Medicine across Borders

Exploration of Grey Zones

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SUSANNE LUNDIN, RUI LIU,
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EDITORS

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Editors
Susanne Lundin, Rui Liu,
Elmi Muller and Anja Smith

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INTRODUCTION: MEDICINE ACROSS BORDERS

Susanne Lundin, Rui Liu, Elmi Muller and Anja Smith

On 9 January 2020 the World Health Organization (WHO) reported on a mysterious coronavirus-related pneumonia in Wuhan, China. Just two months later, the WHO declared a pandemic, which meant the world faced a health crisis with the number of infections and deaths escalating rapidly. At the same time, it began its search for cures and vaccines. So, too, did individual members of the public, albeit, on an entirely different premise from those of scientists and healthcare practitioners. The first stage of the pandemic saw hoarding of goods, including medicines, thought to be running out. As a result of this stockpiling, some medicines did indeed run out in pharmacies, and, to manage the shortages, governments around the world took the decision to ration the dispensing of medicines. This, in turn, led people to seek medical products at places other than authorised pharmacies and drugstores.

Hoarding, as well as seeking goods outside established formal systems, are historically well-known strategies in times of crisis. By the same token, this has also brought risks to societies in the form of the provision of substandard goods,

plagiarism, and falsifications. Just a few months after the official announcement of the pandemic by the WHO, Interpol warned of the accelerating illicit trade of medical products, including face masks, personal protective equipment (PPE), vaccines and (not least) medicines – both genuine and falsified – in digital and physical marketplaces. The COVID-19 pandemic created criminal opportunities around production and distribution of medical products and substances, directly exposing medicine users to risk (UNODC, 2020). In the most salient way, it highlighted the existence of an underworld market of medical products.

The circulation of medicines and medical products on the informal market is well-known. Stakeholders, including governmental agencies and Biotech enterprises, invest much effort in designing and implementing macrolevel interventions to limit the spread of such products. Nevertheless, there is a lack of knowledge and understanding of how informal markets function in everyday medicine access and use. This applies to professionals within and beyond academia, state governments, as well as the general public.

There are several reasons for this. One is that many countries have inadequate regulations and active development in the pharmaceutical sector. Another reason may be that medicines in the informal markets regularly involve low-income countries or those with already socioeconomically vulnerable people. Both these countries and this group of people are not always a high priority for the more affluent parts of the world, whether geographic or as part of the population (Seeberf, 2012; Barber, et al., 2019). Initially at least, there is nothing good about the global impact of a new, extremely hazardous, virus. Yet, the illegal activities related to COVID-19 protections may have provided an opportunity for addressing long-standing risks posed by all kinds of illegal medicines in a more internationally coordinated way. The risks are not only clinical, but also related to societal concerns, such as health equality, risk awareness and public and private collaboration. Some good practices and positive initiatives are already in place. However, more can be done to understand what gives rise to ambiguities in the health systems, to unpack tension in everyday interaction with medicines, and to evaluate and look back at what insights have been gained. *Medicine Across Borders: Exploration of Grey Zones* aims to explore the knowledge and tools for a variety of stakeholders and actors to better respond to the spread of unsafe medicines and medical products.

Approaching the field

Since the beginning of the 21st century, the spread of malfunctioning and spurious medicines has been recognised as a global problem (Sweileh, 2021). The products pose major risks to the public's health. They affect every region

of the world, and have been identified in all major therapeutic categories. The World Health Organization (WHO) estimates that the increasing spread not only leads to adverse drug reactions, increased morbidity or even death and economic losses, but also to diminished public confidence in health systems (World Health Organization, 2017). Scientists from the subjects of medicine, law and public health dominate this research area, with a primary focus on the supply side, emphasising innovating tracking technologies and advocating international legal frameworks (Hamilton, et al., 2016). The spread of the risky medical products, however, cannot be understood without information about both the demand and supply sides. There is a need to explore the perceptions, experiences and, ultimately, the behaviour of all actors involved. Thus, a wide range of in-depth knowledge is necessary.

