this paper's section "Proposed Method for Sentinel Surveillance" below.

Existing surveillance of medicine quality

At the international level, surveillance of medicine quality takes the form of passive reporting of detected cases. As with disease case reporting, this provides information by demographic, geographic, environmental, or other factors, which is invaluable in helping to identify clusters of risk. However, case reporting does not provide any idea of the number of products tested. No case reports may mean there is no problem in a particular country, but it may also mean there is no capacity or willingness to detect or report cases.

At the national level, medicine regulators in many countries conduct some form of postmarket surveillance. In some countries, this is largely passive, limited to collating

reports of adverse events submitted by health care providers through pharmacovigilance systems. Again, this means the denominator is unknown. However, in other countries, the regulator actively samples medicines from supply chains for inspection and testing. Where they report the number of products inspected or tested, as well as the number of out-of-specification products, this active surveillance allows for the calculation of prevalence in the segment of the market from which samples were drawn.

Sample selection in active surveillance varies widely, from random to convenience sampling, although regulators do not always state which method they use. Academic groups and WHO have published recommended methods for conducting surveys of medicine quality (Newton et al., 2009; WHO Expert Committee on Specifications for Pharmaceutical Preparations & World Health Organization, 2015), as well as for sampling high-risk medicines from the internet (Vida et al., 2020). While not focused specifically on sentinel surveillance, these methods have informed the guidance provided by technical and regulatory agencies on surveillance approaches that focus on selecting products at the highest risk for inspection and testing, including at the point of import (Aroca & Guzmán, 2017; FDA, 2014; FDA Center for Drug Evaluation and Research, 2021; General European OMCL Network (GEON), 2007; United States Pharmacopeial Convention, Babigumira, et al., 2018; United States Pharmacopeial Convention, Nkansah, et al., 2018). To date, the criteria for determining risk have focused largely on the risk of impact to public health, factors intrinsic to the molecules (eg, stability and therapeutic index), and regulatory history. Not all agencies share information about risk profiling, for fear of helping those who produce poor-quality medicines to circumvent targets. However, as far as we know, market-related drivers of the risk of falsification are rarely considered. Furthermore, none of the guidelines or tools currently in the public domain explicitly differentiate between the risks for falsification and the risks for substandard production or degradation. However, attention paid to risk-based, postmarket surveillance is growing; the WHO Member State Mechanism on falsified and substandard medicines chose the development of methods and tools for risk-based surveillance as a prioritized activity in its current workplan (World Health Organization, 2017b), and work is ongoing.

Sentinel surveillance of substandard or falsified medicines is a form of postmarket surveillance designed explicitly to select samples in reproducible ways over time, so that trends can reliably be measured. This is rare in the case of substandard or falsified medicines, although some repeat random surveys have been conducted (Tabernero et al., 2015). Site-based sentinel sampling has also been attempted in some locations. This may suffer from bias if people, including falsifiers, become aware of the practice and change behavior to avoid supplying known sentinel sites (WHO Expert Committee on Specifications for Pharmaceutical Preparations & World Health Organization, 2015).

In the context of medicine quality, case-finding efforts focus on trying to identify individual products that are most likely to be substandard or falsified, so that they can quickly be recalled or otherwise removed from the market. In some high-income

countries with strong pharmacovigilance systems, these efforts coexist with active sampling from the supply chain.

Market-wide estimates of prevalence are virtually non-existent. Reasons for this include the apparent complexity of the task and the expense of pharmacopeial testing. Even small countries will typically have many thousands of registered medicines and vaccines on the market. Meanwhile, well-staffed medicine testing laboratories are scarce – there are fewer than 50 WHO-prequalified drug testing laboratories across all low and middle income settings (World Health Organization, 2020a). Local pharmaceutical reference standards and reagents which allow for testing of the content and quality of medicines are often unavailable, while international "gold standard" products run to hundreds of dollars for even the most common molecules (U.S. Pharmacopeia, 2020). In addition, medicine regulators may be wary of systematic approaches, seeing transparent surveillance and robust estimation processes as an unwelcome evaluation of regulatory performance.

In short, while postmarket surveillance exists in different forms, there is currently no global guidance on the purpose or shape of national surveillance systems for substandard or falsified medicines and no standardized methods for translating the results of surveillance into market-wide estimates of prevalence.

The remainder of this paper proposes candidate methods, expanding on existing risk-based approaches. We aimed to review the risk factors that underlie (1) substandard and (2) falsified medicines; to propose a method for case finding based on the identified risk factors; to propose a sentinel surveillance method based on the identified risk factors; and to propose a method for developing nation-wide estimates for the prevalence of substandard and falsified medicines, based on sentinel surveillance. Our proposal is based on exploratory work undertaken in Indonesia. We believe the proposed methods are feasible in many resource-limited settings.

Risk factors for poor quality medicines

Both falsified and substandard medicines exist because there is money to be made selling them. In the same way that a spike in opportunistic infections once signalled a potential cluster of undetected HIV infections, dymanics in medicine markets can act as crude predictors of clustered cases of substandard or falsified medicines. In earlier works, we reviewed available academic literature; examined reports of the case-reporting database, WHO Global Surveillance and Monitoring System for substandard and falsified medical products; and conducted detailed case studies in 4 middle-income countries, using an epidemiological approach to identify risk factors associated with substandard and falsified medicines (Pisani et al., 2019; World Health Organization, 2017c). We

identified a limited number of market-related factors that combine to increase the possibility that certain products in a market will be substandard, as shown in Table 2.

Table 2. Market risk factors for substandard medicines

Risk factor	Quality risks
High or rising pressure on profit margins	Incentivises cost cutting
Stretched technical capacity	Increases risk of production errors or degradation during distribution
Limited oversight	Allows substandard products to flow through the supply chain
Low risk of damage to corporate reputation	Reduces incentive to invest in quality assurance

Some of these market factors operate at the level of a particular brand, others operate at the company level, others relate to the level of the supply chain, and others relate to a specific molecule. These market factors interact and further combine with other factors already considered in risk-based surveillance for medicine quality, such as the stability of a molecule or the complexity of the production or packaging process, to signal the likelihood that a medicine will be substandard or falsified.

A comprehensive review of academic literature describing interventions to control falsified medicines found few studies that addressed market drivers of falsification (Hamilton et al., 2016). However, we find market-related factors strongly shape incentives for falsifiers, leading to increased risk of falsification, as shown in Table 3.

Table 3. Market risk factors for falsified medicines

Risk factor	Falsifier incentive
Shortage of (or restricted access to) affordable, desired product	Criminals prefer to make/sell product where there is a ready market (where demand exceeds accessible supply)
High priced medicine, or relatively high priced brand	Profit opportunity influences choice of product and brand falsified
Limited risk of discovery or punishment	Risk of retribution shapes choice of distribution channel

We propose adding indicators of the market factors shown in Tables 2 and 3 to increase the specificity of existing risk-based sampling and to more easily distinguish between products at risk for falsification and those more likely to be substandard.

Proposed method for case finding: sample based on an index of risk

Effective case-finding systems may appeal to regulators, politicians and the public because they inform product recalls and other immediate actions to protect patients. On the downside, these systems are data-hungry, and sampling is relatively resource-intensive. They do not systematically test a specific number of samples from a well-defined population, and thus cannot easily be used to measure trends over time or to estimate the magnitude of the problem.

These limitations notwithstanding, many sources of routinely-collected data related to medicine markets do exist, including in middle and some lower-income countries. These include data collected by medicine regulators, health authorities and insurers, customs and excise departments and market research firms. We propose using these data to guide case-finding as shown in Textbox 1. Steps 2-5 should be undertaken separately for substandard and falsified medicines.

Textbox 1: Steps for systematic case finding for falsified and substandard medicines

Step 1: Define indicators of public health importance (e.g. burden of disease, vulnerability of affected population, narrow therapeutic index, sales volume of brand or dosage form).

Step 2: Define 1 or more objective indicators for each of the risk factors for substandard medicine) and for falsified medicine, specifying the level at which it operates. Identify potential collinearity, and weights for importance.

Step 3: Create risk scores for each numeric indicator (e.g.: none; minimal; some; high), and calculate indicators and scores for each product (examples in Supplementary Tables A and B in (Reference 42))

Step 4: For each product, add risk scores to create a total index of risk. Select products to be sampled, prioritising those with the highest risk index.

Step 5: For sampled products, weigh by risks related to geography and supply chain, and draw up sample frame.

Step 6: Sample selected products (from specified locations, if indicated in Step 5).

Step 7: Test sampled products. For potentially falsified products, screen visually and using rapid or low-cost device such as hand-held spectrometer or field-based thin layer chromatography. For potentially substandard products, perform quantitative assay and dissolution tests.

Step 1 is carried out in consultation with health authorities, while steps 2 and 3 take into account available data sources and the opinion of experts from the many sectors involved in the production, procurement, sale, and use of medicines. In Table 4, we provided a single example of a possible indicator for each area of risk for substandard production

or degradation. These suggestions derive from ongoing exploratory work in Indonesia, a large middle-income country with substantial domestic medicine production and a single-payer health insurance system. Exact specifications of the indicators, as well as decisions about potential weighting, may differ by country and will be determined, in large part, by the data available. A more comprehensive list of alternative indicators, together with suggested data sources, is provided in the supplementary tables (Pisani, 2021).

Because the medicine market is extremely heterogeneous, several indicators use relative measures, such as ratios compared with the median. These indicators must then be turned into scores that can be added together to create a total index of risk as described in Textbox 1. Supplementary Table A (Pisani, 2021) suggests methods for turning indicators into risk scores.

To provide a single example for the first indicator in Table 4, examine the ratio of price to weighted market median price for the same product. If the ratio is above 1, the product is priced above the market median and, thus, not deemed irrationally cheap or at risk of cost cutting. Deciles of risk are calculated only for those products with a price–to–median-price ratio of less than one. Products closest to the median (deciles 7-10) may also be considered at no risk. Those in deciles 5 and 6 may score at 1 risk point (at minimal risk for cost cutting), and those in the second to fourth deciles score 2 points (at some risk). Brands (or nonbranded products from a specific market authorization holder) that fall into the first decile—the products selling at the deepest discount—are awarded 3 risk points (at high risk for cost cutting). Narrower gradations would allow for greater specificity; expert committees may decide what is most appropriate in the local context.

A similar process can be undertaken for products at risk for falsification, but the indicators will be different. Table 5 provides examples for each of the major risk-factor groupings. Again, a more comprehensive list of alternative indicators, together with suggested data sources, is provided in the supplementary tables (Pisani, 2021).

The success of the case-finding approach will depend, to a significant extent, on the willingness of data custodians to share these data with those conducting case finding. The sensitivity and specificity of case finding will additionally depend on the ways in which indicators are combined. While Textbox 1 describes a simple index, weighting is possible. If weighting is used, it is likely that brand-specific indicators, which have greater specificity, will carry a greater weight than market-wide indicators relating to molecules. However, we propose working with regulators to use retrospective data to find the model that best predicts poor-quality products in specific markets. Regulators with higher capacity for analysis may wish to develop more complex algorithms, including "big data" approaches, that combine price and volume data in ways that more closely pinpoint risk in specific markets.

Table 4. Indicative components to flag potentially substandard medicines

Indicates	Indicator	Level at which indicator applies	Rationale
Profit pressure: cost-cutting	Ratio of price to weighted market median for same product (same molecule and dose-form)	Brand and doseform	Although premium brands are usually available, products produced by a large number of companies will tend towards the lowest cost of quality-assured production, plus a fair profit (Hill et al., 2018). If a particular product sells significantly below the market median, it may signal insufficient investment in quality assurance, or other cost-cutting measures.
Technical limitation: production errors	Number of years continuously producing this molecule	Manufacturer (per molecule)	As companies and their staff gain experience and streamline their standard operating procedures in the production of a new medicine, the risk of production errors falls. Mistakes in production are more common among newly registered manufacturers.
Limited oversight	Time since most recent Good Manufacturing Practice (GMP) inspection of any facility	Manufacturer (by production site)	Medicine regulators aim to inspect production facilities on a regular basis; some additionally include risk-based inspection. In practice, frequency of inspection depends on regulatory capacity, and intervals may vary. The risk of detectable deviations from GMP grows with time since last inspection.
Production history	Number of regulatory warnings or sanctions given to manufacturer over reference period	Manufacturer (all products)	Investment in quality assurance is embedded in corporate culture. Manufacturers who repeatedly receive warnings for GMP violations may systematically underinvest in quality assurance, meaning all their products are at higher risk.
Reputational risk	Number of years of marketing authorization (MA) holder in the market	MA holder (all products)	Most companies are incentivized to invest in quality assurance (QA), in part, because they wish to maintain their reputation as a provider of quality goods. New companies may be established opportunistically, especially, in rapidly growing markets. With less investment in building a reputation than older firms, new companies may have less to lose if found to be marketing substandard products.
Intrinsic risk: degradation	Stability of molecule	Molecule (all products)	Some molecules are less stable than others and more sensitive to variations in humidity, temperature, light, or other factors. Less stable molecules are more likely to degrade, becoming substandard before consumption.

Table 5. Indicative components to flag potentially falsified medicines

Indicates	Indicator	Level at which it applies	Rationale
Market opportunity: limited affordability	Product is on patent but not listed in current national formulary	Brand	On-patent products usually have premium prices. When they are not listed in current national formularies, they are usually not covered in the national insurance scheme, indicating limited affordability for patients. Patients or health care providers may seek these products at cut prices outside of the regulated supply chain.
Market opportunity: desirability	Molecule is used recreationally or off-label	Molecule	Some narcotics and psychotropic medicines are used recreationally or otherwise abused, including use for purposes for which they are not licensed. Additionally, access to some medicines is tightly restricted for political reasons, such as their potential use as abortifacients. Since the sale of these products is regulated, users without prescriptions commonly seek them outside of the regulated supply chain or from vendors who do not observe due diligence.
Profitability	Ratio of (price × retail channel sales volume) to market median, for the same dosage form	Brand	Falsifiers want to sell products for which there is a lucrative market, for which a large number of patients are prepared to pay a high price. For any given medicine for which there is a choice of brands, those brands with a combination of a relatively high retail price and a relatively large sales volume will be attractive targets.
Low risk of detection	Number of listings for product on 2 largest internet marketplaces	Brand	General internet marketplaces provide an unregulated but commonly used space for trading medicines without official licenses. The vast number of online transactions creates difficulty for regulatory monitoring, and anonymity limits the possibility of repercussions. More listings of products on the largest general online marketplaces also indicate high demand.

Proposed method for sentinel surveillance: tracking trends in risk groups

Sentinel surveillance is a form of post-market surveillance that is less data-intensive than case finding and has a different purpose. Systematic testing of comparable samples over time allows health authorities to: establish the likely prevalence of substandard medicines and, separately, of falsified medicines; inform estimates of the health and economic impacts of these medicines; make a case for additional investment in quality assurance in production or procurement, if necessary, including more investment in regulatory enforcement; plan and implement policies and programs to reduce prevalence of poor-quality medicines; and track progress over time toward achieving that goal.

The principal challenge in developing a robust, risk-based sentinel surveillance system for substandard and falsified medicines is in identifying "risk groups" of medicines, within which most poor-quality medicines cluster. These risk groups are the functional equivalent of the risk behaviors that circumscribe sentinel populations for another invisible threat to health, HIV infection.

Similar to HIV sentinel surveillance, the specific sentinel groups may vary from country to country, depending on market dynamics and the risks and opportunities they create. The critical point is that groups are defined based on the feasibility of drawing samples and in ways that are replicable over time.

Drawing from existing risk-based approaches and the additional market risk factors identified in Table 2 and Table 3, and, again, with reference to ongoing exploratory work in the Indonesian market, we propose sentinel groups for both substandard medicines (Table 6) and falsified medicines (Table 7). We underline that these groupings are not intended to encompass all at-risk products, nor do we suggest that all of the products in these groupings are at risk. Rather, these factors act as proxies that may yield a higher concentration of at-risk products, compared with a random sample.

Most sentinel groups should be sampled in the public, private, and (if applicable) nonprofit sectors; the obvious exceptions are samples specific to unregulated channels, which should not exist in the public sector. A sentinel surveillance system may be established following a process similar to that described in Textbox 2.

Table 6. Suggested sentinel groups for substandard medicines

Sentinel group	Definition	Signals potential problem of	Rationale
Irrationally low priced essential medicines	In public system, medicine price < 75% of international reference price; in retail pharmacies: cheapest available version of target medicine	Cost cutting	Irrationally low prices are a strong predictor for cost-cutting. Selection of samples from the public system can be brand-specific and price data are available in advance, so clear price threshold can be set. For private provision and retail sampling, brand-specific sampling is not feasible, so the cheapest medicine available should be sampled. Molecules should be selected for local public health importance.
Contract manufactured medicines	Products randomly selected from those that are manufactured by a company other than market authorisation holder	Reduced oversight	Contract manufacturing is a frequent means of lowering production costs (by outsourcing to companies that can achieve economies of scale). The market authorisation holder does not always have clear oversight of quality assurance practices at contract manufacturers.
Poor regulatory history	Medicines randomly selected from those made by companies with history of regulatory violations and involuntary recalls within a time reference period	Inadequate quality assurance	Though regulators work with past violators to improve manufacturing and distribution practice, corporate culture and incentives appear to act as enablers of cost-cutting, and other practices which increase the risk of substandard production or degradation.
Technically vulnerable	Medicines randomly selected from those that are technically challenging to manufacture or distribute, including those with unstable molecules, limited therapeutic index, or sterile forms.	Higher potential for production errors	These product-specific characteristics require particular investment in quality assurance. It would be possible to restrict this sentinel group to newer (less experienced) manufacturers or market authorisation holders. For unstable molecules, sample may be drawn from retail outlets in geographically remote areas.

Table 7. Suggested sentinel groups for falsified medicines

Sentinel group	Definition	Signals potential problem of	Rationale
High irrational demand	Medicines that are used for recreation or other off-label purposes, for which alternatives are restricted or expensive; randomly sampled from retail outlets.	Market opportunity	Demand planning is based on authorised uses only; off-label use creates shortages which provide market opportunities for falsifiers. Sample frame may be weighted towards independent pharmacies/medicine shops.
Life-saving but unaffordable	Medicines that are known/reputed to be life-saving, that retail at >10% of average per capita household spending, but that are not covered by national insurers; brand-specific sample from retail outlets.	Market opportunity	Patients with life-threatening conditions are highly motivated to acquire these medicines. High profit margins incentivise their sale, which may diminish due diligence even in the regulated supply chain. This sample may include products not locally authorised; these should also be screened for falsification.
Sold on unregulated internet platforms	Random sample of "prescription-only" medicines sold through unlicensed internet sellers (sentinel group may be combined with signals of profit potential though purposive sampling of brands retailing at >200% market median for the dose-form)	Evasion of regulation	Falsifiers favour internet sales because the potential for detection and successful prosecution is low. While the sample may be weighted toward medicines with high irrational demand, it should include other medicines of public health importance, such as antibiotics.

Textbox 2: Steps to establish sentinel surveillance for falsified and substandard medicines

Step 1: Define indicators of public health importance (e.g. burden of disease, vulnerability of population, sales volume of brand or dose-form, publicly procured), and list medicines by public health importance.

Step 2: Review local data sources and market conditions to define proxy "sentinel groups", in which the highest concentration of a) falsified and b) substandard medicines of public health importance are likely to be found.

Step 3: Define indicators (or combinations of indicators) that best circumscribe those sentinel groups.

Step 4: Draw up a sample frame for each sentinel group, including in it the public and private sectors, as appropriate, and sample a pre-determined number of products for testing.

Step 5: Test samples. For sentinel groups containing potentially falsified products, screen visually and using rapid or low-cost device such as hand-held spectrometer or field-based thin layer chromatography. For sentinel groups containing potentially substandard products, perform quantitative assay and dissolution tests.

Figure 2. Illustration of risk-based sentinel surveillance for substandard and falsified medicines

Pharmacopeial testing is expensive. The risk-based sentinel approach aims to reduce costs of routine surveillance in two ways: first, it increases the "yield" of testing by focusing it on the clusters of medicines most likely to be at risk (Figure 2). Second, it provides an initial triage for testing technologies. Products selected in sentinel groupings for falsification risk can be screened visually and using lower-cost field-based devices (Vickers et al., 2018); only those at high risk of substandard production need to undergo assay and dissolution testing.

Developing national estimates for the prevalence of substandard and falsified medicines

Steps to estimate the prevalence of poor-quality medicines

In the same way that HIV prevalence among sex workers or drug injectors does not represent the prevalence of the virus in a whole population, the prevalence of poor-quality medicines in risk-based sentinel groups does not represent medicine quality across a whole national market. However, if the size of each of those sentinel groups can be calculated and if assumptions can be made about their relationships with the wider population, then sentinel surveillance can provide a starting point for making robust estimates of national prevalence (World Health Organization & UNAIDS, 2010). The same is true for medicine surveillance groups and their relationships with the wider market. Textbox 3 suggests a process for developing such estimates.

The approach in Textbox 3 has the great advantage of transparency. In addition, the process will highlight important data gaps that can be rectified over time. Assumptions can easily be corrected as more complete data are collected or shared. For example, step 6 might initially include the assumption that imported, on-patent oncology drugs that do not fall into any of the groups in Table 6 are substandard 0% of the time. The assumption may change if regulators in producing countries issue product recalls for products that are also exported.

Estimation process

Health-related estimates tend to improve in accuracy and local relevance (and thus potential utility) if potential end-users are involved in their production (Pisani & Kok, 2017). This is, in part, because these actors can identify and contribute data to the process, and their expertise provides critical insights in informing necessary assumptions (UNAIDS/WHO Working Group on Global HIV/AIDS and STI Surveillance et al., 2004). Estimation of the prevalence of substandard and falsified medicine should be led by medicine regulators and ministries of health. We would strongly encourage active consultation with pharmaceutical manufacturers and distributors, insurers, procurement authorities, consumer and patient advocates and professional associations

(for example doctors and pharmacists) in deciding on methods and assumptions. The policies, decisions and behaviours of these actors shape markets and influence the quality of medicines that patients consume (Hasnida et al., 2021). Besides enriching the process, their participation increases the likelihood that estimates will be broadly accepted, and acted upon. However, the motivations and interests of these groups are rarely aligned; careful annotation and transparent publication of all assumptions and data sources used in the estimation process can guard against capture by any interest group, protecting the integrity of the estimates (UNAIDS/WHO Working Group on Global HIV/AIDS and STI Surveillance et al., 2004).

Textbox 3: Steps to estimate the national prevalence of falsified and substandard medicines

Step 1: Conduct risk-based sentinel surveillance for falsified and substandard medicines to obtain prevalence estimates for each sentinel group.

Step 2: Calculate the interaction between sentinel groups.

Step 3: Use market, procurement and regulatory data to estimate the total volumes of medicines in each sentinel group.

Step 4: Apply the prevalence estimates (step 1) to the volume data (step 3) to estimate the total number of substandard medicines across all sentinel groups for substandard medicines, correcting for interactions where necessary. Repeat for falsified medicines.

Step 5: Use market, procurement and regulatory data to estimate the total volumes of medicines in (lower risk) market sub-sectors that do not fall in the sentinel groups.

Step 6: Use all available data sources (e.g. regulatory data, academic studies, case reporting data, data from other countries) to make assumptions about the residual prevalence, comparing with prevalence in sentinel groups. Document each assumption, and, then, estimate the prevalence of substandard and falsified medicines in each sector.

Step 7: Apply the prevalence estimates (step 6) to volumes (step 5) to estimate the total number of poor-quality medicines outside of sentinel groups.

Step 8: Calculate the national prevalence estimate, where national prevalence estimate = (step 4 + step 6)/(step 3 + step 5)

Next steps

The national estimates that result from this process will not capture the full complexity of medicine markets, especially in initial rounds of estimation. However, we think it important to begin to work towards that goal with tools that are most likely to be adopted by regulators in resource-constrained settings. We believe that simple, spreadsheet-based national models which clearly document all data sources and assumptions, and which are based on clearly defined and repeatable sentinel surveillance, are a feasible

and important first step in better quantifying the threat posed by substandard and falsified medicines. Later, more sophisticated models may embrace more complexity, and be expanded to estimate the extent to which these products undermine health and wellbeing, and the damage they do to family and national budgets.

Our suggested methods may seem complex, and the processes may seem institutionally daunting, but, again, we draw inspiration from the experience of HIV surveillance. The current state of information systems for medicine quality closely resembles HIV surveillance systems circa 1995. Many low- and middle-income countries had no system at all. In those that did, incomplete case reporting was the norm; sentinel surveillance focused mainly on pregnant women even in countries where most infections were in men; behavioral risk surveillance was in its infancy; and estimation of population size was unheard of. Meanwhile, most estimates of national prevalence were made by a handful of people working for international organizations, using assumptions that did not reflect the diversity of national epidemics (Pisani, 2008).

Now, the picture is very different. Most countries have developed surveillance systems based around the specific risks that drive their national epidemic and gather data related to risk behaviors and treatment outcomes in ways that are comparable across time. Population size estimation allows for the development of prevalence estimates that are useful in informing programming and measuring risks. Many different sectors cooperate in the implementation of these systems, which are largely country-led (Mahy et al., 2017).

This transition in HIV surveillance was made possible by the vast, disease-specific investments in HIV seen from the early 2000s, investments that were themselves triggered, in part, by findings in countries such as Thailand, an "early-adopter" of risk-based surveillance for HIV. While we do not imagine that similar investments will be forthcoming in the field of medicine quality, we believe that increased national investments in medicine procurement through expanded efforts to achieve universal health coverage will increase the urgency of ensuring that public money is invested in medicines that actually cure patients or prevent disease, rather than in their substandard or falsified doppelgangers. It is, thus, a good time to start building the capacities and systems that will improve the ways in which health systems measure; understand; and, ultimately, curtail the extent and distribution of substandard and falsified medicines.

Prioritizing surveillance approaches for medicine quality

As with infectious disease surveillance, the 2 approaches we have suggested for surveillance of medicine quality—case finding and sentinel surveillance—have different purposes. Case finding aims to pinpoint problems for an immediate response, while sentinel surveillance allows for more reliable quantification of the problem and for the monitoring of the effectiveness of interventions. It is unclear in situations where resources are constrained, which one a regulator should prioritize.

In the short term, especially, from the point of view of the medicine regulator who will be held responsible if substandard or falsified medicines are shown to harm patients, case finding will probably be the more attractive option. This is true despite the fact that case finding is more data intensive and, likely, more technically challenging to implement, because it requires greater specificity to succeed than sentinel surveillance. Case finding is likely to be the more valuable approach in settings where the regulator is well resourced and where substandard and falsified medicines are comparatively rare.

Where it is suspected that falsified and, especially, substandard medicines may be rather more prevalent, however, the calculus changes, at least, from a broader public health point of view. Here, a more robust understanding of the extent of the problem, provided by estimates based on sentinel surveillance, may be more valuable. In such settings, which may include many low- and middle-income countries, the prevalence of substandard and, to a lesser extent, falsified medicines will likely have a system-wide effect on health outcomes, as well as on public and private finances. Only after estimating prevalence can one reliably estimate impact. Robust estimates of impact are politically persuasive and may encourage policy makers to change health financing, procurement, and industrial policies in ways intended to erode the factors that incentivize the production and sale of substandard medicines and to shrink the market for falsified products. In addition, a clear understanding of the magnitude of the problem may prove a powerful argument for adequate resourcing for medicine regulators, especially, in lower-income settings.

We are currently consulting closely with the Indonesian national medicine regulator to trial risk-based case-finding, as well as to plan and implement sentinel surveillance and develop national estimates using the methods suggested in this paper. We welcome challenges to our thinking and suggestions to improve the proposed methods, and look forward to continued debate on the subject.

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Chapter 4.

Assessing the quality of amoxicillin and testing the relationship between medicine price and quality

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Abstract

Objectives
To assess the quality of amoxicillin products in Indonesia's private market by surveying the range of products available across different areas, followed by product sampling and laboratory testing.

Design
A cross-sectional survey employing mystery shoppers to purposively sample the widest possible range of amoxicillin products available to patients across different areas in Indonesia.

Setting
Licensed and unlicensed medicine outlets in remote, rural and urban areas and online.
Participants
Amoxicillin products that are sold to patients as oral solid and dry liquid formulations.

Main outcome measures
Quality of amoxicillin products, assessed using compendial testing of active pharmaceutical ingredient content and dissolution. Samples that failed any quality test were classified as substandard or out-of-specification (OOS). The raw prevalence of substandard amoxicillin was adjusted based on the national market volume of each product variant.

Results
We surveyed 476 outlets, mostly pharmacies (68.5%), websites (19.7%) and drug stores (10.9%). Among the 120 collected samples, there were 59 distinct products, collectively representing 95% of the estimated market volume for oral solid products and 65% for dry syrups. 12 out of 110 oral solid samples tested OOS (10.9%), as did 3 out of 10 dry syrups (30%). The samples that failed originated from various areas and types of outlets. We found no relation between the price and quality of amoxicillin.

Conclusions
The oral solid amoxicillin products that tested OOS represent an estimated 12.7% of the national market volume. We found no relation between the price and quality of amoxicillin. Combining product-variety sampling with data on market volume presents a promising approach to gain insight into the prevalence of poor-quality medical products using a relatively small sample size.

Introduction

Substandard and falsified medicines pose a threat to patient health, lead to waste of resources, undermine confidence in health systems and contribute to antimicrobial resistance (Newton et al., 2010). Substandard, often referred to as 'out-of-specification,' denotes an authorized product that fails to meet either its quality standards, specifications, or both. Falsified medicines deliberately or fraudulently misrepresent their identity, composition, or source (World Health Organization, 2017). Despite an increased focus on medicine quality prompted by alarming incidents (Lateef, 2023; Schier et al., 2023; WHO, 2023), robust evidence about the prevalence of poor-quality medicines remains scarce (Pisani et al., 2021; Rasheed et al., 2023).

Medicine regulators are tasked with assuring the quality, safety, and efficacy of medicines on the market by routinely sampling and testing products that are available to patients (United States Pharmacopeial Convention, 2021). It is essential that regulators sample medicines at the point where patients get them, as poor storage and distribution practices may lead to the degradation of medicines along the supply-chain (Yong et al., 2015) and outlets may also sell expired, unauthorized and falsified products (Fernandez et al., 2011).

Regulators face many challenges in conducting effective post-market surveillance. They have to choose which products are most at-risk, collect them from the market, and conduct quality tests (USP Promoting the Quality of Medicines, 2018). In most countries, thousands of medications have received market authorization. For most medicines, there are multiple product variations on the market. For examples, amoxicillin is available in diverse forms (tablets, capsules, dry syrup) and varying strengths (250 mg, 500 mg, 1000 mg). Multiple companies manufacture amoxicillin, with some marketing it under distinct brand names, and others offering an unbranded generic option.

After a regulator decides to sample a specific product variation, the subsequent operational challenge is sampling that product in the market (United States Pharmacopeial Convention et al., 2018). The sales volume and distribution of product varieties can vary significantly. Some products have large market volumes and are sold across the country, while others may be sold in small volumes and available only in specific areas.

Since medicines may degrade along the supply chain (Yong et al., 2015), regulators also need to choose from which location, market segment, and type of outlets they will sample (United States Pharmacopeial Convention et al., 2018). A private pharmacy in a bustling metropolis, a small clinic in a remote village, or an outlet that is not licensed to sell prescription-only medicines, which could be a drug store, market vendor, health workers or a website (Jean-Baptiste et al., 2020; Vida et al., 2017). Testing the quality of medicine in the laboratory is also not straightforward, as there are different testing parameters and quality standards. Meanwhile, many regulators struggle to perform

their routine tasks due to high cost of testing and insufficient human, financial and physical resources and a lack of enforcement capacity (Twesigye et al., 2021; United States Pharmacopeial Convention, 2021; WHO, 2018).

The different factors that make post-market surveillance challenging are all present in Indonesia. Its 278 million citizens (Indonesia, 2023) are spread across 7,000 inhabited islands (Ministry of Foreign Affairs of Indonesia, 2018). The pharmaceutical market is huge. There are over 19,000 registered pharmaceutical products (National Medicines Regulatory Authority of Indonesia, 2023c), produced by 225 manufacturers of which 88% are domestic companies (Pharmaboardroom, 2017). Most manufacturers are located on Java Island in the center of the country (National Medicines Regulatory Authority of Indonesia, 2023a), from which there are complex supply chains to the outer islands of the archipelago, which can be thousands of kilometers away (Fanda, Probandari, Kok, et al., 2024; Fanda, Probandari, Yuniar, et al., 2024). Medicines are provided to patients by roughly 10,100 primary health centers, 3,100 hospitals and sold in 22,000 authorized retail pharmacies (Indonesia, 2020; Wulandari et al., 2021). In addition, there are 10,800 registered drug stores that are allowed to dispense over-the-counter medicines, but often also sell prescription-only medicine, such as antibiotics (Ferdiana et al., 2021; Wulandari et al., 2021).

The vibrant private sector plays a large role in the direct provision of medicines to patients. While most Indonesians have social health insurance and are entitled to free essential medicines from public facilities, 79% of expenditures on medicines is still paid out-of-pocket to private outlets (WHO Regional Office for South-East Asia, n.d.). Patients are driven to private outlets because public facilities are out of stock (Soewondo et al., 2020) or difficult to reach (Pratiwi et al., 2021) or overburdened, leading to longer waiting times (FHI 360, 2019). Patients also choose to buy medicines from private outlets because they believe the more expensive branded medicines are of higher quality (Hasnida et al., 2021; Pisani et al., 2022).

Despite the widely documented incidents – such as falsified vaccines in 2016 and contaminated cough syrup in 2022 (Karmini & Mason, 2016; Telegraph, 2022)- there are very few studies assessing the quality of medicines available to patients in Indonesia, particularly in the private sector (Dewi et al., 2022; Pisani et al., 2024). In this study, we focus on amoxicillin trihydrate, the most widely used antibiotic in outpatient settings (Akhavan et al., 2022), including in Indonesia (Limato et al., 2022). As in many countries, hundreds of amoxicillin products are authorized for the Indonesian market (National Medicines Regulatory Authority of Indonesia, 2023c). Ensuring their quality is crucial, as substandard antibiotics not only pose risks to patients' health but can also contribute to the escalation of antimicrobial resistance (Zabala et al., 2022).

To our knowledge, there are no studies that purposively examine the variety of products of a specific antibiotic that are available to patients within a country, taking into account brand variations, market volume and type of outlets, to test their quality.

The aim of this study is to assess the quality of amoxicillin within the Indonesian private market by examining the diversity of products sold across different areas and various types of medicine outlets. Additionally, we analyzed the market volume of the tested products and assessed the relationship between the price and quality of amoxicillin.

We focused on the private sector, as this is where the majority of patients obtain their medicines and we expected to encounter the widest variety of available products. In four different regions and the online market, we surveyed the range of product available and purposively sampled the widest possible variety of amoxicillin products. Subsequently, we conducted pharmaceutical analysis to evaluate their quality. This included assay testing to quantify the percentage of active ingredients and dissolution testing to determine if the products released the active substance in a timely manner (Davani & Bhattacharyya, 2005; Koech et al., 2020; United States Pharmacopeia, Undated).

Methods

Methods are described following the Medicine Quality Assessment Reporting Guideline (Newton et al., 2009) (online supplemental file 1). Our study design is a cross-sectional survey of product varieties, prices, and pharmaceutical quality testing analysis.

Study medicine

Our study focused on amoxicillin, considering its public health importance, as it is among the antibiotics with the highest utilization in Indonesia (Limato et al., 2022). Poor-quality amoxicillin might also trigger antimicrobial resistance (Cavany et al., 2023), a true concern in the country (WHO Indonesia, 2023). In addition, many amoxicillin products are registered with different price points (Alfajri & Diveranta, 2024; National Medicines Regulatory Authority of Indonesia, 2025), enabling us to examine the product variety and medicine prices and assess their quality. We also discussed our study design with the Indonesian medicine regulators (Hasnida et al., 2025), who suggested including amoxicillin based on their previous inspection records.

Samples definition

We defined a single sample as one finished pharmaceutical product (with amoxicillin as active pharmaceutical ingredient/API), of one dosage (strength and form), of one brand, from one manufacturer, and collected at one location, at one time) (WHO Expert Committee on Specifications for Pharmaceutical Preparations, 2016). We classified medicine types as branded generics and unbranded, International Nonproprietary Name (INN) generics.

Sampling areas and types of outlets

Samples were collected between November 2020 and November 2021 in four geographic regions and online (online supplemental file 2). Based on the initial assumption that

the long chain of medicine supply might introduce degradation risks (United States Pharmacopeial Convention et al., 2018), we purposively selected four different areas: remote (East Nusa Tenggara province/NTT), semirural (Malang district in East Java province) and two urban areas of the Greater Jakarta region (Jakarta and the satellite city Bekasi). In the remote and semi-rural districts, we visited one location with a larger population (e.g., provincial capital) and one with a smaller size (e.g., district or administrative city).

Our sampling encompassed both licensed outlets, such as pharmacies, and outlets not authorized to sell prescription-only medicines, including drug stores, health providers, and online platforms. The distribution of outlets varied across sampling areas, determined by outlet availability in each region and the feasibility of on-site visits. We located these outlets by cross-referencing medicine outlet directories from the sub-national health authorities with empirical location mapping from previous surveys (Dewi et al., 2022; Ferdiana et al., 2021) and by conducting product searches on various Indonesian online marketplace platforms. In the Greater Jakarta area, our sampling of drug stores focused on two concentrated medicine trade areas (Kompas, 2015). For online sources, we specifically selected unlicensed vendors without permission to trade prescription-only medicines.

Secondary data collection and analysis

To prepare for sampling, we started by creating a sampling plan with an overview of the different amoxicillin products in the Indonesian market and the market volume for each distinct product. We combined data about registered medicines from the public regulatory database (National Medicines Regulatory of Indonesia, 2016-2018) and the products listed in public procurement data (National Procurement Agency, 2018) and obtained market data from IQVIA, a pharmaceutical data services firm (IQVIA MIDAS ® Quarterly Sales Data from 2020, which were obtained under licensed from IQVIA and reflect estimates of market activity). These MIDAS data estimate market sales volumes and list prices of most amoxicillin products in the Indonesian market. We used the Indonesian Total Market Audit data, which estimates product supply by combining the actual sales from pharmaceutical companies with sales projections from retail channels such as pharmacies, drug stores, and hospitals.

Amoxicillin forms

We defined form as the way a medicine is presented (European Medicines Agency, n.d.). We chose to focus on oral solid products (tablets and capsules) as these have the highest estimated market volume in the Indonesian market. In the final stage of the data collection, an expert from the World Health Organization suggested including dry syrup as well. We collected 10 dry syrup samples, only in the Greater Jakarta area.

Sampling strategy

We aimed to collect a total of 120 samples. Initially, we planned to target preselected amoxicillin products that had specific risk factors for being substandard, based on our

previous assessments (Pisani et al., 2021), and collect an equal number of samples in each area. In the first area, we learnt that the variety of products available from outlets was very limited. We, therefore, decided to focus our sampling strategy on purposively collecting the largest possible variety of amoxicillin products available on the market, which we will refer to as product variety sampling. The total sample size (N=120) is based on the maximum feasible budget for sampling and pharmaceutical analysis. We expect this sample size to cover around 90% of the estimated market share.

Prior to sampling, the data collectors surveyed product variety by recording all brands and dosage forms sold in a particular outlet. In each new area, we focused on trying to sample new product varieties. In case a product was available from a different type of outlet we would sample it again (e.g., brand X in area 1 from a pharmacy, and brand X in area 2 from an unlicensed drug store). For dry syrup, we collected each different brand for each sample based on the availability at the outlet (N=10).

Product survey and sample collection

In each area, we recruited local enumerators with experience in health research (17 in total). We trained them for 2 days on the purchasing methods using vignettes, samples handling, storage, and delivery. We also prepared medical prescriptions to collect the samples as necessary.