One such essential insight, is about the lack of a common understanding of what should be defined as risky medicines. There is a myriad of terms used to refer to medicines traded on illicit or informal markets. This, in turn, leads to various and often conflicting sanctions – ranging from legislative to everyday attitudes and actions. To address this, in 2017, the WHO proposed the term 'substandard and falsified (SF) medical products' to refer to medicines that do not meet quality standards or deliberately misrepresent their composition or sources (World Health Organization, 2017). The term covers factors such as products that are of poor-quality or falsified. The term also includes medicines produced legally and of sufficient standard, but being traded in informal or illicit markets.

In this introductory chapter we highlight two notions that link each chapter in this anthology. First, the term 'SF medical products'. We editors employ the WHO's definition 'SF medical products' here to denote the wide range of unsafe medicines, as the WHO term is well-recognised among scholars. On the other hand, we are aware of and stress the need for critically examining the terms used to describe medical products that, for various reasons, fall into the categories of 'substandard' and 'falsified'. The variety of definitions is also one of the key issues with which authors in this anthology seek to grapple.

Recognising the complexity of SF medical products also means being aware that the investigative gaze studying the phenomenon can be limiting. A narrow focus on medicines alone can cause researchers to miss the local particularities that give rise to the spread of SF medical products (Van der Geest, 2019; Hardon & Sanabria, 2017; Quet, 2017). Such work implicitly takes for granted that markets can be grouped into legal or illegal, while the interaction and interflow between them is overlooked (Dewey, 2016). Rather than delineating a clearly bounded legal world, we draw on anthropologist Carolyn Nordstrom's delineation of extra-legal to highlight an in-between space where political boundaries do not

match economic domains (Nordstrom, 2011). Along increasingly globalised supply chains, medicines often move from one jurisdiction to another, where different medication categorisation and qualification systems might be applied. Differences in legal systems suggest that the extra-legal domain is not confined to a single market structure. It is, as Nordstrom points out, "interwoven with states, but not bounded by them." The fact that both the quality of medicines and the value attributed to them are being challenged in such an extra-legal space is observed by several of the book's authors. This understanding reinforces that markets are open, fluid and also often possess conflicting constructs (Baxerres & Cassier, 2022).

The second notion we highlight is closely related to the complexity in the definition of SF medical products. And that is, grey zones. Scholars from different disciplines will have different ideas of what they mean. In this anthology, which collects contributions from multiple fields of studies, we choose a broader definition of grey zones, to denote medicine markets that do not have official sanctions. The starting point of the anthology is that SF medical products must be understood as medical and sociocultural objects. They are commodities in constant transformation, and attributed diverse meanings depending on contexts (Appadurai, 1986). As such, they transcend and cross not only medical, geographical and legal borders, but also moral and cultural boundaries. It is this movement that contributes to the creation of spaces where there is a clear demand for a particular type of medicine or medical product, but where its presence may not be legally sanctioned, despite the need being real. Thus, various types of grey zones take shape. The existence, causes and consequences of illicit medicines, also legal medicines traded in extra-legal markets, must be explored from multi-disciplinary perspectives.

In this book, researchers from different subjects and organisations share knowledge about SF medical products and the different forms of grey zones in which they circulate. In addition, the connections to acute medical crises such as the COVID-19 pandemic are examined. The pandemic exposed several pre-existing societal fault lines and although many of these were already well-known, the weakness of healthcare systems in many countries, both rich and poor, became alarmingly clear (World Health Organization, 2022). Drawing on the authors' research and knowledge base, the anthology provides an in-depth understanding of what drives the spread of SF medical products globally. The chapters contribute with multi-disciplinary analyses that explore how medicines and health are embedded in a web of social relations, material resources and glocalisation where universalising tendencies in political and social systems interplay with local particularities. Medical, legal, and law

enforcement authorities have called for actions to stop the development of the phenomenon (Newton & Bond, 2019). In addition to its scientific contributions, the book offers analyses that can serve as sources of knowledge for healthcare and international, medical regulatory agencies. We furthermore address organisations such as the WHO and Interpol, to develop informed policies and awareness campaigns around SF medicines and medical products.

The book shares knowledge from a range of places and contextually different locations In the world: from Sweden in northern Europe, to Ghana, Zimbabwe and South Africa on the African continent. Although both geographic and social conditions vary, the presence of SF medical products brings about a number of commonalities, especially in relation to demand-side needs. *Medicine Across Borders: Exploration of Grey Zones* is organised in three sections and framed by an introduction and a concluding chapter.

Section I: Searching for medicines

In the first section, 'Searching for medicines', three chapters examine the demand for medicines and the situations that may give rise to medical grey zones. The actors we meet include the public, health-sector stakeholders, the pharmaceutical industry and organisations that all are operating in physical arenas in the Global North and the Global South, as well as on digital platforms. The first two chapters have Sweden as a field of investigation, while the third chapter explores the situation in Zimbabwe.

In 'The spread of substandard and falsified medical products to the Swedish market: a discussion from pharmacists' point of view', Persson and Lenander take their starting point in Swedish society. The discussion is based on their research as medical scientists and their professional experiences as pharmacists. Sweden is a high-income country and has a legislation and control programmes, making it extremely difficult for SF medical products to enter the legal pharmacies and the formal markets. However, the situation may look different in the informal market. For Swedes, online shopping for all kind of goods is a part of everyday life, the extent of which increased further during the COVID-19 pandemic. In 2022, as many as 94% of the population uses the Internet, and almost everyone uses it on a daily basis (The Internet Foundation, 2022). For many people, it is easy to look for medicines online instead of asking a doctor or pharmacist for advice. At the same time online shoppers do not know how to identify illegal Internet pharmacies, where unsafe medicines may be sold. Only 63% of respondents in a study from 2020 knew about the common EU logo for legally operating online pharmacies (European Commission, 2014). Pharmacists

surveyed by the authors are aware that there is a gap between regulations and people's everyday practices. The Swedish system's solid control of medicines does not correspond with and even clashes with the public's actions that may entail risks of obtaining SF medical products. Persson and Lenander point at pharmacists in Sweden having a high credibility among citizens and they therefore play an important role as mediators, also informing the public on how to buy medications safely online.

'Controlling the machinery of knowledge: Google and access to COVID-19 grey-zone medicines', by Sundin, Andersson and Söderström, explores the relationship between search engines and individuals. However, in a different way than in the previous chapter, Sundin et al., with backgrounds in information studies, delve into the digital system that Google Search represents and how it governs the people who use it. The starting point is that Google Search is a critical building block of today's information infrastructure for finding out about things, including epistemic content, products and services, which in this case are products to protect against the coronavirus. Thus, the search engine becomes a digital intermediary that guides users to online pharmacies and pharmaceutical information. The search engine strives to provide users with the information they are looking for and at the same time wanting to create the appearance of social responsibility. Importantly, infrastructures governing information are neither neutral nor stable and fixed, which means that the answers to people's questions vary depending on what search queries are used, and how websites adjust to the algorithmic circumstances. Network analysis of search engine results provides insight into how quickly, how likely, and by what digital route a person might land on a website that contains misinformation about a particular COVID-19 medicine. This means that Google Search, interacting with individuals' search terms, potentially opens the door to platforms selling illegal, substandard, and falsified medical products. However, depending on how searches are managed by the back-end of Google, individuals may also not always be able to access the medicines they are looking for.

In 'Drug stock-outs and district poverty in Zimbabwe: A spatial analysis approach', health and development economists Chari, Von Fintel and Burger explore the spatial correlation between socioeconomic status and drug stock-outs in Zimbabwe. Drug stock-outs can be a result of improper supply chain management, lack of proper storage at health facilities, or pharmaceutical theft. In this chapter, the authors situate this issue in a larger societal context where the formal health system is not robust enough to sustain necessary drug supply, and thus may risk exacerbating health inequality among populations with a low socioeconomic status. A consequence of drug stock-outs is the emergence of

informal markets where medicine quality can be questionable. The authors use a geo-spatial quantitative mapping technique and identify that health facilities are not evenly distributed in the country. However, surprisingly, the quantitative mapping also suggests a weak correlation between poverty and drug stock out. The authors speculate that this can be due to prevalent and high-level poverty in the entire country. Furthermore, the authors argue that this finding brings forth other social and material constraints experienced by people with socioeconomic disadvantages. For example, the poorer parts of the population are typically not as active as their counterparts in more economically prosperous regions globally, regardless of their geographical location or the composition of their population. The more socioeconomically vulnerable population tends to more frequently turn to sellers in informal markets or traditional healers as their first port of access to healthcare as these alternatives are less time-consuming than formal health facilities with long waiting times.