On arrival at the sampling outlet, data collectors asked which amoxicillin products were sold, which they recorded on their mobile phones. If asked regarding specific symptoms by the pharmacists or storekeepers, they responded by presenting a case of acute sore throat that persisted for more than 3 days, either for themselves or another family member (for their child in the case of dry syrup samples). Only on request, they provided the prescriptions.

To select which products to sample, the enumerators referred to a daily sampling plan of targeted product varieties yet to be collected.

To meet the technical requirements of pharmaceutical analysis, for each sample the enumerators aimed to purchase 40 tablets or capsules (usually in 4 foil strips or blisters) or 5 bottles of dry syrup. When there were no new variations available at the outlet, or the quantity of the available product was less than the minimum units required, the enumerators left the outlet without any purchase.

The enumerators recorded the collected samples data on an open-source mobile application called KoBo Collect (Kobo Inc., 2022). Data about the details of the outlet and sampling location were recorded on site. Product details were completed in the field office (forms are available in online supplemental file 3). Data collectors visually inspected the samples using a magnifying glass to inspect any damaged packaging.

Sample handling and storage

We labelled each sample with a unique barcode. Each sample was stored in a zipper bag labelled with a barcode, the date of data collection, and sampling location. We stored the samples in tight containers before pharmaceutical analysis following the procedure of proper amoxicillin storage at controlled room temperature (United States Pharmacopeial Convention, n.d., p. 42). We included a temperature data logger in the container. The identity, quantity, and expiry dates of the samples were verified again by the laboratory personnel.

Pharmaceutical analysis

Samples were tested at PT Equilab International in Jakarta, a private laboratory certified with ISO/IEC 17025, referring to the US Pharmacopoeia (USP) 42 National Formulary 37 (United States Pharmacopeial Convention, n.d., p. 42) from December 2020 – January 2022 on average 93 days (17-331 days) after sample collection. The laboratory validated all methods for all dosage forms before testing (detailed testing protocol is in online supplemental file 4).

The laboratory staff performed visual inspections by examining the physical attributes of each sample, for example, color and shapes of the tablets or bottles of the dry syrups. We conducted assay testing to quantify the percentage of active ingredients and dissolution testing to determine if the products released the active substance in a timely manner (Davani & Bhattacharyya, 2005; Koech et al., 2020; United States Pharmacopeia, Undated).

Assay and dissolution were performed using HPLC-UV (Waters Alliance 2695, with UV Detector 2489), Spectrophotometer (Shimadzu, UV-1800) and Dissolution Tester with USP Paddle All-Teflon 15" Long. Per protocol, the staff handling the packaged samples was different from the staff conducting the tests. All samples (N=120) were tested in terms of simple visual inspection and assay. Dissolution was only performed on solid dosage forms (tablets and capsules).

The laboratory staff used the sample barcodes throughout the testing procedure. The research team and a quality assurance adviser reviewed the raw measurement data and certificates of analysis. The quality testing parameters and compliance standards are summarized in online supplemental file 5. Q is the targeted amount of active ingredient, expressed as a percentage of the labelled content of the dosage unit, which should be dissolved within a certain time (United States Pharmacopeia, Undated).

Following USP42 NF37, we considered a sample as out-of-specification (OOS) if it falls into any of these following categories:

- Assay results are outside the stated limits.
- Dissolution stage 1 result shows each unit is lower than Q + 5%.
- Dissolution stage 2 average result of 12 units is < Q, and at least a unit <Q – 15%.

- More than 2 units are <Q-15%, and at least a unit is <Q – 25%.

Given the limited number of tablets, capsules or bottles of each sample that can be collected using mystery shopping, we performed dissolution stage 1 and 2 (United States Pharmacopeia, Undated). The assay protocol was adjusted and validated using two units of tablets instead of five as stated in USP 42 NF 37. This testing protocol was designed in consultation with experts from USP and in line with a review indicating a minimal likelihood of atypical performance in stage three for products that pass stages 1 and 2 (Marroum, 2014).

Medicine prices and quality assessments

When purchasing the samples on-site, the enumerators recorded the price they paid in the respective outlets on the KoBo collect, later referred to as the patient purchase price. Price was analysed in the smallest counting units, e.g., per capsule or tablet for oral solid dosage forms and 5 mL for dry syrups. As we captured the actual price paid in the market, no reference prices were used in this study.

Data management and analysis

Data were analyzed using STATA MP V.18. For five oral solid products, market volume data were unavailable. To address this, we performed imputation using the median of all sampled oral solid products.

To get an indication of the prevalence of poor-quality amoxicillin in the private market, we weighted the results by the sales volume of each product. For each product, we multiplied the percentage of samples that failed a quality test by the market volume of that product. To examine the relationship between price and quality, we conducted logistic regression. The independent variable was the price paid by patients (selling price, which we calculated per standard counting units for tablets and dry syrup) sourced from our empirical mystery shopping survey, and the dependent variable was the outcome of pharmaceutical analysis, indicating whether the product was within or outside of specification. We also conducted logistic regression to study the relationship between the estimated market volume for oral solid products (independent variable) and at least the one-time failure of pharmaceutical analysis (dependent variable).

Ethical clearance

This study has obtained the ethical approval from the Ethics Committee of the Faculty of Medicine, University of Indonesia number KET-354/UN2.F1/ETIK/PPM.00.02/2019. The study protocol was discussed with the National Medicines Regulatory Authority.

Patient and public involvement

We did not involve patients in this study. We consulted the study design with the Indonesian National Medicine Regulatory Authority (NMRA) in a series of meetings prior to the empirical data collection between July and October 2019.

Results

Amoxicillin product variety in the Indonesian market

At the beginning of 2020, the Indonesian regulator had authorized 185 amoxicillin products for the market, including 104 different oral solid products (tablets or capsules) and 81 different dry syrup products. The oral solid products were available in 250, 500 and 1000 mg tablets and capsules, while dry syrups were available as 125 and 250 mg/5 mL.

Pharmaceutical market data provided the sales volume estimates for 174 products (95 oral solid and 79 dry syrup) (illustrated in online supplemental file 6). The estimated market volume of the oral solid products was 359 million doses and 97 million doses of dry syrups. The market leader was accounting for 24.3% of the volume of oral solid products and 7.1% (dry syrup) of the total market share. Branded generics products dominated both dosage forms (66 out of 95 oral solid and 59 out of 79 dry syrups).

Visited outlets, product variety identified and sampled

In total, we visited 476 outlets in the four sampling areas and online (details are in online supplemental file 7). We started our data collection in the remote NTT area, where the availability of drug stores was notably limited. Through visits to 47 outlets, we gathered 14 samples encompassing seven distinct amoxicillin product varieties. In the second area (East Java), we visited 132 outlets, identified 38 different products, most of which were not present in the first sampling area. We gathered 34 samples, including 27 distinct products. In the third area (Jakarta), we visited 144 outlets, including 43 drug stores, from which we accumulated 29 samples, introducing ten new product variations into our dataset. Moving on to Bekasi, a satellite city of Jakarta, we identified a total of 31 distinct products and bought 18 samples. As a final step, we conducted targeted online searches to buy any additional product varieties available. Through online sources, we pinpointed an additional nine new products, and bought seven of them.

In total, we identified 57 different oral solid products in the four sampling regions and online and collected 49 different product varieties. Eight products were not sampled because they were not sold in sufficient quantities for pharmaceutical analysis (minimum 20 tablets) or online vendors did not respond to our attempts to order products.

Description of collected samples

We collected samples as finished pharmaceutical products. In total, we collected 110 oral solid samples in the four sampling areas and online as summarized in Table 1. This encompasses 59 different varieties of amoxicillin products, and in several cases, multiple samples of the same product variety, gathered from different types of outlets. In the fourth sampling area, we also collected ten dry syrup samples, leading to a total of 120 samples. Most samples (93.3%) were obtained without medical prescriptions, and almost all samples (99.2%) were manufactured in Indonesia. We had no information about the

source of APIs in each sample. We collected one sample from an online vendor that had no information about the country of origin. In accordance with an agreement with the Indonesian medicine regulator, we are not able to report the brands or manufacturers of the tested samples.

Table 1. Descriptions of collected samples

Categories	Frequency	Distinct products*
Total collected samples	120	59
Products characteristics as labelled		
Un-branded/INN generic products	28 (23.3%)	12 (20.3%)
Branded generic products	92 (76.7%)	47 (79.7%)
Dosage forms		
Capsule 250 mg	7 (5.8%)	2 (3.4%)
Capsule 500 mg	18 (15%)	5 (8.5%)
Tablet 500 mg	83 (69.2%)	40 (67.8%)
Tablet 1000 mg	2 (1.7%)	2 (3.4%)
Dry syrup 250 mg / 5 ml	2 (1.7%)	2 (3.4%)
Dry syrup 125 mg / 5 ml	8 (6.7%)	8 (13.6%)
Packaging		
Strip	109 (90.8%)	48 (81.4%)
Blister	1 (0.83%)	1 (0.83%)
Bottle	10 (8.3%)	10 (8.3%)
Other characteristics**		
Split batch (>1 batch numbers)	8 (6.7%)	N/A
Damaged packaging	2 (1.7%)	N/A
Obtained from air-conditioned outlets	22 (21%)	N/A
Collected without prescriptions	112 (93.3%)	
Manufacturing		
Domestic producer (Indonesia)	119 (99.2%)	58 (98.3%)
Origin unknown	1 (0.8%)	1 (1.7%)

*Distinct product: one amoxicillin brand, of one dosage, in tablets or capsules or dry syrups, and from one manufacturer

**Distinct products are not applicable for these categories since one product can have multiple versions of characteristics

Pharmacopeial testing results

All samples were identified as amoxicillin and no samples were entirely depleted of amoxicillin or contained a different API. The visual inspection reported no crushed solid forms in their primary packaging. There was one dry syrup sample with suspension powder which leaked in a bag separate from the primary packaging (bottle).

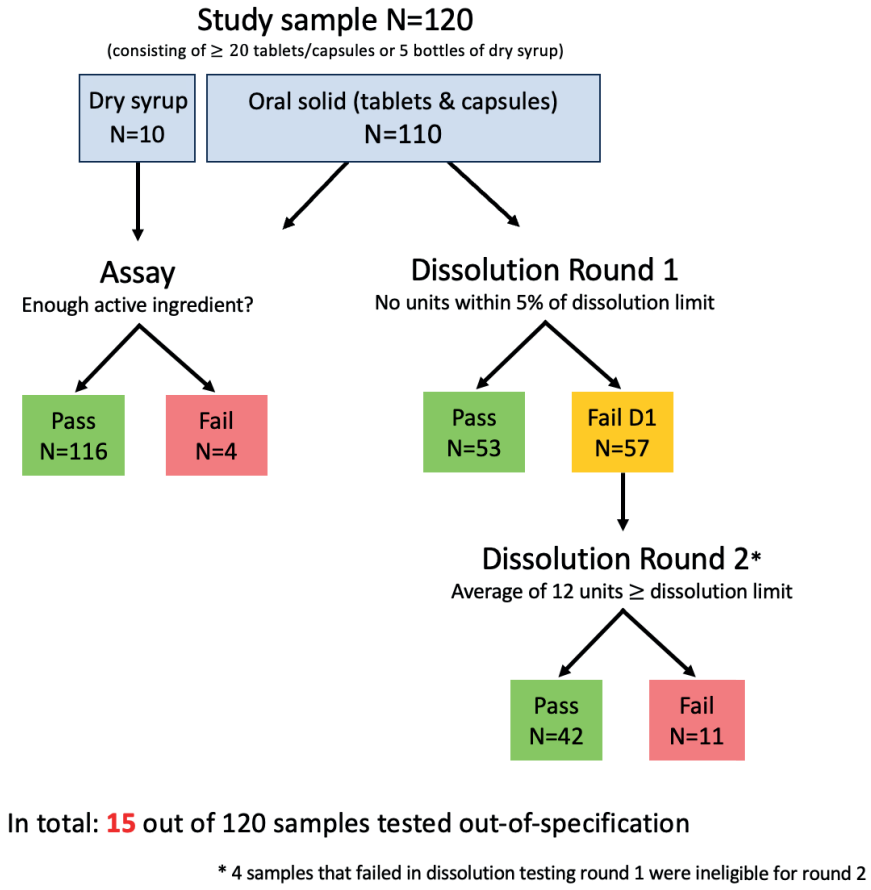

Figure 1. Flowchart of pharmaceutical analysis and results

Figure 1 provides a flowchart of the assay and dissolution testing and an overview of the results. Four out of 120 samples tested out-of-specification (OOS) on assay, three of which were dry syrups. All 110 oral solid samples were tested in stage 1 dissolution testing. 57 samples failed in stage 1, but we only included 53 in stage 2 testing. Four samples had to be excluded for the second round, as insufficient tablets or capsules were available (N=1) or samples beyond their expiry date (N=3). Of the 53 samples that were tested in dissolution stage 2, 11 samples were OOS. In total, we report that 15 out of 120 samples were OOS (12.5%). The OOS samples were tested on average of 700 days (113-1,026 days) before their expiry date for assay and 587 days (-1-920 days) for dissolution stage 2.

The OOS samples in assay consist of the following dosage forms: tablets 500 mg, dry syrup 250 mg/5 mL and dry syrup 125 mg/5 mL (N=2). The dosage forms of the eleven samples that were OOS in dissolution testing were: 250 mg capsule (N=1), 500 mg capsule (N=1), 500 mg tablets (N=9). The sample without information on manufacturing country or market authorization number did meet both the assay and dissolution specifications criteria. The dry syrup sample with leaked powder failed in assay with the lowest percentage of labelled amoxicillin (72.8%).

We found OOS samples in both licensed and unlicensed outlets as summarized in Table 2. We only collected dry syrup samples in Jakarta and Bekasi. We sampled the most from pharmacies where we found the highest numbers of OOS samples (12.1% for oral solid and 60% for dry syrup). Out of two OOS oral solid samples purchased from online vendors, one tablet has the lowest dissolution percentage (45.2%, well below the minimum of 75%). None of the samples that failed a laboratory test came from the most remote area (NTT). Bekasi had the highest proportion of OOS samples both for oral solid (16.7%) and dry syrups (50%). One of the fifteen samples that tested OOS came from a split batch.

Table 2. Proportion of quality testing outcomes by sampling areas & types of outlets

Oral Solid Dosage Forms			
By sampling regions			
Regions	**Total samples collected (N=110)**	**Meet specification**	**Out-of-specification (OOS)**
Jakarta	29	25 (86.2%)	4 (13.8%)
East Java	34	31 (91.2%)	3 (8.8%)
Bekasi	18	15 (83.3%)	3 (16.7%)
Online	15	13 (86.7%)	2 (13.3%)
East Nusa Tenggara (NTT)	14	14 (100%)	0 (0%)
By types of outlets			
Outlets	**Total samples collected (N=110)**	**Meet specification**	**Out-of-specification (OOS)**
Pharmacies	66	58 (87.9%)	8 (12.1%)
Drug stores*	25	23 (92%)	2 (8%)
Health providers (i.e., physicians & midwives)*	4	4 (100%)	0 (0%)
Online vendors*	15	13 (86.7%)	2 (13.3%)
Dry Syrup Dosage Forms			
By sampling regions			
Regions	**Total samples collected (N=10)**	**Meet specification**	**Out-of-specification (OOS)**
Jakarta	6	5 (83.3%)	1 (16.7%)
Bekasi	4	2 (50%)	2 (50%)
By types of outlets			
Outlets	**Total samples collected (N=10)**	**Meet specification**	**Out-of-specification (OOS)**
Pharmacies	5	2 (40%)	3 (60%)
Drug stores*	5	5 (100%)	0 (0%)

**Unlicensed outlets to sell antibiotics*

Figure 2 provides the estimated share of market volume of the sampled amoxicillin products and the volume of the products that tested OOS in pharmaceutical analysis. Figure 2 shows that the 49 distinct amoxicillin products we sampled represent 95.3% of the estimated market volume for oral solid products. There were five distinct products for which at least one sample tested within specification and at least one sample tested OOS.

After imputing the estimated market volume of one OOS product (2.4 million) and weighting the frequencies of testing failures (per product), we calculated the estimated total volume of out-of-specification branded oral solid products in the private market to exceed 46 million, constituting 12.7% of the total private market. We found no relation between the estimated market volume of oral solid products and quality outcomes (OOS on assay and dissolution) (OR=1, 95% CI 0.99 to 1.00).

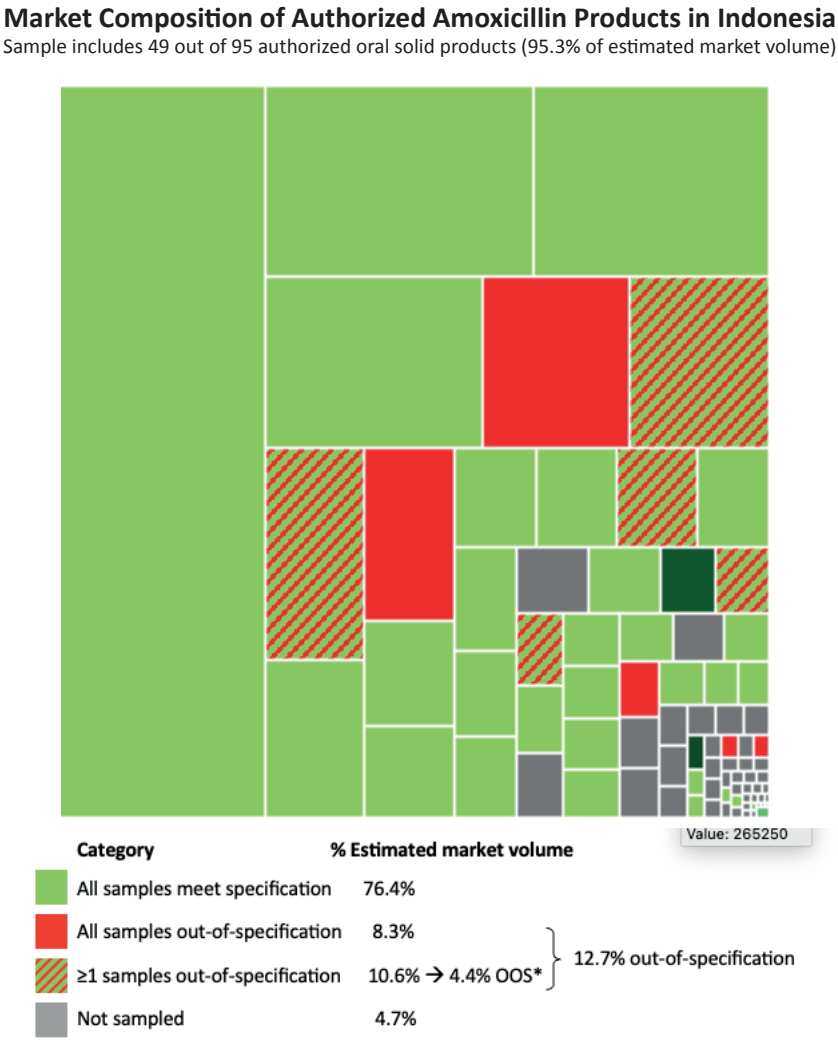

Figure 2. Estimated market volume of amoxicillin oral solid products (N=95) sold in the Indonesian market from October 2019-September 2020; mapped to sampled and tested products. *after weighting for % of sampled product that tested OOS. Source: This is based on internal analysis by (Hasnida et al., 2025) using data from the following source: IQVIA MIDAS Quarterly Sales for the period (October 2019-September 2020) reflecting estimates of real-world activity.

Online supplemental file 8 provides the estimated share of market volume of the 10 dry syrup products that we sampled. Two OOS products in assay (N=2) had low market volume and one had no market volume data, hence, these are not indicated in this figure.

Medicine prices and quality outcomes

There were large variations in the patients purchase price of amoxicillin. Calculated per tablet or capsule, the cheapest amoxicillin product of 250mg cost IDR400, while the most expensive cost IDR2525. Large price variations were also found for 500 mg (IDR320 – IDR6500) and 1000 mg (IDR7000 – IDR14286). For dry syrup, the price also varied significantly (per 5 mL) for both 125 mg (IDR292 - IDR1917) and 250 mg (IDR458 – IDR833).

Figure 3 provides two scattered plots of ratio for each medicine price to cheapest per dosage forms in log scales for assay and dissolution test, respectively. We found no relation between the price of amoxicillin and quality outcomes (OOS on assay or dissolution) (OR=1, 95% CI 0.99-1.00).

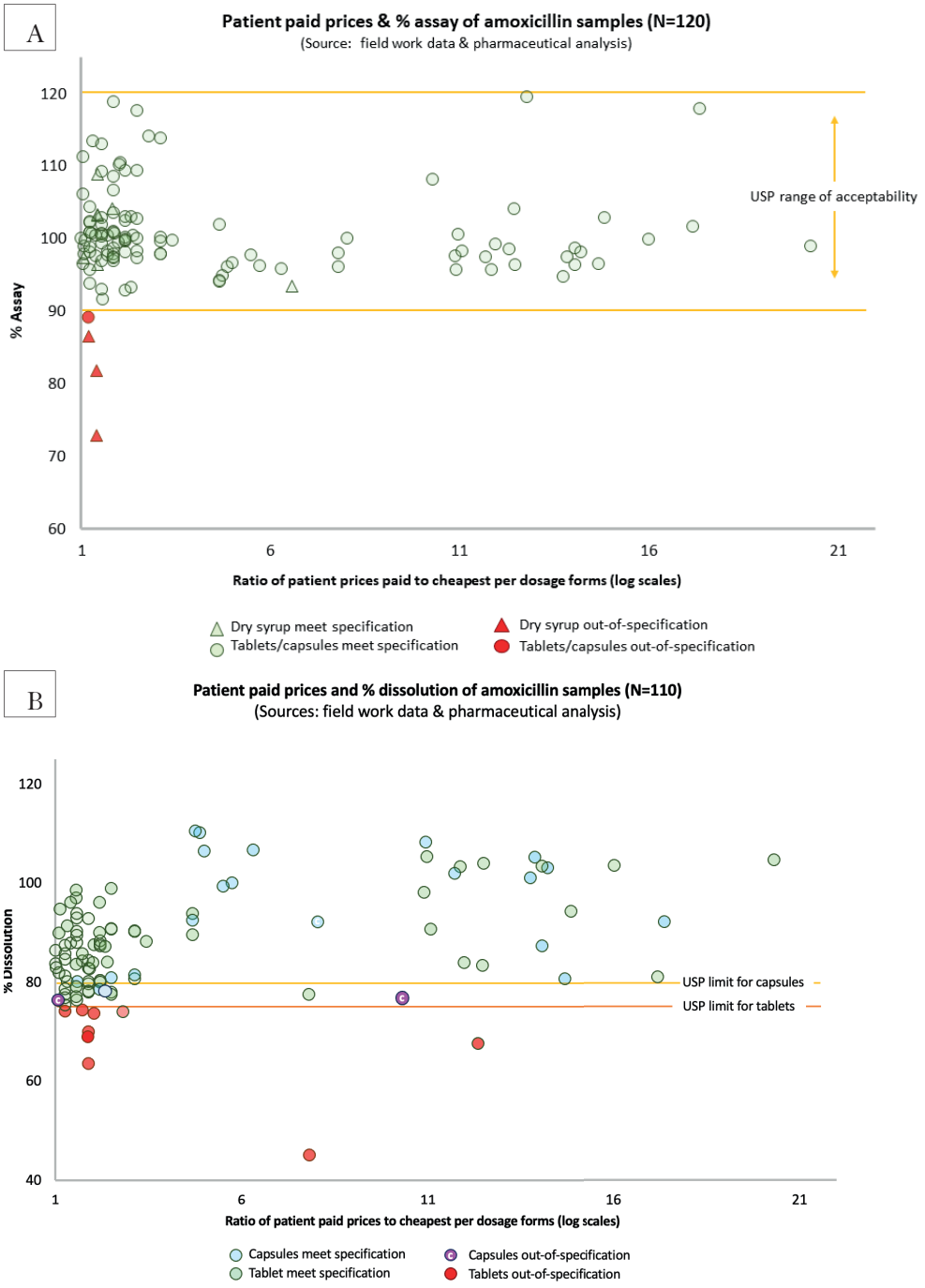

Figure 3. Scattered plots of ratio of patient paid prices to cheapest per dosage forms and percentage of assay testing results (N=120) (figure 3A, above) or dissolution (N=110) (figure 3B, below)

Discussion

Our study assesses the quality of amoxicillin available in the Indonesian private market by examining a large variety of products sold in different areas and from different types of outlets. We surveyed 476 outlets and collected 120 samples that include 59 different products. These 59 products make up 95.3% of the estimated market volume for oral solid products and 65.2% for dry syrups. 15 out of 120 samples (12.5%) tested out-of-specification, of which 4 samples failed in assay and 11 in dissolution. The samples that failed came from different areas and types of outlets. We found no relation between the price of amoxicillin and the results of quality testing. We did not identify any samples indicative of falsified medicines (eg, those completely lacking amoxicillin or containing an alternative API).

The percentage of samples testing out-of-specification (N=15/120) needs to be carefully interpreted. Most failed samples were within 10 percentage points of the allowed limits for assay or dissolution. While the threat to individual patients may be confined to only the lowest-scoring products, the danger posed by substandard antibiotics is substantial (Zabala et al., 2022).

Insufficient amounts of APIs or poor dissolution features could contribute to the development of antimicrobial resistance (Cavany et al., 2023), a significant concern given the hundreds of millions of amoxicillin doses consumed annually in Indonesia. Amoxicillin is frequently identified as a poor-quality antibiotic in surveys in other countries (Kelesidis & Falagas, 2015). Comparing our results to data from the Indonesian medicine regulator is not possible. While the regulator implements a proactive post-market surveillance program, it does not release disaggregated results of quality per medicine (National Medicines Regulatory Authority of Indonesia, 2023b).

A particular concern is that 3 out of 10 dry syrup samples tested OOS in the assay. Dry syrup amoxicillin is commonly prescribed for pediatric patients who face challenges in swallowing tablets or capsules. Its liquid form allows for easier administration, making it a suitable choice for young patients who require accurate doses. Prior studies have predominantly focused on the quality of tablets and capsules, with limited attention to dry syrup formulations (Fadeyi et al., 2015; Hegazy, 2021; Kyriacos et al., 2008). We urgently recommend a more detailed examination of the quality compliance parameters for dry syrup formulations, particularly in larger sample sizes. Additionally, more research with experts such as pharmaceutical scientists and chemists is paramount to understanding the technical factors behind the quality testing results of amoxicillin in liquid formulations (Markman et al., 2014), including dry syrups or adding more evidence on dissolution testing in general (Gabel et al., 2024; Pisani, 2015).

In terms of methodology, our sampling strategy, which focused on collecting the broadest variety of products available to patients from private outlets, offers insights

into distribution variability. Previous studies assessed the quality of various medicines in Indonesia but did not focus on product variability in their sampling strategies (Dewi et al., 2022; Hadi et al., 2010; Khairani et al., 2024; Pisani et al., 2024). Amoxicillin products were not evenly distributed across the four sampling areas and the online market. In our initial and most remote sampling area, we found a very limited variety of available products. In the subsequent areas, we found a much larger variety of products. Despite an open market system, it is worth noting that almost all of the samples collected were manufactured locally, indicating that Indonesia has a large domestic pharmaceutical production to meet national demand (Pharmaboardroom, 2017).

The combination of product-variety sampling and data about the market volume of distinct products enables the use of a relatively small and focused sample (110 oral solid samples, including 49 out of 95 authorized oral solid products) to provide an indication of the quality of a substantial portion of the estimated market volume (95.3%). The 12 oral solid samples that tested OOS account for an estimated 12.7% of the market volume, equivalent to over 46 million doses.

An advantage of our sampling strategy is its focus on the most informative samples, a crucial consideration given the expense of testing the quality of medicines (Valente de Almeida et al., 2024). However, as demonstrated in our results, it is noteworthy that multiple samples of the same product could yield different quality testing results. This underscores the importance of further investigation into the factors influencing product quality, including batch-to-vatch variation and product degradation in the field.

One of the challenges in assuring medicine quality is that poor handling, storage, and distribution practices along the supply chain can lead to product degradation. We anticipated that, due to lengthy and vulnerable supply chains, products sold in more remote areas and unlicensed outlets were more likely to test OOS (United States Pharmacopeial Convention et al., 2018). Our results do not support this hypothesis. While we observed notable variation in the results of quality testing between areas and types of outlets, our sampling strategy focused on product variety and was not designed to compare differences between areas and outlet types.

The proportion of OOS samples recorded in this study should not be interpreted as a prevalence estimate of all substandard amoxicillin across Indonesia. Our study specifically focused on tablets and capsules available to patients in private outlets, representing an estimated market volume of approximately 340 million doses per year. While public sector facilities are supplied by the same manufacturers, they may source from a smaller number of manufacturers, making challenging to generalize our findings (Pisani et al., 2024).

Our study illustrates the potential of combining product-variety-sampling with market volume data, indicating how a relatively small and focused sample can provide insight into a significant portion of the market volume. Before proposing this approach to

regulators as an efficient post-market surveillance strategy, we recommend comparing results from different sampling approaches and conducting further analysis of the extent to which a sample, consisting of four different primary packaging and forty tablets or capsules, accurately represents a product.

A recent study in Indonesia reported that health workers, regulators, and medicine producers share concerns that the pressure to reduce medicine prices in the public sector could lead to an increase in the exposure to poorly produced substandard medicines (Hasnida et al., 2021). Patients are also inclined to buy more expensive versions in the private market, assuming they are of better quality. We found no relationship between the price of amoxicillin and the results of assay and dissolution testing. This finding aligns with recent studies conducted in Indonesia and elsewhere, suggesting that significant savings could be achieved by procuring relatively cheaper product varieties (Bate et al., 2011; Ochekpe et al., 2010; Pisani et al., 2023).

Our study also identified several problematic practices related to the provision of antibiotics that align with previous research in Indonesia and elsewhere (Jean-Baptiste et al., 2020; Schäfermann et al., 2018; Wulandari et al., 2021). Mystery shoppers, also known as simulated patients, have frequently been used to purchase medicine samples in outlets (Newton et al., 2009), including unregulated channels (Dewi et al., 2022; Hadi et al., 2010; Tabernero et al., 2022; Wulandari et al., 2021). In the majority of outlets (94.6%), our mystery shoppers did not require a medical prescription when purchasing antibiotics. Additionally, amoxicillin was easily accessible in unlicensed outlets, including drug stores where selling antibiotics is prohibited. We also found that amoxicillin was readily available from numerous unlicensed online vendors, one of which provided the sample exhibiting the lowest dissolution profile.

Previous studies have mainly highlighted online purchases from unlicensed platforms with the associated risk of falsified and illegal medicines (Dean et al., 2010; Sanada et al., 2020; Zhu et al., 2020). Our study shows that this illicit practice also carries the risk of exposure to substandard products (Wang et al., 2015; Westenberger et al., 2005). Our results underscore the need for increased attention to counteract the unauthorized provision of antibiotics by unlicensed and online outlets. Addressing this issue requires collaboration among government agencies at both national and local levels. A key step is to prevent patients from resorting to unlicensed outlets by ensuring that medicines are adequately available in public facilities (Hasnida et al., 2021; Nistor et al., 2023). Another promising strategy involves leveraging technology to increase transparency regarding medicines procurement, supply chain, and availability (Parmaksiz et al., 2020).

Strengths and limitations

The strength of the study lies in the comprehensive survey of a substantial number of outlets (N=476) across four areas, including licensed, unlicensed, and online vendors, and the diverse sample of amoxicillin products in the private market that represents 95% of the total market volume. The first limitation of this study is that although the 120 collected samples include 59 different products covering 95% of the estimated total market volume, numerous oral solid products authorized for the Indonesian market were still not included, including those in the public channels. Second, we only collected 10 dry syrup products in the Greater Jakarta area, which limits the understanding of quality assessment for the remaining products in the market.

Future research

Future research could take into account diverse quality testing parameters for both active ingredients and excipients (McManus & Naughton, 2020; Rasheed et al., 2023). Additionally, it is crucial to investigate the root cause of product degradation, differentiating it from substandard production.

Conclusion

With the aim of collecting the largest possible variety of amoxicillin products available in the Indonesian market, we gathered 120 samples from licensed and unlicensed outlets in four areas, as well as from online vendors. 15 samples tested as out-of-specification (12.5%). We found no relation between the price and quality of amoxicillin. Combining product-variety sampling with data on market volume presents a promising approach to gain insight into the prevalence of poor-quality medical products using a relatively small sample size.

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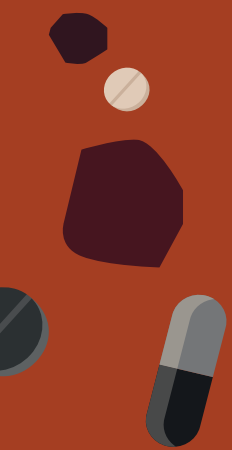
Chapter 5.

Testing risk-based sampling approach to identify substandard medicines



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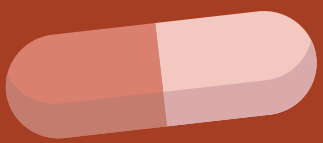
Supplementary materials for this chapter can be found at https://doi.org/10.7910/DVN/OWLN2L



Abstract

Introduction

Post-market surveillance is a critical yet challenging task for regulators worldwide. Protecting patients by detecting substandard medicines is complicated by the vast and dynamic pharmaceutical market, as well as the high costs associated with quality testing. This study tests a novel risk-based sampling approach designed to improve the efficiency of identifying poor-quality medicines.

Methods

Building on previous research, we developed a composite risk index based on seven risk indicators for substandard medicines, including low prices or a history of substandard production. We applied this risk-flagging approach in the Indonesian market by scoring all registered amoxicillin product varieties. We then purposively sampled a diverse range of amoxicillin brands and dosage forms from private pharmacies and drug stores in three areas and online marketplaces. All samples underwent independent laboratory testing using assay and dissolution methods to assess their quality.

Results

Fifteen out of 120 samples (12.5%) failed at least one quality test. While products with higher risk index scores were more likely to fail quality tests, the association was not statistically significant. Additionally, no individual risk indicator showed a significant correlation with the laboratory results.

Conclusion

Our findings suggest that while a risk-based sampling approach has potential, it requires further refinement and validation with larger sample sizes. Regarding feasibility, we recognize that the risk-flagging approach is highly context-dependent and data-hungry. Effective implementation of this method depends on a robust regulatory framework capable of responding to flagged product risks to safeguard the quality of medicines and public health.

Introduction

Poor-quality medicines, manufactured to lower quality specifications, known as substandard or deliberately imitated from genuine products or falsified (World Health Organization, 2017) have caused many public health concerns. Substandard and falsified medicines (SFM) disrupt proper disease treatment, waste financial resources, and threaten the credibility of the health system (Newton et al., 2010). The WHO Global Monitoring and Surveillance System (WHO GSMS) database shows that SFM has been found in different parts of the world (World Health Organization, 2025b); however, previous studies suggested that this problem is particularly concerning in low- and middle-income countries (LMICs) (Ozawa et al., 2018).

Protecting the public from SFM circulated in the market is a complex task. Responsibility usually lies with the National Medicines Regulatory Authority (NMRA) (United States Pharmacopeial Convention, 2021). This authority undertakes post-market surveillance (PMS) that encompasses a range of regulatory actions from routine inspections of medicine dispensing channels and quality control testing to reporting adverse events of medicines consumed by patients or pharmacovigilance to removal and disposal of non-compliant products or product recalls (United States Pharmacopeial Convention, Nkansah, et al., 2018). However, the extent to which regulators undertake PMS activities varies across health systems. Many regulatory authorities operating at maturity level 4 (ML-4) or the regulators with stringent quality standards in their product review processes for marketing authorization (World Health Organization, 2025a) are known to not undertake routine product sampling and laboratory quality testing in the market (Department for Business, Energy & Industrial Strategy, 2016; Research, 2020; Zaken, 2015). In this paper, we delineate the focus of PMS into the scope of medicine sampling and quality testing, which regulators in LMICs are continuing to seek to implement and improve (United States Pharmacopeial Convention, Babigumira, et al., 2018; United States Pharmacopeial Convention, Nkansah, et al., 2018; USP Promoting the Quality of Medicines, 2018).

The type of surveillance can be either passive, relying on routine data reporting from health providers or manufacturers (e.g., pharmacovigilance) or active (e.g., medicine regulators regularly sample products and test their quality) (Pisani et al., 2021). On the one hand, pharmacovigilance has the specific purpose of reporting adverse events following the consumption of medicines. Therefore, it is not specifically designed to detect or find substandard products in the market (World Health Organization, 2015). On the other hand, the latter type is more resource-intensive given the large number and variety of products in a market (United States Pharmacopeial Convention, Babigumira, et al., 2018), complex supply chain networks including unlicensed channels or informal markets (Alfajri & Diveranta, 2024; Gaudiano et al., 2007; Mengesha et al., 2024), and expensive medicine testing costs in the laboratory, partly contributed by the prices of quality reference standards (Valente de Almeida et al., 2024). Meanwhile, many medicine regulators in LMICs continue to face challenges regarding resources and

technical capacity to conduct PMS adequately (Twesigye et al., 2021; WHO, 2018).

To better allocate limited resources and reduce the high costs of medicine sampling and testing, one approach to active surveillance is to identify, test, and eliminate at-risk products in the market, which we will refer to as case finding (Pisani et al., 2021), thereby enabling a risk-based approach in PMS. This approach aims to find more substandard or falsified products in a given market, but does not quantify the prevalence or estimate the magnitude of the problem itself. The latter aim aligns with another active surveillance approach, sentinel surveillance.

Although many regulators in LMICs are seeking to strengthen PMS, policy objectives may differ from country to country (National Medicines Regulatory Authority of Indonesia, 2024; South African Health Products Regulatory Agency, 2022; Tanzania Medicines & Medical Devices Authority, 2019). On the one hand, regulators can increase their capacity to find substandard or falsified products by implementing case finding approaches. On the other hand, they can also ensure that a larger proportion of products circulating in the market are of good quality by implementing sentinel surveillance (Pisani et al., 2021). These policy objectives can then be translated into different strategies. For example, when implementing a case finding approach, regulators may choose to increase the yield of SFM in the market. Meanwhile, regulators can also save costs by collecting and testing fewer samples. The policy choice is likely to depend on several aspects, such as budget and resource allocation, key performance indicators of each regulator, and political sensitivity in finding and reporting poor-quality products to the public.

Recently, there has been increasing attention to developing or refining a risk-based, case finding approach (World Health Organization, 2021). Furthermore, a technical agency has proposed a tool to identify the most vulnerable medicines for sampling by combining different risk dimensions, including risks inherent to the medicine type, geographic location, and supply chains (United States Pharmacopeial Convention, 2021). Other authors have suggested various approaches by combining different risk factors that comprise risks to the product and public health (Aroca & Guzmán, 2017; Badan Pengawas Obat dan Makanan - Republik Indonesia, n.d.; FDA, 2014; United States Pharmacopeial Convention, 2021). However, current approaches combine different risk factors altogether without explicitly distinguishing whether these risks relate to specific product characteristics (e.g., narrow therapeutic index and stability) or public health in general (e.g., medicines administered in vertical infectious disease programs or national health insurance).

Although the need to improve the targeted sampling of poor-quality medicines is well recognized, the specific risk factors that could enhance the effectiveness of such strategies remain largely unknown. Notably, no studies have yet integrated market-related risks into risk-based sampling approaches. Addressing this gap is crucial for developing more precise and efficient detection methods, ultimately strengthening efforts to identify and

remove compromised products from the supply chain and safeguard patient health. In the current study, we aim to test a novel risk flagging approach, for which we combine seven risk factors into a composite risk index that is used to select products at the highest risk of being substandard. Considering the resources available for this research, I chose to examine the risk of substandard quality in the selected study drug, amoxicillin, as it is more prone to substandard issues than to falsification risks.

We conduct this trial in Indonesia, a middle-income country with a population of over 280 million individuals (Indonesia, 2023), where the universal health coverage (UHC) scheme has put extreme downward pressures on medicine prices, leading to some scientific inquiries as to whether medicine quality will be compromised (Hasnida et al., 2021) and where the medicine regulator is responsible for ensuring the quality of approximately 18,700 medicines in circulation in one of the world's largest archipelagic countries (National Medicines Regulatory Authority of Indonesia, 2023).

The Indonesian medicine regulatory agency conducts annual PMS based on random and case finding or targeted sampling (Direktorat KMEI, BPOM, 2023; National Medicines Regulatory Authority of Indonesia, 2024). The agency tested over 13,500 samples by combining both sampling approaches in 2021 (Pisani et al., 2024). The medicine regulator also developed a risk-based sampling strategy based on several risk factors, including product and public health risks. However, the weighting of the risk factors remains unclear, and sampling is implemented by 34 different sub-national offices, which may cause variations in practice (Badan Pengawas Obat dan Makanan - Republik Indonesia, n.d.; Direktorat KMEI, BPOM, 2023). Further, the regulator has not included market risk factors, namely, medicine price, into their current approach. Since we do not have complete information about the regulator's case finding strategy, we will refer to it as the "predicted regulatory approach". We provide an overview of the differences in risk dimensions between the risk factors in our risk-flagging approach and the predicted regulatory approach in Indonesia in Table 1.

In this trial, we first operationalized the risk-based indicators in the Indonesian setting based on the data availability and accessibility, further tailored the risk scoring following feasibility and workability in practice, and tested it by conducting sampling and pharmaceutical analysis for an antibiotic, amoxicillin (Akhavan et al., 2022). Further details on the selection of study medicine, sampling processes, and laboratory compendial testing have been described elsewhere (Hasnida, Rahmi, et al., 2025). We will now specifically look at whether adding market risk-based indicators will increase the likelihood of finding products at the highest risk of being substandard.

Table 1. The difference in risk factor dimensions between risk-flagging and the current regulatory approach

Approach	Risk factors	
	Product risks	**Public health risks**
1. Risk-flagging	Market risks (medicine price)	
	Regulatory risks (manufacturing compliance, history of substandard products and companies producing them)	
	Technical risks (years of product manufacturing, expired market authorization)	
2. Predicted regulatory approach	Regulatory risks (manufacturing compliance, history of substandard products and companies producing them, evaluation of previous years of sampling and testing)	Products manufactured in a large quantity
		Therapeutic index
		Disease prevalence
		Medicine used in the national health insurance scheme

Methods

Our aim was to purposively find at-risk substandard samples across multiple locations where patients can obtain them in the Indonesian market and to test whether this approach would improve the likelihood of finding amoxicillin products at the highest risk of being substandard.

General workflow

We present an overview of the workflow in developing and testing a market risk-based approach (Figure 1A), specifically for the Indonesian setting (Figure 1B). As a first step, we conducted multiple stakeholder engagements with Indonesian public and private organizations, non-governmental organizations (NGOs), professional associations, and technical agencies working in areas as diverse as regulation, pharmaceutical policy, health care and services, patient advocacy, procurement, industry and trade, environment, supply chain and logistics and bilateral aid agencies (Hasnida, Bal, et al., 2025). Among our objectives from these engagements was to explore potential datasets to inform the risk indicators. During the engagements, we also discussed potential study medicine with the medicine regulators. Given its importance in public health,

we selected amoxicillin as described elsewhere (Hasnida, Rahmi, et al., 2025). Details of the fieldwork for sampling and pharmaceutical quality testing or analysis have also been described earlier.

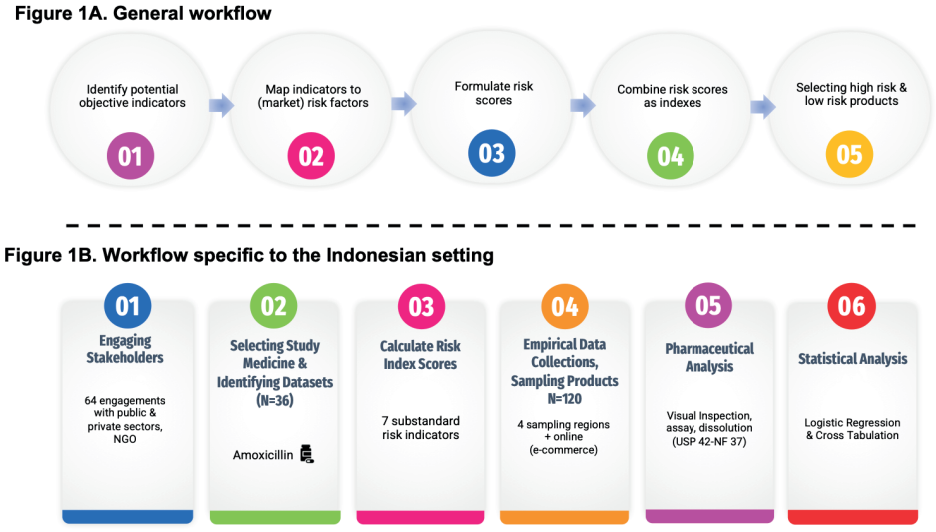


Figure 1. Workflow in developing and testing market-based approach

Secondary data collection, management, and analysis

To operationalize the risk indicators into a sampling frame, we collected secondary data from public and private organizations and non-governmental and/or technical agencies from April 2019 to July 2020. A complete list of explored datasets is included in Supplementary Material 1 (files can be found at https://doi.org/10.7910/DVN/OWLN2L). We obtained publicly available data from official agency websites or publications; confidential or proprietary data were obtained through formal requests or approvals. We used the pharmaceutical market (IQVIA MIDAS ® Quarterly Sales Data from 2020, which were obtained under licensed from IQVIA and reflect estimates of market activity), regulatory (i.e., product registration, Good Manufacturing Practice (GMP) inspection records, and history of substandard products and companies), and procurement data as primary sources of information, using these to calculate risk indicators at the company and product levels as described in the results. The final merged dataset consists of observations related to product characteristics, price, and regulatory history for each unique brand and dosage form of all amoxicillin authorized in Indonesia. In this paper, "unique products" are unique brands and dosage forms of amoxicillin, with unbranded generics identified by the market authorization holder. Meanwhile, "samples" refer to specific products collected at a single sampling location at a specific point in time. Data management and indicators analysis were performed using Microsoft Excel and STATA MP 18.

Operationalizing the risk indicators

In operationalizing the substandard risk indicator, we aimed to specify a generic version and turn it into a more relevant, applicable version corresponding to the specific setting in Indonesia. To achieve this, we reviewed academic literature, policy documents, regulations, and reports from governmental and technical agencies. We reviewed recordings undertaken for an earlier study on risks to medicine quality in Indonesia (Hasnida et al., 2021). We also conducted informal discussions and consultations with stakeholders, including the Indonesian medicine regulator, and took detailed meeting notes (Hasnida, Bal, et al., 2025). We discussed the insights and feedback from the stakeholders in weekly research team meetings and modified the indicators accordingly.

We considered two key issues that differentiated Indonesia from other middle-income markets and influenced the operationalization of risk indicators. First, Indonesia has a substantial domestic manufacturing sector, with over 200 companies supplying medicines both domestically and internationally (Pharmaboardroom, 2017). Second, we assume that the pharmaceutical industry employs cross-subsidization between products in their portfolio with different profit margins (Maria et al., 2024, p. 2; Pisani et al., 2022). This can apply to the same or various types of medicines, e.g., amoxicillin International Non-proprietary Name or INN generic, and branded generic. Following downward price pressures in the national health insurance scheme, some products are sold at very low profit margins. Thus, revenues from other products sold at higher price points with higher profit margins subsidize the indispensable costs associated with manufacturing, including quality assurance.

Sampling plans

We targeted a sample size of 120 amoxicillin samples that we deemed financially feasible for data collection and pharmaceutical analysis. The specific amoxicillin products we sought in the Indonesian market are described in the results. We targeted oral solid dosage 250 mg, 500 mg, and 1000 mg and dry syrups of 125 mg/ 5 ml and 250 mg / 5 ml. We provided a detailed justification for the targeted product dosage forms elsewhere (Hasnida et al., 2024).

Flagging the products and sampling strategy

This study focuses on the risk of substandard amoxicillin products. Hence, we defined a "flagged" product as one that is indicated to be at risk of being substandard based on individual risk indicators (see results). Each amoxicillin product in the Indonesian market will have its risk scoring from individual risk indicators *and* a total index risk score from all risk indicators.

In this trial, for practical purposes, we used a binary system for each risk indicator, indicating no risk (i.e., score 0) *or* at risk (i.e., score 1). Our initial aim was to collect samples with the highest total risk index scores (i.e., score 7) as *cases* and the lowest risk index scores (i.e., score 0) as *controls*. Our initial analysis plan was to consider the market

risk-based flagging approach works effectively if the proportion of products flagged as cases was statistically significant for failing any of the laboratory quality measures (see the section below) compared to the proportion of products used as controls. As previously described elsewhere (Hasnida, Rahmi, et al., 2025), we collected samples in five sampling areas in Indonesia, both licensed (e.g., private pharmacies) and unlicensed outlets (e.g., drug stores, health care providers, and websites). We primarily aimed to collect samples evenly in each area (N=24).

However, we encountered difficulties finding the targeted products, both the highest risks index and the lowest total index scores, in equal numbers across the five areas. Consequently, we could not conduct the initial case-control analysis since we collected very few samples with the highest and lowest total risk index scores (see results).

Based on our initial fieldwork experiences, we refined our sampling design. We adjusted the strategy to capture a wider variety of products while continuing to prioritize those with the highest and lowest risk index scores across the five sampling areas. Therefore, this also meant that collecting the same unique product as multiple samples from different outlets was possible. In practice, we collected most samples with a risk score of 3 and a score of 1 (see results). We conducted empirical data collection or sampling from November 2020 to November 2021. Additional details about the sampling process can be found elsewhere (Hasnida, Rahmi, et al., 2025).

Measures of quality

The collected samples were then tested at a third-party laboratory in Jakarta, Indonesia, for pharmaceutical analysis to identify the active pharmaceutical ingredients (API), assay or quantification of the percentage of API, and dissolution or determination of whether the sample releases the API in a timely manner. Table 2 provides an overview of the quality testing parameters. Further details on the testing protocol are described elsewhere (Hasnida, Rahmi, et al., 2025).

Table 2. Quality testing parameters and limits of compliance of amoxicillin by dosage forms (based on United States Pharmacopoeia 42 National Formulary 37)

Dosage forms	Quality testing parameter					
	Identification	Assay	Dissolution		Numbers of units tested	
			[Q]%	[Q + 5] %	Dissolution Stage 1 (S_1)	Dissolution Stage 2 (S_2)
Tablet	RT* of sample peak as standard assay %	90-120	75**	80	6	12
Capsule	RT of sample peak as standard assay %	90-120	80***	85	6	12
Dry syrup	RT of sample peak as standard assay %	90-120	Not applicable	Not applicable	Not applicable	Not applicable

*RT = sum of all the peak responses from the Sample solution

**For tablets, 75% of the labelled active ingredients should be dissolved within 30 minutes

***For capsules, 80% of the labelled active ingredients should be dissolved within 60 minutes

Since the term substandard encompasses a specific set of quality parameters for each active pharmaceutical ingredient (API) that we did not test in this study, we used the term "out-of-specification" instead. Following the United States Pharmacopeial Convention (USP) 42 National Formulary 37, we considered a sample to be "out-of-specification" if it fell into any of the following categories:

- Assay results are outside the stated limits or
- Dissolution stage 1 result shows each unit is lower than Q + 5%
- Dissolution stage 2 average result of 12 units is < Q, and at least a unit <Q – 15%
- More than 2 units are <Q-15%, and at least a unit is <Q – 25%

Missing data imputation & risk scoring adjustments

We lacked information on the list price for some products we collected without market data (see results). Thus, we imputed the missing data by calculating the estimated list price from the highest retail price. Every product authorized by the regulator and circulated in Indonesia has information on this price. We followed the Ministry of Health's regulations, where the list price was the highest selling price, minus 28% (Peraturan Menteri Kesehatan Republik Indonesia Nomor 98 Tahun 2015 Tentang Pemberian Informasi Harga Eceran Tertinggi Obat, 2016).

After we imputed the missing price data, we adjusted the risk indicator assessment related to profit pressure from all collected samples. We then used these adjusted risk indicators to test with the pharmaceutical analysis results.

Statistical analysis

We first performed a two-tailed Cochrane-Armitage test, a nonparametric test for trend, to examine the association between failures in pharmaceutical analysis or quality testing and the total risk index scores (Ghodsi et al., 2016). Considering this study's relatively small sample sizes (N=120), we reported the exact p-value calculated using the true distribution. We set the level of statistical significance at p=. 05.

For individual risk indicators, we performed logistic regression to calculate the odds ratio (OR) and measure the association between any individual risk indicator and failures in quality testing. We analyzed OR to measure the association between "exposure", which we defined in this study as being flagged by any risk indicator as at-risk for substandard, and a "disease or condition", defined here as out-of-specification (OOS) samples as indicated by failures in pharmaceutical quality testing or analysis.

We performed the Chi-Square test of independence to determine whether there is a significant relationship between group risk indicators (i.e., market, regulatory, and technical risks) and failure in pharmaceutical analysis or quality testing. We performed all statistical analyses in this study with STATA MP 18.

Ethical clearance

This study has obtained ethical approval from the Ethics Committee of the Faculty of Medicine, University of Indonesia, number KET-354/UN2.F1/ETIK/PPM/00.02/2019. We also consulted with the Indonesian medicine regulator on the study protocol in a series of meetings from July to October 2019.

Results

Identification of risk-based indicators in the Indonesian setting

Operationalization of risk-based indicators

Risk indicators are defined as specific parameters that indicate whether a medicine product is at risk of being substandard. In our previous viewpoint, we proposed several generic indicators for finding products at risk of being substandard (Pisani et al., 2021). Following the availability, accessibility, and interpretation of secondary data in the Indonesian context, we further formulated seven objective risk-based indicators to be combined as a total risk index score, which indicates profit pressures and cost-cutting risks, production history, and technical limitations. Table 3 summarizes the seven individual risk indicators, their abbreviated names, the level at which they operate (e.g., companies, products, molecules), the rationales behind these indicators, and the secondary data sources for risk-scoring. We provide an example of detailed steps in operationalizing a market risk indicator in Textbox 1.

Table 3. Substandard risk indicators in the Indonesian setting

No	Indicates	Risk indicators	Abbreviated indicators name	Applies to	Rationale	Scoring criteria	Main data sources
Risk group: market risks							
1A	Profit pressure: Cost cutting	Market authorization (MA) holders sell amoxicillin at the most expensive price, namely below the 20th percentile of the list price (net price) of the same dosage form	Low-price amoxicillin	Companies (market authorization holders)	MA holders sell amoxicillin products below certain price threshold are assumed to indicate inadequate investment in quality assurance, or other cost-cutting measures. Net price is used as a proxy for the MA holder's manufacturing price added with profit and distribution margins. Price below the 20th percentile of the market is used as a hypothetical low market price threshold price aiming for higher specificity in markets with a large number of product types and variations because medicine prices are not normally distributed. . If MA holders sell multiple amoxicillin products, we select the most expensive product with the highest sales volume. The "cost-cutting risk threshold" price is calculated in the smallest unit price (i.e., per tablet or capsule for oral solid and per 5 ml for dry syrup).	Score 1 (at-risk): if the MA holders sell the most expensive amoxicillin product at a price below the 20th percentile of the net price of the same dosage form Score 0 (no-risk): if the MA holders sell the most expensive amoxicillin products at a price above or equal to the 20th percentile of the net price of the same dosage form	Pharmaceutical market data (Q4 2018 – Q3 2020)

No	Indicates	Risk indicators	Abbreviated indicators name	Applies to	Rationale	Scoring criteria	Main data sources
1B	Profit pressure: Cost cutting	Percentage (%) of ALL products sold by a market authorization (MA) holder with the highest price below the 20th percentile of Pharmacy Purchase Price (net price) of the same molecule & dosage form to the total products sold by the same MA holders	Low-price products portfolio	Companies (market authorization holder)	Indications of cost-cutting or low investment in quality assurance are measured across the product portfolio of a particular MA holder. The assumption is that cost-cutting may occur for other molecules or products. Another underlying assumption here is that there is a cross-subsidization between different molecules and products sold by the same MA holder. This means that the investment in quality of a particular product with a lower price and, thus, lower profit margin is assumed to be compensated by a more expensive product with higher margin. Although this indicator does not operate at the level of specific amoxicillin product, it indicates companies with indications of low investment in quality assurance. Net price is used as a proxy for the manufacturing price of the MA holder added with profit and distribution margins. Price below the 20th percentile of the market is used as a hypothetical threshold of low market price aiming for higher specificity.	Score 1 (at-risk): if the MA holder sells the most expensive product at a price lower than the 20th percentile of the net price of the same molecule & dosage form to the total products sold by the same MA holder Score 0 (no-risk): if the MA holder sells any product at a price above or equal to the 20th percentile of the net price of the same molecule & dosage form to the total products sold by the same MA holder	Pharmaceutical market data (Q4 2018 – Q3 2020)

Risk group: regulatory risks							
2A	Production history	Manufacturer previously had Good Manufacturing Practice (GMP) violations	GMP violations	Companies (manufacturers)	Manufacturers who repeatedly violate GMP principles may have less investment in quality assurance; their products may be at higher-risk of substandard. Applies to manufacturers and not MA holders to capture companies that are actually inspected by the NMRA; this is especially relevant in the case of contract manufacturing.	Score 1 (at-risk): if the manufacturer has violated one or more GMP inspection components (see the main text) as reported by the NMRA in the period of 2016-2018 Score 0 (no-risk): if the manufacturer has not violated any GMP inspection components as reported by the NMRA in the period of 2016-2018	Regulatory inspection data (2016 – 2018)
2B	Production history	Market authorization (MA) holders with a history of substandard product	Substandard company	Companies (market authorization holder)	MA holders with a history of producing substandard products repeatedly may indicate lower investment in quality assurance which places the product at the higher risk of being substandard. Applies to MA holders because, under the rules, regulatory sanctions are applied to MA holders.	Score 1 (at-risk): if the MA holder has marketed substandard products (see the main text) as reported by the NMRA in the period of 2016-2018 Score 0 (no-risk): if the MA holder has not marketed substandard products as reported by the NMRA in the period of 2016-2018	Regulatory inspection data (2016 – 2018)

No	Indicates	Risk indicators	Abbreviated indicators name	Applies to	Rationale	Scoring criteria	Main data sources
2C	Production history	Amoxicillin product with substandard history	Substandard product	Product (unique amoxicillin brand and dosage form)	Amoxicillin products (with unique brand names and dosage forms) with substandard production records may indicate poor investment in quality assurance.	Score 1 (at-risk): if the amoxicillin product has tested substandard as reported by the NMRA in the period of 2016-2018 Score 0 (no-risk): if the amoxicillin product has not tested substandard as reported by the NMRA in the period of 2016-2018	Regulatory inspection data (2016 – 2018)
Risk group: technical & oversight risks							
3A	Technical limitation: production errors	Manufacturer with < 5 years' experience in producing amoxicillin	Manufacturing experience	Molecule (amoxicillin)	Manufacturers who have recently produced amoxicillin in a given period may have a higher risk of production errors leading to a higher-risk of substandard products. Since amoxicillin can be considered a "mature" molecule developed since the 1960s, we considered manufacturers who produce molecule less than 5 years ago before the last empirical survey period (November 2021) to have a higher risk of production errors. We obtained information on the year of manufacture from the product's market authorization number codification.	Score 1 (at-risk): if amoxicillin has been produced by a particular manufacturer within less than 5 years prior to the last empirical survey period in 2021 Score 0 (no-risk): if amoxicillin has been produced by a particular manufacturer within or more than 5 years prior to the last empirical survey period in 2021	Regulatory database of registered medical products (as of November 2021)

No	Indicates	Risk indicators	Abbreviated indicators name	Applies to	Rationale	Scoring criteria	Main data sources
3B	Technical limitation: production oversight risks	Amoxicillin product with expired market authorization	Expired market authorization	Product (unique amoxicillin brand and dosage form)	Products with expired market authorization (MA) must not be distributed or sold on the market. These products have an MA that is not valid for various technical reasons as issued by the NMRA which may include production. Products with expired market authorization circulating on the market indicate that these products have a higher-risk of being substandard.	Score 1 (at-risk): if the amoxicillin product has an invalid market authorization number based on the regulatory database in the last data collection (November 2021) Score 0 (no-risk): if the amoxicillin product has valid market authorization number based on the regulatory database in the last data collection period (November 2021)	Regulatory database of registered medical products (as of November 2021)

Textbox 1. Steps for calculating the risk indicators

Indications: Profit pressure: cross-cutting
Risk indicator (abbreviated name): 1A Low-price amoxicillin
1. Calculate the "cost-cutting risk threshold" price for each dosage form of interests of amoxicillin or and other medicines as intended in the Indonesian market.
2. For each market authorization (MA) holder, determine if it sells amoxicillin products in dosage form of interests with the most expensive price lower than the "cost-cutting risk threshold".
3. If the same MA holder sells another product in dosage form of interest, determine which products with the highest estimated market volume sold in the Indonesian market. This particular product will be the reference of the most expensive prices sold by the MA holder.
4. Score the MA holder as 1 if it sells amoxicillin products in dosage forms of interests with the most expensive prices below the "cost-cutting risk threshold". This is called as the "flagged" MA holder meaning that this MA holder might have the risk to sell substandard amoxicillin product.
5. Alternatively, score the MA holder as 0 if it sells amoxicillin products in dosage forms of interests with the most expensive prices above than or equal to the "cost-cutting risk threshold". This is called as the "non-flagged" MA holder meaning that this MA holder might not have the risk to sell substandard amoxicillin product.
6. Add the risk score of this indicator to the total index scores for substandard.

We included two market risk indicators aiming to flag market authorization (MA) holders at risk of selling substandard products based on low prices. While the low-price amoxicillin risk indicator directly points to MA holders that sell amoxicillin products at prices lower than the "cost-cutting risk threshold", the low-price product portfolio indicator flags MA holders that sell other low-price products, in addition to amoxicillin, in a certain proportion of their overall portfolio. Our underlying assumption is that quality assurance requires certain investments (Pisani et al., 2022). To do so, MA holders can implement cross-subsidy whereby quality assurance investments for products with lower profit margins can be subsidized by profits earned from other products with higher margins. Following this, within the same MA holder, there is a plausibility that amoxicillin, a widely known product with low-profit margins, is being cross-subsidized with other products.

Market risk for quality arises when cross-subsidization is carried out without considering the same investment standards for quality assurance (Pisani et al., 2022). For the low-price amoxicillin risk indicator, we consider cross-subsidy for the same amoxicillin molecule but different products and price points sold by the same MA holder. Meanwhile, for the low-price product portfolio, we considered cross-subsidy across different product

portfolios sold by the same MA holder. We assume that each MA holder flagged by this risk indicator carries the "spillover effect" risk for pressured profit margins from cross-subsidy, leading to cost-cutting for other products, including amoxicillin.

Product history risk indicators encompass various components of Good Manufacturing Practice (GMP) violations and substandard products identified through regulatory inspections. The first indicator is a combination of eight violations: regular warning, severe warning, production suspension, production ban, market authorization license revoked, GMP permit revoked, industrial permit revoked, and product recall. Meanwhile, the latter indicator comprises a group of five substandard product findings, including active pharmaceutical ingredient (API) level, high impurity level, low dissolution profiles, visual inspection, and acidity level. In identifying product history risk indicators, our source of information is the regulatory case finding reports, which do not include a denominator value. This implies that we had no information on whether "non-flagged" products were meeting specifications or whether they had been tested at all.

Distribution of substandard total risk index scores in the Indonesian market

We added the binary risk scores for the risks shown in Table 1 into a total risk index for each of the 174 amoxicillin products in the Indonesian market for which we had market data. Out of a potential maximum risk score of 7, the highest recorded risk was 5. Most products scored 3 (N=73) or 2 (N=50); only two products were flagged as the highest risk or scored 5. We also calculated the estimated total product volume at each scoring level in the year preceding sample collection. The proportion of risk scores for unique amoxicillin products in the Indonesian market in the year preceding sample collection, mapped to the estimated market volume, is shown in Figure 1.

The majority of marketed products, which have scored 3, account for over 275 million dosages and comprise 60% of the total market volume. Products with the lowest risk (score 0) had the lowest selling volume for over 2.4 million dosages. In contrast, products with the highest risk (score 5) had a slightly higher selling volume of approximately 2.6 million.

Our aim in mapping the products was to gain insight into the available products in the market. Therefore, this mapping serves only as an indicative guideline for sampling. In other words, this mapping is not prescriptive, considering the time gaps between this analysis and the empirical data collection. Hence, we anticipated the likelihood of obtaining the recently authorized products previously uncaptured in the regulatory and market data.

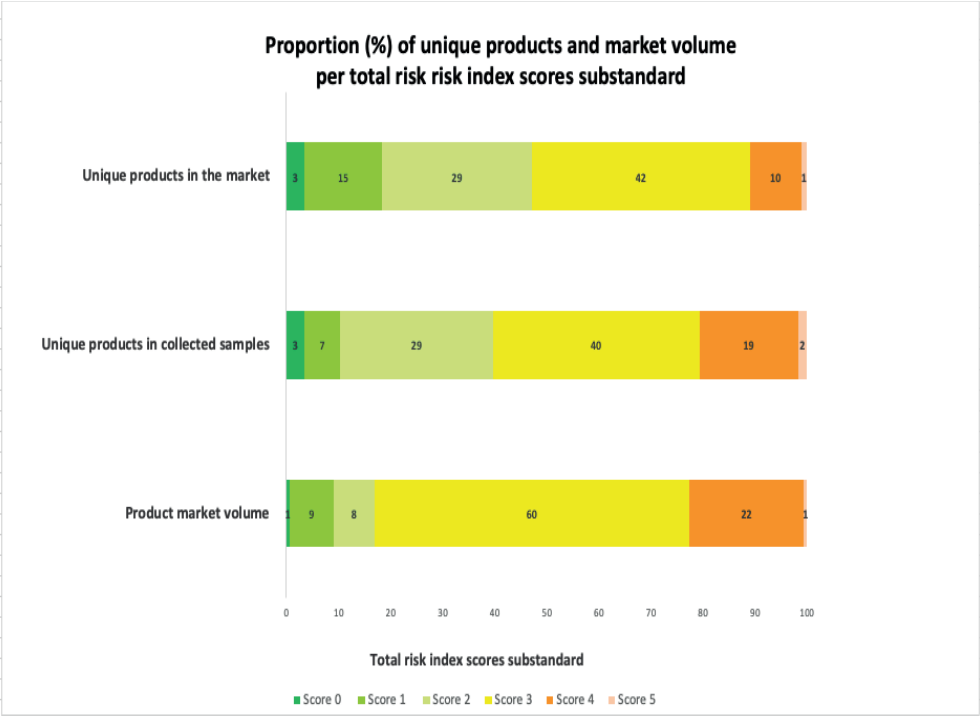


Figure 1. Proportion of unique products and market volume per substandard risk index scores in the Indonesian market in the year preceding data collection (October 2019-September 2020)

Source: This is based on internal analysis by (Hasnida et al., 2025) using data from the following source: IQVIA MIDAS Quarterly Sales for the period (October 2019-September 2020) reflecting estimates of real-world activity. Copyright IQVIA. All rights reserved.

Analysis of total risk index scores

Distribution of total risk index scores in the collected samples

We collected all samples we could find of products scoring 0 and 5, and we started collecting scores 1 and 4, and, finally, scores 2 and 3, aiming to obtain the greatest possible unique product diversity. We collected a total of 120 samples. Out of 120 samples, we collected eleven products previously unlisted in our scoring dataset but were found in the field. Therefore, these samples did not have list prices, so we imputed the missing price data and adjusted for the low-price amoxicillin risk indicator and the low-price products portfolio. As a result, for the low-price amoxicillin risk indicator, the highest product price in the same company changed for two products in our dataset. Additionally, for the low-price products portfolio, the percentage of products with prices lower than 20% of the same product in the market also changed for one product. We also found one sample

without information on prices and regulatory authorization; therefore, we could not calculate its risk score and excluded it from this analysis.

At the sample level, we present the distribution of total risk index scores of all collected samples (N=119) mapped to the pharmaceutical analysis results in Figure 2. We collected the most samples with a score of 3 (N=47); we sampled very few samples with the highest risk (N=4), and non-flagged ones or zero risk (N=3). Additionally, we collected scores 1 (N=23), scores 2 (N=25), and scores 4 (N=18).

Based on the pharmaceutical analysis, all samples were identified as amoxicillin. Out of 120 samples, we reported fifteen out-of-specification (OOS) samples (12.5%). Four samples were OOS in the assay, and eleven were OOS in dissolution; no samples failed both assay and dissolution testing. Overall, medicines scoring higher on the risk index are more likely to be OOS. As shown in Figure 3, the OOS samples were distributed from risk scores 2 to 5. Score 5 had the highest proportion of the OOS samples (N=3), for which we collected the same products for all samples (N=4). The lowest proportion of OOS (N=6/25) was identified in score 2 samples. One excluded sample passed the assay and dissolution tests.

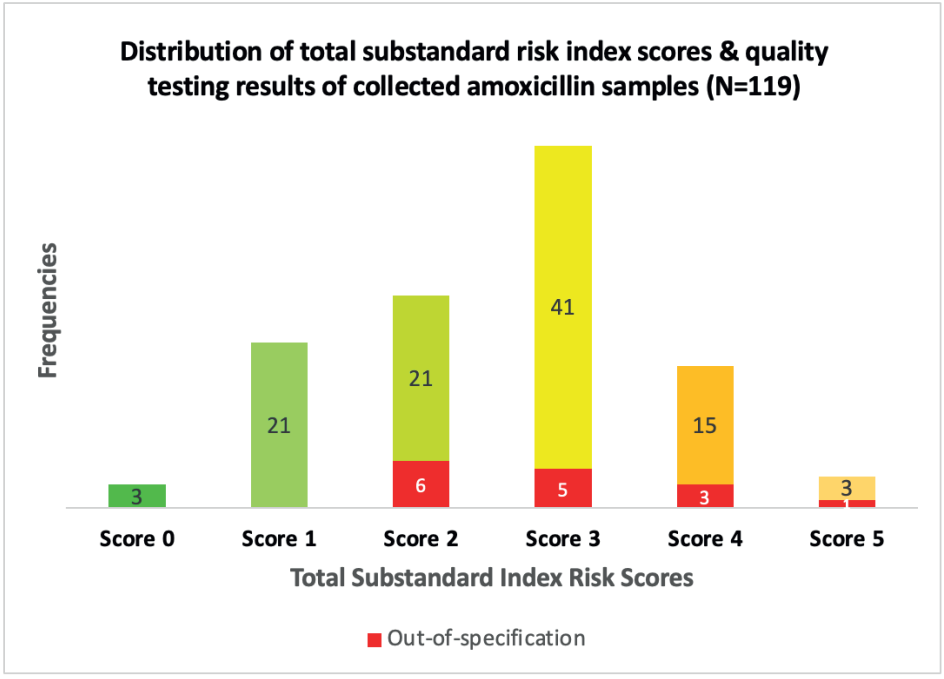


Figure 2. Distribution of total substandard index risk scores and pharmaceutical analysis results of collected samples

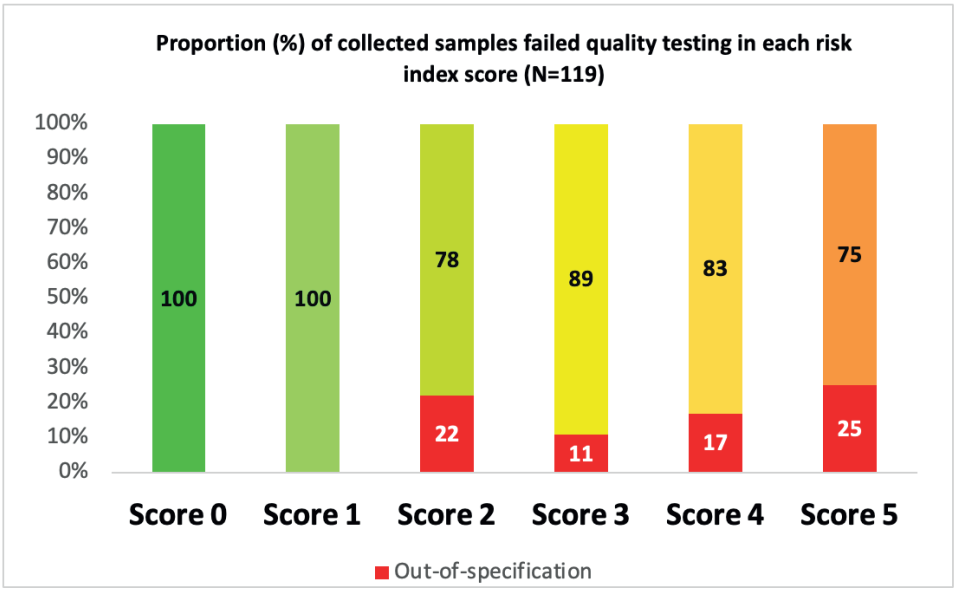


Figure 3. Proportion of collected samples failed quality testing in each risk index score

At the product level, we collected 58 unique products, including several unique amoxicillin products, for each risk index score (Table 4). For scores 3 and 2, we observed different pharmaceutical analysis results for the same unique products. For each score, two unique products failed and passed samples. Meanwhile, at both scores, one unique product was collected from a total of two samples, and all samples consistently failed the pharmaceutical analysis (N=2).

Table 4. Distribution of unique products per total index scores and pharmaceutical analysis of multiple samples of the same unique products

Total substandard risk index scores	Total samples*	Unique products**	Multiple samples with the same unique products but different test results (failed & passed)			Multiple samples with the same unique products and same failed test results		
			Unique products	Samples failed	Samples passed	Unique products	Samples tested	Samples failed
0	3	2	Not applicable			Not applicable		
1	21	4	Not applicable			Not applicable		
2	27	17	2	2	3	1	2	2
3	46	23	2	3	3	1	2	2
4	18	11	Not applicable			Not applicable		
5	4	1	1	3	1	Not applicable		
Total	119	58						

*Samples: particular products collected at one sample location at one point in time

**Unique products: unique brand and dosage form of amoxicillin

Statistical analysis

We performed a two-tailed Cochrane-Armitage test to determine the trend between the total risk index score and failure in pharmaceutical analysis testing (i.e., yes/no) in both dissolution and assay. We found no significant association between the total risk index score and failure in pharmaceutical analysis (P=. 16).

Analysis of individual risk indicators

We calculated the odds ratio (OR) for each individual market and regulatory risk indicator (N=5). However, we were unable to calculate the OR for all technical risk indicators (N=2) because there were zero sub-groups in the pharmaceutical analysis that failed or passed. Table 5 shows an overview of the logistic regression.

Table 5. Logistic regression of individual risk indicators

Market risks	**(N= 120)**	**Quality testing**		**Odds Ratio (OR)**	**Confidence Interval (CI)**	**P-value**
		Failed	**Passed**			
Low price amoxicillin						
Flagged	15	2 (13%)	13 (87%)	1.1	(0.22, 5.32)	0.93
Not flagged	104	13 (12%)	91 (88%)			
Missing	1	0 (0%)	1 (100%)			
Low price products portfolio	**(N=120)**	**Quality testing**		**Odds Ratio (OR)**	**Confidence Interval (CI)**	**P-value**
		Failed	**Passed**			
Flagged	80	12 (15%)	68 (85%)			
Not flagged	39	3 (7%)	36 (93%)	2.1	(0.56, 7.99)	0.27
Missing	1	0 (0%)	1(100%)			
Regulatory risks						
Manufacturer previously had GMP violations	**(N=120)**	**Quality testing**		**Odds Ratio (OR)**	**Confidence Interval (CI)**	**P-value**
		Failed	**Passed**			
Flagged	96	11 (11%)	85 (89%)			
Not flagged	23	4 (17%)	19 (83%)	0.6	(0.18, 2.14)	0.45
Missing	1	0 (0%)	1 (100%)			
Market authorization holder with any substandard product history	**(N=120)**	**Quality testing**		**Odds Ratio (OR)**	**Confidence Interval (CI)**	**P-value**
		Failed	**Passed**			
Flagged	91	14 (15%)	77 (85%)			
Not flagged	28	1 (3%)	27 (97%)	4.9	(0.61, 39.12)	0.13
Missing	1	0 (0%)	1 (100%)			
Amoxicillin product with substandard history Substandard product history	**(N=120)**	**Quality testing**		**Odds Ratio (OR)**	**Confidence Interval (CI)**	**P-value**
		Failed	**Passed**			
Flagged	20	4 (20%)	16 (80%)			
Not flagged	99	11 (11%)	88 (89%)	2	(0.57, 7.07)	0.28
Missing	1	0 (0%)	1 (100%)			
Technical risks						
Manufacturer < 5 years' experience in producing amoxicillin	**(N=120)**	**Quality testing**		**Odds Ratio (OR)**	**Confidence Interval (CI)**	**P-value**
		Failed	**Passed**			
Flagged	1	1 (100%)	0 (0%)	N/A (zero sub-group)		
Not flagged	118	14 (12%)	104 (88%)			
Missing	1	0 (0%)	1 (100%)			
Amoxicillin product with expired market authorization	**(N=120)**	**Quality testing**		**Odds Ratio (OR)**	**Confidence Interval (CI)**	**P-value**
		Failed	**Passed**			
Flagged	2	0 (0%)	2 (100%)	N/A (zero sub-group)		
Not flagged	117	15 (13%)	102 (87%)			
Missing	1	0 (0%)	1 (100%)			

Analysis of group risk indicators

We mapped all samples (N=120) to each risk indicator to understand the risk distribution in Supplementary Material 2. We noticed that we flagged only a very limited number of samples for technical risks. Only one sample was flagged by the risk indicator manufacturer's experience in producing amoxicillin in less than 5 years, and two were flagged by expired market authorizations. Meanwhile, almost all samples (N=116) were flagged by any regulatory risk indicators, and 80 samples were flagged by any market risk indicators. No sample was flagged solely by market risks without also being flagged by regulatory risks. Following this, we further investigated the market and regulatory risk indicators.

Regulatory and market risk independence test

We performed a Chi-Square test of independence between the pharmaceutical analysis failures and samples flagged by any market risk indicators (e.g., low-price amoxicillin and low-price products portfolio) and any regulatory risks (e.g., GMP violations, substandard company, and substandard product). As shown in Table 6, we found no statistically significant relationships between any regulatory risks (.51) and any market risks (.26).

Table 6. Test of independence of group of risk indicators and failure in pharmaceutical testing

Group of risk indicators	Degrees of freedom	Sample size (N)	Chi-square value	P-value
Any regulatory risks	1	119	0.44	.51
Any market risks	1	119	1.27	.26

Discussion

This study explores a novel risk-based approach to identifying products that are at risk of being substandard medicines. Previously, we conceptualized several risk indicators for substandard medicines (Pisani et al., 2021). In this paper, we operationalized these indicators in a middle-income setting—Indonesia—and tested their effectiveness through pharmaceutical analysis. We developed a total risk index score based on seven substandard risk indicators, comprising two market risk indicators, three regulatory risk indicators, and two technical risk indicators. To evaluate our approach, we collected 120 amoxicillin samples from a diverse range of products available to patients in the Indonesian market (Hasnida et al., 2024).

Our findings suggest that medicines with higher risk scores were more likely to test out-of-specification, though this trend was not statistically significant. We found no significant correlation between the individual risk indicators or clusters and the pharmaceutical analysis results.

The distribution of risk scores among sampled medicines was uneven, with only three samples scoring 0, four scoring the highest value of 5, and a large concentration (N=41) at a mid-range score of 3. Notably, no out-of-specification samples were observed at the lowest risk scores (0 and 1), while the highest proportion (25%) was found among samples with a risk score of 5. While the results suggest that medicine with a high-risk score is more likely to be substandard, the trend is not statistically significant, and a larger sample would be necessary to improve statistical power and further validate this approach (Tekindal, 2016).