Section II: Frictions and transitions

While the first section deals with unmet demand for medicines and the contexts and situations that give rise to these markets , the second section focuses on the nature of these markets and the different ways in which they are expressed and sustained. The first chapter in this section reports fieldwork conducted in an informal low-income settlement in South Africa.

In 'Poor-quality medical products in times of crisis', by medical scientists Van Assche, Caillet, Kitignavong and Newton, the authors zoom out to examine the mechanism of grey zone medicines. They draw on medical alerts during the COVID-19 pandemic to demonstrate both short-term and long-term impacts of poor-quality medical products on the society. The authors, with their academic training in the discipline of pharmacy and medicine, take a public health approach to highlight the need to address the complexity entailed in the various ways of categorising medical products as poor quality. These different categorisations ask for different political approaches and health interventions. Historical accounts show that falsification of medical products has been around for centuries and that a deep understanding of current health crises, such as the COVID-19 pandemic, is insightful to prepare us for future ones. Drawing on media reports and governmental report the authors demonstrate that similar falsification patterns can be drawn in nearly all types of medical products apart from medicines. The collected medical alerts in this chapter also indicate that spread of poor-quality medical products can happen in both illegal and legal manufacturing and supply chains, and in both developing and developed countries. Populations that are negatively affected are not limited to medicine

users but also health service workers and workforces outside healthcare that regularly use personal protection products at work. Although the impact of the pandemic is yet to be analysed, the authors point to health inequality as a larger issue than supply-demand imbalance and its need to be addressed continuously through multil-disciplinary and multi-sectorial collaborations.

The chapter 'When the State cannot (yet) assure the quality of medical products – What to do?' is a contribution from public-health researchers Ravinetto, Macé, Mohamed Ali and Caudron. The authors draw on real-life cases from their fieldwork and discuss how material constraints are negotiated on international, national and local levels, in countries with inadequate financial and technical capacity to assure medicine quality. A grey zone in the regulatory system emerges where countries with weak regulatory capacities are left to decide on their own whether to import non-fully quality-assured medical products. This leads the authors to a closer examination on the decision-making process followed when procuring these medicines. The authors argue that supply-chain innovations may be effective, but are not likely to be adopted by countries with limited resources due to the high economic cost. On the other hand, cases presented in this chapter show that national and international procurement organisations have the potential to assure medicine quality by collaborating with medicine suppliers and implementing low-cost techniques, such as visual inspection. Furthermore, the authors propose to break the assumption between the high quality and high price commonly held among actors in all levels from policy-makers to medicine users. While the state governments certainly have the main responsibility to ensure the supply of good-quality medicines at affordable prices, the authors call for self-organised advocacies from local communities and active engagement with frontline health workers to tackle the spread of SF medical products.

In 'To reach the unreachable: Migration, health vulnerabilities, and the problem of non-response bias in health research' by ethnologists Mirsalehi and Hansson, take the COVID-19 pandemic to an entry point for a methodological discussion. The pandemic struck very unevenly between different groups in Sweden. One of the reiterative topics that has been highlighted in public health reporting was the high rate of mortality among foreign-born and migrants in Sweden. Several reasons have been given, but above all that these groups are not reached through official channels and are therefore not aware of the risks posed by the virus or how to protect themselves. It is not a new phenomenon, the authors note, that the health of vulnerable groups receives little attention. However, the pandemic has emphasized the need to find appropriate strategies to reach these groups. Based on their research on asylum seekers and migrants, the authors explore

different methods for investigating how marginalised perceive and respond to a collective health hazard.