Our study design raises several methodological points that may help explain the absence of a significant association between risk indicators and medicine quality. First, we included interactions between risk indicators or collinearity for two market risk indicators (i.e., low-price amoxicillin and low-price product portfolio) and two regulatory risks (i.e., a substandard company history and products). The logistic regression we performed to analyze the association between individual risk scores and pharmaceutical analysis failure is susceptible to multicollinearity among predictors (Bayman & Dexter, 2021).

We have several suggestions for improving the design of this study. The first is to omit one of the correlated variables (Midi et al., 2010) by selecting risk indicators that are more specific to the same risk groups which are more specific to flag samples as at-risk. We consider risk indicators more specific when they yield a higher proportion of medicine samples that are not correctly flagged by the risk-flagging approach as truly meeting specifications. For example, based on the logistic regression, the low-price product portfolio yielded a higher proportion of non-flagged samples that passed the quality assessment (93%; OR 2.1), indicating that this indicator is more specific than low-price amoxicillin (88%; OR 1.1). In Indonesia, the medicine regulator asserts that, by regulation, all products manufactured by the same company must undergo the same standard of quality assurance, even if their market price differ (Peraturan Kepala Badan Pengawas Obat dan Makanan Republik Indonesia nomor 24 tahun 2017 tentang kriteria dan tata laksana registrasi obat, 2017, p. 24). In addition, other scholars have found no significance in cross-subsidies protecting the quality assurance of lower-priced medicines by selling more expensive products with the same active ingredients and formulation (Maria et al., 2024). Their findings may explain the non-significance of cross-subsidization at the same molecule level, such as the low-price amoxicillin risk indicator. Meanwhile, we believe that cross-subsidization across all products, represented by the low-price product portfolio indicator, has the potential to be further explored.

Another plausible alternative to improve the design would be to apply weighting based on the severity of the implications of each risk for the quality of the flagged product. We did not have the capacity for this weighting because of information asymmetries about pharmaceutical market dynamics (Hill et al., 2018; Moon et al., 2020) and regulatory risk (USP Promoting the Quality of Medicines, 2018), for example, as mentioned above, about cross-subsidization of products at the same molecule level or across products sold by the same company or cost-cutting price threshold. Information about fair pricing, particularly in relation to quality assurance, has been consistently obscured by the industry, prompting a push for transparency from researchers and policymakers (Ferrario et al., 2020; Hill et al., 2018; Morgan et al., 2020).

Another point of methodological discussion concerns the binary scoring system. For this trial, we decided to simplify the scoring approach by categorizing risk scoring into a binomial system (i.e., score 1 for products "flagged" or deemed risky and score 0 for products "non-flagged" or deemed not risky). We realize this is a relatively simplistic approach in a complex pharmaceutical market and carries the consequence of missing the nuances of different risk weights. Furthermore, fewer categories, such as binary risk scoring, require large sample sizes to determine trends, while more categories can provide statistical power with smaller sample sizes compared to two categories (Tekindal et al., 2016). However, we found the process of deciding the cut-offs for more tiered risk levels to be too arbitrary, given the limited evidence at this early stage of the trial. Moreover, we consider the instrumental and conceptual utility in practice by striking an adequate balance of sophisticated concepts and simplicity across model elements (Thompson et al., 2022). Further study could consider stratified risk scoring, for example, using a three-tiered scale (i.e., low, medium, and high risks) combined with weighted individual risk indicators.

Our risk-flagging approach is specific to indicating product quality risks. Thus, we differentiate our approach from other case finding strategies that vaguely combine the risks to product and public health, including predicting higher-risk antibiotics for substandard (Ching et al., 2022) or other commodities weighted by market volume (Aroca & Guzmán, 2017) and the predicted current regulatory approach (Badan Pengawas Obat dan Makanan - Republik Indonesia, n.d.). The development and trial of our risk-flagging approach aim to contribute to the detection of substandard and falsified medicines as one of the key strategies recommended by the WHO (Working Group of the Member State mechanism on SSFFC medical products, 2017). However, these developments are mostly concerned with tools or technologies (Opuni et al., 2019; Pan & Ba-Thein, 2018) but rarely with sampling approaches (Pisani et al., 2024), especially case finding strategies.

Central to developing the risk-flagging approach is the consideration of market dynamics, including product price and market volume, which remains scarce in the literature except for prevalence estimation methods using weighted product volume (Pisani et al., 2024). Our study shows that case finding strategy benefits from understanding which products

are *actually* circulated in the market, as indicated by their sales volume. The samples we collected eventually reflect market volume more than the number of registered products at each score level. Several plausible explanations for this observation are that some products may be registered but not *actually* sold in the market, or products may be sold in different areas other than the sampling location due to market segmentation (Pisani et al., 2022), or products might have a history of substandard quality, so that the medicine regulator has withdrawn them from the market.

We reflect on several implications for policy and practice as follows. In theory, we expected that a case finding strategy such as the "risk-flagging" approach would be effective in settings with a low prevalence of substandard medicines (Pisani et al., 2021). In Indonesia, previous research has shown that the prevalence of antibiotics and cardiovascular and diabetic medicines is quite low (Dewi et al., 2022; Hadi et al., 2010; Pisani et al., 2024, p. 202). These findings resonated with the results of annual regulatory post-market surveillance, which reported a prevalence of 4% of out-of-specification (OOS) products based on over 13,500 tested samples, with a proportion of 18.9% sampled using a case finding or targeted strategy (Pisani et al., 2024). Our risk-flagging approach shows that adding the market risk factors does not significantly increase the likelihood of finding products at the highest risk of being substandard. One practical explanation is that, as academic researchers, we had limited access to regulatory data, which limits the operationalization of the risk indicators. We recognize that the feasibility and applicability of this proposed approach are highly dependent on the availability, accessibility and cost of secondary data from various data custodians. In particular, data specific to companies and products are not widely available in middle-income markets and are expensive. However, based on our exploration of the Indonesian environment, other potential routine data sources provide information on market sales or distributions, such as medicine distribution data from the Ministry of Health. Furthermore, we argue that this approach requires reasonable and functional regulatory capacity to implement and conduct the necessary follow-up actions.

Our risk indicators for substandard products rely heavily on marketing authorization information. We did find, however, a sample without marketing authorization information that meets specifications, but we were unable to score it. Therefore, we suggest that this risk-flagging approach for substandard medicines is not suitable for use in situations with a high prevalence of unlicensed or illegal products on the market.

We also observed that regulatory risks simultaneously flagged all samples that are also flagged by market risk indicators. This may indicate that market risks have been captured in the regulators' current regulatory indicators. To our knowledge, the Indonesian regulators consider the medicines used in the national health insurance scheme, which are often priced substantially lower than products in the private market (Anggriani et al., 2020; Pisani et al., 2022, p. 202). However, we did not know precisely other market factors or any weighting strategies used by the medicine regulator in practice.

We conducted this trial based on our previous research on market dynamics, including low-price resulting from pressured profit margins, as a risk factor for substandard quality (Hasnida et al., 2021; Pisani et al., 2019). Our results showed no statistically significant association between any total risk index scores, group risk scores, and individual risk scores with failure in pharmaceutical analysis. This finding contributes to the ongoing debate about whether the price of medicine can serve as a reliable indicator of quality (Bate et al., 2012, 2015). The literature shows mixed evidence from different countries, while previous research in Indonesia suggests no relationship between price and quality (Pisani et al., 2023, 2024). Overall, adding market risk to the case-finding strategy warrants further caution, considering the context-dependent operationalization of risk indicators, the availability and accessibility of secondary routine data, and the regulatory capacity to implement this approach and take necessary follow-up actions.

Strengths and limitations

Our study is the first to test the integration of market-related risks, including price and market volume, with regulatory and technical risks into a risk-based sampling approach to identify specific products at the highest risk of being substandard. We collected a wide variety of amoxicillin products that are *actually* circulated in the Indonesian market, covering most of the market volume. We also operationalized the risk indicators based on the routinely collected data within and outside the health sector, making the risk-flagging a unique, intersectoral, data-driven approach.

Our study has several limitations. First, we collected multiple samples of the same product, which added to the variety of products but, at the same time, increased sample variance. This design is a mitigation plan since, as academic researchers, we have fewer resources, such as data and authority, to locate the circulation of products in the market than the medicine regulators. We also note that five unique products for which samples were collected in different areas and types of outlets yielded different pharmaceutical analysis results that require further investigation into the addition of the supply chain as a factor for public health risk. Second, although in our previous viewpoint (Pisani et al., 2021), we proposed the addition of market risk factors to increase specificity in existing risk-based case findings, we did not systematically analyze diagnostic measures, including specificity. We had no information about the denominator value of samples tested by the regulators; hence, we had no means of knowing which samples produced true or false positive or negative results from the quality testing. In addition, we collected a relatively small sample size (N = 120), which reduced the likelihood of obtaining meaningful conclusions from this particular analysis. However, as mentioned above, specificity is useful at this stage to explore which risk indicators within the same risk groups may be more specific to indicate risky products.

Conclusions

In developing the "risk-flagging" approach, we operationalized seven substandard risk indicators to be combined as a total or composite risk index score in the Indonesian setting. The index comprises individual market risk indicators (N=2), regulatory risk (N=3), and technical risk (N=2). While products with higher risk index scores were more likely to fail laboratory quality tests, the association was not statistically significant. Additionally, no individual risk indicator showed a significant correlation with the laboratory results. Our findings suggest that while a risk-based sampling approach has potential, it requires further refinement and validation with larger sample sizes. Regarding feasibility, we recognize that the risk-flagging approach is highly context-dependent and data-hungry. The effective implementation of this method depends on a robust regulatory framework capable of responding to flagged risks to safeguard the quality of medicine and public health.

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Chapter 6.

Examining stakeholder engagement in broadening the frame and operationalizing the problem definition of substandard and falsified medicines

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Abstract

Background

Tackling falsified and substandard medicines requires intersectoral collaboration, impact-oriented research, and the effective application of research findings. However, the best way to organize research and involve stakeholders from different sectors to ensure that results are used remains unclear. We aimed to assess how intersectoral stakeholder engagement in research on medicine quality in Indonesia evolved, influenced the research processes and participants, and affected the uptake of the results.

Methods

For this prospective case study, we adopted an abductive approach inspired by Contribution Mapping and Collaborative Governance. We conducted 37 interviews with key informants, observed 24 meetings, and analyzed 121 documents to systematically map the engagement of stakeholders in a study on medicine quality, focusing on processes, influences, and research-related contributions.

Results

From the outset, it proved feasible, but challenging, to effectively engage stakeholders in research into falsified and substandard medicines in Indonesia. After a cautious start and persistent efforts, stakeholders, such as the national medicine regulatory authority, became increasingly involved and developed a shared understanding of the need for intersectoral collaboration to tackle problems with medicine quality. While the research findings did not lead to a different estimate of the magnitude of the problem, the involvement of stakeholders was beneficial. After formalizing the collaboration, stakeholders provided data needed to study potential risk factors, product varieties and sales volumes and contributed to decisions during the research and interpretation of the findings. Due to frequent personnel changes and diverging priorities, stakeholder engagement required more effort than anticipated and necessitated a strategic and adaptive approach. This approach had to account for the varying priorities and interests of stakeholders, the evolving framing of the problem, the implications of the findings, and the nature of the field, where regulators must operate cautiously, balance interests and respond to critical incidents.

Conclusion

Intersectoral stakeholder engagement in medicine quality research is challenging but beneficial. Engagement contributed to building trust and relationships between researchers and stakeholders, helped forge an intersectoral network focused on medicine quality, exposed the medicine regulator to new methods, inspired stakeholders to take on new roles and make better use of existing data, and furthered a research-policy partnership forum on pharmaceutical topics.

Background

Substandard and falsified medicines represent a significant and growing threat to human health (Newton et al., 2010). Poor-quality medicines can aggravate illness, leave patients uncured, and, in some cases, poison or kill people. Poor-quality medicines include substandard medicines, which are made by registered pharmaceutical companies, but do not meet quality standards, and falsified medicines, which are made, repackaged, or sold by criminals who seek to deliberately misrepresent the identity, composition, or source of the product (World Health Organization, 2017).

Recent incidents involving medicine quality, such as the lethal cough syrup that killed hundreds of children in Indonesia, West Africa and India, underscore the critical importance of ensuring medicine quality (Schier et al., 2023). While the attention to these tragedies might suggest that combating falsified and substandard medicines is a political priority, the reality is often different (Kingori et al., 2023). Despite lethal consequences, public outcry and media attention, sustained political commitment and resource allocation for addressing this issue remain insufficient, leaving significant gaps in the global pharmaceutical oversight framework (Newton et al., 2019).

Governments have long viewed the ensuring of medicine quality as a specialized technical task, primarily the responsibility of the national medicines regulator. The regulator sets standards for the production and distribution of medicines and decides which products are allowed on the market. Manufacturers and distributors must follow these standards, implement quality control measures, and ensure the proper storage, transportation, and handling of medications before they reach consumers. Regulators inspect and monitor compliance with these standards, as well as verify the quality of drugs circulating in the market. In practice, many national regulators are unable to fulfill their duties. In 2019, the World Health Organization (WHO) stated that "fewer than 30% of the world's medicines regulatory authorities have the capacity to perform the functions required to ensure medicines, vaccines and other health products actually work and do not harm patients"(World Health Organization, 2018).

Gaining insight into the prevalence of falsified and substandard medicines poses a significant challenge to regulators (World Health Organization, 2017). In most countries, thousands of authorized medicines, produced by both domestic and foreign manufacturers, move through complex supply chains. Meanwhile, many countries also contend with unauthorized medicines in circulation, as well as expired and falsified products. Although regulators are tasked with overseeing a complex market, they often lack the funding, facilities, and specialized staff required to test medicine quality and thus gain little or no insight into the prevalence of falsified and substandard medicines (Hamill et al., 2021)(Pisani et al., 2021). As long as the extent of the problem remains unknown and its health impact remains invisible, issues with medicine quality will not feature prominently on the political agenda and regulators will struggle to obtain

sufficient funding.

Meanwhile, the limited data that is available offers a bleak picture. A recent review estimated that nearly 20% of antimalarials and over 12% of antibiotics in low and middle income countries are substandard or falsified (Ozawa et al., 2018). Every year, the WHO receives hundreds of reports concerning suspected products, which are likely only the tip of the iceberg (World Health Organization, 2017).

To more effectively combat poor quality medicines, experts have called for a more collaborative and research-based strategy (Mengesha et al., 2024; Newton et al., 2019). At the core of this new strategy is an understanding that problems with medicine quality are not just a technical issue that needs to be dealt with by the regulator, but are influenced by several risk factors that are deeply intertwined with the functioning of pharmaceutical markets, health systems and larger political and economic forces, and can only be addressed through a coordinated collective effort (Newton et al., 2019; Pisani et al., 2019). An example of such a risk factor is a medicine stock-out, which pushes patients towards unregulated outlets, creating a market opportunity for those who sell fake products (Nistor et al., 2023). Another risk may emerge from procurement systems that push prices so low that companies are incentivized to produce substandard products (Hasnida et al., 2021). To address these risks, the regulator needs to collaborate with others organizations, such as ministries of health, finance and trade, medicine producers and distributors and law enforcement agencies.

A more effective approach to tackling poor-quality medicines also requires more impact-oriented research and regulators who make better use of research findings (Newton et al., 2019; World Health Organization, 2017). Regulators operate within a complex landscape of diverse goals and interests, which necessitates a careful, cautious and confidential approach (Hamill et al., 2021). This closed way of working hinders the sharing of valuable lessons and innovation. Academic researchers can help regulators by developing new methods and strategies for understanding medicine quality issues and creating and evaluating interventions.

A key aspect of impact-oriented research is stakeholder engagement. Numerous studies, in the health sector and beyond, have shown the benefits of engaging stakeholders in research: stakeholders can provide valuable knowledge and experience, help align research to local needs and circumstances, and improve its usefulness and legitimacy (Boaz et al., 2018; Borst et al., 2023; Kok et al., 2012, 2016). There is also evidence that engaging potential key users in research increases the likelihood that results will be used (Kok et al., 2016; Lavis et al., 2003).

While several evaluations point to the benefits of engaging stakeholders, recent studies have shown that it can actually be challenging to engage stakeholders in research (O'Shea et al., 2021). Stakeholders may be uninterested or too busy, and constructively involving the right actors can require a lot of time and effort (Boaz et al., 2021a; Oliver et

al., 2019; Pisani & Kok, 2017). In Indonesia, it is standard practice to engage stakeholders during the dissemination of results, but intensive stakeholder involvement throughout the course of a study is uncommon (Nugroho et al., 2018).

In this article, we examine an attempt to combine an impact-oriented, engaged research approach with intersectoral collaboration in medicine quality research in Indonesia. There are three reasons why this medicine quality research was conducted in Indonesia. First, in 2016, the country experienced a widely-publicised case of vaccine falsification, which resulted in approximately 1,500 children being injected with fake products (Hasnida et al., 2021). This created a policy window to work on medicine quality. Second, the government had recently reformed pharmaceutical procurement and significantly pushed down prices, raising concerns regarding medicine quality (Anggriani et al., 2020; Hasnida et al., 2021). Third, Indonesia has a large domestic pharmaceutical market, with over 26,000 authorized medicines, and a relatively well developed regulator who was interested in developing new methods to detect unsafe medicines (Karensa, 2016). The research team pursued an impact-oriented research strategy that required intersectoral stakeholder engagement. Throughout their project, the researchers sought collaboration with the regulator and other relevant stakeholders, anticipating that these partners would contribute to understanding issues with medicine quality, designing new methods and approaches, and interpreting and applying findings.

While there is a clear need for more impact-oriented research on falsified and substandard medicines, the best way to organize this research and engage stakeholders remains unclear. Insights into strategies for intersectoral stakeholder engagement could help to better organize research and apply the findings, thereby contributing to the fight against substandard and falsified medicines.

The aim of our study is to assess how intersectoral stakeholder engagement in research collaborations on medicine quality evolved and influenced research, people and organizations, as well as the uptake of the results. While we followed three interlinked research projects, this prospective analysis focuses on STARmeds, the most recent project, which set out to estimate the prevalence of substandard and falsified medicines in Indonesia. We present data from interviews, observations, and document analysis that show that intersectoral stakeholder engagement was feasible, yet challenging.

We argue that intersectoral engagement requires a significant effort and a strategic and adaptive approach, effective coordination and platforms for engagement, a careful framing of the problem, and attention to the nature of the field.

Analytical framework

To guide our analysis of stakeholder engagement in medicine quality research, and illuminate its processes and influences, we draw upon insights from the literature on Knowledge Translation and Collaborative Governance.

Stakeholder engagement in impact-oriented research

Recent studies on research utilization provide an empirically grounded perspective on how research and engagement processes evolve and how results are translated into policy and practice (Borst et al., 2023; Hegger et al., 2016; Kok et al., 2016). These studies show that the use of research is influenced not only by the results and efforts of users but also by the embedding of research processes, the involvement of stakeholders in designing, conducting, and interpreting the research, and developments in the broader context. These studies also show that the ideas that researchers formulate about how results will be used influence who they perceive to be stakeholders and how and when they engage these stakeholders (Borst et al., 2019; Kok et al., 2016; Kok & Schuit, 2012).

These insights inspired our study of stakeholder engagement in research. Specifically, we:

1. Adopt a process perspective and analyze how research, embedded in a specific context, develops, progresses, and gains meaning, as well as how efforts are made to apply the results.
2. Explore the ideas of researchers and other stakeholders about how results should be used, and how this itself shapes the stakeholder engagement strategy.
3. Examine how stakeholders are involved in the research process and how their involvement influences research activities and vice versa.
4. Analyze the influence of broader structures and dynamics in the context, including recent events and policy changes that affect the research activities and stakeholder engagement.

Key elements in Collaborative Governance

An interesting aspect of the stakeholder engagement strategy in the STARmeds project is that it required intersectoral collaboration. The literature on Collaborative Governance provides inspiration for analyzing how diverse organizations can work together to achieve a public goal (Ansell & Gash, 2008). According to the literature, such intersectoral collaboration requires four key elements:

1. **A shared objective**: the willingness of diverse stakeholders to work towards a common goal.
2. **Effective coordination**: a neutral facilitator needs to coordinate the process.
3. **A forum for deliberation**: a platform for stakeholders to meet, discuss, and make decisions.

4. **Inclusive participation**: engaging all stakeholders that are relevant to solving the problem.

Our prospective study focuses on stakeholder engagement in research. The four elements of Collaborative Governance provide inspiration specifically for our analysis of the intersectoral aspect of the stakeholder engagement.

Methods

Study design

For this prospective case study, we combined interviews, observations and document analysis to investigate how a research project and its intersectoral stakeholder engagement strategy evolved over time and how different research-related contributions were realized. More details about our methodological approach are available in the supplementary material of Consolidated Criteria for Reporting Qualitative Research (COREQ) reporting form (Supplement 1).

Analytical approach

Our analytical approach was inspired by Contribution Mapping, a method that is designed to analyze how research and translation processes evolve and are shaped by the actions of the researchers and those with whom they interact (Hegger et al., 2016; Kok et al., 2016; Kok & Schuit, 2012). This approach focuses on how these processes evolve, and how they are shaped by historical developments, pre-existing networks and larger structures and dynamics in the context, and how these influence the uptake of the findings. As is common in Contribution Mapping, we focused on the actors involved in, or interacting with, the research project and the most likely key users in Indonesia.

A key part of Contribution Mapping is the development of a chronological process map, which contains a detailed analytical description of core activities, interactions and events that happen before, during and after a research project (Kok & Schuit, 2012). This three-phase project map provides a structure for data collection and analysis and for the presentation of the results. The chronological approach helps assess how actions, interactions and developments in the preparation and initial phase of a study influence how research and engagement processes evolve and results are interpreted and taken up.

While our study focuses on the process of stakeholder engagement in the STARmeds project, we drew inspiration from the literature on Collaborative Governance to analyze the intersectoral aspects of the stakeholder engagement strategy.

The case

In this analysis, we focus on the stakeholder engagement in the STARmeds research project. This project was the third of three interlinked studies into medicine quality in Indonesia (see Figure 1). We chose the STARmeds project because it had the most comprehensive stakeholder engagement strategy, which included an intersectoral working group. One of the work packages of the STARmeds project focused on analyzing the process of stakeholder engagements and how this shaped both the research and the uptake of the results. The current paper results from that part of the STARmeds study.

In the result section, we explain how the STARmeds project was developed upon the foundation of the two other projects (Figure 1). As we will show in the paper, these previous engagements were formative in that they contributed to the underlying framings of the issues at hand and established relations with the stakeholders who were subsequently engaged in STARmeds, including the national medicine regulator, the Ministry of Health, the national health insurance agency and representatives from the pharmaceutical industry.

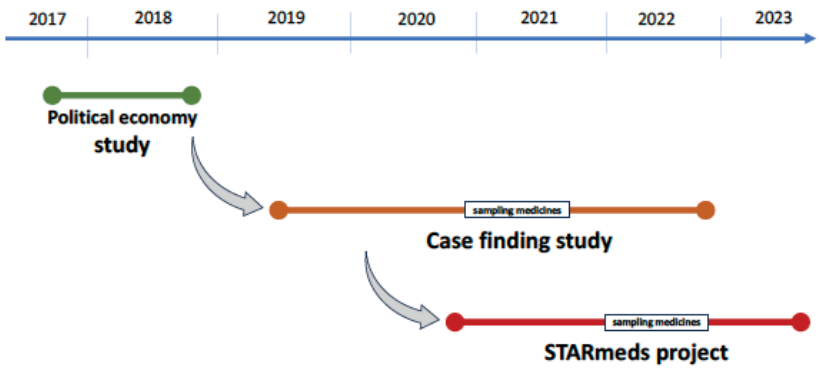
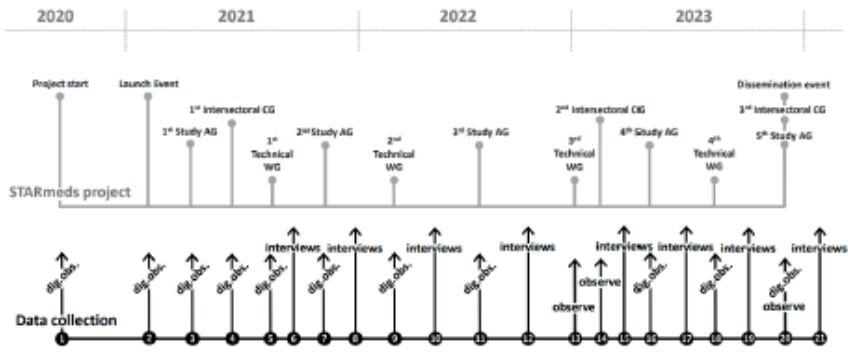


Figure 1. Timeline of different medicine quality studies in Indonesia

Data collection

Figure 2 provides an overview of the data collection during the STARmeds project.



Year 2020

1. Digital observation: Project start

Year 2021

2. Digital observation: Launch event
3. Digital observation: 1st Study Advisory Group
4. Digital observation: 1st Intersectoral Consultative Group
5. Digital observation: 1st Technical Working Group
6. Interviews (N=2): after 1st Technical Working Group
7. Digital observation: 2nd Study Advisory Group
8. Interviews (N=2): after 2nd Study Advisory Group

Year 2022

9. Digital observation: 2nd Technical Working Group
10. Interviews (N=2): prior to 3rd Study Advisory Group
11. Digital observation: 3rd Study Advisory Group
12. Interviews (N=12): after 3rd Study Advisory Group

Year 2023

13. Observation: 3rd Technical Working Group
14. Observation: 2nd Intersectoral Consultative Group
15. Interview (N=4): after 2nd Intersectoral Consultative Group
16. Digital observation: 4th Study Advisory Group
17. Interviews (N=5): after 4th Study Advisory Group
18. Digital observation: 4th Technical Working Group
19. Interviews (N=3): between Technical Working Group & 3rd IWG & dissemination meeting
20. Observation: dissemination meeting & 3rd ICG, and digital observation of 5th SAG
21. Interviews (N=5): after 5th Study Advisory Group

Figure 2. Timeline of data collection of policy learning study throughout the STARmeds project

Observing meetings

Between October 2020 and the end of 2023, we observed 24 meetings, with AH mostly acting as observer. There were different types of meetings. For the intersectoral consultative group (ICG) (n=3), the STARmeds team invited senior officials, key opinion leaders, and decision-makers from various public, private, and non-governmental organizations. The Technical Working Group (TWG) meetings (n=4) were organized to get technical input from stakeholders regarding data collection, analysis, and interpretation. The Study Advisory Group (SAG) meetings (n=5) involved national and international experts and practitioners to advise on research plans and activities. There were also institutional audiences (n=11) with particular organizations to discuss substantive topics such as obtaining a research permit or interpreting laboratory testing results. At the end of the project, the researchers organized a large dissemination meeting. Meetings lasted on average 2 hours. Due to the Covid-19 pandemic, most meetings (18 out of 24) were held and observed online. Twenty-two (out of 24) meetings were audio-visually recorded; the recordings were not transcribed verbatim. Consent to record as part of the data collection was sought before the meetings started. Two meetings could not be recorded due to the confidential nature of what was being discussed. We were, however, allowed to observe these meetings and made detailed notes. Our observations focused on the group dynamics between the STARmeds researchers and other stakeholders as guided by Contribution Mapping and key elements of Collaborative Governance. For more information about key observational points and other technical details, see the COREQ reporting form (Supplementary material 1).

Interviews

To gain further insight into how the stakeholder engagement and research processes evolved, we conducted semi-structured interviews with 37 purposively selected key informants as detailed in Table 1. Interviewees were selected based upon their roles in the research, the stakeholder engagement activities and/or in the engaged organizations (e.g., SAG members, research teams, the medicine regulator, Ministry of Health).

We used an interview topic guide (Supplementary material 2). Our topic guide was structured based on Contribution Mapping and informed by theoretical concepts from Collaborative Governance, and adapted to the role and situation of the participant. We adopted a 'rolling triangulation' approach in which we used the data gathered from earlier interviews, observations and a documentary review to inform the creation of a specific schedule for each interview (Hanney et al., 2003). For more about the development of the topic guide, see the COREQ reporting form.

Interviews were structured chronologically based on the Contribution Mapping approach. First, we asked participants about their background and previous roles and responsibilities and their perceptions regarding medicine quality. We continued by asking participants about their current roles and responsibilities and perspective on medicine quality in Indonesia. We asked participants how they expected results should,

and would, be used, and who and what would play a role in that process. We focused specifically on the engagement strategy and on how the engagement influenced the study and those who were engaged. Regarding the future, we discussed the potential uptake of the results, including any indications that results were informing policy and practice. Lastly, we asked participants to articulate what follow-up actions were needed in the light of the study findings and who should initiate these actions. We recruited interviewees by approaching them by email or in person during a project meeting. Two participants from the public sector did not respond to our interview requests.

Table 1. List of interviewees by roles

Roles	**Frequency**
Medicine regulator	9
Ministry of Health	3
National insurance	2
Pharmaceutical industry	4
Sub-national district authority	1
Procurement agency	1
Other ministries	4
World Health Organization	2
National research agency	1
Knowledge sector professional	1
Other study collaborators	4
STARmeds research team	5
Total number of interviews	37

As shown in Figure 2, we conducted the interviews at various points during the research project.

Interviews were conducted both online and face-to-face, depending on the preference of the participants, research practicalities and the restrictions due to the COVID-19 pandemic. Interviews were conducted either in Indonesian (n=29) or English (n=8), and lasted 40 minutes on average. Thirty-six interviews were audio recorded. During the one interview that could not be recorded, the interviewer made detailed notes. AH led most of the interviews (n=36); one interview was led by MK.

Document analysis

To gain a deeper insight into the background of the project and triangulate our interview and observation data, we analyzed a variety of documents produced throughout the STARmeds project (N=121). We included documents which informed us about how the STARmeds study objectives were initially planned based on research proposals and amendments (n=2), then how the research design was changed and evolved following stakeholder engagement based on meeting minutes (n=95), and ultimately realized

and publicized based on periodic activity reports (n=17) as well as project publications in the media and scientific journals (n=6). We also included one field note from the political economy and risk-flagging study to understand how stakeholder engagement during these two projects shaped the initial STARmeds research design. We excluded internal meeting minutes which were specifically about operations and managerial aspects.

Data analysis

Interviews were transcribed verbatim. Data analysis started with developing a general timeline of the case study, including the research activities, stakeholder engagement processes and influence of events in the context. This general timeline was structured according to the three-phase process map (before the start of STARmeds, during STARmeds and after the results were finalized). We used an abductive approach and thematic analysis to identify patterns of information emerging from the data (Iddo Tavory & Stefan Timmermans, 2014). We developed a coding tree by performing open coding followed by axial coding (Mays & Pope, 2000). During three workshops, AH, MK, RM, SS, YN and FF read multiple sets of interview transcripts and highlighted important information. Emerging themes were discussed during the plenary sessions and we agreed on a first list of codes. Next, during the axial coding steps, the codes were refined by coding another set of transcripts. Our coding tree is included in Supplementary material 3. We then applied these codes to all transcripts, observation notes and documents for analysis.

We then linked the emerging themes to the process map to present our results in a detailed chronological narrative. Between these steps, we organized several sessions between AH, RB and MK to discuss emergent theoretical themes, leading to the use of Collaborative Governance theory to enrich the analysis. We used ATLAS 24.2 as qualitative data analysis software. For more information about data analysis, see the COREQ reporting form.

Results

We present the results chronologically in three consecutive phases: (1) the research and policy context prior to the study and during proposal development, (2) the conduct of the STARmeds study, and (3) the finalization and dissemination of results. In each phase, we examine how research activities and engagement processes evolved, the role of stakeholders, and the influence of contextual structures and dynamics.

Setting the stage: medicine quality incidents in Indonesia

In 2016, Indonesia was rocked by the discovery of fake measles vaccines given to children for over a decade, propelling the issue of medicine quality to the top of the political agenda and prompting a major overhaul of the national medicine regulator. The following year, a multinational research team, coordinated from Erasmus University Rotterdam, began investigating the political and economic factors driving the proliferation of falsified and substandard medicines in middle-income countries (Hasnida et al., 2021; Nistor et al., 2023; Parmaksiz et al., 2020; Pisani et al., 2019). The developments in Indonesia were highly relevant. Besides the scandal with fake vaccines, there were also worries about substandard medicines entering the regulated supply chain. The Indonesian government had reformed procurement policies, resulting in significantly reduced medicine prices (Anggriani et al., 2020). In various forums, manufacturers, distributors and patients voiced concerns that these low prices might compromise product quality.

An Indonesian researcher on the multinational team investigated the root causes of a fake vaccine scandal. Her analysis revealed that unmet patient demand created an opportunity for criminals to sell falsified vaccines (Hasnida et al., 2021). Additionally, she found that procurement systems, by pushing prices excessively low, could incentivize companies to cut corners, potentially resulting in substandard medicines. After presenting their findings in 2018, the team initiated a follow-up study to identify which medicines were at the highest risk of poor quality. They aimed to test whether market-risk indicators—such as low prices or company history—could reliably predict medicine quality. Developing these indicators required detailed data on the pharmaceutical market and regulatory inspections. To conduct the study, the researchers collaborated with scholars from a university in Jakarta which had experience studying medicine prices in Indonesia and a strong working relationship with the national drug regulator (Anggriani et al., 2020). Using the risk indicators, the researchers planned to send mystery shoppers to three regions in Indonesia to buy specific products, which would then be quality-tested in a lab.

How the engagement evolved in previous research

During the initial two studies, the research team actively engaged stakeholders, expecting them to provide valuable data and insights that would enhance the research's relevance and increase the chance of its results being applied. The researchers focused on engaging the national medicine regulator. The researchers presented their proposals and conducted a formal meeting with the regulator, discussing the uncertainties surrounding the prevalence of poor-quality medicines in Indonesia. The regulator expressed interest in new methods for post-market surveillance and agreed to future meetings. Engagement with the regulator continued in 2019 as part of the risk-flagging study.

Developing the STARmeds research proposal

While the risk-flagging study was ongoing, the research team submitted a proposal to a

UK funder for a larger study on the prevalence of poor-quality medicines in Indonesia. This new study, called STARmeds, was led by a principal investigator from Imperial College London, in collaboration with researchers from Universitas Pancasila in Indonesia and Erasmus University in the Netherlands. The primary aim of STARmeds was to estimate the prevalence of substandard and falsified medicines in Indonesia, as well as to assess the societal costs associated with poor-quality medicines. STARmeds was designed based on the groundwork of the risk-flagging project, building upon the same team, network, and sampling locations.

Planning intersectoral stakeholder engagement

From the beginning, stakeholder engagement was ingrained in the research strategy. The researchers had designed a specific engagement strategy with three components. First, the project would establish an intersectoral consultative group, with representatives from public, private, and non-governmental organizations who would contribute data, knowledge, and experience to jointly develop the new prevalence estimation method. Second, the researchers envisioned an institutionalized partnership between academia and policymakers, which would be convened by an Indonesian ministry with an overarching coordinating role. Third, to foster collaboration, the researchers proposed to conduct part of the work from the regulator's office.

During the first two studies, the researchers had learned that engaging the regulator was not a straightforward process. One of the challenges was that the medicine regulator had a distinct role within the system, necessitating independence, confidentiality and strict adherence to formal procedures. One of the researchers explained:

> *"Regulators should follow the strict line of authority …[…]...they have a different mindset, while researchers are way more flexible." (notes from observations)*

Preparing to implement STARmeds during COVID-19

In May 2020, the researchers learned that the STARmeds project was approved. Meanwhile, the world had drastically changed. The COVID-19 pandemic had reached Indonesia, significantly impacting research planning and stakeholder engagement. The regulator was occupied with evaluating and authorizing pandemic-related medical products, leaving little time for joint activities. In-person collaboration at the regulator's office was no longer feasible, and all stakeholder engagement had to shift online.

While the regulator was busy with COVID-19, the researchers wanted to secure institutional support from the regulator. To guide this effort, they enlisted a former chief medicine regulator as an advisor. Securing institutional commitment for collaboration proved challenging due to rapid turnover of senior staff, organizational fragmentation, and concerns about data usage.

> *"We had to present (the research design) in many directorates. It was not only to the post-market surveillance directorate but also to the research directorate, to high-level decision makers...[]…But sometimes the people changed, then we started presenting again…[]…In the beginning we put the (proposal) letter with the name (of the official) but when we followed up two weeks later, the people were changed. After that we just put the name of the directorates (on the letter)."* (researcher)

Forging a network and building trust

As Indonesia entered lockdown, the research team started to implement its stakeholder engagement strategy. A first challenge was to develop a shared commitment among diverse stakeholders and gather their input for refining the study design. The researchers aimed to convene stakeholders in an intersectoral working group hosted by a government organization. However, the initial response from stakeholders revealed that fostering collaboration toward a common goal was not easily accomplished.

> *"One of the challenges […] the silos between institutions and even within institutions. You know between deputy X and deputy whatever. It's kind of a complete silo effect. You know that sectoral ego thing is huge, particularly in this space. You've got civil war basically between the regulator and ministry… Within the ministry between the different divisions. Then you've got the procurement agency struggling with the ministry about sectoral versus national. Then, on top of that, the insurance agency doesn't speak to the ministry. And then, oh, the regulator won't speak to the industry at all."* (researcher)

Given the differing perspectives and priorities among stakeholders, and with many preoccupied by the COVID-19 pandemic, the researchers decided to adapt their engagement strategy. The researchers decided to serve as conveners for the intersectoral consultative meetings, using their status as neutral outsiders to facilitate collaboration.

During the online intersectoral meeting, senior staff from key ministries and other government organizations attended, and a member of parliament delivered remarks in support of the project.

> *"The theme of this research is currently an ongoing discussion (in parliament). The role of medicines in the Indonesian health system is very vital, especially as we have seen so far during this pandemic. It is important to provide a rational dosage of medicines to patients and it is also equally important to ensure the safety and quality of medicines on the market." (notes from observation)*

Formalizing the collaboration with the regulator proved more challenging than anticipated. While the regulator maintained interest in the project, it became increasingly clear that they saw the study not only as an opportunity but also as an added task and potential risk. Some officials expressed concerns that the study could

serve as an evaluation of their performance, while others questioned how to structure the collaboration to avoid the risk of the regulators becoming mere data suppliers. The researchers reassured the regulators that the study was not intended to evaluate their work and promised to discuss findings before making them public. Data confidentiality emerged as another concern, resulting in lengthy negotiations over contracts and multiple meetings and presentations.

> *"Again and again, like more than five times. Until we were very bored. Oh my god, its again and again. And even though there are no changes, a new person came in and asked again similar things and then sometimes they were very vocal. They say it's not possible, it's a big change. But we already agreed in the previous meetings. But the new person came and said: 'This is a no. Not possible'. And then, fortunately, some person from the old discussions explained to them that we already discussed this in the previous meeting."* (researcher)

The regulator also expressed concern about the workload involved in managing the data that the researchers had requested to develop the risk indicators. To avoid overburdening the regulator, the researchers agreed that they would handle the bulk of the data management and analysis. A senior official explained that the trust that had been built during previous interactions with the Indonesian scholars proved instrumental in addressing these concerns and fostering the collaboration.

> *"I have trust…[]…Trust in the study leader also influenced me. So trust grows from the people we already know."* (regulator)

While the formal agreements laid the groundwork for data sharing, the responsibility for the data within the regulator's large organization was less defined. Multiple departments were involved in managing key datasets, raising questions about roles and responsibilities and necessitating internal coordination. Some data requests that the researchers anticipated to be simple proved to be complex for the regulator, resulting in lengthy waiting periods.

Engaging stakeholders in selecting which medicines to sample

The researchers engaged the Ministry of Health and other key stakeholders in designing the sampling strategy. A crucial decision was determining which of the thousands of medicines on the market would be included in the study. With a budget sufficient to collect and test approximately 1,200 samples, the researchers planned to select five or six different medicines. Different stakeholders proposed different criteria for selecting the medicines. The researchers focused on public health importance, risk groups and the feasibility of collecting samples. The Ministry of Health was concerned about antimicrobial resistance and proposed the inclusion of antibiotics. The regulator advised medicines with a record of abuse, such as tramadol. After careful deliberation, the researchers decided to include five prescription-only medicines: amoxicillin, amlodipine, cefixime, allopurinol and dexamethasone.

Changing the research design

In June 2021, after numerous meetings and negotiations, the formal agreements between the universities and the regulator were finally concluded, and the researchers gained access to existing inspection data that had been collected by the regulator. Using the data from the regulator, the researchers started to model and test their ideas about the risk categories, and soon found that there was no clear association between the risk-indicators and the results of previous inspections. The researchers presented these findings during a technical working group with the regulator and decided to modify their study design. Instead of trying out a risk-based sentinel surveillance approach, the researchers opted for a sampling strategy that focused on price variation, as this was thought to be the most likely risk factor influencing the quality of medicines.

Another incident influencing stakeholder engagement

In early 2022, while the researchers had started data collection, another major incident with dangerous medicines emerged, propelling the issue of medicine quality to the top of the political agenda once again and influencing stakeholder engagement (MohanaSundaram et al., 2023). Several Indonesian manufacturers failed to test a medicine's raw ingredients and used a highly toxic chemical to produce children's cough syrup. The contaminated syrup caused acute kidney failure, killing over 200 children. This tragic case demanded the full attention of the regulator, limiting its ability to participate in other research. The incident, however, did underscore the importance of medicine quality and inspired other stakeholders to participate more actively in the STARmeds study.

Deliberation on the estimation methods

While data collection for the STARmeds study was ongoing, two other medicine quality studies in Indonesia reported their findings (Dewi et al., 2022). These studies had tested medicines that were also included in the STARmeds study. Both studies found that the prevalence of substandard medicine was low and there was no relation between the price and quality of the medicines.

Once the laboratory testing results became available, the STARmeds team began estimating the national prevalence of falsified and substandard medicines in Indonesia. During the risk-flagging study, the researchers had obtained data on medicine sales volumes in the Indonesian market, which showed that many common medicines had numerous product varieties with diverse market shares. If a product with a large market share was found to be substandard, it would impact many more patients than a product with a smaller sales volume. Therefore, the researchers proposed incorporating sales volume data into their prevalence estimates.

Meanwhile, stakeholders in the technical working group began questioning the goal of estimating the nationwide prevalence of poor-quality medicines. The primary concern, raised by the regulator and other stakeholders, was that the researchers planned to

present a national prevalence estimate based on a study that included only five types of medicines, despite thousands being authorized for the Indonesian market.

> *"My real concern is that the systems thinking is good, but the data is very limited. So, if the data is only for five medicines, then we assume (quality) per product types, for example amoxicillin tablets … […] But if the quality of all medicines is estimated (nationwide), where does the data come from? We need more data to conclude that. The most sensible thing is to only make estimates of the prevalence of these five types of medicines."* (manufacturer)

A changing perspective on the role of stakeholders

Once the initial results became available, the dynamics of the stakeholder engagement process shifted. The researchers observed that several stakeholders became more active in the discussions.

> *"I remember when we had our very first working group where it was like you were talking into a big blackhole, there were no questions, there was no engagement, there was nothing…[] and I think last week when we had the technical working group there was more engagement. I could see that. I think it had also to do with the fact that…[]…maybe beforehand they couldn't quite imagine what kind of research would look like that we are producing. And I think that it wasn't until it was on paper that they understood what this is about. They kind of saw the value of it."* (researcher)

The researchers' perspectives on the stakeholders had also evolved. After nearly two years of interactions, the researchers had gained a deeper understanding of the stakeholders' roles, responsibilities, and ways of working. Initially, the researchers focused primarily on the regulator, expecting it to be the key user of the study results. While some staff expressed interest, the regulator remained unconvinced about the necessity of a new prevalence estimation method and continued to adopt a formal and risk-averse approach to collaboration.

Meanwhile, the researchers began to recognize the strategic role that the Ministry of National Planning (MNP) could play in utilizing the findings. Responsible for overseeing key development indicators, the MNP was interested in the study's results, as the prevalence estimate provided an independent validation of the regulator's performance.

The researchers also reconsidered their approach to engaging industry. Despite recommendations from other stakeholders, the research team had opted against involving industry from the start, fearing it would hamper the engagement of the regulator. This lack of early engagement led to issues in the project's second year when the researchers sought industry assistance to confirm medication packaging for identifying fake products. Industry representatives were taken aback by the request, as they had received

minimal information about the study, and many did not respond.

Finalizing the results and disseminating them to stakeholders

Despite skepticism from some stakeholders, the researchers proceeded with their plan to calculate a national prevalence estimate. On the basis of 1,274 tested samples, they estimated that the prevalence of substandard and falsified medicines in Indonesia was 4.4%. Although the researchers employed a different method, their estimate did not differ much from the regulator's routine inspection results, which reported a prevalence of 4% in 2022.

In October 2023, the results were presented at a large dissemination meeting attended by a diverse group of stakeholders. During the presentation, the researchers compared their prevalence estimate with the regulator's inspection results, concluding that post-market surveillance was effectively implemented in Indonesia. At the meeting, senior staff from the regulator responded positively to the study results, expressing relief that the findings aligned closely with their own inspection results. During a follow-up interview, the regulator adopted a more skeptical stance, continuing to question the validity of a nationwide prevalence estimate based on a sample that included only five different types of medicines.

Another finding highlighted by the researchers was that there was no relationship between the price and quality of medicine. This finding meant that the government's efforts to reduce the prices of publicly procured medicines did not compromise their quality. This conclusion drew critical comments from industry representatives, who argued that the researchers had only assessed the active pharmaceutical ingredients. They pointed to the recent cough syrup case, where many children died due to the poor quality of excipients—an aspect not tested in the STARmeds project (Schier et al., 2023).

A second finding was the ease of purchasing prescription-only medicines from unlicensed outlets. The researchers pointed out that many Indonesians obtain their medicines from unlicensed outlets. In routine inspections, the regulator only checked to see whether the products that were illicitly sold were falsified, but did not assess their quality. The researchers recommended to test for substandard products as well. During the follow-up interviews, the regulator remained critical of this idea, and argued that it was not part of its mandate to ensure the quality of medicine that was sold illegally.

The STARmeds project had also resulted in outputs that could be used in other countries, including a method for estimating the cost of sampling and testing and a toolkit (Valente de Almeida et al., 2024). A regulatory expert highlighted the possibilities of these methods, but warned that applying them elsewhere would not be easy.

> *"Certainly, countries should be able to apply this methodology. But..[]… having academics carrying this (methods) out is one thing. Having a regulator is another, who has a range of other duties. So, I think there's a good argument there for engaging with academic institutions."* (Regulatory expert)

Intersectoral collaboration as output

While there were no indications that the findings were directly applied in Indonesia, the study did result in the formation of an intersectoral network focused on medicine quality. Stakeholders noted that their involvement in the study made them aware that ensuring medicine quality is not solely the responsibility of the regulator, but is also influenced by other organizations.

> *"As a person who procures goods and services, I now feel I am responsible for this. Why? Because the medicines purchased by the government follow our rules. Is it sufficient to use market authorization as a preliminary quality assurance? So far, we have never made specific criteria for the quality of medicine that must be listed on the procurement platform. So far, we assumed that if a market authorization has been issued, it means the drug is fit for distribution."*

Several stakeholders praised the collaboration between the study and government organizations. A regulator staff member emphasized that this experience increased their awareness of the benefits of partnering with academia and other sectors to address medicine quality issues. One of them explained:

> *"We did not realize what potential (work) can be maximized by joining forces with other stakeholders."*

During the last intersectoral meeting, researchers asked stakeholders about the future of the intersectoral forum following the study. Stakeholders expressed interest in continuing the platform, suggesting it be broadened to include pharmaceutical policy and access to medicines (Fanda et al., 2024).

While participants agreed to continue the forum, there was uncertainty about who should organize it. Researchers advocated for government leadership, while some stakeholders proposed that the regulator take charge. Others suggested that the Ministry of National Planning serve as the overarching coordinator. A staff member from the MNP proposed to convene a meeting to discuss this plan and to organize a first meeting in 2024.

Discussion

The aim of our study was to assess how intersectoral stakeholder engagement in medicine quality research evolved, influenced research processes and participants, and affected the uptake of results. Our findings show that while engaging stakeholders was challenging, it proved beneficial. Stakeholders provided valuable data and insights that informed the research process. They were introduced to new ideas, methods, and roles, becoming integral members of an intersectoral network focused on medicine quality. However, engaging stakeholders was labor-intensive and required an adaptive and strategic approach, taking into account the diverse priorities and interests of stakeholders as well as the cautious nature of the field.

Our analysis provides insights into the efforts and strategies required for effective stakeholder engagement in impact-oriented research. Our results show that stakeholder engagement requires considerable effort and substantial time and dedication (Boaz et al., 2021b; O'Shea et al., 2021). Rapid turnover of staff and organizational changes among stakeholders can further complicate engagement, necessitating persistence, patience, and a willingness to continually build relationships with new staff. Our analysis highlights the importance of formalizing collaborations and aligning them with institutional goals to reduce dependence on individual support (Hoekstra et al., 2020).

Previous research highlights the role of trust in effective engagement of stakeholders (Boaz et al., 2018; Kok et al., 2016). We found that stakeholder engagement benefitted significantly from personal relationships and trust developed during previous projects, as well as the strategic involvement of trusted individuals, such as a former director of a key stakeholder organization. Moreover, as actors frequently change, trust-building is a continuous effort. These findings underscore the importance of investing in long-term partnerships that extend beyond a single project and in building relationships with both individuals and institutions (Oortwijn et al., 2024; Zych et al., 2020). Developing procedural arrangements, such as memorandums of understanding, can help sustain collaborations during transitions in personnel.

We found that a lot of efforts necessary to engage stakeholders and establish effective collaboration did not take place during formal meetings, but rather behind the scenes. While much of the work for organizing the formal meetings could be handled by junior staff and an engagement manager, senior researchers, who held significant respect and trust, had to engage in informal discussions before and after meetings, which was key to making the collaborations work. The need for both front-stage and backstage work has also been highlighted in other studies (Bekker et al., 2010). We would add that effective coordination is essential between activities conducted in front of and behind the scenes, as well as among the various individuals involved.

Our analysis shows that stakeholder engagement requires a strategic approach. The first element of this strategic approach is the development of a framing of the research that is suitable for gaining support and commitment from stakeholders. To develop an appealing framing, the research team explained to each stakeholder how they could contribute to tackling an important problem, while also taking into account the different needs, concerns and interests of the individual stakeholders. This actor-specific framing occurred, for example, when the researchers sought to alleviate the regulator's concerns by emphasizing that the project should not be viewed as an evaluation of the regulator, but as an opportunity to jointly develop new methods and approaches.

The second element of this strategic approach is to carefully consider who should be engaged, when, and for what purpose. Whereas the literature about Collaborative Governance suggests that stakeholder identification is something that should be done at the start of a project, we found that this is actually a continuous undertaking and dependent on evolving ideas about the meaning of the results, how results could be used and who should play a role in that process (Boaz et al., 2018).

Our analysis also shows that one should be aware of the limits of stakeholder engagement. In the STARmeds project, the research team initially focused on the regulator as the potential key user and engaged them from the start. At their preference, the researchers involved the industry only towards the end of the study. While this may have helped secure the regulator's engagement, it ultimately complicated the process of confirming sample packaging. This finding aligns with other studies that emphasize the importance of carefully considering who is involved and when, as there are trade-offs and a limited number of stakeholders that can be actively engaged (O'Shea et al., 2021). In future research, experimenting with strategies to involve a more diverse array of stakeholders, such as civil society and community representatives, may be beneficial.

We also found that researchers need to be flexible in order to benefit from the input from the stakeholders. The research team that we observed had planned a study in which they could incorporate the input of the stakeholders, for instance in the selection of medicines. The input of the stakeholders, including the data that they provided, inspired the researchers to make significant changes to their study design. While in this case study the research funder agreed with this change in research design, this flexibility is not always provided. Other studies report similar adaptations that are made as a result of the input of stakeholders, and suggest that these adaptations help align research to needs and increase the likelihood that results will be used (Kok et al., 2016).

We observed that, in relation to this flexibility, there was also a willingness of the research team to adapt to the needs of stakeholders, by giving updates and presenting some preliminary results or providing some analytical support. While these efforts may have sometimes distracted the researchers from their core tasks, they helped forge the collaboration. This finding suggests that it can be helpful to allocate some dedicated resources for stakeholder engagement and arrange for operational flexibility in the

planning of research (Boaz et al., 2018).

According to the literature, inter-organizational collaboration to achieve a public goal needs a forum for deliberation and coordination by a relatively neutral facilitator (Ansell & Gash, 2008). In the STARmeds project, there were multiple platforms for engagement. The most ambitious platform was the intersectoral consultative group, in which a variety of stakeholders was brought together, who had to be convinced that they could play a role in better understanding and tackling problems with falsified and substandard medicine. The researchers organized and facilitated these meetings, which had both advantages and disadvantages. The researchers took on the role of convenor of the intersectoral meetings after they became aware of the difficult relationships and lack of cooperation between some of the organizations that played a role in the field of medicine quality. The researchers were eager to make the collaboration work, had a dedicated budget for the engagement, and had a relatively neutral position which allowed them to navigate the politically charged topic and coordinate the process. We found that the meetings facilitated the collaboration of diverse stakeholders, fostered a shared framework for addressing medicine quality issues, and helped develop and strengthen relationships.

Having academics organize such meetings also has disadvantages. As relative outsiders to policy processes, they have little formal authority, which can make it more difficult to involve high-level decision makers. A second disadvantage is their dependence on project funding, which can cause carefully built partnerships to disintegrate when a project concludes. In Indonesia, there seems to be sufficient interest among those involved to continue the platform, and by broadening the subject there seems to be a good chance that this collaboration will continue.

We found no indications that the research results were directly applied in Indonesia. This is not unusual, as studies of research use suggest that results are often not applied immediately, but only over time, in a more conceptual way, and contribute to change through a more cumulative process (Hanney et al., 2015; Weiss, 1980). We did find that the stakeholder engagement led to several relevant developments and beneficial outcomes. One key outcome was the formation of an intersectoral network of organizations that recognized their role in combating poor-quality medicines in Indonesia. At the heart of this network was a shared understanding that market dynamics, such as product shortages, price pressures, and financing flows, could influence the production, distribution, and consumption of poor-quality medicine. This suggests that the engaged research strategy succeeded in reframing the problem of medicine quality and fostering collaboration, which are crucial steps toward protecting patients from ineffective and unsafe products and ensuring that the medicines they receive work as intended.

Based upon our analysis, we have formulated 12 suggestions for intersectoral stakeholder engagement, which are presented in Table 2.

Table 2. Practical recommendations for intersectoral stakeholder engagement

- **Recognize that effective stakeholder engagement is a continuous process requiring substantial effort and resources.** Ensure the allocation of adequate resources – such as time, funding, and personnel – to support engagement activities.
- **Map key stakeholders and strategically plan when and how to engage them.** Recognize that stakeholders have distinct roles and vary in influence and interest. Anticipate the potential consequences of each engagement choice, as engaging with one stakeholder can impact your ability to engage others.
- **Engage stakeholders from the start.** Involve stakeholders early in the research process to collaboratively shape priorities, objectives, and methodologies. This early engagement fosters a sense of ownership and promotes long-term commitment to the project.
- **Introduce the study and engagement process thoughtfully.** Tailor the approach and framing to align with each stakeholder's needs and priorities. Providing clear terms of reference helps set expectations and build trust.
- **Jointly develop a shared vision that aligns the goals of different stakeholders.** A shared vision helps bridge differences in priorities and enables stakeholders to work together toward mutually beneficial outcomes.
- **Acknowledge that stakeholders need time to become familiar with the research topic, engagement process, and their potential contributions.** Providing training can enhance their ability to contribute meaningfully, allowing them to grow into their roles over time.
- **Build relationships with individual stakeholders and their organizations.** Staff turnover may necessitate engaging new individuals; therefore, formalizing agreements with organizations can help sustain progress and ensure continuity during staff changes.
- **Ensure flexibility in project planning and stakeholder engagement.** Emerging challenges and unexpected results may alter stakeholders' roles. Be prepared to adapt the research and engagement strategies based on shifting priorities, new insights, and changing problem framings.
- **Build trust by transparent communication, active listening and delivering on promises.** Clarify roles, responsibilities and expectations. Share information regularly, respect diverse perspectives, interests and concerns, and consistently follow through on commitments.
- **Keep stakeholders engaged throughout the project.** Provide regular progress updates on milestones and developments, showcase quick wins and encourage stakeholders to ask questions and provide feedback.
- **Monitor the engagement processes and adapt as necessary.** Solicit feedback from stakeholders and reflect on the process to enhance engagement efforts.
- **Develop a long-term stakeholder engagement strategy**. Build meaningful relationships with stakeholders beyond the scope of a single project and plan continuous engagement activities.

Strengths and weaknesses

Prospectively studying stakeholder engagement in research has both strengths and weaknesses. By conducting a prospective study, we were able to closely monitor and comprehensively capture the changing dynamics of involvement in a multi-year project. However, as resonating with earlier work, this study is quite interdependent (O'Shea et al., 2021) with the progress of the research project that we studied. We would have liked to interview some stakeholders more often. This was not always possible, because stakeholders were also expected to provide input to the STARmeds project and we did not want to overload them with multiple research-related requests in the same period. Our strategy then was to triangulate the information obtained from observations with interviews and document analysis. Although the participants were aware of the fact that our research team observed them as part of stakeholder engagement in research, some still asked us about our opinions regarding this process and the interpretations of the STARmeds study findings, which we politely declined to answer. They nonetheless indicated that they were not disturbed by our presence and their awareness of it did not influence our findings.

Conclusions

Tackling substandard and falsified medicines requires collaboration, impact-oriented research, and the effective application of results. Our study demonstrates that intersectoral stakeholder engagement in medicine quality research is challenging yet beneficial. Engagement helped build trust and relationships between researchers and stakeholders, forged a diverse network of organizations committed to combating poor-quality medicines, exposed the medicine regulator to new methods, inspired stakeholders to adopt new roles and better utilize existing data, and advanced a research-policy partnership forum on pharmaceutical topics. However, making intersectoral stakeholder engagement effective posed challenges: it required sustained efforts from a dedicated team, a strategic approach, careful framing of which actors to involve, and thoughtful consideration of when and how to engage. Meaningful engagement also necessitated operational flexibility to seize opportunities and adapt plans based on stakeholder input and contextual changes.

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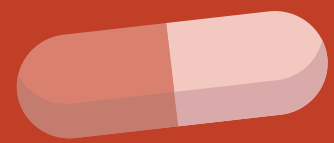
Chapter 7.

Discussing the lessons learned from using a political economy perspective to tackle substandard and falsified medicines

The English language in this chapter has been edited using Grammarly, an artificial intelligence software



In this thesis, I aim to explore insights into broadening the frame and problem definition of substandard and falsified medicines (SFM) by taking a political economy perspective and operationalizing it to contribute to policy agenda-setting. The main question underlying this study is **what can we learn from a political economy approach and how can it shape efforts to tackle SFM.** In this chapter, I will outline the **answers to the sub-research question** of each chapter, followed by a synthesis of the **main insights from the findings** and then reflect on and position the findings within the current literature. I will then discuss the **implications for research policy and practice**. Next, I will provide some **reflections on positionality**. Finally, I will conclude with some **final notes** on this thesis.

Answers to the sub-research questions

Sub-question 1: What is the problem definition of SFM from a political economy perspective?

The historical path in defining the scope of poor-quality medicines globally has shown that although substandard and falsified are described as different types, little has been done to distinguish their risk factors independently from technical and non-technical aspects (World Health Organization, 2017). Chapter 2 of this thesis investigated the political and economic factors driving the production and trade of substandard and falsified medicines (SFM) in Indonesia. Based on a literature review and semi-structured interviews, I incorporated the political economy perspective by taking the political promise of achieving Universal Health Coverage (UHC) as my analytical starting point. Thus, rather than viewing SFM as a purely technical and regulatory problem, my investigation seeks to broaden the scope to understand how SFM is defined as a problem by different actors and organizations and what factors contribute to SFM.

From a political economy perspective, market dynamics are integral to shaping the incentives of various actors within and outside the healthcare system. Market dynamics result from the interaction between procurement, trade, and taxation policies, as well as sociocultural factors such as religious affairs. I argue that the political promise to achieve an ambitious UHC scheme in Indonesia, without a solid structural financial capacity (Pisani et al., 2016), creates various incentives for actors to maintain profit at both the micro and macro levels.

Market dynamics influence the production and trade of SFM, respectively, but with different incentives to protect profits. On the one hand, several factors that reduce revenue, including political promises to provide UHC amidst structural deficits and procurement policies that do not explicitly consider quality, have pushed for extreme price pressure. On the other hand, policies such as trade, religious affairs, and the requirement to certify all medical products as halal, as well as taxation, contribute to increasing production and distribution costs. Consequently, market forces from the pharmaceutical industry may react in two different ways, depending on their incentives.

The first scenario is that the industry may implement cost-cutting, leading to the production and distribution of substandard medicines. In the second scenario, the industry may opt for market withdrawal, resulting in product shortages. Furthermore, I described scenarios where different actors in the health system – e.g., the pharmaceutical industry and healthcare providers – implement profit protection, which leads to a risk to medicine quality.

Broadening the problem definition of SFM using a political economy perspective also leads to identifying distinct market factors for SFM. My research also conceptualized a bridge between the market dynamics as a risk factor for SFM and the technical and regulatory domains. I argue that using a political economy perspective does not mean ignoring that SFM is also a technical issue requiring stringent regulatory oversight. In addition, I described other policy gaps beyond the authority of medicine regulators that may pose risks to quality. For example, procurement policies that do not explicitly consider quality criteria or impose sanctions on pharmaceutical manufacturers that do not comply with the supply of products as contracted in the tender process. Or the lack of capacity to test the quality of medicines. I concluded that, given the systemic nature of the SFM problem, when viewed through the broader frame of a political economy perspective, the quality of medicine is a shared responsibility among various actors both within and outside the health system.

Sub-question 2: How can the SFM problem definition and related assumptions from a political economy perspective be operationalized and tested?

In Chapter 3, I proposed several risk categories and indicators as a case finding system that uses secondary data to flag poor-quality medicines in a resource-constrained market. This is based on the enormous size and diversity of the pharmaceutical market, as well as the high costs associated with testing medicine samples in the laboratory (Valente de Almeida et al., 2024). These factors can complicate the task of medicine regulators in ensuring the quality of medicines in the market or post-market surveillance.

I proposed operationalizing risk factors for substandard and falsified medicines based on the political economy perspective in Chapter 2 into risk indicators. Adapting the principles of disease outbreak response in epidemiology, I divided the risk factors into different risk categories for SFM. These risk categories combine market risks (e.g., profit pressure for substandard or profitability for falsified products) and technical risks (e.g., low detection risk for falsified products or production history for substandard products). Furthermore, I provided some examples of potential risk indicators, the level at which indicators apply, and some rationales behind the formulation of indicators.

I also discussed the utility of case finding and sentinel surveillance as potential approaches to strengthen post-market surveillance, depending on the specific public health objectives. While case finding helps identify products at the risk of being substandard or falsified for immediate market withdrawal, sentinel surveillance aims to measure the prevalence of SFM in the risk clusters where they are most likely to be

found. Concerning priority setting, a clear understanding of the market dynamics and risk factors driving the production and trade of SFM will enable regulators to allocate their resources effectively. While this case finding system is designed to be adaptable in different resource-constrained settings, I have not tested this conceptualized suggestion to understand how it would work in practice.

I further described the operationalization and testing of the case finding approach in Chapters 4 and 5, respectively. To do so, I studied amoxicillin to represent one of Indonesia's antibiotics with the highest utilization volume. In Chapter 4, I described the setup of the quality survey of amoxicillin by considering market dynamics and organization in the Indonesian private market. In the same chapter, I also specifically studied the relationship between medicine price and quality. Meanwhile, in Chapter 5, I operationalized and tested the risk indicators to flag amoxicillin products at the highest risk of being substandard in Indonesia. In this chapter, I refer to the case finding strategy as the risk-flagging approach. Hence, in other words, I explained the process of collecting and testing the samples in Chapter 4, while I described whether and how market risk factors work in practice in Chapter 5.

In Chapter 5, based on the risk categories conceptualized in Chapter 3, I further operationalized them in the Indonesian context into seven substandard risk indicators consisting of market (n=2), regulatory (n=3), and technical risk indicators (n=2), which collectively form the substandard risk index scores. Although I initially targeted substandard index scores of high-risk (score 5) and low-risk products (score 0), the challenges I encountered in finding them in the field led to a different strategy in collecting various risk indices, with the middle-risk (score 3) products constituting the majority of the sample. Therefore, as described in Chapter 4, I adjusted my new sampling strategy to product variety sampling, which aims to collect different brands and dosage forms until saturation in the Indonesian private market.

Chapter 4 aims to assess the quality of amoxicillin products in Indonesia's private market by surveying the variety of products available in different regions and types of outlets, followed by sampling and quality testing, and to understand the relationship between price and the quality of the medicine. I sampled amoxicillin from various locations, such as remote, semi-rural, urban areas, and online. During the sampling, I identified that amoxicillin, a prescription-only antibiotic, is available for purchase and sampling at various outlets, including unlicensed channels. I surveyed 476 outlets selling amoxicillin products, with the majority being pharmacies (68.5%), unlicensed websites (19.7%), and drug stores (10.9%). The latter two outlets are unlicensed to sell amoxicillin. Ultimately, I collected 120 samples, of which 93% were obtained without a prescription. The quality of samples is determined by an independent quality testing laboratory using an assay or the percentages of active pharmaceutical ingredients (API) and their dissolution rates.

Sub-question 3: What are the findings from operationalizing and testing the SFM problem definition and assumptions from a political economy perspective?

In Chapter 4, I described the findings related to quality testing results. I used the technical term 'out-of-specification' instead of 'substandard' to point out samples that did not meet the quality criteria. Among the 120 samples collected, 59 distinct products have unique brands and dosage formulations. These samples collectively represent 95% of the estimated market volume for oral solid formulations and 65% of dry syrup formulations. Fifteen of the 120 samples (12.5%) tested out-of-specification, including 3 out of 10 dry syrups. The tested out-of-specification samples came from both licensed and unlicensed outlets, as well as multiple sampling locations. Considering the product market volume, the oral solid samples tested out-of-specification represented 13.2% of the total market volume, which equates to over 46 million dosages per year.

Another finding refutes the assumption that medicine price can signal quality, which dominates the narrative in the previous chapter. Although I recorded a wide range of prices paid by patients for amoxicillin, I found no relationship between the price and quality parameters of either assay or dissolution.

When testing the risk-flagging approach in Chapter 5, the results indicated that medicines scoring higher on the risk index are more likely to fail the laboratory quality test. However, I found no statistically significant association between the total substandard risk index scores, individual risk scores, group risk indicators, and pharmaceutical analysis results. Therefore, the addition of market risk factors, developed based on operationalizing SFM risk factors from a political economy perspective, did not significantly increase the likelihood of finding products at the highest risk of being substandard. Furthermore, my findings suggest that the risk-flagging approach is highly context-dependent and data-hungry, andas such, requires reasonable and functional regulatory capacity to implement and undertake necessary follow-up actions, including product recalls and enforcement.

Despite the results mentioned above, I believe that the risk-flagging approach has the potential for further exploration to strengthen case finding. One argument is that, in this trial, the distribution of risk scores among sampled medicines was uneven. I collected only three samples scoring 0, four scoring the highest value of 5, and a large concentration (N=41) at a mid-range score of 3. I observed no out-of-specification samples at the lowest risk scores (0 and 1), while the highest proportion (25%) was found among samples with a risk score of 5. While the results suggest that medicine with a high-risk score is more likely to be substandard, the trend is not statistically significant, and a larger sample is required to improve statistical power and further validate this approach.

Another potential lies in one of the market risk factors, namely the low-price product portfolio. Considering the market volume, price, and cross-subsidization across product portfolios within the same market authorization holder, this indicator demonstrated a higher proportion of correctly indicating non-flagged products that meet quality specifications compared to others, namely, low-price amoxicillin. This suggests an

opportunity to refine and further develop this indicator. However, I propose several conditions for its advancement, including combining it as an index with regulatory risk indicators and measuring its specificity objectively. In addition to a larger sample size, as mentioned above, it will benefit from more comprehensive pharmaceutical market and regulatory data, such as fair prices, to determine the threshold for cost-cutting prices. Furthermore, a comprehensive dataset would enable weighting individual risk indicators according to their consequences for quality assurance and selecting arbitrary thresholds for stratified risk scoring, for example, using a three-tiered scale (i.e., low, medium, high risks).

Sub-question 4: How does intersectoral stakeholder engagement contribute to broadening the frame and problem definition of SFM and its operationalization in a research collaboration?

In Chapter 6, I assessed how intersectoral stakeholder engagement in research on medicine quality in Indonesia evolved and influenced the research process, participants, and the uptake of the results. To do so, I followed the stakeholder engagement process in the multi-year Systematic Tracking of At-Risk Medicines (STARmeds) study. The objective of the STARmeds study was to develop methods for estimating the prevalence of SFM. This method was initially designed as a sentinel surveillance, as explained earlier in Chapter 3. It was largely informed by the political economy perspective presented in Chapter 2 and insights from empirical data collection, as outlined in Chapters 4 and 5, the latter of which focused on risk-flagging studies.

From my research in Chapter 6, I understand that effectively engaging stakeholders in SFM research in Indonesia is feasible but challenging. Stakeholder engagement in research requires persistent and cautious effort, including the use of an appropriate framing of the study (i.e., "this research is not an evaluation of the authority") and the operational flexibility of the research team. Engaging stakeholders in SFM research is challenging due to varying stakeholder priorities and needs, and frequent organizational and personnel changes. However, stakeholder engagement is facilitated by trust and relationships built upon previous research projects, as outlined in Chapters 2 to 5 of this thesis.

Since stakeholders have different priorities and perspectives on the problem of SFM in Indonesia, intersectoral consultative forums serve as a stakeholder engagement strategy to create shared objectives across interests. Engaging stakeholders helps forge an intersectoral network, inspiring them to take on new roles and use existing data more effectively. The intersectoral consultative forum serves as a platform for the researchers to socialize their ideas around market dynamics based on the political economy perspective, such as using product market volume to weigh medicines' prevalence and the assumption that medicine price signals quality. Additionally, these forums facilitate mutual learning between researchers and other stakeholders. For example, researchers learn about the evolving framing of SFM problems in Indonesia in relation to other pharmaceutical policy issues, public health objectives, or contextual dynamics, such as

the COVID-19 pandemic. In addition, the researchers also test their assumptions and inform the operationalization of the research. For example, the researchers found that the risk factors proposed in the sentinel surveillance group are not suitable for measuring SFM prevalence.

Stakeholder engagement also informs the researchers about who could use their study findings. Since medicine quality has traditionally been viewed as a technical and regulatory issue, the researchers initially framed the medicine regulator as a potential primary user of the STARmeds study findings. However, the researchers later discovered that the Ministry of National Planning, as the overarching coordinating agency for development, also has a relevant interest in the findings. This discovery inspired the researchers to refine the framing and problem definition of SFM iteratively, thereby engaging relevant stakeholders in the research. This iterative and ongoing engagement led to a collective initiative between researchers and stakeholders to further a research-policy partnership forum on broader pharmaceutical topics post-STARmeds. Hence, the political economy perspective helps to view the problem of SFM in a broader picture and mobilizes initiatives and commitments from different stakeholders to tackle it.

Main insights from the findings

In this section, I reflect on five main insights from the abovementioned findings, situate them in the literature, and synthesize their meaning to answer the main research question comprehensively.

Adding a political economy perspective provides new substantive insights, but is inherently complicated to operationalize

At the beginning of this thesis, I assumed that broadening the SFM frame and problem definition by taking a political economy perspective and operationalizing it in combination with the technical domain can strengthen risk-based sampling and post-market surveillance. However, the results showed a more grounded but contrasting finding. I found no relationship between the price of medicine and its quality. In addition, there was no relationship between quality and market risk factors in the risk-flagging approach. In this trial, the results suggested that adding market risk factors into an existing case finding strategy does not significantly increase the likelihood of finding products at the highest risk of being substandard.

I learned that operationalizing SFM risk factors from a political economy perspective is inherently complex and highly context-dependent, particularly when pricing is one of the risk factors. One argument is that the relationship between medicine price and quality is complex, as demonstrated by other scholars who previously attempted to conceptualize it (Bate et al., 2011, 2015; Gabel, Difäm-EPN Minilab Network, et al.,

2024; Pisani et al., 2023; Rahman et al., 2021; Schiavetti et al., 2018). In addition, other plausible aspects need to be in place to study the relationship between medicine price and quality comprehensively. For example, more accessible empirical data is required in either primary (e.g., prevalence data) or secondary datasets (e.g., pricing from public and private sectors, market volume, regulatory inspection results). Further, the type of evidence may vary beyond APIs quality, for instance, including inactive ingredients or excipients or diverse quality testing parameters such as impurities. I will elaborate on these aspects further in a later section, where I discuss the research implications of this thesis.

However, the operationalization difficulties in constructing the risk-flagging model do not diminish the additional insights gained from taking a political economy perspective. Reflecting on my findings, several insights point to the value of broadening the SFM frame and problem definition. I will summarize these insights here, but more detailed explanations will follow in the subsequent sub-section. First, a political economy perspective illuminates the mechanisms by which political and economic factors drive the production and trade of SFM. Furthermore, risk factors for SFM based on the interaction of political promises, different policies, and incentives for actors are conceptualized in a market-risk based framework, which has been published elsewhere (Pisani et al., 2019). Second, it uncovers the social constellation of actors and raises awareness of the roles and responsibilities of other relevant actors, as reflected in the case of the falsified vaccine in Chapter 2. Third, it describes the fluidity of the link between licensed and unlicensed channels through which patients can purchase medicines, sometimes without a prescription, as identified in Chapters 2 and 4. Fourth, it inspires the use of market volume to inform product prioritization for sampling with different consequences in public health.

Taking a political economy perspective redefines the problem of SFM and articulates the socioeconomic dimension

Broadening the frame of SFM using a political economy perspective redefines the problem, articulating and foregrounding its socioeconomic dimension. In other words, a political economy perspective expands the risk factors for SFM beyond the scope of the existing technical and regulatory domain (World Health Organization, 2017), ultimately identifying other relevant (policy) actors. Previous studies have noted a lack of agreement among actors about the nature of the problem or, more precisely, whether there is a problem (Mengesha et al., 2024), which requires more research to refine the understanding of this issue. Furthermore, while the role of medicine regulators in ensuring the quality of medicines is

well-known, little is understood about the interplay between their role and other actors, such as procurement agencies (Kohler et al., 2025). In Chapter 2, I described the drivers or risk factors that drive the production and trade of SFM from the sides of supply, demand, and regulatory enforcement. In describing these risk factors, I paid close

attention to socioeconomic dimensions, for example, in exploring patient preferences for particular vaccine brands despite universal access to a range of other products. Other scholars have argued that misplaced patient expectations or demand for prescriptions shaped by limited medical knowledge contribute to the irrational or inadequate use of medicines (Ahmed et al., 2025), while WHO reported a significant increase in incidence during COVID-19 of the relationship between perceived efficacy, demand, and increased numbers of SF medical products of interest (World Health Organization, 2024). In this way, my research contributes to the growing body of insights from actors beyond medicine regulators and within and outside the health system to define the SFM problem. Taking a political economy perspective and discussing the dynamics in the market serves as an "umbrella" lens for actors to agree on defining the problem, including other types of actors in the discussion, and considering the interrelatedness of seemingly non-linked policies to influence medicine quality.

Political economy also foregrounds the problem of SFM and links it to a more significant priority agenda in the health system: UHC (Ozawa et al., 2020). Regarding the socioeconomic dimension, my research in Chapter 2 suggests that ambitious political promises to provide healthcare access without balancing various incentives for different actors, including profit protection, pose some risks to quality. Furthermore, the political economy articulates problems that tend to receive less attention and priority in agenda setting regarding poor-quality medicines. In Chapter 3, my empirical findings show that out-of-specification samples, also referred to as substandard, continue to be a problem in both licensed and unlicensed outlets. While historically falsified medicines tend to attract more attention in the policy arena (Ozawa et al., 2022) due to their association with criminal activity, my findings in Chapter 3 underscore the importance of giving adequate priority to substandard medicines as postulated in previous research (Gabel, Lächele, et al., 2024).

Taking a political economy perspective also bridges different areas of pharmaceutical policy. Previous research has highlighted the insufficient attention to the complex interrelatedness among other areas within the health system, such as access to medicines and affordability (Mhazo & Maponga, 2022). Political economy articulates the connections between the risks to quality with availability, and pharmaceutical pricing or affordability and the irrational or inadequate use of medicines, which also have socioeconomic dimensions (Fanda, Probandari, Kok, et al., 2024; Maria et al., 2024; Ahmed et al., 2025). Furthermore, it adds to the available evidence about the complexity of pharmaceutical supply chains in LMICs that pose risks to SFM (Wulandari et al., 2021). Eventually, a political economy perspective challenges traditional technical and regulatory approaches to tackling SFM. It offers a new angle that more regulation and enforcement are not always the answer to every problem (Mengesha et al., 2024), especially without considering and balancing the multiple interests at stake and incentives of each relevant actor, including individuals or organizations newly identified as a implication of broadening the framing.

Problem definition is a social process that creates a path towards interagency silos

Defining the complex problem of SFM is both a substantive and a social process. The definition of the problem is shaped based on the frames of each actor. Furthermore, frames are built on underlying structures, common values, and the actors' beliefs (Behr et al., 2015, p. 2). Depending on the policy positions of the actors, the frames indicate prevailing views about what is considered a problem and the choice of responsible actors who need to be involved in addressing the problem. Therefore, the differences in frames can create silos between different actors or organizations that work in their own ways and lack integration with the outside parties.

The prevailing frame that I identify throughout the chapters in this thesis is that, in Indonesia, poor-quality medicines are a technical problem that requires specific expertise and authority to address. In line with previous research, this framing of the issue leads to the perception of the medicine regulator as the organization with primary responsibility (Gostin et al., 2020; Orubu et al., 2020; Twesigye et al., 2021). In addition, I also observed the existence of interagency silos in the field of medicine quality in Indonesia, as reported in previous work (USP Promoting the Quality of Medicines, 2018). In a complex bureaucratic environment, these silos undermine efforts to collaborate across sectors, a process highlighted in Chapter 6.

Interagency silos manifest in fragmented data and information between different actors and organizations. One of the opening quotes in Chapter 1 is a striking illustration of how it is considered inappropriate to talk about quality with a pharmacist at the Ministry of Health. The tendency to keep topics around SFM within the expertise of the medicine regulator is also observed in Chapters 2 and 6. While collecting secondary data to inform Chapters 4 and 5, it came to my attention that the data was fragmented in different directorates of organizations, such as the medicine regulator or across organizations, making it difficult to merge and interoperate datasets. Materials such as datasets reflect organizational framings with varying levels of granularity. This example illustrates how silos operate, making it more challenging to bring different actors together to collaborate.

My findings in Chapters 2 and 6 highlight that various actors have distinct roles to play in addressing SFM in Indonesia. Using a political economy perspective, in Chapter 2, it becomes evident that there are different interplays of incentives for each actor based on the dynamics in the market. Previous publications have called for actions to collaborate between actors to combat SFM (Newton et al., 2019) and to sustain cooperation (World Health Organization, 2024). However, unless there is an alignment of framing between actors (Xu, 2022) to understand how problems are framed and agendas are set at the national level (Mhazo & Maponga, 2022), the initiatives or movements towards intersectoral collaboration remain as rhetoric and, thus, challenging to implement, let alone sustain.

Broadening the frame, redefining problems and bridging silos entail policy learning across actors

Broadening the frame and reshaping the problem definition of SFM using a political economy perspective does not necessarily mean replacing policy instruments. However, policy learning between actors is still required. In Chapter 6, the intersectoral research partnership between researchers and stakeholders resulted in a prevalence estimation method for SFM that considers market dynamics, including product market volume. However, there are insofar no indications that stakeholders will use the study results to replace the existing policy instruments.