Section III: Solutions and lessons learnt

All sections of the anthology deal with medicines in grey zones and SF medical products. Although the authors refer to the concepts in different ways, the overall theme is to examine the conditions and problems inherent in the phenomenon. The third section brings together three chapters that specifically discuss what lessons can be learnt from the research on SF medical products.

In 'Medicine quality and medicine traceability: A focus on prevalence, context and responsibility' medical scientists and pharmacists Naughton and McManus review data based on published evidence on SF medical products. Their focus is on examining the topics of medicine quality and medicine traceability in lower and higher income countries. They review the challenges associated with medicine traceability legislation and technology in high-income country contexts. They then consider broader challenges related to the adoption of serialisation and traceability technology and legislation in middle- and low-income country contexts. They argue that in order to develop strategies to track and prevent SF medical products, a contextual understanding is required. More specifically, the contextual factors that contribute to the greater presence of SF medicines in low- and middle-income country contexts have to be identified, and traceability solutions developed that address these challenges. Two specific solutions are identified. The first solution is to develop and roll-out a comprehensive training programme for staff dealing with medicines that would enable them to detect SF medicines. The second solution entails adopting a socially responsible approach to innovation (on medicine traceability through broad engagement with all relevant stakeholders). Both proposed solutions speak to the challenges but also opportunities provided by particular contexts.

In 'How technology can help solve substandard medicine problems: A case study on the digital medicine supply chain platform Med4All' by Sunkwa-Mills, Kretchy, Afful, De Wit and Antwi, researchers and implementers working in the larger public health space, explore how in Ghana digital technology significantly shortened and also integrated the formal medicine supply chain, reducing the availability of SF medicines. Ghana is a country characterised by the high frequency of drug stock outs in the formal health sector and a fragmented medicine procurement process, contributing to weak quality control. Med4All is an initiative that aims to address access, affordability and quality of essential medicines in Ghana through a regulated digital supply chain platform. Selected

health facilities that form part of the Christian Health Assocation of Ghana (CHAG), a large proportion of Ghana's health facilities, are onboarded onto Med4All. They make their need for medicines known on the platform and onboarded, participating providers are able to submit tenders for medicines. Once a tender has been accepted, the movement of the barcoded medication is tracked on the platform until its safe arrival at the facility. The lead times for arrival of medicine has been reduced to less than 48 hours after orders are placed and it has also contributed to the availability of high-quality medication in facilities, thereby addressing drug stock out issues.

In 'Risk awareness in medicine access: Methodological reflections from fieldwork in a low-income setting in South Africa' by Liu, Lundin, Smith, Gosa, Khambule and Muller, two social scientists, an economist, development practitioners and a health scientist, the empirical field shifts from the relatively homogeneous high-income country of Sweden to the socially and economically differentiated South Africa. The country has a strong pharmaceutical sector. However, the high public-health expenditure due to the burden of communicable diseases (HIV/TB), as well as non-communicable diseases, poses major challenges and has opened up for SF medical products to spread. This chapter examines whether, and to what extent, there is knowledge about the prevalence of SF medical products among residents in a lower-income neighbourhood in the Southern Cape province. The results indicate a relatively low awareness of falsified medicines among the local people. There was an attitude that all medicine should never be assumed to be genuine and that it was a matter of taking what you could get. Based on the mixed-methods approaches, the authors found inconsistencies between what respondents answered on the paper-based questionnaire and what they told interviewers in the recorded conversation that took place in parallel to their formal, paper-based responses. It turned out that the fairly good level of trust in the formal healthcare service they indicated in the questionnaire was not matched by what they actually thought and did in accessing medicines. In many cases, people chose to informally share medicines with each other or to turn to the local healers. The different answers, on the paper-based questionnaire on the one hand, and in conversations on the other, point to an unwillingness to offend the church. On this account, the authors argue that risk awareness and medicine access should be contextualised in people's life worlds and sociocultural structures.

Conclusion

The anthology ends with sociologist Heather Hamill's chapter, 'Medicines across borders Conclusion', which summarises the book's contributions.