One of the key findings in Chapter 6 is that creating a shared objective is instrumental to aligning different framings, fostering intersectoral collaboration, and ultimately bridging the interagency silos. Several arguments underline the importance of creating shared objectives in tackling SFM. The historical path of SFM in the global policy arena provides examples of contestations about which aspects of the issue should be prioritized in policy action, for instance, criminal prosecution, supply chain management, consumer protection, or intellectual property rights (IPR) protection (Xu, 2022). Furthermore, as described in Chapter 1, some actors resisted redefining the issues when it came to poor-quality medicines. In addition, although the responsibility to tackle SFM transcends borders and sectors, maintaining a collective commitment remains challenging (World Health Organization, 2024). Therefore, a shared objective serves as a foundation among various actors to safeguard public health amidst differing institutional priorities.

Mutual learning occurs among the various actors engaged in discussing SFM in Indonesia, leading to the creation of shared objectives. Previous research highlighted the active participation of multiple stakeholders during this process (Fimbo et al., 2024). It fostered conversations between the regulatory interface and other policy areas, such as procurement, contributing to a joint effort in addressing SFM (Kohler et al., 2025; Lee et al., 2025). In Chapter 6, the intersectoral consultative forum facilitated a learning process between researchers and stakeholders. Researchers introduced the political economy perspective, forming the foundation for the prevalence estimation method they wish to develop jointly with other stakeholders. During the deliberation process, it became apparent that each stakeholder has their own perspectives and framing on the issue of SFM, leading to different approaches in developing the estimation method. Although this diversity led to a lengthy discussion during the forum, the process by which different existing, often competing, visions of the issues are challenged is sometimes necessary to embrace diverse stakeholders, interests, and perceptions of the problem inclusively (Xu, 2022). Furthermore, the learning process is pivotal in technically complex areas potentially subject to powerful societal and political influences (Hall, 1993).

The learning processes outlined above produced substantive and relational outputs. For researchers, this helps to inform research designs and interpret results. Meanwhile, the learning exposes stakeholders to new methods for estimating prevalence from a political economy perspective and forges networks between actors and organizations who might not otherwise have sat together discussing SFM issues. Previous scholars

have also reported these relational outputs, adding that interdisciplinary projects have changed allocations, power, authority, expertise, and material resources (van Egmond & Bal, 2011). As described in Chapter 6, more substantive outputs in policy and practice, such as designing new policies, were not observed during the writing process of this thesis. Other scholars have suggested that recording these impacts might require a more extended period beyond the research project (Hanney et al., 2015).

Researchers as policy entrepreneurs in navigating and bridging silos

Researchers play a critical role as policy entrepreneurs in broadening the frame and problem definition of SFM by adopting the political economy perspective and navigating and bridging interagency silos. Crises, such as medicine quality incidents, open a policy window for action on the issue, sometimes leading to policy and organizational changes for medicine regulators (Ariyanti, n.d.). However, what happens afterwards is still undecided and uncertain. Once the policy window is opened, competing frames of problematizations may persist. Moreover, considerable effort is still required to gain acceptance of a particular issue. The prominence of an item or proposal on the agenda depends on the climate within the government and the receptivity to particular types and ideas, regardless of their sources (Béland, 2016). This is where researchers come in.

Examples of researchers' roles as policy entrepreneurs are shown in Chapters 2 to 6. In Chapter 2, researchers can propose a broader framing using a political economy perspective and conceptualize risk factors for SFM based on a reformulated problem definition, further operationalize the problem definition into risk indicators in Chapter 3, and test the assumptions and risk indicators to inform policy and practice in Chapters 4 and 5, while engaging various stakeholders throughout the process to enrich the insights and gain legitimacy for their findings in Chapter 6.

Researchers are commonly perceived to represent reality objectively, but conversely, researchers also create or frame reality. By broadening the frame and redefining the issue of SFM from a political economy perspective, the composition of researchers influenced their inquiries, assumptions, and approaches. My research is a collaboration with a team that has diverse expertise in epidemiology, public health sciences, pharmacy, public administration, and criminology. The diversity of expertise enables a broader research focus and engagement with actors beyond medicine regulators.

Part of the effort to reframe the problem involves categorising the various risk factors of SFM. Beyond values, classifying perceived problems within concrete policy categories is an ideational process that shapes the politics of problem definition (Béland, 2016). As Kingdon (2014) says, "The first cut of analyzing anything is to place it in its proper category" (Kingdon, 2014). Furthermore, the category structures people's perception of the problem. SFM, as argued in this thesis, is a different category of problem, thus requiring distinct policy solutions (Pisani et al., 2019; World Health Organization, 2017). To structure the perception of the SFM problem, I placed the risk factors indicating SFM in different categories in Chapter 3 and further operationalize risk indicators

for substandard in Chapter 5. In this thesis, I use the political economy perspective to argue that substandard and falsified products have different root causes. While the risks associated with substandard products stem from squeezed profit margins and technical limitations, falsified ones result from criminal activity and inadequate law enforcement. This distinction contributes to subsequent steps towards formulating potential solutions: it shapes the operationalization of risk indicators for a case finding approach, informs potential data sources from various stakeholders inside and outside the health system, and directs stakeholder engagement, including with the data custodians. Therefore, while the trial or testing in this thesis suggests that the risk-flagging approach did not significantly increase the likelihood of finding at-risk products, these steps demonstrate the type of work researchers, as policy entrepreneurs, can do to redefine the SFM problem and operationalize it to make it more actionable.

When attempting to bridge interagency silos, the role of researchers as policy entrepreneurs is also affected in the process. Considering the political economy perspective and market dynamics when developing the risk-flagging approach in Chapter 5, the process will benefit from expanding the interaction with different actors, especially if the modelling requires various datasets. However, it is known that the modelling process considers technological and organizational elements and the connection to policies (Kraemer, 1987). Researchers form certain configurations with particular sections of government that share similar framing, approaches to problem definitions, values, and political goals (van Egmond & Bal, 2011). At times, this is not something that happens by choice. In this thesis, the configuration between researchers and medicine regulators in the post-market surveillance department resulted from a top-down appointment by senior leaders of the organization and is facilitated by a previous working relationship with one of the researchers, as described in Chapter 6.

Navigating silos exposes the boundaries of possible actions in research and may limit the researcher's efforts to broaden the frame and problem definition of SFM and operationalize it. For example, in Chapter 5, I categorized risk scoring as binary scores (i.e., score 1 as at-risk and 0 as no-risk). On the one hand, I recognized that this is a relatively simplistic approach in a complex pharmaceutical market and carries the risk of missing nuances of different risk weights or levels. On the other hand, limited evidence on market dynamics and considerations about the instrumental and conceptual utility of the model in practice (Thompson et al., 2022) also contributed to this decision. Information asymmetries about market organization, dynamics, and incentives constrain the operationalization of risk indicators to flag products at the highest risk of being substandard. This type of information is available mainly from the pharmaceutical industry. However, it is widely acknowledged that information about fair prices for manufacturing and distributing quality-assured medical products remains obscure and is a subject of calls for greater transparency from the industry (Moon et al., 2020; World Health Organization, 2021).

On top of that, in Chapter 6, institutionalized research partnerships with the medicine regulators run the risk of constraining more flexible engagement with other actors,

including the industry. Modelling practice, such as the risk-flagging approach, is a form of boundary work between policy and science; it defines what values and perspectives on the subject can be modelled and thus prioritized (van Egmond & Bal, 2011). This raises the question of how perspectives and information can further enrich the modelling practice if silos do not necessarily limit the researchers' entrepreneurial role in policy.

The above dynamics reflect the politics of broadening the frame and problem definition of SFM through the lens of the political economy perspective. While seeking to broaden the scope of SFM, researchers must compromise strategically to produce sound policy solutions and set their ideas on the agenda. Therefore, researchers may form alliances with particular actors or organizations that may limit the operationalization of the problem definition itself.

Research implications, study limitations, and suggestions for future research

The main results of this thesis are (1) opening the scope of problem definition and broadening the existing framing to understand the mechanisms that drive the production and trade of SFM, and (2) understanding the work that researchers as policy entrepreneurs can do in broadening the frame and problem definition of SFM. This thesis then contributes to research on medicine quality governance in several ways, including conducting an interdisciplinary study of SFM with a participatory approach, broadening the frame related to policy priorities to address a politically sensitive subject, making explicit the roles and responsibilities of other relevant actors, operationalizing the problem definition using routinely collected datasets, testing the assumed relationship between medicine price and quality, and examining stakeholder engagement in research. In this section, I discuss some of the strengths and limitations of my approach and provide suggestions for future research.

Broadening the frame and problem definition of SFM using a political economy perspective to bridge interagency silos entails conducting interdisciplinary research on the quality of medicine. Collaboration across disciplines and expertise is considered critical in medicine quality (Masini et al., 2022; Newton et al., 2019; Spink et al., 2016). In this thesis, I used a participatory approach to answer the research question by working closely with the stakeholders and incorporating their insights to inform relevant research questions and refine the study design. I collaborated with other researchers from different backgrounds in pharmaceutical science, epidemiology, public administration, criminology, and chemistry. Furthermore, I combined quantitative and qualitative methods to answer the main research question. I used various study designs, such as cross-sectional surveys with a detailed mystery shopping approach in Chapters 4 and 5 and longitudinal observations in Chapter 6. Previous scholars have studied the multiple framings surrounding SFM issues and how different framings drive priority settings for addressing them (Borup & Traulsen, 2016; Lamy, 2017; Xu, 2022). However, they have not taken a participatory approach to broaden the frame and deliberately reshape the problem definition.

The active roles of interdisciplinary researchers in broadening the frame and problem definition of SFM and further operationalizing it have several implications for research. In studying a politically charged subject such as medicine quality, reframing this specific issue into a broader focus and linking it to policy priorities such as UHC allows researchers to openly discuss the "big elephant in the room", or a subject where almost every relevant actor understands the importance of the problem but is reluctant to talk about it due to its sensitivity. In doing so, researchers can clarify whether there is a problem at all and the magnitude of the problem. For example, previous research reported that the prevalence of SFM identified was lower than what was speculated in the lay press (Gabel, Lächele, et al., 2024).

Researchers can study the roles of various actors that shape the problem definition of SFM using a political economy perspective. In addition, they make explicit their roles and responsibilities, leading to an understanding that some actors or organizations can become more or less critical in addressing SFM. Knowledge about the roles and responsibilities of different actors is pivotal to comprehensively understanding the mechanisms leading to SFM, the latter of which, according to previous research, is a contribution from social and political sciences into policy response research (Xu, 2022). In this thesis, partly due to the engagement strategy and research focus on developing the risk-flagging approach, I mostly interacted with stakeholders at the national level, particularly with medicine regulators. As a result, I had fewer opportunities to study the roles of other stakeholders, including those at the sub-national, district, or community levels. Previous scholars have emphasized that health research is most likely to be used when aligned with local needs (Kok et al., 2016), indicating the importance of stakeholders' roles at other governance levels. Therefore, future studies may benefit from further identifying, mapping, and researching the roles of various stakeholders relevant to medicine quality and the context of the respective health system. Some examples of actors in the context of Indonesia's decentralized health system are patients, community health workers, religious leaders, grassroots organizations, and the media (Kurniadi et al., 2025 & Moore et al., 2025).

The SFM problem definition operationalization using a political economy perspective was demonstrated in developing the risk-flagging approach. Detection is one of the key areas WHO recommends in addressing SFM, and it has received considerable attention from academic researchers in several methods, techniques, or tools under development (Bharucha et al., 2024; Lächele et al., 2024; Mosca et al., 2023; Opuni et al., 2024). However, little has been done to develop sampling approaches and incorporate risk factors related to market dynamics (Dewi et al., 2022; Pisani et al., 2024), especially case finding. The risk-flagging approach is specific to indicating product quality risks, which differs from other case finding strategies that vaguely combine product and public health risks (Aroca & Guzmán, 2017; Badan Pengawas Obat dan Makanan - Republik Indonesia, n.d.; Ching et al., 2022; FDA, 2014; United States Pharmacopeial Convention, 2021). The formulation of objective risk indicators and their trials highlights the importance of contextualization by adjusting to local priority settings, political and policy contexts (Biermann et al., 2025; Hasnida et al., 2017), and public health objectives

in close collaboration with local authorities. For instance, by selecting study medicines appropriate to the burden of disease, with a substantial market volume, consider their impact on public health (Pisani et al., 2024), such as different types of anti-infectives, considering the high number of infectious diseases in Indonesia, especially in remote regions (Mboi et al., 2022).

Knowledge sharing among actors is instrumental in developing the risk-flagging approach. Limited data has been a key challenge for researchers conducting modelling studies on medicine quality (Cavany et al., 2023; Lee et al., 2025). When developing the risk-flagging, I realized that many potential routine datasets in the market are fragmented across multiple data custodians (WHO Indonesia, 2025a). However, while a variety of country-specific data is available in principle, it does not always mean that it is accessible in practice (Khaki et al., 2025). Thus, it influenced the development of the risk-flagging approach. On the one hand, information asymmetry from key stakeholders in the market, such as pharmaceutical manufacturers, regarding fair prices for quality (Bate et al., 2011; Kohler et al., 2015), limits the formulation of cost-cutting price thresholds in market risk factors. On the other hand, limited data is accessible from different public sector stakeholders (Duga et al., 2024; Gray & Suleman, 2025), which constrains the identification and operationalization of other risk indicators. Greater transparency in data sharing on fair prices for quality-assured products and regulatory inspection results would be useful to operationalize the risk-flagging approach further, for example, by selecting the appropriate market price for cost-cutting thresholds and understanding regulatory case finding and weighting strategies. While I will explain more practical implications of data sharing and transparency among actors in the next section, I encourage future studies to generate more knowledge from sub-national, district, or community-level stakeholders. This knowledge may help further identify and operationalize risk indicators, map corresponding datasets, and select relevant study medicine for priority setting. In this thesis, I only operationalized the substandard risk indicators in Chapter 5, while the falsification risk indicators were also conceptualized in Chapter 3. Therefore, it would be useful if future research operationalizes risk indicators using relevant study medicines for falsification, for example, tramadol with a higher risk of abuse in Indonesia (Nugroho, 2023) or particular types of medicines that are out of stock in the regions (Fanda, Probandari, Yuniar, et al., 2024).

Testing the assumption of the relationship between medicine price and quality in Chapter 4 adds to the evidence in Indonesia with the same conclusion of no associations (Dewi et al., 2022; Pisani et al., 2024). The link between pharmaceutical pricing and quality has been a pressing policy question, especially since UHC has become a priority on the agenda amid rising medicine costs (Shafie et al., 2024) and cost-containment policies, including in Indonesia (Anggriani et al., 2019; Khairani et al., 2024; Sarnianto et al., 2022). Therefore, evidence on this topic is critical to further access to affordable and quality-assured products, such as generics and biosimilars, in achieving UHC (Deviani, 2024; Zhou, 2025, p. 20). My thesis focused on amoxicillin as an active ingredient, which I tested in the laboratory for assay and dissolution and did not include further quality criteria, similar to other studies (Gabel, Difäm-EPN Minilab Network,

et al., 2024). Understanding the quality assurance of medicines in the market would be more profound if future research considers the testing of inactive substances or excipients (Global Pharma Health Fund, 2024), especially in light of the recent cough syrup incidents in several countries (*Medical Product Alert N°6/2022*, n.d.; World Health Organization Indonesia, 2023).

Furthermore, previous research in Indonesia speculated that low-price and low-margin products are also manufactured with lower-price APIs of lower quality (Sarnianto et al., 2022), which requires further evidence. Therefore, quality testing using other parameters, such as impurities, can further test the anecdotal evidence that price can signal medicine quality (Johnston & Holt, 2014; Ndichu et al., 2019). However, impurities have received less attention in research than other quality parameters, such as assay and dissolution. A plausible rationale is that impurity testing requires more advanced and expensive standards and techniques that are beyond the capacity of academic or third-party commercial laboratories, especially in LMICs (United States Pharmacopeia, n.d.). Hence, an embedded collaboration in research policy partnerships with national medicine regulators may facilitate this effort. In the next section, I will discuss research policy partnerships as they have implications for practice.

This thesis also prospectively examined stakeholder engagement as a strategic way to reframe the problem definition of SFM and operationalize it. Stakeholder engagement is increasingly recognized as an important element in policy-focused research (Boaz et al., 2021; Borst et al., 2019). I observed that implementing stakeholder engagement early in a project creates meaningful interactions between researchers and stakeholders, effectively informing the research design and interpreting results, as noted in previous research (Boaz et al., 2018). Because stakeholder engagement can be time-consuming and vulnerable to political and institutional dynamics, its benefits will be more significant if it builds on previous projects or is part of long-term collaborations. Furthermore, stakeholder engagement requires operational flexibility from funders and researchers (Biermann et al., 2025; Boaz et al., 2018). For example, stakeholders can ask time-sensitive requests to researchers to investigate specific questions of interest to them within the project timeline. Prospectively studying stakeholder engagement comes with a constraint in accessing data (O'Shea et al., 2021), as I sometimes could not follow all meetings and interactions between the research team and stakeholders due to confidentiality. Another limitation of prospectively studying stakeholder engagement and its influence on research is that it covered a time frame different from policymaking.

Meanwhile, stakeholders' actual uptake of results may extend beyond the project timeline in a more conceptual, cumulative process (Hanney et al., 2015). Therefore, I recommend continuing to study the uptake of these results in future research on pharmaceutical policy and understanding the impact of researchers' roles as policy entrepreneurs in priority settings. This follow-up study is particularly relevant because, as stated in Chapter 6, stakeholders agreed to further intersectoral consultative groups on the broader topic of pharmaceutical policy.

Practical and policy implications

This thesis raises practical questions regarding addressing the problem of SFM. Based on my findings, I will reflect on several implications in policy and practice.

One dominant notion from the political economy perspective I use in this thesis is the assumed relationship between price and quality of medicines. Since I found no relationships between these two aspects, my findings resonated with previous research that suggested higher-priced medicines do not equate to higher quality (Gabel, Difäm-EPN Minilab Network, et al., 2024). Although I mentioned earlier that this finding supports efforts to expand access to affordable and quality-assured generics in countries striving for UHC with cost containment policies, I argue that quality assurance remains an important item on the agenda or priority setting and, as such, requires commitment from stakeholders to put it forward. As part of the investment in quality assurance, stakeholders such as governments and researchers can proactively inquire about fair prices for quality-assured medicines. The Indonesian MoH has prioritized several inquiries and evaluations on the affordability and transparency of medicine prices within the national insurance scheme (Yumna & Nurfitra, 2024). However, regarding this agenda, the discourse on quality is less prominent (Bhwana, 2025) and is only made explicit by the medicine regulator. Quality, therefore, remains relatively disconnected from other priority areas on the agenda, such as affordability. My research findings on out-of-specification products, even in licensed outlets, suggest that quality assurance is a continuum; it does not stop at the market authorization of a product before it enters the market (Wilder et al., 2025). Post-market surveillance is an integral part of protecting public health from SFM. Thus, it deserves explicit attention in the priority setting of pharmaceutical policy.

Broadening the problem definition of SFM through a political economy perspective offers a holistic view of the interrelationships between seemingly disparate policy areas, clarifying the gap between regulation and practice, and facilitating a deeper understanding of the interplay of incentives among actors. These implications are particularly relevant considering the persistent inequalities in global, sustainable and equitable access to quality products, which necessitates a change in perspective that medicines are public goods (Ravinetto et al., 2024). One of my main findings in Chapter 2 is that the factors driving the production and trade of SFM resulted from the interactions between policies from within and outside the health sector, such as procurement, taxation, and religious affairs. Furthermore, in Chapter 4, I described the gaps between existing policies and implementations as I sampled prescription-only antibiotics in unlicensed outlets across the sampling areas, including on unlicensed websites or platforms, as also identified by other scholars in Indonesia (Ramadaniati et al., 2024 & Moore et al., 2020) and other LMICs (Satheesh et al., 2025). My findings, therefore, underscore the fluidity of licensed and unlicensed channels and the diversion of products between those channels. Unlicensed channels pose a risk to patients by enabling access to falsified and substandard products. Hence, despite the existing

regulatory framework prohibiting product diversion, I encourage medicine regulators to sample products for substandard risks in unlicensed channels as part of their routine post-market surveillance. To increase efficiency and possibly save costs, regulators can consider market volume to prioritize which products to sample from the market and which retail outlets are mainly accessible to the public (Pisani et al., 2024). Overall, the empirical findings I have generated in this thesis suggest the linkages between medicine quality and other areas of pharmaceutical policy, such as affordability, availability, irrational or inadequate use of medicines, and its potential consequences in triggering AMR (Muhamad & Difa, 2024, p. 202; Ravinetto et al., 2024; WHO, 2024; Hembre et al., 2025; Ahmed et al., 2025; WHO Indonesia, 2025), and, therefore, can facilitate the bridging of the silos that stand between them.

The holistic view mentioned above helps bridge the interagency silos between different actors and, therefore, can foreground the quality of medicine in the agenda setting. In the policy environment, it may be useful to comprehensively review interrelated SFM policies using a political economy perspective to develop medium and long-term national planning. Aligning the frames and incentives of different actors (Mhazo & Maponga, 2022; Xu, 2022) is also necessary during this review by fostering policy dialogue with other stakeholders beyond medicine regulators in selecting policy priorities. This process can be institutionalized as a national forum led by a coordinating agency responsible for harmonizing development plans across sectors. In line with this, Biermann et al. (2025) argued that implementation research and knowledge translation should be institutionalized in governments, and researchers should be involved in decision-making (Biermann et al., 2025). However, since the issue of SFM requires rapid regulatory follow-up and action, the roles of researchers may be more substantial in a research-policy partnership rather than decision-making, as I will explain later in this section.

Adopting the political economy perspective to address SFM issues calls for greater utilization and sharing of routine data across governance levels, such as national, sub-national and district levels. When operationalizing risk indicators in Chapter 5, I explored several potential datasets from the public and private sectors. In LMICs, where surveys or additional data collection require more public sector costs or greater dependence on external donors (Khaki et al., 2025; WHO Indonesia, 2025a), depending on political dynamics, routine datasets generated as part of official duties are of higher importance for evidence-based policy-making. Additionally, using existing data collection tools can encourage authorities to collect and share information systematically in a standardized manner (Kohler et al., 2025). Thus, I encourage investment in the health and related sectors, including technical support, to strengthen authorities' capacity to independently collect routine data according to their duties and functions (Khaki et al., 2025). Indonesia has an ongoing initiative to leverage digital health to enhance data collection and analysis for more effective and targeted public health interventions (WHO Indonesia, 2025b).

However, routine datasets collected can be underused if they are not shared timely, transparently, and responsibly with various actors (World Health Organization, 2024).

As SFM is politically charged, various concerns are associated with the multiple actors or data custodians involved. For example, in Chapter 6, I learned that medicine regulators had concerns about confidentiality before sharing their routine data with the researchers. Enforcement of data confidentiality in LMICs is generally less stringent than in HICs, which require legal or regulatory frameworks, such as agreements on information sharing and supporting infrastructure, such as secure data storage (Khaki et al., 2025; World Health Organization, 2024). In Chapters 4 and 5, proprietary pharmaceutical market data is critical in providing market volume and product price data for developing risk indicators. While I later learned that other datasets inform market trends sourced from public agencies such as the MoH, public-private partnerships may be a viable solution to leverage proprietary data for greater public health purposes, including advancing health equity (Khaki et al., 2025).

A research-policy partnership provides an avenue to support comprehensive policy reviews with interrelated themes mentioned above and facilitate the sharing of data. Instead of institutionalized decision-making meetings (Biermann et al., 2025), this forum serves as a platform to exchange knowledge and insights between research agendas, findings and their implementation in practice. As explained in Chapter 6, these forums require a convenor where researchers can take on this role with several advantages and disadvantages. On the one hand, researchers can serve as neutral facilitators who can bridge various interests and concerns, especially when discussing sensitive subjects such as SFM. On the other hand, researchers lack the authority and political legitimacy to advocate for necessary actions or enforce laws related to SFM consequences. Therefore, when organizing these partnerships, I recommend tailoring the convenor's role to the forum's purpose. For example, for horizon scanning and knowledge exchange purposes, researchers can take on the role of convenor, while for more strategic purposes and action-oriented policy outcomes, such as task forces, a public agency with a coordinating role can lead the forum. Research-policy partnership forums could also benefit from using an overarching public health-driven framework to foster a health-needs-driven innovation ecosystem (Ravinetto et al., 2024). The Indonesian medicine regulator has recently formed a consortium comprising academia, business companies, and the government to encourage the development of the medicine research ecosystem (Budiyanti & Sulistiyandari, 2024). However, whether this forum prioritizes medicine quality or SFM is unclear.

While a political economy perspective broadens the scope of the definition of the SFM problem beyond the technical dimensions, I extend my support for greater investment in regulatory agencies and their strategic positioning in setting the policy agenda. As noted earlier, taking a political economy perspective does not mean downplaying the importance of the technical dimension and the capacity to implement it. Instead, a political economy perspective complements the technical aspect to strengthen the medicine regulator's efforts to address the issue of SFM. A political economy perspective can guide regulators in understanding the socioeconomic and political dimensions of SFM, thereby shifting their focus away from prescriptive regulatory functions and technical aspects (Fimbo et al., 2024). Regulators, especially in middle-income settings,

can use this perspective in their routine post-market surveillance, for example, by considering market dynamics such as product market volume, price, and unlicensed outlets where patients can purchase medicines. However, taking a political economy perspective and operationalizing and institutionalizing it in the current regulatory practice can be a major leap from the traditional training and experience of medicine regulators, who are largely pharmacists (Meilianti et al., 2025). Therefore, as noted in Chapter 5, this requires stable and functioning regulatory agencies equipped to expand their capacities beyond the basic functions standardized in the WHO Maturity Levels (World Health Organization, 2025).

Additionally, other scholars have recommended creating adaptive systems that respond to changing needs to improve regulatory effectiveness (Fimbo et al., 2024). In the Indonesian context, the national medicine regulator is committed to developing its capacities and aims to be listed in the WHO Stringent Regulatory Authority list (Ikrar, 2024). Furthermore, the agency has recently highlighted that its work in accelerating the licensing process contributes to providing access to quality-assured and affordable medicines (Ashari & Sulistiyandari, 2024; Budiyanti & Sulistiyandari, 2024). In general, I suggest that a political economy perspective would be most useful to strengthen the regulator's work when the following conditions are met: mutual learning, knowledge exchange, data sharing, and transparency between actors. In this way, it foregrounds the work of the medicine regulator as a key actor in the health system, which has traditionally been more in the background and only emerges when major incidents occur, and generates more political support, commitment, and investment in agenda setting.

Reflexivity

If SFM is such a complex issue, studying the subject also entails its own particular complexity. In this section, I will reflect on the sensitivity of the research topic and my positionality, followed by some strategies to overcome the challenges I have encountered in my fieldwork and further reflections on researching the socioeconomic dimension and governance of medicine quality.

Sensitivity of the topic and becoming a policy entrepreneur

As explained in Chapter 1, SFM is a politically sensitive topic. At the beginning of my fieldwork and data collection for Chapter 2, I found it utterly difficult to broach the subject of medicine quality. Initially, many individual or organizational actors, including the medicine regulators, were unwilling to discuss it openly. Most of the time, these actors assumed that product quality was ensured before medicines were released onto the market. For many of these actors, there is little point in discussing what happens to the quality of medicines on the market after they have been evaluated and authorized

in the pre-market phase.

However, major incidents of SFM in Indonesia changed this landscape. As I stipulated in my key insights, crises such as the 2016 vaccine falsification incidents opened a policy window. Incidents are indeed unfortunate tragedies for patients and public health, but at the same time, they create public pressure and draw the attention of policymakers. Hence, this policy window enables open discussions among various actors regarding the quality of medicine. As part of my policy entrepreneurial role in broadening the frame and problem definition of SFM using a political economy perspective, I also steered the discussion to touch on a higher priority in policy setting, namely, UHC policy or Indonesia's JKN. Combining UHC with the major SFM incidents in Indonesia has provided an entry point for investigating my sub-question one and, eventually, all the other sub-questions across three different research projects.

My role as a researcher and policy entrepreneur in broadening the frame and operationalizing the problem definition based on a political economy perspective in this thesis was implemented differently. From Chapters 2 to 5, I took a zoom-in perspective as I was fully involved in leading all the studies, including intentionally shaping interactions with relevant actors to inform the study design and conduct data collection. Meanwhile, in Chapter 6, I was more distant as I observed stakeholder engagement in the STARmeds project to jointly develop a method for estimating SFM prevalence, where I did not make any decisions about the engagement myself. I believe the unique combination of zoom-in and zoom-out perspectives in this thesis allowed me to immerse myself in the experience as a policy entrepreneur while also being able to take a step back as a researcher, triangulate my initial findings or observations on some aspects that may have been overlooked, and reflect on their meanings. In other words, both perspectives enriched my analysis and provided insights into answering the research question.

Positionality

My professional background and current affiliations inevitably shape my positionality in this thesis (Adhikari & Mishra, 2025). I am not a trained pharmacist or other healthcare provider. As such, my educational qualifications have led to some questions from the actors about whether I have adequate background information and understanding when discussing technical aspects such as medicines or post-market surveillance. I often had to respond to statements such as "So, what do you know about medicines?" If it was already difficult to convince my study participants or stakeholders that I am a competent researcher or discussion partner, talking about a sensitive subject such as SFM was even harder.

Fortunately, my previous working experience in a multinational pharmaceutical company in Indonesia came to my rescue. Before entering academia, I worked for almost three years in market access, public procurement, and government affairs. My initial interest in the relationship between price and medicine quality emerged

while negotiating medicine prices with the government during the first two years of Indonesia's UHC scheme. My work experience in this industry provided me with the technical, regulatory, and market trends in pharmaceuticals and network information for my thesis research. It is also fair to say that my assumptions when broadening the frame and operationalizing the problem definition of SFM using a political economy perspective were primarily shaped by my experience in this industry.

Although I am Indonesian, my primary affiliation with a Dutch university has posed some challenges. In the initial data collection phase, some actors or study participants considered me "not local enough." The actors I interacted with during informal conversations or data collection questioned whether I could fully understand the local context. Additionally, some actors were suspicious whether I was merely acting as a "knowledge broker" or, to put it bluntly, an "intellectual crony."

To be institutionally embedded in the research environment, my main strategy was establishing two collaborative partnerships with reputable organizations (Hasnida et al., 2017). In Chapter 2, I collaborated with Migunani Research Institute, a non-profit organization with extensive experience in socio-economic research. In Chapters 3 to 6, I collaborated with a research group specializing in pharmacoeconomics, social, and administrative pharmacy at Pancasila University.

These partnerships enabled fruitful collaboration, knowledge exchange, and mutual understanding between me and other researchers, making the research more locally relevant and valid (Hasnida et al., 2017). I gained many insights to understand the political sensitivity of SFM in the Indonesian context, how to navigate it, and the societal challenges surrounding the topic. Interdisciplinary collaboration can also be challenging and time-consuming due to the differing paradigms and experiences of each researcher. However, over time, we learned to align our perspectives during regular team meetings or thematic workshops organized to empower the research team's capacity. It is vital to align the research team's objectives before we interact with other actors or stakeholders to gain their trust and legitimacy (Biermann et al., 2025), given the sensitivity of the SFM topic.

Further reflections

SFM has the most significant impact on patients. Patients consume medicines hoping to cure or prevent a disease, while reality might speak differently because of SFM (Khuluza et al., 2025). It is, therefore, important to include patient perspectives in research, particularly those of marginalized groups who lack access to affordable and quality-assured medicines (Wagnild et al., 2025). In Chapter 2, I discussed the factors driving the production and trade of SFM with several patient representatives. However, when further operationalizing risk indicators to develop the risk-flagging approach, a deliberate decision was made to engage more closely with medicine regulators and other actors in the policy environment.

Nevertheless, I remain a proponent of further patient involvement in research to understand the complex socioeconomic dimensions of SFM. At the outset of this thesis, I stated that medicine is one of the building blocks or key pillars of healthcare delivery to provide universal quality healthcare for all (Basu, 2024). Therefore, ensuring that all patients receive safe, affordable, and quality-assured medicines should remain a priority on the policy agenda.

Based on my fieldwork experience, in the absence of major incidents, I believe that medicine quality will remain a low priority on the agenda setting as long as there are more visible and pressing issues surrounding pharmaceuticals in the health system. These issues include affordability (Masresha et al., 2024), which has recently been a priority for the Indonesian Minister of Health (Bhwana, 2025), as well as availability (Van Gurp et al., 2024), as illustrated in the opening quotes in Chapter 1. While affordability and, more generally, access to medicines remain important issues (Fanda, Probandari, Yuniar, et al., 2024 & Hembre et al., 2025), I argue that access and quality should go hand in hand. Thus, it is necessary to move away from silos and evaluate issues of quality, availability, affordability, and other relevant areas comprehensively.

Concluding thoughts

SFM is a complex and politically sensitive issue that requires greater attention and commitment from multiple actors to address the problem. However, fragmented policy environments and interagency silos complicate the effort and governance to do so. Using a political economy perspective, I hope to have offered an alternative frame to redefine the problem, bridge interagency silos, and illustrate the contributions of actions by multiple actors to either create risks to medicine quality or address them. In the research domain, I aspire to encourage more research to frame and define the problem of SFM because what is not defined ultimately does not get discussed and solved. In policy and practice, I hope this work stimulates and supports the interagency or intersectoral initiatives to consider medicine quality when different actors plan and evaluate different health system building blocks. Reflecting on the opening quotes in Chapter 1, I also hope to contribute in a way that ensures no health provider or other actors have to choose between giving a patient poor-quality medicine or not providing medicine at all. Researchers or policymakers may use different frames to look at the problem of SFM, but the hard truth remains. There is no UHC without quality-assured medicines that work.

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Appendices

Summary

Bridging the Interagency Silos

Taking a political economy perspective to tackle substandard and falsified medicines in Indonesia

In 2022, WHO Director-General Dr Tedros Adhanom Ghebreyesus emphasized that "There is no universal health coverage or UHC, no health security, without access to quality medicines". His statement remains highly relevant, given the widespread occurrence of poor-quality medicines globally – a challenge that is both complex and multifaceted. The consequences of poor-quality medicines are far-reaching, impacting not only individual patients but also health systems and society at large. Current frameworks for targeting poor-quality medicines are largely technical in nature. In this thesis, I introduce a new and broader framing of the problem of poor-quality medicines, operationalize it based on this perspective, and test its potential to better tackle the issue.

The social process of framing and defining the problem of poor-quality medicines

In **Chapter 1**, I begin by describing the process of defining poor-quality medicines, which is historically complex. Diverse actors and organizations, including global health institutions, pharmaceutical experts, and the pharmaceutical industry, have influenced and reshaped the definition by framing the issue in different ways, such as through the lens of intellectual property infringement. To drive more concerted efforts in tackling the problem, the WHO, in the end, adopted a public health-focused definition in 2017. According to this definition, *substandard* medicines refer to "authorized medical products that fail to meet either their quality standards or their specifications, or both", while *falsified* medicines are those "products deliberately or fraudulently misrepresented with regard to their identity, composition, or source".

Although substandard and falsified medicines are defined from a public health perspective, the technical and regulatory domains primarily influence the problem scoping and policy responses that follow. This framing positions the national medicines regulator as the primary authority for addressing substandard and falsified medicines issues. As a technical agency, the regulator is responsible for ensuring the quality of medicines through activities such as post-market surveillance. This technical focus tends to separate quality issues from other critical areas of pharmaceutical policy, such as medicines availability, affordability, and irrational or inadequate use of medicines.

Similar problem framing and policy solutions – yet the problem persists

Various technical interventions and policy efforts have been implemented to help countries combat substandard and falsified medicines; however, poor-quality medicines

continue to wreak havoc around the world, especially in low- and middle-income countries. Over a nearly two-decade span, WHO reports from 1999 and 2017 present similar causes, risk factors, and recommendations, predominantly focusing on technical and regulatory domains, while paying little attention to the underlying social, political and economic factors behind the production and trade of substandard and falsified medicines. Additionally, challenges related to governance – such as market structure, the complex network of stakeholders in the pharmaceutical supply chain, political sensitivities surrounding substandard and falsified medicines, and issues with data availability, standardization, and sharing – underscore the multifaceted nature of the problem, involving many actors from different domains. Consequently, overlooking political and socioeconomic dimensions may overshadow the role of other (policy) actors and limit the development of alternative solutions.

Highlighting interagency silos

The constellation of multiple actors, as described above, often leads to shifting responsibilities and results in what is known as "siloisation". This occurs when differing framings and perspectives, such as technical and regulatory approaches, cause actors or organizations to operate independently, with a lack of integration with outside parties. In this thesis, *silos* are understood as distinct areas within pharmaceutical policy, including medicine quality, availability, affordability, and the irrational or inadequate use of medicines. The term *interagency* refers to different sections, departments, or directorates within the same *or* between different organizations.

The circumstances described above call for an alternative perspective that incorporates both political and socioeconomic dimensions to effectively address the issue of substandard and falsified medicines.

Broadening the frame and problem definition of substandard and falsified medicines: a political economy perspective

This thesis argues that incorporating political and socioeconomic perspectives can offer valuable insights into the nature and underlying risks of substandard and falsified medicines. Such perspectives can help overcome or bridge interagency silos, strengthen intersectoral collaboration, and support the development of more effective policy responses. The objective of this thesis is to broaden the scope and redefine the problem of substandard and falsified medicines by adopting a political economy perspective and operationalizing it to address the issue in practice. The main research question guiding this work is "*What can we learn from a political economy approach, and how can it shape the efforts in tackling substandard and falsified medicines?*".

To explore this, the thesis is structured around the following sub-questions:

1. What is the problem definition of substandard and falsified medicines from a political economy perspective?

2. How can the substandard and falsified medicines problem definition and related assumptions from a political economy perspective be operationalized and tested?
3. What are the findings from operationalizing and testing the substandard and falsified medicines problem definition and assumptions from a political economy perspective?
4. How does intersectoral stakeholder engagement contribute to broadening the frame and problem definition of substandard and falsified medicines and its operationalization in a research collaboration?

This thesis consists of two parts. First, I broaden the current definition of the problem and reframe the existing approach to better understand the underlying mechanisms that drive the production and trade of substandard and falsified medicines (Chapter 2). Second, the thesis explores understanding the work that can be done to operationalize the political economy perspective and combine it with technical and regulatory approaches to strengthen post-market surveillance (Chapters 3 to 6). In this context, I pay particular attention to the role of researchers as policy entrepreneurs in broadening how substandard and falsified medicines is framed and defined.

Approaching the issue of substandard and falsified medicines from a political economy perspective involves conducting a mixed-methods study focusing on several key areas. First, I explore how substandard and falsified medicines relates to other policy priorities and agenda-setting topics, such as Universal Health Coverage (UHC) and national prosperity. Second, I examine the roles and responsibilities of various intersectoral actors, with a particular emphasis on the interactions between researchers and policymakers. Finally, I utilize the political economy perspective to foreground the connections between medicine quality and (a) affordability, including the relation between price and quality, (b) availability, with attention to the estimated volume of substandard medicines in the market, and (c) patient preferences and irrational or inadequate use of medicines, including purchasing antibiotics from informal sources or without prescriptions.

My thesis focuses on Indonesia, the world's fourth most populous nation, which has a competitive domestic pharmaceutical industry. Particular products, such as antibiotics, are available in a wide variety of brands, formulations, and price points. Aiming to provide health coverage to its entire citizens, Indonesia launched the world's largest single-payer insurance (*Jaminan Kesehatan Nasional / JKN*) in 2014, now covering more than 90% of the population. Despite JKN's goal to provide free access to essential medicines, challenges persist within the healthcare system regarding availability and affordability, particularly related to out-of-pocket payments. This thesis examines medicines circulating both in regulated and unregulated markets. My core premise is that broadening the framing and problem definition of substandard and falsified medicines by integrating a political economy perspective alongside technical and regulatory approaches creates new opportunities to tackle the issue. Furthermore, I operationalize and test this broader perspective to understand its usefulness in strengthening post-

market surveillance. To test this, I have focused on amoxicillin, as this antibiotic is widely available in Indonesia. My approach includes sampling amoxicillin products from patient-access points, such as pharmacies or drug stores, and conducting quality testing of active pharmaceutical ingredients (APIs) in a third-party laboratory.

Lessons learned from the political economy approach and its influence in shaping research, policy, and practice

Drawing on the primary findings from **Chapters 2 to 6**, I present five key insights that address the main research question in detail in **Chapter 7**.

Key insight #1: Adding a political economy perspective provides new substantive insights, but is inherently complicated to operationalize

Adopting a political economy perspective to the issue of substandard and falsified medicines reveals several important insights; however, operationalizing this perspective into practice presents inherent complexities.

First, it helps uncover the mechanisms by which political and economic factors shape the production and trade of substandard and falsified medicines. As discussed in Chapter 2, the political commitment to achieve UHC served as the starting point for analyzing how various policy areas, such as procurement, trade, taxation, and even religious affairs, interact to create complex market dynamics. These interactions shape the incentives of different actors involved within and beyond the healthcare system.

Second, this approach highlights the social constellation of actors and clarifies their roles and responsibilities. Chapter 6 illustrates this by examining stakeholder engagement in intersectoral research collaboration focused on substandard and falsified medicines.

Third, the perspective brings to attention the fluidity or blurred boundaries between formal (regulated) and informal (unregulated) medicine distribution channels, particularly in the case of antibiotics. I sampled amoxicillin (N = 120), with the majority (93.3%) purchased without a prescription, across a range of locations, including remote, semi-rural, urban areas, and online. Substandard antibiotics (12.5%) were reported in both regulated and unregulated outlets, underlining the need for stronger regulatory oversight and enforcement, particularly in the informal sector.

Fourth, it inspires the use of market volume data to guide sampling priorities based on public health impact. In Chapter 4, I mapped quality testing results with estimated market volume and found that substandard amoxicillin accounted for 12.7% of the total market volume, equivalent to approximately 43 million doses annually, highlighting the scale of the issue and its relevance to public health policy.

While a political economy perspective offers valuable insights, operationalizing it in practice proves to be complex. In Chapter 3, I introduced several risk categories and indicators designed as a case-finding tool that leverages secondary data to flag potential substandard and falsified medicines products in a resource-constrained setting. By

combining market-related factors, including pricing and technical or regulatory risk factors, I developed separate sets of indicators for substandard and falsified medicines, respectively. However, the empirical findings from testing these assumptions told a different story. For example, I found no relationship between medicine price and quality. Future studies could explore testing non-active substances, such as excipients, and apply more advanced quality parameters, such as impurities.

In Chapter 5, I further operationalized and tested these risk indicators (N = 7) by applying them to flag amoxicillin products considered most at risk of being substandard. The results indicated that integrating market-related risk factors into the existing case-finding approach did not significantly increase the likelihood of detecting substandard, high-risk products. To strengthen and validate this approach, future work will require a larger sample size and more comprehensive regulatory and pharmaceutical market data, including benchmarks for fair pricing of quality-assured medicines.

Key insight #2: Taking a political economy perspective redefines the problem of substandard and falsified medicines and articulates its socioeconomic dimension

Applying a political economy perspective to substandard and falsified medicines broadens the problem definition by foregrounding socioeconomic dimensions. This is illustrated in Chapter 2, where patient preferences for certain vaccine brands reflect broader social and economic influences. Redefinition is further demonstrated in Chapter 3 through the development of distinct risk categories and objective indicators, connecting substandard medicines to factors such as pressured profit margins and falsified ones to topics such as product shortages and market opportunities. A "conceptual bridge" is formed by integrating technical or regulatory measures, and market dynamics.

In Chapter 6, intersectoral consultative meetings revealed that a political economy perspective can act as an "umbrella lens" or unifying framework, enabling actors to agree on defining the problem in a broader sense. It also helps to include other types of actors in the discussions, contributing to a more inclusive understanding of the problem and mobilizing commitment across stakeholders. In practical terms, using a political economy perspective may facilitate alignment of different stakeholder frames, perspectives, and incentives, especially when harmonizing multisectoral development plans and policies related to substandard and falsified medicines. Institutionalizing this process in a coordinating public agency could strengthen long-term policy coherence and collaboration.

Key insight #3: Problem definition is a social process that creates a path towards interagency silos

Defining the problem of substandard and falsified medicines is not only a substantive process, but also a social one, and the frames of each actor shape it. In a complex bureaucratic environment, this often results in interagency silos that undermine the intersectoral collaborative efforts, as discussed in Chapter 6. These silos become evident in the fragmented data and information on substandard and falsified medicines and the pharmaceutical market between various actors and organizations, as shown in Chapters

4 and 5. Materials, such as datasets, reflect the framing of each organization, often differing in detail and structure, which complicates data integration, interoperability, and collaborations.

This insight suggests that adopting a political economy perspective to tackle substandard and falsified medicines encourages the use and sharing of routine data across different sectors and levels of governance, such as national and sub-national, to support more coordinated policy responses.

Key insight #4: Broadening the frame, redefining problems and bridging silos entail policy learning across actors

While using a political economy perspective to broaden the framing and redefine the problem of substandard and falsified medicines does not necessarily call for replacing policy instruments, it does enable policy learning among involved actors. These learning processes yield both substantive outputs (e.g., knowledge on new methods for estimating substandard and falsified medicines prevalence) and relational outputs (e.g., stronger networks between researchers and policymakers.

As illustrated in Chapter 6, intersectoral consultative forums served as a key strategy in engaging stakeholders in a research collaboration. These forums facilitate policy learning and the creation of shared objectives across various interests. Establishing shared objectives was essential for aligning different framings, fostering intersectoral collaboration, and ultimately, bridging interagency silos.

Key insight #5: Researchers as policy entrepreneurs in navigating and bridging silos

While researchers are often seen to represent reality objectively, they also play an active role in shaping and framing how issues are understood. In the case of substandard and falsified medicines, the backgrounds and perspectives of researchers influenced their way of defining the problems, the assumptions, and the approaches they used. For instance, the effort to redefine the problem of substandard and falsified medicines included developing categories of risk factors and objective indicators (Chapter 3) and testing these assumptions (Chapter 5).

As researchers work to broaden the framing of substandard and falsified medicines and shape policy agendas, they must make strategic compromises and build alliances with particular actors or organizations (Chapter 6). While necessary, this strategy can limit the flexibility in operationalizing the problem definition and may constrain broader engagement with broader actors.

Furthermore, existing silos also hinder researchers' ability to broaden the framing of substandard and falsified medicines by creating information asymmetries, particularly around market organization, dynamics, and incentives, which the pharmaceutical industry or commercial data providers typically hold. Establishing a public-private partnership could help leverage proprietary data for public health use.

More broadly, and aligning with key insight #4, a research-policy partnership led by researchers can act as a platform for mutual learning, enabling open and transparent

data sharing across sectors and contributing to more coordinated policy responses to complex public health issues, such as substandard and falsified medicines.

Joining hands for universal quality healthcare

In closing, I echo Dr Tedros' central message: UHC cannot exist without access to quality-assured medicines. Through the lens of political economy, this thesis seeks to broaden our understanding and definition of the complexities surrounding substandard and falsified medicines, contributing both depth and evidence to the ongoing scientific and policy discourse. Medicine quality should not be considered in isolation within the UHC agenda; it is closely tied to availability, affordability, and the irrational or inadequate use of medicines. This thesis clearly demonstrates that providing quality-assured healthcare for all depends on coordinated efforts among stakeholders and collaboration across sectors to prevent anyone from being affected by substandard and falsified medicines.

Samenvatting

Het overbruggen van de silo's tussen agentschappen

Een politiek-economisch perspectief om ondermaatse en vervalste medicijnen in Indonesië aan te pakken

In 2022 benadrukte Tedros Adhanom Ghebreyesus, directeur-generaal van de WHO, dat "er geen universele gezondheidszorg, geen gezondheidszekerheid bestaat zonder toegang tot kwaliteitsgeneesmiddelen." Zijn uitspraak blijft zeer relevant, gezien de wijdverbreide aanwezigheid van geneesmiddelen van slechte kwaliteit wereldwijd – een uitdaging die zowel complex als veelzijdig is. De gevolgen van slechte kwaliteit geneesmiddelen zijn verstrekkend en hebben niet alleen invloed op individuele patiënten, maar ook op gezondheidszorgstelsels en de samenleving als geheel. De huidige kaders voor het aanpakken van geneesmiddelen van slechte kwaliteit zijn grotendeels technisch van aard. In dit proefschrift introduceer ik een nieuwe, bredere framing van het probleem van slechte kwaliteit geneesmiddelen, maak ik deze framing operationeel en test ik het potentieel ervan om het probleem beter aan te pakken.

Het sociale proces van het framen van het probleem van geneesmiddelen van slechte kwaliteit

In hoofdstuk 1 begin ik met een beschrijving van het proces om medicijnen van slechte kwaliteit te definiëren, wat historisch gezien complex is. Verschillende actoren en organisaties, waaronder mondiale gezondheidszorginstellingen, farmaceutische deskundigen en de farmaceutische industrie, hebben de definitie beïnvloed en hervormd door het probleem op verschillende manieren te framen, bijvoorbeeld vanuit het perspectief van inbreuk op intellectueel eigendom. Om meer gezamenlijke inspanningen te leveren om het probleem aan te pakken, heeft de WHO uiteindelijk in 2017 een op de volksgezondheid gerichte definitie aangenomen waarbij een onderscheid wordt gemaakt tussen ondermaatse en vervalste geneesmiddelen. Volgens deze definitie zijn geneesmiddelen van ondermaatse kwaliteit "toegelaten medische producten die niet voldoen aan hun kwaliteitsnormen of specificaties, of beide", terwijl vervalste geneesmiddelen "producten zijn die opzettelijk of frauduleus verkeerd worden voorgesteld met betrekking tot hun identiteit, samenstelling of herkomst."

Hoewel geneesmiddelen van ondermaatse kwaliteit en vervalste geneesmiddelen worden gedefinieerd vanuit het oogpunt van de volksgezondheid, zijn het vooral de technische en regelgevende domeinen die van invloed zijn op de omvang van het probleem en de beleidsreacties die daarop volgen. Deze framing positioneert de nationale geneesmiddelenautoriteit als de belangrijkste instantie voor het aanpakken van ondermaatse en vervalste geneesmiddelen. Als technisch agentschap is de autoriteit verantwoordelijk voor het waarborgen van de kwaliteit van geneesmiddelen door middel van activiteiten zoals post-market surveillance. Deze technische focus heeft de neiging

om kwaliteit te scheiden van andere cruciale aspecten van het geneesmiddelenbeleid, zoals de beschikbaarheid en betaalbaarheid van geneesmiddelen en irrationeel of onjuist gebruik van geneesmiddelen.

Gelijkblijvende framing – maar het probleem blijft bestaan

Er zijn verschillende technische maatregelen en beleidsinitiatieven genomen om landen te helpen bij de bestrijding van ondermaatste en vervalste geneesmiddelen. Toch blijven geneesmiddelen van slechte kwaliteit wereldwijd grote schade aanrichten, vooral in landen met lage- en middeninkomens. Over een periode van bijna twee decennia presenteren WHO-rapporten uit 1999 en 2017 vergelijkbare oorzaken, risicofactoren en aanbevelingen, waarbij de nadruk vooral ligt op technische en regelgevende aspecten en weinig aandacht wordt besteed aan de onderliggende sociale, politieke en economische factoren. Bovendien onderstrepen uitdagingen op het gebied van governance – zoals de marktstructuur, het complexe netwerk van belanghebbenden in de farmaceutische toeleveringsketen, politieke gevoeligheden rond ondermaatse en vervalste geneesmiddelen en problemen met de beschikbaarheid, standaardisatie en uitwisseling van gegevens – het veelzijdige karakter van het probleem, waarbij veel actoren uit verschillende domeinen betrokken zijn. Het negeren van politieke en sociaaleconomische dimensies miskent daarmee de rol van andere (beleids)actoren en verhindert de ontwikkeling van alternatieve oplossingen.

De nadruk op silo's tussen instanties

De constellatie van meerdere actoren, zoals hierboven beschreven, leidt vaak tot verschuivende verantwoordelijkheden en resulteert in wat bekend staat als 'siloïsering'.

Dit doet zich voor wanneer verschillende frames en perspectieven, zoals technische en regelgevende benaderingen, ervoor zorgen dat actoren of organisaties onafhankelijk opereren, zonder integratie met andere (externe) partijen. In dit proefschrift worden silo's opgevat als afzonderlijke gebieden binnen het farmaceutisch beleid, waaronder de kwaliteit, beschikbaarheid en betaalbaarheid en het irrationele of inadequate gebruik van geneesmiddelen. De term interagency verwijst naar verschillende afdelingen, departementen of directoraten binnen dezelfde of tussen verschillende organisaties.

De hierboven beschreven omstandigheden vragen om een alternatief perspectief dat zowel politieke als sociaaleconomische dimensies omvat om de kwestie van ondermaatse en vervalste geneesmiddelen effectief aan te pakken.

Verruiming van het frame en de probleemstelling van ondermaatse en vervalste geneesmiddelen: een politiek-economisch perspectief

Dit proefschrift stelt dat het integreren van politieke en sociaaleconomische perspectieven waardevolle inzichten kan bieden in de aard en onderliggende risico's van ondermaatse

en vervalste geneesmiddelen. Dergelijke perspectieven kunnen helpen om silo's tussen instanties te overwinnen of te overbruggen, de intersectorale samenwerking te versterken en de ontwikkeling van effectievere beleidsmaatregelen te ondersteunen. Het doel van dit proefschrift is om het zicht op de reikwijdte van ondermaatse en vervalste geneesmiddelen te verbreden en het probleem opnieuw te definiëren door een politiek-economisch perspectief te hanteren en dit te operationaliseren om het probleem in de praktijk aan te pakken. De belangrijkste onderzoeksvraag die als leidraad voor dit werk dient, is: "*Wat kunnen we leren van een politiek-economische benadering en hoe kan deze de inspanningen om ondermaatse en vervalste geneesmiddelen aan te pakken vormgeven?*"

Om dit te onderzoeken, is het proefschrift opgebouwd rond de volgende deelvragen:

1. Wat is de probleemdefinitie van ondermaatse en vervalste geneesmiddelen vanuit een politiek-economisch perspectief?
2. Hoe kunnen de probleemdefinitie van ondermaatse en vervalste geneesmiddelen en de daarmee samenhangende aannames vanuit een politiek-economisch perspectief worden geoperationaliseerd en getoetst?
3. Wat zijn de bevindingen van het operationaliseren en toetsen van de probleemdefinitie en aannames van ondermaatse en vervalste geneesmiddelen vanuit een politiek-economisch perspectief?
4. Hoe draagt intersectorale betrokkenheid van belanghebbenden bij aan het verbreden van het frame en de probleemdefinitie van ondermaatse en vervalste geneesmiddelen en de operationalisering ervan in een onderzoekssamenwerking?

Dit proefschrift bestaat uit twee delen. Eerst verbreed ik de huidige definitie van het probleem en herformuleer ik de bestaande benadering om de onderliggende mechanismen die de productie en handel van ondermaatse en vervalste geneesmiddelen aansturen beter te begrijpen (hoofdstuk 2). Ten tweede onderzoek ik hoe het politieke-economische perspectief kan worden geoperationaliseerd en gecombineerd met technische en beleidsmatige benaderingen om het toezicht na het in de handel brengen te versterken (hoofdstukken 3 tot en met 6). In dit verband besteed ik bijzondere aandacht aan de rol van onderzoekers als beleidsondernemers bij het verbreden van de manier waarop ondermaatse en vervalste geneesmiddelen wordt geframed.

Ik hanteer daarbij verschillende methodologische benaderingen die zich richten op verschillende hoofdgebieden. Ten eerste onderzoek ik hoe ondermaatse en vervalste geneesmiddelen zich verhouden tot andere beleidsprioriteiten en agendabepalende onderwerpen, zoals universele gezondheidszorg (universal health coverage, of UHC) en nationale welvaart. Ten tweede onderzoek ik de rollen en verantwoordelijkheden van verschillende intersectorale actoren, met bijzondere aandacht voor de interacties tussen onderzoekers en beleidsmakers. Ten slotte gebruik ik het politiek-economische perspectief om de verbanden tussen de kwaliteit van geneesmiddelen en (a) betaalbaarheid, met inbegrip van de relatie tussen prijs en kwaliteit, (b) beschikbaarheid, met aandacht voor de geschatte hoeveelheid geneesmiddelen van ondermaatse kwaliteit op de markt, en (c) patiëntenvoorkeuren en irrationeel of inadequaat gebruik van geneesmiddelen, waaronder de aankoop van antibiotica uit informele bronnen of zonder recept, op de

voorgrond te plaatsen.

Mijn proefschrift richt zich op Indonesië, het op vier na meest bevolkte land ter wereld, dat een concurrerende binnenlandse farmaceutische industrie heeft. Bepaalde producten, zoals antibiotica, zijn verkrijgbaar in een grote verscheidenheid aan merken, formuleringen en prijsklassen. Met als doel alle burgers van gezondheidszorg te voorzien, lanceerde Indonesië in 2014 ‘s werelds grootste single-payer-verzekering (*Jaminan Kesehatan Nasional* / JKN), die nu meer dan 90% van de bevolking dekt. Ondanks het doel van JKN om gratis toegang tot essentiële geneesmiddelen te bieden, blijven er binnen het gezondheidszorgstelsel uitdagingen bestaan met betrekking tot de beschikbaarheid en betaalbaarheid, met name in verband met eigen bijdragen. Dit proefschrift onderzoekt geneesmiddelen die zowel op gereguleerde als op ongereguleerde markten circuleren. Mijn belangrijkste uitgangspunt is dat het verbreden van het frame en de probleemdefinitie van ondermaatse en vervalste geneesmiddelen door een politiek-economisch perspectief te integreren naast technische en regelgevende benaderingen, nieuwe mogelijkheden creëert om het probleem aan te pakken. Verder operationaliseer en test ik dit bredere perspectief om het nut ervan te begrijpen voor het versterken van het toezicht na het in de handel brengen. Om dit te testen, heb ik mij gefocust op amoxicilline, omdat dit antibioticum overal verkrijgbaar is in Indonesië. Mijn aanpak omvat het nemen van monsters van amoxicillineproducten bij punten waar patiënten toegang toe hebben, zoals apotheken of drogisterijen, en het uitvoeren van kwaliteitstests van actieve farmaceutische ingrediënten (API’s) in een onafhankelijk laboratorium.

Lessen die zijn getrokken uit de politiek-economische benadering en de invloed daarvan op de vormgeving van onderzoek, beleid en praktijk

Op basis van de belangrijkste bevindingen uit de **hoofdstukken 2 tot en met 6** presenteer ik in **hoofdstuk 7** vijf belangrijke inzichten die de hoofdvraag van het onderzoek in detail behandelen.

Inzicht #1: Het toevoegen van een politiek-economisch perspectief levert nieuwe inhoudelijke inzichten op, maar is inherent complex om te operationaliseren

Ten eerste helpt het toevoegen van een politiek-economisch perspectief om de mechanismen bloot te leggen waarmee politieke en economische factoren de productie en handel van ondermaatse en vervalste geneesmiddelen beïnvloeden. Zoals besproken in hoofdstuk 2, diende de politieke toezegging om UHC te realiseren als uitgangspunt voor het analyseren van hoe verschillende beleidsterreinen, zoals inkoop, handel, belastingen en zelfs religieuze aangelegenheden, op elkaar inwerken om een complexe marktdynamiek te creëren. Deze interacties vormen de incentives van verschillende actoren binnen en buiten het gezondheidszorgsysteem.

Ten tweede benadrukt deze benadering de sociale constellatie van actoren en verduidelijkt zij hun rollen en verantwoordelijkheden. Hoofdstuk 6 illustreert dit door de betrokkenheid van belanghebbenden bij intersectorale onderzoekssamenwerking

gericht op ondermaatse en vervalste geneesmiddelen te onderzoeken.

Ten derde vestigt dit perspectief de aandacht op vage grenzen tussen formele (gereguleerde) en informele (ongereguleerde) distributiekanalen voor geneesmiddelen, met name in het geval van antibiotica. Ik heb amoxicilline (N = 120) bemonsterd, waarvan het merendeel (93,3%) zonder recept was gekocht, op verschillende locaties, waaronder afgelegen, semi-landelijke en stedelijke gebieden, en online. Zowel in gereguleerde als in niet-gereguleerde verkooppunten werden antibiotica van ondermaatse kwaliteit (12,5%) aangetroffen, wat de noodzaak van strengere regelgeving en handhaving onderstreept, met name in de informele sector.

Ten vierde inspireert dit tot het gebruik van marktvolumegegevens om de prioriteiten voor bemonstering te bepalen op basis van de impact op de volksgezondheid. In hoofdstuk 4 heb ik de resultaten van de kwaliteitstests in kaart gebracht met het geschatte marktvolume en vastgesteld dat amoxicilline van ondermaatse kwaliteit 12,7% van het totale marktvolume uitmaakte, wat overeenkomt met ongeveer 46 miljoen doses per jaar, wat de omvang van het probleem en het belang ervan voor het volksgezondheidsbeleid onderstreept.

Hoewel een politiek-economisch perspectief waardevolle inzichten biedt, blijkt de praktische toepassing ervan complex te zijn. In hoofdstuk 3 heb ik verschillende risicocategorieën en indicatoren geïntroduceerd die zijn ontworpen als een instrument voor het opsporen van gevallen, waarbij gebruik wordt gemaakt van secundaire gegevens om potentiële ondermaatse en vervalste geneesmiddelen in een omgeving met beperkte middelen te signaleren. Door marktgerelateerde factoren, waaronder prijs- en technische of regelgevingsrisicofactoren, te combineren, heb ik afzonderlijke sets van indicatoren ontwikkeld voor respectievelijk geneesmiddelen die niet aan de normen voldoen en vervalste geneesmiddelen. De empirische bevindingen uit het toetsen van deze aannames vertelden echter een ander verhaal. Zo vond ik geen verband tussen de prijs en de kwaliteit van geneesmiddelen. Toekomstige studies zouden kunnen kijken naar het testen van niet-werkzame stoffen, zoals hulpstoffen, en meer geavanceerde kwaliteitsparameters kunnen toepassen, zoals onzuiverheden.

In hoofdstuk 5 heb ik deze risico-indicatoren (N = 7) verder geoperationaliseerd en getest door ze toe te passen om amoxicillineproducten die het grootste risico lopen om onder de maat te zijn te signaleren. De resultaten wezen uit dat het integreren van marktgerelateerde risicofactoren in de bestaande aanpak voor het opsporen van gevallen de kans op het detecteren van producten van ondermaatse kwaliteit en met een hoog risico niet significant vergrootte. Om deze aanpak te versterken en te valideren, is voor toekomstig onderzoek een grotere steekproefomvang en uitgebreidere regelgevings- en farmaceutische marktgegevens nodig, waaronder benchmarks voor een eerlijke prijsstelling van geneesmiddelen waarvan de kwaliteit is gewaarborgd.

Inzicht #2: Door een politiek-economisch perspectief te hanteren, wordt het probleem van ondermaatse en vervalste geneesmiddelen opnieuw gedefinieerd en wordt de sociaaleconomische dimensie ervan duidelijker

Door een politiek-economisch perspectief toe te passen op ondermaatse en vervalste geneesmiddelen wordt de probleemdefinitie verbreed door de sociaaleconomische dimensies op de voorgrond te plaatsen. Dit wordt geïllustreerd in hoofdstuk 2, waar de voorkeuren van patiënten voor bepaalde vaccinmerken een weerspiegeling zijn van bredere sociale en economische invloeden. Herdefinitie wordt verder geïllustreerd in hoofdstuk 3 door de ontwikkeling van verschillende risicocategorieën en objectieve indicatoren, waarbij medicijnen die niet aan de normen voldoen worden gekoppeld aan factoren zoals onder druk staande winstmarges en vervalste medicijnen en onderwerpen zoals producttekorten en marktkansen.

In hoofdstuk 6 bleek uit intersectorale overleggen dat een politiek-economisch perspectief kan fungeren als een verbindend frame, waardoor actoren overeenstemming kunnen bereiken over een bredere definitie van het probleem. Het helpt ook om andere soorten actoren bij de discussies te betrekken, wat bijdraagt aan een meer inclusief begrip van het probleem en het mobiliseren van betrokkenheid bij alle belanghebbenden. In praktische termen kan het gebruik van een politiek-economisch perspectief de afstemming van verschillende frames, perspectieven en prikkels van belanghebbenden vergemakkelijken, met name bij het harmoniseren van multisectorale ontwikkelingsplannen en beleidsmaatregelen met betrekking tot ondermaatse en vervalste geneesmiddelen. Door dit proces te institutionaliseren in een coördinerende overheidsinstantie kan de samenhang en samenwerking op het gebied van langetermijnbeleid worden versterkt.

Inzicht #3: Probleemdefinitie is een sociaal proces dat leidt tot silovorming tussen instanties

Het definiëren van het probleem van ondermaatse en vervalste geneesmiddelen is niet alleen een inhoudelijk proces, maar ook een sociaal proces, en wordt gevormd door de frames van elke actor. In een complexe bureaucratische omgeving leidt dit vaak tot silovorming tussen instanties, wat de intersectorale samenwerking ondermijnt, zoals besproken in hoofdstuk 6. Deze silo's komen duidelijk naar voren in de gefragmenteerde gegevens en informatie over ondermaatse en vervalste geneesmiddelen en de farmaceutische markt tussen verschillende actoren en organisaties, zoals blijkt uit hoofdstukken 4 en 5. Materialen, zoals datasets, weerspiegelen het frame van elke organisatie, die vaak verschilt in detail en structuur, wat de integratie van gegevens, interoperabiliteit en samenwerking bemoeilijkt.

Dit inzicht suggereert dat het hanteren van een politiek-economisch perspectief om ondermaatse en vervalste geneesmiddelen aan te pakken, het gebruik en delen van routinegegevens tussen verschillende sectoren en bestuursniveaus, zoals nationaal en subnationaal, stimuleert om meer gecoördineerde beleidsreacties te ondersteunen.

Inzicht #4: Het verbreden van het frame, het herdefiniëren van problemen en het overbruggen van silo's vereist beleidsleren tussen actoren

Hoewel het gebruik van een politiek-economisch perspectief om het frame te verbreden en het probleem van ondermaatse en vervalste geneesmiddelen te herdefiniëren niet noodzakelijkerwijs vraagt om vervanging van beleidsinstrumenten, maakt het wel beleidsleren mogelijk onder de betrokken actoren. Deze leerprocessen leveren zowel

inhoudelijke resultaten op (bijvoorbeeld kennis over nieuwe methoden voor het schatten van de prevalentie van ondermaatse en vervalste geneesmiddelen) als relationele resultaten (bijvoorbeeld sterkere netwerken tussen onderzoekers en beleidsmakers).

Zoals geïllustreerd in hoofdstuk 6, dienden intersectorale overlegfora als een belangrijke kernstrategie om belanghebbenden te betrekken bij een onderzoekssamenwerking. Deze fora faciliteren beleidsleren en het creëren van gedeelde doelstellingen tussen verschillende belangen. Het vaststellen van gedeelde doelstellingen was essentieel voor het op één lijn brengen van verschillende frames, het bevorderen van intersectorale samenwerking en uiteindelijk het overbruggen van silo's tussen instanties.

Inzicht #5: Onderzoekers fungeren als beleidsondernemers bij het navigeren en overbruggen van silo's

Onderzoekers spelen ze een actieve rol bij het vormgeven en framen van hoe kwesties worden begrepen. In het geval van ondermaatse en vervalste geneesmiddelen beïnvloedden de achtergronden en perspectieven van onderzoekers hun manier van definiëren van de problemen, de aannames en de benaderingen die ze gebruikten. Dit betreft bijvoorbeeld de inspanning tot het herdefiniëren van het probleem van ondermaatse en vervalste geneesmiddelen waaronder het ontwikkelen van categorieën van risicofactoren en objectieve indicatoren (hoofdstuk 3) en het toetsen van deze aannames (hoofdstuk 5).

Omdat onderzoekers werken aan het verbreden van het frame van ondermaatse en vervalste geneesmiddelen en het vormgeven van beleidsagenda's, moeten ze strategische compromissen sluiten en allianties aangaan met bepaalde actoren of organisaties (hoofdstuk 6). Hoewel deze strategie noodzakelijk is, kan ze de flexibiliteit bij het operationaliseren van de probleemdefinitie beperken en een bredere betrokkenheid van meer actoren in de weg staan.

Bovendien belemmeren bestaande silo's ook het vermogen van onderzoekers om het frame van ondermaatse en vervalste geneesmiddelen te verbreden door informatie-asymmetrieën te creëren, met name rond marktorganisatie, dynamiek en prikkels, waarover de farmaceutische industrie of commerciële gegevensleveranciers doorgaans beschikken. Het opzetten van een publiek-privaat partnerschap zou kunnen helpen om gegevens te benutten voor volksgezondheidsdoeleinden.

Meer in het algemeen, en in overeenstemming met kerninzicht #4, kan een door onderzoekers geleid partnerschap tussen onderzoek en beleid fungeren als een platform voor wederzijds leren, waardoor open en transparante gegevensuitwisseling tussen sectoren mogelijk wordt en wordt bijgedragen aan beter gecoördineerde beleidsreacties op complexe volksgezondheidskwesties, zoals ondermaatse en vervalste geneesmiddelen.

Samenwerken voor universele kwaliteitsgezondheidszorg

Tot slot sluit ik me aan bij de centrale boodschap van dr. Tedros: universele gezondheidszorg (UHC) kan niet bestaan zonder toegang tot geneesmiddelen van goede kwaliteit. Vanuit politiek-economisch perspectief tracht dit proefschrift ons begrip en onze definitie van de complexiteit rond ondermaatse en vervalste geneesmiddelen te verbreden en zowel diepgang als bewijs te leveren voor het lopende wetenschappelijke en beleidsdiscours. De kwaliteit van geneesmiddelen mag niet los worden gezien van de agenda voor universele gezondheidszorg; deze hangt nauw samen met de beschikbaarheid, betaalbaarheid en het irrationele of inadequate gebruik van geneesmiddelen. Dit proefschrift toont duidelijk aan dat het bieden van kwaliteitsvolle gezondheidszorg voor iedereen afhankelijk is van gecoördineerde inspanningen van belanghebbenden en samenwerking tussen sectoren om te voorkomen dat patiënten door ondermaatse en vervalste geneesmiddelen worden getroffen.

Ringkasan

Menjembatani Sekat Antarlembaga

Perspektif ekonomi politik untuk menangani obat-obatan substandar dan palsu di Indonesia

Pada tahun 2022, Direktur Jenderal WHO Dr Tedros Adhanom Ghebreyesus menekankan bahwa "Tidak ada cakupan kesehatan semesta (*Universal Health Coverage / UHC*) atau keamanan kesehatan tanpa akses terhadap obat-obatan berkualitas". Pernyataan ini tetap sangat relevan, mengingat penyebaran obat-obatan berkualitas rendah secara global – sebuah tantangan yang kompleks dan bersegi banyak. Dampak obat-obatan berkualitas rendah sangat luas, tidak hanya mempengaruhi pasien individu tetapi juga sistem kesehatan secara keseluruhan dan struktur sosial-ekonomi. Kerangka kerja saat ini untuk menargetkan obat-obatan berkualitas rendah sebagian besar bersifat teknis. Dalam tesis ini, saya memperkenalkan kerangka pemikiran baru dan lebih luas mengenai masalah obat-obatan berkualitas rendah, mengoperasionalisasikannya berdasarkan perspektif ini, dan menguji potensinya untuk mengatasi masalah tersebut dengan lebih baik.

Proses sosial dalam membuat kerangka dan mendefinisikan masalah obat-obatan berkualitas rendah

Pada Bab 1, saya mulai dengan menjelaskan proses mendefinisikan obat-obatan berkualitas rendah, yang secara historis kompleks. Seperti dijelaskan dalam Bab 1, proses mendefinisikan obat-obatan berkualitas rendah secara historis kompleks. Berbagai aktor dan organisasi, termasuk lembaga kesehatan global, ahli farmasi, dan industri farmasi, telah mempengaruhi dan merumuskan ulang definisi tersebut dengan memandang masalah ini dari sudut pandang yang berbeda, seperti melalui lensa pelanggaran hak kekayaan intelektual. Untuk mendorong upaya yang lebih terkoordinasi dalam menangani masalah ini, WHO pada akhirnya mengadopsi definisi yang berfokus pada kesehatan masyarakat pada tahun 2017. Menurut definisi ini, obat-obatan substandar merujuk pada "produk medis yang resmi namun tidak memenuhi standar kualitas atau spesifikasinya, atau keduanya", sementara obat-obatan palsu adalah "produk yang secara sengaja atau dipalsukan terkait identitas, komposisi, atau sumbernya".

Meskipun obat-obatan substandar dan palsu didefinisikan dari perspektif kesehatan masyarakat, domain teknis dan regulasi selalu mempengaruhi penentuan lingkup masalah dan respons kebijakannya. Kerangka ini menempatkan regulator obat nasional sebagai otoritas utama dalam menangani masalah obat substandar dan palsu. Sebagai lembaga teknis, regulator bertanggung jawab untuk memastikan kualitas obat melalui kegiatan seperti pengawasan pasca-pasar. Fokus teknis ini cenderung memisahkan masalah kualitas dari area kritis lain dalam kebijakan farmasi, seperti ketersediaan obat,

keterjangkauan, dan penggunaan obat yang tidak rasional atau tidak memadai.

Kerangka masalah dan solusi kebijakan yang serupa – namun masalah tetap berlanjut

Berbagai intervensi teknis dan upaya kebijakan telah diterapkan untuk membantu negara-negara memerangi obat-obatan berkualitas rendah dan palsu; namun, obat-obatan berkualitas rendah terus menimbulkan dampak serius di seluruh dunia, terutama di negara-negara berpendapatan rendah dan menengah. Selama hampir dua dekade, laporan WHO tahun 1999 dan 2017 menyoroti penyebab, faktor risiko, dan rekomendasi yang serupa, dengan fokus utama pada aspek teknis dan regulasi, sementara sedikit memperhatikan faktor sosial, politik, dan ekonomi yang mendasari produksi dan perdagangan obat-obatan substandar dan palsu. Selain itu, tantangan terkait tata kelola – seperti struktur pasar, jaringan kompleks pemangku kepentingan dalam rantai pasok farmasi, sensitivitas politik seputar obat-obatan substandar dan palsu, serta masalah ketersediaan, standarisasi, dan pemanfaatan data – menyoroti kompleksitas dari masalah ini, yang melibatkan banyak pihak dari berbagai bidang. Akibatnya, mengabaikan dimensi politik dan sosioekonomi dapat mengaburkan peran aktor kebijakan lain dan membatasi pengembangan solusi alternatif.

Menyoroti sekat antarlembaga

Konstelasi berbagai pemangku kepentingan, seperti yang dijelaskan di atas, seringkali menyebabkan pergeseran tanggung jawab dan mengakibatkan apa yang dikenal sebagai "siloisasi", atau penyekatan antar lembaga. Ini terjadi ketika kerangka acuan dan perspektif yang berbeda, seperti pendekatan teknis dan regulasi, menyebabkan pemangku kepentingan atau organisasi beroperasi secara mandiri tanpa integrasi dengan pihak luar. Dengan demikian, dalam tesis ini, silo dipahami sebagai area-area terpisah dalam kebijakan farmasi, termasuk kualitas obat, ketersediaan, keterjangkauan, dan penggunaan obat yang tidak rasional atau tidak memadai. Istilah antarlembaga merujuk pada bagian, departemen, atau direktorat yang berbeda dalam organisasi yang sama atau antara organisasi yang berbeda.

Kondisi yang dijelaskan di atas memerlukan perspektif alternatif yang menggabungkan dimensi politik dan sosioekonomi untuk menangani masalah SFM secara efektif.

Memperluas kerangka dan definisi masalah obat substandar dan palsu: perspektif ekonomi politik

Tesis ini berargumen bahwa memasukkan perspektif politik dan ekonomi sosial dapat memberikan wawasan berharga tentang sifat dan risiko mendasar obat substandar dan palsu. Perspektif-perspektif ini dapat membantu mengatasi atau menjembatani sekat antarlembaga, memperkuat kolaborasi antarsektor, dan mendukung pengembangan respons kebijakan yang lebih efektif. Tujuan tesis ini adalah untuk memperluas cakupan dan mendefinisikan ulang masalah obat substandar dan palsu dengan mengadopsi perspektif ekonomi politik dan mengimplementasikannya untuk mengatasi masalah

tersebut dalam praktik. Pertanyaan penelitian utama yang mengarahkan tesis ini adalah "*Apa yang dapat kita pelajari dari pendekatan ekonomi politik, dan bagaimana hal itu dapat membentuk upaya dalam menangani obat substandar dan obat palsu*?".

Untuk mengeksplorasi hal itu, tesis ini disusun berdasarkan pertanyaan-pertanyaan berikut:

1. Apa definisi permasalahan obat substandar dan palsu dari perspektif ekonomi politik?
2. Bagaimana definisi permasalahan obat substandar dan palsu dan asumsi terkait dari perspektif ekonomi politik dapat dioperasionalkan dan diuji?
3. Apa temuan dari pengoperasionalan dan pengujian definisi permasalahan obat substandar dan palsu dan asumsi dari perspektif ekonomi politik?
4. Bagaimana keterlibatan pemangku kepentingan lintas sektor berkontribusi dalam memperluas kerangka dan definisi permasalahan obat substandar dan palsu serta pengoperasionalannya dalam kolaborasi penelitian?

Tesis ini terdiri dari dua bagian. Pertama, saya memperluas definisi masalah yang ada dan merumuskan ulang pendekatan yang ada untuk memahami mekanisme mendasar yang mendorong produksi dan perdagangan obat substandar dan palsu (Bab 2). Kedua, tesis ini mengeksplorasi pemahaman apa yang dapat dilakukan untuk mengimplementasikan perspektif ekonomi politik dan menggabungkannya dengan pendekatan teknis dan regulasi untuk memperkuat pengawasan pasca-pasar (Bab 3 hingga 6). Dalam konteks ini, saya memberikan perhatian khusus pada peran peneliti sebagai *policy entrepreneurs* dalam memperluas cara obat substandar dan palsu didefinisikan dan dikerangkakan.

Menghadapi isu obat substandar dan palsu dari perspektif ekonomi politik melibatkan studi yang beragam metodenya dengan fokus pada beberapa area kunci. Pertama, saya mengeksplorasi bagaimana obat substandard dan palsu terkait dengan prioritas kebijakan lain dan topik penetapan agenda, seperti Cakupan Kesehatan Semesta (*Universal Health Coverage / UHC*) dan kemakmuran nasional. Kedua, saya menganalisis peran dan tanggung jawab berbagai aktor lintas sektor, dengan penekanan khusus pada interaksi antara peneliti dan pembuat kebijakan. Akhirnya, saya memanfaatkan perspektif ekonomi politik untuk menyoroti hubungan antara kualitas obat dan (a) keterjangkauan, termasuk hubungan antara harga dan kualitas, (b) ketersediaan, dengan memperhatikan volume perkiraan obat-obatan substandar di pasar, dan (c) preferensi pasien dan penggunaan obat yang irasional atau tidak memadai, termasuk pembelian antibiotik dari sumber informal atau tanpa resep.

Tesis ini berfokus pada Indonesia, negara dengan populasi keempat terbesar di dunia, yang memiliki industri farmasi domestik yang kompetitif. Produk-produk tertentu, seperti antibiotik, tersedia dalam berbagai merek, formulasi, dan rentang harga. Dengan tujuan memberikan jaminan kesehatan bagi seluruh warganya, Indonesia meluncurkan program asuransi kesehatan tunggal terbesar di dunia (Jaminan Kesehatan Nasional /

JKN) pada tahun 2014, yang kini mencakup lebih dari 90 persen populasi. Meskipun tujuan JKN adalah menyediakan akses gratis ke obat-obatan esensial, tantangan tetap ada dalam sistem kesehatan terkait ketersediaan dan keterjangkauan, terutama terkait pembayaran pribadi. Tesis ini menganalisis obat-obatan yang beredar di pasar yang diregulasi maupun tidak. Premis utama saya adalah bahwa memperluas kerangka acuan dan definisi masalah terkait obat-obatan substandar dan palsu dengan mengintegrasikan perspektif ekonomi politik bersama pendekatan teknis dan regulasi menciptakan peluang baru untuk menangani masalah tersebut. Selain itu, saya mengimplementasikan dan menguji perspektif yang lebih luas ini untuk memahami kegunaannya dalam memperkuat pengawasan pasca-pasar. Untuk menguji ini, saya fokus pada amoksisilin, karena antibiotik ini tersedia secara luas di Indonesia. Pendekatan saya meliputi pengambilan sampel produk amoksisilin dari titik akses pasien, seperti apotek atau toko obat, dan melakukan pengujian kualitas bahan aktif farmasi (API) di laboratorium pihak ketiga.

Pelajaran yang dipetik dari pendekatan ekonomi politik dan pengaruhnya dalam membentuk penelitian, kebijakan, dan praktik

Berdasarkan temuan utama dari Bab 2 hingga 6, saya menyajikan lima wawasan kunci yang menjawab pertanyaan penelitian utama secara rinci dalam Bab 7.

Wawasan utama #1: Menambahkan perspektif ekonomi politik memberikan wawasan substantif baru, tetapi secara inheren rumit untuk diimplementasikan

Mengadopsi perspektif ekonomi politik terhadap isu obat substandar dan palsu mengungkapkan beberapa wawasan penting; namun, mengimplementasikan perspektif ini ke dalam praktik menimbulkan kompleksitas inheren.

Pertama, hal ini membantu mengungkap mekanisme di mana faktor politik dan ekonomi membentuk produksi dan perdagangan SFM. Seperti dibahas dalam Bab 2, komitmen politik untuk mencapai UHC menjadi titik awal untuk menganalisis bagaimana berbagai bidang kebijakan (seperti pengadaan, perdagangan, perpajakan, dan bahkan masalah yang terkait dengan agama) berinteraksi menciptakan dinamika pasar yang kompleks. Interaksi ini membentuk insentif bagi berbagai aktor yang terlibat di dalam dan di luar sistem kesehatan.

Kedua, pendekatan ini menyoroti konstelasi sosial para aktor dan memperjelas peran serta tanggung jawab mereka. Bab 6 menggambarkan hal ini dengan menganalisis keterlibatan pemangku kepentingan dalam kolaborasi penelitian lintas sektor yang berfokus pada obat substandar dan obat palsu.

Ketiga, perspektif ini menyoroti keluwesan atau batas yang kabur antara saluran distribusi obat formal (teregulasi) dan informal (tidak teregulasi), terutama dalam kasus antibiotik. Saya mengambil sampel amoksisilin (N = 120), dengan mayoritas (93,3%) dibeli tanpa resep, di berbagai lokasi, termasuk daerah terpencil, semi-pedesaan, perkotaan, dan daring. Antibiotik substandar (12,5%) dilaporkan di outlet

yang diregulasi maupun tidak, menyoroti kebutuhan akan pengawasan dan penegakan regulasi yang lebih kuat, terutama di sektor informal.

Keempat, hal ini menginspirasi penggunaan data volume pasar untuk mengarahkan prioritas pengambilan sampel berdasarkan dampak kesehatan masyarakat. Dalam Bab 4, saya memetakan hasil uji kualitas dengan volume pasar yang diperkirakan dan menemukan bahwa amoksisilin substandar menyumbang 12,7% dari total volume pasar, setara dengan sekitar 46 juta dosis per tahun, menyoroti skala masalah dan relevansinya bagi kebijakan kesehatan masyarakat.

Meskipun perspektif ekonomi politik menawarkan wawasan berharga, mengimplementasikannya dalam praktik terbukti kompleks. Dalam Bab 3, saya memperkenalkan beberapa kategori risiko dan indikator yang dirancang sebagai alat identifikasi kasus yang memanfaatkan data sekunder untuk mengidentifikasi produk obat substandar dan palsu potensial dalam lingkungan dengan sumber daya terbatas. Dengan menggabungkan faktor-faktor pasar, termasuk harga dan faktor risiko teknis atau regulasi, saya mengembangkan set indikator terpisah untuk obat-obatan substandar dan palsu. Namun, temuan empiris dari pengujian asumsi-asumsi ini mengungkapkan informasi yang berbeda. Misalnya, saya tidak menemukan hubungan antara harga obat dengan kualitasnya. Studi masa depan dapat mengeksplorasi pengujian zat non-aktif, seperti eksipien, dan menerapkan parameter kualitas yang lebih canggih, seperti impuritas.

Dalam Bab 5, saya lebih lanjut mengimplementasikan dan menguji indikator risiko ini (N = 7) dengan menerapkannya untuk mengidentifikasi produk amoksisilin yang dianggap paling berisiko menjadi substandar. Hasil menunjukkan bahwa mengintegrasikan faktor risiko terkait pasar ke dalam pendekatan penemuan kasus yang saat ini digunakan tidak secara signifikan meningkatkan kemungkinan mendeteksi produk berisiko tinggi. Untuk memperkuat dan memvalidasi pendekatan ini, penelitian di masa depan memerlukan ukuran sampel yang lebih besar dan data pasar farmasi serta regulasi yang lebih komprehensif, termasuk acuan harga yang wajar untuk obat-obatan yang terjamin kualitasnya.

Wawasan Utama #2: Penggunaan perspektif ekonomi politik mendefinisikan ulang masalah obat substandar dan palsu dan menguraikan dimensi sosial-ekonominya.

Mengaplikasikan perspektif ekonomi politik pada obat substandar dan palsu memperluas definisi masalah dengan menonjolkan dimensi sosial-ekonomi. Hal ini diilustrasikan dalam Bab 2, di mana preferensi pasien terhadap merek vaksin tertentu mencerminkan pengaruh sosial dan ekonomi yang lebih luas. Pendefinisian ulang ini lebih lanjut ditunjukkan dalam Bab 3 melalui pengembangan kategori risiko yang berbeda dan indikator objektif, menghubungkan obat-obatan substandar dengan faktor seperti margin keuntungan yang tertekan, dan obat-obatan palsu dengan topik seperti kelangkaan produk dan peluang pasar. Sebuah "jembatan konseptual" terbentuk dengan mengintegrasikan langkah-langkah teknis atau regulasi, dan dinamika pasar.

Dalam Bab 6, pertemuan konsultatif antar sektor mengungkapkan bahwa perspektif

ekonomi politik dapat berfungsi sebagai "lensa payung" atau kerangka kerja unifikasi, memfasilitasi kesepakatan para pemangku kepentingan dalam mendefinisikan masalah secara lebih luas. Hal ini juga membantu melibatkan jenis pemangku kepentingan lain dalam diskusi, berkontribusi pada pemahaman yang lebih inklusif tentang masalah dan menggerakkan komitmen di antara para pemangku kepentingan. Dalam praktiknya, penggunaan perspektif ekonomi politik dapat memfasilitasi penyelarasan kerangka, perspektif, dan insentif berbagai pemangku kepentingan. Terutama untuk mengharmonisasikan rencana dan kebijakan pembangunan multisektor yang terkait dengan obat substandar dan palsu. Menginstitusionalisasikan proses ini dalam lembaga publik yang bersifat koordinatif akan memperkuat keterpaduan kebijakan dan kolaborasi jangka panjang.

Wawasan Utama #3: Definisi masalah merupakan proses sosial yang membentuk jalur menuju sekat antarlembaga

Definisi masalah obat substandar dan palsu tidak hanya merupakan proses substansial, tetapi juga proses sosial yang dibentuk oleh kerangka acuan masing-masing aktor. Dalam lingkungan birokrasi yang kompleks, hal ini sering kali menghasilkan sekat antarlembaga yang menjadi kendala kolaborasi lintas sektor, seperti yang dibahas dalam Bab 6. Sekat-sekat ini terlihat jelas dalam data dan informasi yang terfragmentasi tentang obat substandar dan palsu dan pasar farmasi di antara berbagai aktor dan organisasi, seperti yang ditunjukkan dalam Bab 4 dan 5. Materi, seperti dataset, mencerminkan kerangka acuan masing-masing organisasi, seringkali berbeda dalam detail dan struktur, yang mempersulit integrasi data, interoperabilitas, dan kolaborasi.

Wawasan ini menyarankan bahwa mengadopsi perspektif ekonomi politik untuk menangani obat substandar dan palsu mendorong penggunaan dan pemanfaatan data rutin di berbagai sektor dan tingkat pemerintahan, seperti nasional dan sub-nasional, untuk mendukung respons kebijakan yang lebih terkoordinasi.

Wawasan Utama #4: Memperluas kerangka, mendefinisikan ulang masalah, dan menjembatani sekat memerlukan pembelajaran kebijakan di antara aktor

Meskipun menggunakan perspektif ekonomi politik untuk memperluas kerangka dan mendefinisikan ulang masalah obat substandar dan palsu tidak selalu memerlukan penggantian instrumen kebijakan, hal ini memfasilitasi pembelajaran kebijakan di antara aktor yang terlibat. Proses pembelajaran ini menghasilkan keluaran substantif (misalnya, pengetahuan tentang metode baru untuk mengestimasi prevalensi obat substandar dan obat palsu) dan keluaran relasional (misalnya, jaringan yang lebih kuat antara peneliti dan pembuat kebijakan.

Seperti yang diilustrasikan dalam Bab 6, forum konsultatif antar sektor berperan sebagai strategi kunci dalam melibatkan pemangku kepentingan dalam kolaborasi penelitian. Forum-forum ini memfasilitasi pembelajaran kebijakan dan pembentukan tujuan bersama di antara berbagai kepentingan. Pembentukan tujuan bersama sangat penting untuk menyelaraskan kerangka kerja yang berbeda, mendorong kolaborasi antar sektor, dan pada akhirnya, menjembatani sekat antar lembaga.

Wawasan Utama #5: Peneliti sebagai policy entrepreneur dalam menavigasi dan menjembatani sekat-sekat

Meskipun peneliti sering dianggap mewakili realitas secara objektif, mereka juga berperan aktif dalam membentuk dan mengarahkan cara pemahaman terhadap isu-isu tertentu. Dalam konteks obat substandar dan palsu, latar belakang dan perspektif peneliti memengaruhi cara mereka mendefinisikan masalah, asumsi, dan pendekatan yang digunakan. Misalnya, upaya untuk mendefinisikan ulang masalah obat substandar dan palsu meliputi pengembangan kategori faktor risiko dan indikator objektif (Bab 3) serta pengujian asumsi-asumsi tersebut (Bab 5).

Saat peneliti berusaha memperluas kerangka obat substandar dan obat palsu dan membentuk agenda kebijakan, mereka harus membuat kompromi strategis dan membangun aliansi dengan aktor atau organisasi tertentu (Bab 6). Meskipun diperlukan, strategi ini dapat membatasi fleksibilitas dalam mengimplementasikan definisi masalah dan mungkin membatasi keterlibatan yang lebih luas dengan aktor-aktor lain.

Selain itu, sekat-sekat yang ada juga menghambat kemampuan peneliti untuk memperluas kerangka obat substandar dan palsu dengan menciptakan ketidakseimbangan informasi, terutama terkait organisasi pasar, dinamika, dan insentif, yang biasanya dimiliki oleh industri farmasi atau penyedia data komersial. Pembentukan kemitraan publik-swasta dapat membantu memanfaatkan data dengan hak kepemilikan khusus untuk kepentingan kesehatan masyarakat.

Secara lebih luas, dan sejalan dengan wawasan kunci nomor 4, kemitraan riset-kebijakan yang dipimpin oleh peneliti dapat berfungsi sebagai platform untuk pembelajaran bersama, memfasilitasi pemanfaatan data secara terbuka dan transparan antar sektor, serta berkontribusi pada respons kebijakan yang lebih terkoordinasi terhadap isu kesehatan masyarakat yang kompleks, seperti obat substandar dan palsu.

Bergandengan tangan untuk cakupan kesehatan semesta yang berkualitas

Sebagai penutup, saya mengulang pesan utama Dr. Tedros: cakupan kesehatan universal tidak dapat terwujud tanpa akses terhadap obat-obatan yang berkualitas. Melalui perspektif ekonomi politik, tesis ini bertujuan untuk memperluas pemahaman dan definisi kita tentang kompleksitas mengenai obat-obatan substandar dan palsu, memberikan kedalaman dan bukti ilmiah bagi wacana ilmiah dan kebijakan yang sedang berlangsung. Kualitas obat tidak bisa dipertimbangkan secara terpisah dalam agenda UHC; hal ini terkait erat dengan ketersediaan, keterjangkauan, dan penggunaan obat yang tidak rasional atau tidak memadai. Tesis ini dengan jelas menunjukkan bahwa penyediaan cakupan kesehatan berkualitas bagi semua bergantung pada upaya terkoordinasi antar pemangku kepentingan dan kolaborasi lintas sektoral untuk mencegah siapa pun terkena dampak obat substandar dan palsu.

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Completing a PhD can be a daunting journey. However, I feel fortunate to go to work each day knowing I'll be surrounded by colleagues who bring positive energy to the experience.

My gratitude goes to the beloved **Health Care Governance (HCG) section**. A special thanks goes to **Susan**, whose dedication ensures every meeting runs smoothly, all paperwork is in order, and who never fails to remind me—with a smile—to "behave" over the weekend . **Robert**, our interactions date back to our time in Amsterdam. I've always been amused by your boundless inquisitiveness about everything from decolonising global health to the latest binge-worthy series, all delivered with great humour. I'm especially thankful for our early brainstorming session, which helped shape the direction of Chapter 1. To **Regianne**, thank you for your valuable guidance on teaching and for your personal support during some of the more difficult phases of my PhD journey. I also appreciate **Zahra** and **Habib**, who have consistently encouraged me to complete this PhD. **Martijn** has always greeted me with a big smile —I'm grateful for his guidance during my first

teaching experience and for his practical advice that helped with the publication of Chapter 6. Lastly, my thanks to **Bert** for convening the Caring for Crisis group, which has been particularly helpful for shaping my postdoc research themes.

My fellow PhD and postdoc colleagues in HCG—past and present—are too many to name individually, but have been incredible in sharing *gezelligheid*, as well as helping shoulder the challenging moments. A few of you, however, deserve special mention here:

Jolien, thank you for all the lovely meet-ups across different cities and countries, especially during our memorable French summer road trip. **Chiara**, the feminist powerhouse, is always ready for a coffee or drink when needed urgently. **Renee**, I appreciate your adventurous spirit in exploring various Indonesian restaurants in Den Haag and your funny cat stories. **Iris**, always up for a friendly chat between writing sessions, and the one with vivid memories of my many Germany trips. **Margot**, for your excellent teaching and supervision tips, and your passion for sharing research findings in creative ways. **Tessa**, one of the earliest PhD colleagues I met, always honest and helpful with advice on surviving the PhD journey. **Oemar**, the "gangsta" colleague, who not only teaches brilliantly but also opened my eyes to the "politics of snacks." **Nada**, my "Erasmuspedia," a dependable guide for all things university, faculty, and section-related. Cheers to the cultural day we co-organized together! **Mirjam**, for sharing the long metro rides to Hoek van Holland and keeping her positivity even in tough times. I've enjoyed exchanging cultural stories with **Sabrina** about her Balinese family and appreciate **Leonoor**'s easy-going humour at work. **Syb**, always relaxed, provides the latest tips on defending the thesis. **Kyra**, though not yet a PhD, your companionship has been so meaningful that you feel more like family than just a colleague . I also want to mention some of the newer PhD colleagues: **Laura B**, who constantly reminds me when it's lunchtime and is always ready for another matcha run; **Lizette**, known for her hilariously witty remarks; and **Celine and Runnah**, who inspired me to take breaks and hit the gym. **Karin, Janna, and Yael** for their genuine kindness.

I'm also lucky to have got to know other PhDs across various sections of ESHPM, who also add colours to the journey.

Karen— or should I say Karenita? —thank you for all your positive encouragement, for motivating me to exercise or meditate, and for persistently reminding me to cook Indonesian food for you. I truly value your presence during my PhD journey – *gracias por todos*!. **Elena**, thank you for your brilliant sense of humor. **Maria-Jose**, I cherished the relaxing moments we shared in Nusa Dua during the iHEA conference. **Lujia**, thank you for your insights on legal and compliance matters and for a wonderful sunny day trip to Antwerp. **Wenran, Eden, and Fanny**, I appreciate your contributions to making the cultural day such a success. **Vivienne**, thank you for sharing your knowledge of pharmaceuticals and global health aid. And **Mas Pugo** —I'm following your path as the next Indonesian PhD at ESHPM .

As part of my additional engagements this year, I had the privilege of joining the management team of the Rotterdam Global Health Initiative (RGHI). I'm grateful to my fellow team members — **Robert Sparrow, Matthias Rieger, Tanja Houweling, and Carlos Riumallo-Herl** — for the opportunity to collaborate on exciting initiatives that promote health equity, particularly in countries in the Global South. I also extend my thanks to **Caroline Verboom**, whose amazing organisational skills keep RGHI afloat.

The success of several activities within my PhD projects would not have been possible without the dedicated support of the professional staff at ESHPM. I sincerely thank **Patricia van Loo-Kemp** for her assistance with communications, including during the launch of the STARmeds project. My appreciation also goes to **Annette Twigt** and, later, **Hannie Tran** for their efforts in managing the project's financial administration.

Before completing my PhD, I had the opportunity to begin working as a postdoctoral researcher on the PARAATHEID project. I'm grateful to the principal investigator, **Zenlin Roosenboom-Kwee** from **TU Delft**, for her thoughtful leadership and support during the final stages of my dissertation. I also extend my thanks to the core team — **Saba Hinrichs-Krapels**, **Saut Sagala, Ari Nurman**, **and Wahyu Septiono** — for their warm and welcoming reception. I'm excited to collaborate in the successful delivery of the project!

I would also like to thank my friends and personal connections who keep me going in my PhD.

Let me begin with my **former housemates** in Rotterdam, who made the city feel like home away from home. A special shoutout to **Indra**, who has been a reliable presence in countless ways — not least as a fantastic home chef. *Hatur nuhun*, Ndra! Thanks also to **Franklin and Martin**, who shared the house in Alexander and graciously put up with many gatherings. **Alexandra and Domi**, thank you

for your warmth and for the joyful walks through the city centre we shared.

A wonderful **group of friends** has made living in **Roffa** all the more special. **Sofi**, who first introduced me to the city a decade ago, continues to be a steady source of support. **Yolly**, whose bright spirit and amazing Indonesian cooking speak volumes about her kindness. To the 2022 cohort — **Yasmin, Hanna, and Rafid** — thank you for the wonderful companionship during my early days in the city. **Hendra,** my first thesis student, has impressed me with his passion for public health. **Alex and Angel**, frequent visitors to the town, brought refreshing Gen-Z insights and vocabulary**. Ika**, thank you for introducing me to that serene sunset spot at Kralingse Plas. **Alamanda**, for taking me to museums to see beautiful landscape paintings and for being my lifeline on many occasions. I'm also grateful to friends from Erasmus MC and their families **— Yun & Iwan, Rendy & Riani, Anshory & Uni** — for the countless potlucks and delighted moments across seasons. Special thanks to **Riani**, who beautifully designed my book cover! To **Mbak Novika**, thank you for showing me what it means to be a good paranymph. Lastly, to the new wave of Indonesian PhDs and postdocs at Woudestein: **Andini**, for constantly encouraging me to join protests and embrace activism ; **Mbak Nimas**, for connecting me professionally to your network; and **Issa & Zul**, proud residents of Zuid, always up for a scenic lunch on the 14th floor of Mandeville.

Although I now live in a different city, Amsterdam will always be my *ḳawah candradimuḳa* — the place where my journey abroad began when I moved there to pursue my master's degree. Over the years, I've been fortunate to meet many kind-hearted individuals in the city, whose support has remained constant, in some cases for over a decade. My sincere thanks to **Mbak Meta Aurelia**, *mbaḳe*, for your wisdom, cheerfulness, and positivity in the face of challenges. **Leonita** and her husband, **Sunny,** have always welcomed me into their home with warmth and generosity. **Lukas**, even after all this time, your words — "*Selama ḳamu bergerak, pasti ada jalan*" — continue to guide me. **Mbak Leolita,** your perseverance during your PhD journey deeply motivated me. **Finde**, you're my go-to tech advisor, and I truly value your practical take on life. To **Sienna and Mulia** — your consistent kindness means a lot, even though we don't see each other often. Mbak **Agnes Tiwi**, my PhD sister — I'm incredibly proud of everything you've achieved despite the obstacles. I look forward to the next time our paths cross, wherever that may be. **Bagas**, your research is truly inspiring, and I'm excited to attend your defense. **Ferdy**, thank you for sharing your PhD journey with such honesty. And to **Agnes Utari** —for the low-key catch-ups, always full of quality time (even if we always forget to take photos!).

I've also had the pleasure of spending time with the families of long-time friends who have generously welcomed me, especially during Ramadan and Eid, when I've missed being with my own family. For this, I'm truly grateful to **Maya & Ferry** in Deventer, as well as **Dinda & Rezqi** and **Sachira & Fauzan** in Den Haag. **Chira**, your words — "You're the most chill PhD candidate in the final year I've ever seen" — still make me smile every time I think of them.

Having friends around the world who are also at various stages of their PhD journeys has been very valuable for exchanging ideas on academic life. I'm especially grateful to the ever-talented **Viddy Ranawijaya**, who's always a great listener and whose visits from Erfurt during the holidays bring joy. Thanks to **Suci Anatasia** for the cheerful video calls and thoughtful messages from Ohio, and to **Fadila Wirawan**, who always finds time to respond quickly despite her packed schedule in Edinburgh. **Mujab Saiful**, I appreciate you checking in regularly, even with the huge time difference between Rotterdam and Melbourne. And **Dito Alif** — who now spends more time at my house in Jakarta than I do — thank you for the many research discussions with my father! A big thanks to **Soe Yu Naing**, my ASEAN brother, who probably knows more about agriculture and antibiotic use in my home country than anyone else. I'm also grateful to **Rik Lubbers** for his supportive role in another medicine quality project — always contributing with great energy. Lastly, to **Yesi Rodriguez**, for her knowledge of medical devices and pharmacovigilance, and for the wonderful memories we shared in Bogotá.

Many friends scattered around the world cannot be mentioned individually, but they have all supported me in various ways. I will, however, mention a few. To my **high school friends in Jakarta** (sing it like Niki!), you know who you are—thank you for your enduring friendship. Special thanks to **Emma**, whom I can always count on for anything design-related. My **undergraduate friends from SITH ITB**, especially **Finda, Alidi, and Ivanna**, who shared their experiences of navigating a PhD, and **Aldina**, who remains an inspiration for success. Thanks to **Abie** and **Mbak Herma,** who shared their masterful coding skills. I also appreciate **Bramka**, who consistently produces world-class publications. Thanks to **Delfine Pautis** for showing me the impressive MSF facility in Bordeaux. To **Antoine Timmermans**, a GP who patiently answered all my medical questions. And to **Manon Guldemond** and **Joshua Stewart**, for reminding me to enjoy some fun moments along the way.

The true heroes of the ceremony are my paranymphs, **Tanjung Retno Wigati** and **Jonathan Berg**. **Tanjung**, my wonderfully laid-back friend, is my go-to for the latest pop culture updates and savvy shopping advice. Thank you for the easy-going friendship. I also thank your husband, **Edgar**, for sharing his insights about competitive research grants. **Jonathan**, a multi-talented individual who takes on many roles with ease, stands out most as a kind and dependable friend and colleague. Whether it's organizing unforgettable themed parties or offering support during difficult times, you're always there. I've also truly enjoyed chatting with your partner, **Famke**, in your cozy home nestled near a beautiful forest.

As I stipulated in my propositions, finishing a PhD is a powerful reminder to be resilient. I sincerely thank various **healthcare professionals** who supported me in maintaining both my mental and physical health – psychologists, general practitioners, specialists, physiotherapists, and occupational physicians.

And finally, a heartfelt thanks to my **family**, who have carried me all the way in this journey.

I want to express my heartfelt gratitude to **Professor Jan Passchier** and **Joke Hunfeld**, who have been like "academic parents" to me in Amsterdam. **Prof. Jan**, becoming your Bahasa Indonesia tutor back in 2015, marked a turning point in my life. Since then, you and Joke have shown me immense kindness, which has motivated me to complete my academic journey. Along the way, we've shared good conversations about history, politics, culture, travel, and film. *Saya tidak akan pernah bisa membalas semua kebaikan Prof. Jan dan Joke*.

To the extended families in Europe: **Tante Carola Nazir-Kinast** and her lovely family, thank you for the warm welcome in Hannover; **Tante Mady Kohlbrugge** and her family, whose kindness has always extended to my mother's family; and **Tante Shirley Tombokan, Om Denny Nagel, and Pritha** in Soest, who have always treated me with the warmth and care of their own.
Terima kasih sebesarnya kepada **keluarga besar Djamaluddin dan Z.B Ibrahim** *yang telah mendukung perjalanan studi doktor ini dengan segenap doa dan dukungannya. Mohon maaf apabila kesibukan studi ini membuat kita jarang bertemu di Indonesia*.

To dearest **Marie**, whose kindness has always been a gentle comfort, reminding me to pause and care for myself amidst the deadlines and duties. Your thoughtfulness—whether through your uplifting messages or getting a bike ready for me in Haarlem—truly means a lot.

My beloved parents, **Ibu and Bapak**, have wholeheartedly supported their only daughter in pursuing an education abroad, offering their immense trust and prayers along the way.

Ibu, my journey abroad to study has always been inspired by your incredible career path, which has taken you around the world. You're my number one compass for navigating the complex bureaucracy, with advice rooted in your years of experience. Thank you for continuously encouraging me to be patient, to find strength through spiritual reflection, and for always lifting my spirits with your daily dose of cat photos from home.

Bapak, you often tell me how proud you are of my pursuit of a PhD, something you did not have the opportunity to do yourself. But truthfully, that isn't necessary – because anyone who has worked with you, studied under your guidance, or been mentored by you knows that your expertise far exceeds what any diploma could represent. You've set a high bar for me, both as an academic and as an educator whose legacies are widely recognized. Thank you for every thoughtful and in-depth conversation on different topics, and for supporting my academic endeavours, including translating the summary of this thesis into proper, refined Bahasa Indonesia.

If earning a PhD is seen as an accomplishment, then I proudly share that honor with my dearest partner, **Thomas**. We met just before my final year began, and you've been my unwavering support every step of the way. You always remind me of what truly matters in life and keep me grounded with your incredible sense of humor. Your support has wonderfully come in many forms: offering a reassuring pat before presentations, planning joyful getaways that gave me a break from the pressure, or translating the *samenvatting*. Thank you for steadfastly holding my hands throughout this journey, both literally and figuratively. *Terima kasih sayangku!*

At last, I bring this long thread of gratitude to a close by honoring the one who stood at the very beginning. Long before I understood the possibilities life could offer, my late Oma **Evolune Orienta Darman Ibrahim** gently whispered her hopes to me: "*Je moet naar Holland studeren*" (You must study in Holland). Little did I know how far those words would carry me—but here I am.

Academic portfolio

Name : Siti Amalia Hasnida (Amalia)
Place and date of birth : Jakarta, 3 July 1989
PhD promotor : Prof. dr. Roland Bal
PhD co-promotor : Dr. Maarten O. Kok
PhD section : Health Care Governance
PhD period : 2020-2025

PhD training

Courses at Erasmus Graduate School for Social Sciences and the Humanities (EGSH)

- Research grants, opportunities and core skills, June 2024
- Maximise your visibility as a researcher! How to make author profiles and use identifiers, April 2024
- Diversity and inclusion in academia and beyond, December 2023
- Dealing with teaching challenges, September 2023
- Safety and security for fieldwork research, ISS The Hague, June 2023
- Professionalism and integrity in research, September 2022
- Bounce back: handling the mental and emotional challenges of doing a PhD, May 2022

Courses at other institutions

- Preparedness for health crises: a multidisciplinary approach, Pandemic Center at the University of Bergen, Norway, October 2024
- Global health ethics and equity, Utrecht University Summer School, The Netherlands, July 2022
- Pharmaceutical policies in health systems, Institute of Tropical Medicine in Antwerp, Belgium, June 2021
- STATA and statistics, University of Indonesia, February 2021

Scientific presentations

- International Health Economics Association Congress, July 2025, Nusa Dua, Bali, Indonesia, *Maintaining medicine quality while aiming for Universal Health Coverage: a political economy perspective (oral presentation)*
- Utrecht Winter Meeting, Utrecht WHO Collaborating Centre for Pharmaceutical Policy and Regulation, January 2024, Utrecht, The Netherlands, *Ensuring medicine quality in an engaged research collaboration: qualitative evidence from Indonesia (oral presentation)*.
- European Congress on Tropical Medicine and International Health (ECTMIH), November 2023, Utrecht, The Netherlands, *Assessing the quality of amoxicillin in the private market in Indonesia: considering product variety, sampling locations and price (oral presentation)*.
- 8th Biennial Scientific Meeting of Indonesian Health Economics Association (InaHEA), University of Indonesia, October 2023, Depok, Indonesia, *Investigating the persistence of illicit antibiotics sales in drug outlets in Indonesia: a mixed-method study (as co-authors in oral presentation)*
- Start of the Academic Year, Rotterdam Global Health Initiative, Erasmus University

Rotterdam, September 2023, Rotterdam, The Netherlands, *Assessing the quality of amoxicillin in the private market in Indonesia: taking into account product variety, sampling locations and price (poster presentation)*
- Medicine quality informal meeting, Oxford University, March 2023, Oxford, United Kingdom, *PhD research on governance of substandard and falsified medicines in Indonesia (5-minute speed talk)*.
- Utrecht Winter Meeting, Utrecht WHO Collaborating Centre for Pharmaceutical Policy and Regulation, January 2023, Utrecht, The Netherlands, *Is there any relation between price and quality of amoxicillin in Indonesia? (oral presentation)*
- 7th Global Symposium on Health Systems Research, November 2022, Bogota, Colombia, *Implementing an intersectoral risk approach to flag substandard medicines: an empirical analysis in Indonesia (poster presentation)*
- 2021 Indonesia Update: In Sickness and In Health: Diagnosing Indonesia, 17 September 2021, Online, Organized by the Australian National University, *Pill pushers: politics, money, and the quality of medicine in Indonesia (as co-authors of oral presentation)*
- The United States Pharmacopeial (USP) Convention: USP Compendial Science and Policy Meeting, 18 August 2021, Online, *Developing a market-risk based approach for medicine quality (oral presentation)*
- 6th Global Symposium on Health Systems Research, 10 February 2021, Online, *Identifying market risk-based indicators to flag poor quality medicines (oral presentation)*
- ASTMH Annual Conference Medicines Quality Side Meeting, 17 November 2020, Online, *Developing a market risk-based approach for medicine quality (oral presentation)*

Academic appointments

- **Master's thesis supervisor**, Health Economics, Policy, and Law (HEPL) master's program, *Erasmus University Rotterdam*, 2022-2023 & 2024-2025
- **Tutor Comparative Health Policy course**, Health Economics, Policy, and Law (HEPL) master's program, *Erasmus University Rotterdam,* 2022 & 2023
- **Tutor Advanced Research Methods course**, Health Economics, Policy, and Law (HEPL) master's program, *Erasmus University Rotterdam,* 2022
- **Guest lecturer,** Internal training**,** Deputy of Enforcement, National Medicine Regulatory Authority of Indonesia (Badan Pengawas Obat dan Makanan Republik Indonesia), February 2024
- **Guest lecturer**, Policy, Management, and Organization (PMO) master course, Health Sciences master program, Faculty of Science, *Vrije Universiteit Amsterdam,* November 2021
- **Guest lecturer**, Health Care Issues and Social Welfare undergraduate course, Social Welfare undergraduate program, Faculty of Social and Political Sciences, *University of Indonesia*, April 2021

Academic scholarships and awards

- **Nominee for Best PhD Colleague**, PhD Excellence Awards, Erasmus Graduate School of Social Sciences and the Humanities, Erasmus University Rotterdam, awarded March 2023
- **Best Presentation**, Utrecht WHO Winter Meeting on Pharmaceutical Policy and Regulation, awarded January 2023
- **Fellow in Quality of Medical Products**, United States Pharmacopeial Convention

(USP) Quality Institute, awarded 2019
- **Postgraduate Scholarship in Health Sciences**, Indonesia Endowment Education Fund (LPDP), Ministry of Finance, Republic of Indonesia, awarded August 2014
- **Cum Laude graduate**, Microbiology undergraduate program, School of Life Sciences and Technology, Bandung Institute of Technology, awarded October 2011
- **Dean's list of honor students**, Microbiology undergraduate program, School of Life Sciences and Technology, Bandung Institute of Technology, awarded 2008-2011

Publications

Peer-reviewed articles from this thesis

- **Hasnida, A.**, Rahmi, M., Rahmawati, A., Anggriani, Y., Leth, F. C. M. van, & Kok, M. O. (2025). *Assessing the quality of amoxicillin in the private market in Indonesia: A cross-sectional survey exploring product variety, market volume and price factors*. https://doi.org/10.1136/bmjopen-2024-093785
- **Hasnida, A.,** Bal, R., Manninda, R., Saputra, S., Nugrahani, Y., Faradiba, F., & Kok, M. O. (2025). Making intersectoral stakeholder engagement in medicine quality research work: Lessons from the STARmeds study in Indonesia. Health Research Policy and Systems, 23(1). https://doi.org/10.1186/s12961-025-01286-z
- Pisani, E., **Hasnida, A.**, Rahmi, M., Kok, M. O., Harsono, S., & Anggriani, Y. (2021). Substandard and Falsified Medicines: Proposed Methods for Case Finding **and S**entinel Surveillance. *JMIR Public Health and Surveillance*, *7*(8), e29309. https://doi.org/10.2196/29309
- **Hasnida, A.**, Kok, M. O., & Pisani, E. (2021). Challenges in maintaining medicine quality while aiming for universal health coverage: A qualitative analysis from Indonesia. *BMJ Global Health*, *6*(Suppl 3), e003663. https://doi.org/10.1136/bmjgh-2020-003663

Other peer-reviewed articles

- Valente de Almeida, S., Hauck, K., Njenga, S., Nugrahani, Y., Rahmawati, A., Mawaddati, R., Saputra, S., **Hasnida, A.**, Pisani, E., Anggriani, Y., & Gheorghe, A. (2024). Value for money of medicine sampling and quality testing: Evidence from Indonesia. *BMJ Global Health*, *9*(9), e015402. https://doi.org/10.1136/bmjgh-2024-015402
- Newton, P. N., Bond, K. C., & **Oxford Statement signatories**. (2019). Global access to quality-assured medical products: The Oxford Statement and call to action. *The Lancet. Global Health*, *7*(12), e1609–e1611. https://doi.org/10.1016/S2214-109X(19)30426-7
- Pisani, E., Nistor, A.-L., **Hasnida, A.**, Parmaksiz, K., Xu, J., & Kok, M. O. (2019). Identifying market risk for substandard and falsified medicines: An analytic framework based on qualitative research in China, Indonesia, Turkey and Romania. *Wellcome Open Research*, *4*, 70. https://doi.org/10.12688/wellcomeopenres.15236.1
- **Hasnida, A.**, Borst, R. A., Johnson, A. M., Rahmani, N. R., Elsland, S. L. van, & Kok, M. O. (2017). Making health systems research work: Time to shift funding to locally-led research in the South. *The Lancet Global Health*, *5*(1), e22–e24. https://doi.org/10.1016/S2214-109X(16)30331-X

Book chapters

- Pisani, E., Biljers Fanda, R., **Hasnida, A**., Rahmi, M., Nugrahani, Y., Bachtiar, I., Hariadini, A., Lyrawati, D., & Dewi, A. (2022). Pill pushers: Politics, money and the quality of medicine in Indonesia. Chapter in Witoelar and Utomo Eds: 'In Sickness and in Health: Diagnosing Indonesia', IAEAS, Singapore: In press. In F. Witoelar & A. Utomo (Eds.), *In Sickness and in Health: Diagnosing Indonesia*. IAEAS. https://bookshop.iseas.edu.sg/publication/7825#contents

Policy brief

- Fanda, RB, **Hasnida, A**, Dewi, A, Nugrahani, Y, Mawaddati, R, Pisani, E. Medicines shortages in public primary health services: an entry point of higher public financing burdens and the consumption of poor-quality medicines (*Kekosongan Obat di Puskesmas: Pintu Terbuka Terhadap Peningkatan Beban Finansial Masyarakat dan Konsumsi Obat Bermutu Rendah*). Policy brief. Pusat Kebijakan dan Manajemen Kesehatan Fakultas Kedokteran, Kesehatan Masyarakat, dan Keperawatan Gadjah Mada University (2021).
- Mariati, **Hasnida, A**, Setyaningsih, H, Pisani, E. How to increase MRV coverage in Aceh: bottom-up policy suggestions. Policy brief. Center of Health Financing Policy and Insurance Gadjah Mada University (2018).

Audio video

- **Hasnida A,** Simanjuntak R, Prasetya A**.** The distribution of falsified medicines (*Obat palsu dan peredarannya*). 2021. Vote Policy ID. Audio podcast. *Spotify*.
- Pisani E, Nistor A, **Hasnida A**, Parmaksiz K, Xu J, Kok M. What drives market for substandard and falsified medicines: a risk assessment framework. 2019. Presentation video.https://dataverse.harvard.edu/file.xhtml?persistentId=doi:10.7910/DVN/0GGI9D/PXKW4D
- Pisani E, **Hasnida A,** Anggriani Y. Substandard and falsified medicines in the age of JKN: a risk assessment framework for Indonesia. Presentation video. 2018. https://dataverse.harvard.edu/file.xhtml?persistentId=doi:10.7910/DVN/0GGI9D/HRWHO1

Ancillary activities

- **Management team**, *Rotterdam Global Health Initiative (RGHI)*, Erasmus University Rotterdam, May 2025-present
- **Co-initiator,** PhD cultural event, *young ESHPM*, January 2023
- **Adjudicator**, student debate competition (Hatta Debate), *Indonesian Student Association in Rotterdam (PPI Rotterdam)*, May 2022
- **Student mentor,** policy analysis and podcast production, *VotePolicy.ID*, May-October 2021
- **Member of academic and professional associations**:
    - International Health Economics Association (IHEA)
    - Indonesian Intellectual & Professional Association (I&P Indonesia)
    - Indonesian Public Health Expert Association (IAKMI)
    - International Indonesian Scholars Association (I-4)
    - Indonesian Science Communication Lab (IDSCL)

Short Biography

Siti Amalia Hasnida (Amalia), born in Jakarta on July 3, 1989, is a trained microbiologist who graduated cum laude from the Bandung Institute of Technology (ITB) in Indonesia. Her interest in policy emerged while working in market access and government affairs at a multinational pharmaceutical company during Indonesia's transition to Universal Health Coverage (UHC). In 2014, she was awarded a scholarship from the Indonesia Endowment Education Fund (LPDP) to pursue a master's degree in international public health at Vrije Universiteit Amsterdam. Following her studies, she joined a multidisciplinary project examining the political and economic factors of medicine quality, which eventually led her to pursue a PhD at the Erasmus School of Health Policy and Management (ESHPM), Erasmus University Rotterdam.

Amalia is driven by a deep conviction that research should inform and influence policy and practice. At work, she actively promotes the empowerment of early-career researchers and advocates for fair and balanced collaborations between the Global North and South in public health research. Currently, she is a postdoctoral researcher focusing on pandemic preparedness and resilience in Indonesia at ESHPM in collaboration with TU Delft. She also contributes to teaching and supervising master's students. While she now resides in Rotterdam, a part of her heart always stays in Jakarta, where her core family and seven beloved cats live.

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