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SECTION I

SEARCHING FOR MEDICINES

1

THE SPREAD OF SUBSTANDARD AND FALSIFIED MEDICAL PRODUCTS TO THE SWEDISH MARKET: A DISCUSSION FROM PHARMACISTS' POINT OF VIEW

Amelie Persson and Cecilia Lenander

The importance of quality

When someone is ill, medicines are often used to ease or cure the illness. Some medicines are even used to prevent illness. Either way, it is essential that the medicine used is of high quality.

Good Manufacturing Practice (GMP) is applied in the legal production process to ensure quality medicines and to protect the patient (European Parliament and Council, 2014). The first draft for GMP was written by the World Health Organization (WHO) in the 1960s due to several serious accidents with drugs (World Health Organization, n.d.-b, Arayne et al., 2008). An example given by Arayne et al., is the death of nearly 300 people in 1941 after taking sulfathiazole tablets contaminated with phenobarbital. Sulfathiazole is an antibiotic while phenobarbital is a sedative substance that can be lethal, especially if the patient is affected by a general condition, such as an infection. GMP implies that the

production process is described in detail, leaving nothing to coincidence, and GMP also includes control of the quality after packaging.

In Sweden, the Medical Product Agency is the responsible authority for the quality of medicines. However, monitoring of production is not enough to obtain high-quality medicines for the public. Also, the handling and storage of medicines in healthcare is important and monitored. This responsibility lies within the Swedish National Board of Health and Welfare (Swedish National Board of Health and Welfare, 2017).

The sale of medicines to the public is also regulated by law (Ministry of Social Affairs, 2015b; Ministry of Social Affairs, 2015a; Ministry of Social Affairs, 2009) and prescription-only medicines can only be sold at authorised pharmacies. When an authorised pharmacy is open at least one licensed pharmacist must be attending. Some over-the-counter medicines can be sold outside pharmacies, in venues without a pharmacist, but this requires specific permission from the Swedish Medical Product Agency (Medical Product Agency, 2020-a).

When it comes to quality of medicines, pharmacists play a key role. A lot of pharmacists work in the pharmaceutical industry, both with research and development, as well as the production. Pharmacists also work in government agencies, especially the Medical Product Agency. Most pharmacists work in pharmacies and all pharmacies in Sweden are obliged to have a quality responsible pharmacist (Medical Products Agency, 2020).

Substandard and falsified medical products

Although the control of medicines is strictly regulated in Sweden, as in several other countries, poor quality medicines are spreading across the globe.

The production chain of medicines is getting more complex and the market more global. Today, it is not uncommon with production of substances in one country, manufacturing of the medicine in another, and perhaps packaging in a third. Finally, the medicine is distributed or sold to customers in yet other countries.

Although GMP includes all steps in the production, regardless of the country in which the step is taking place, the fractionated production chain described above opens multiple possibilities for criminals to infiltrate the production chain. The GMP-regulations apply globally, but different countries have their own unique laws concerning medicines. This makes it hard to convict criminals working in a global market.

Different countries' regulatory and social contexts also mean that access to quality medicines varies and that unequal access to quality medicines is a global

public health challenge (World Health Organization, 2020). This includes combatting substandard and falsified medical products. There is today no universally accepted definition of medical products that do not fulfil quality criteria. We use the definition by the WHO, "Substandard and Falsified (SF) Medical Products" throughout this chapter (World Health Organization, n.d.-a). 'Substandard medical products' refers to "authorized medical products that fail to meet either their quality standards or specifications, or both," and 'falsified medical products' refers to "medical products that deliberately/fraudulently misrepresent their identity, composition, or source."

To gather information on a global level about SF medical products, the WHO Global Surveillance and Monitoring System was launched in 2013. Antibiotics and antimalarials are the most common groups of medicines reported to WHO as SF medical products. Both these groups can lead to treatment failure (including death), as well as to increased antimicrobial resistance in the world. It is estimated that 10% of the medical products are substandard or falsified in low- and middle-income countries. Corresponding figure for high-income countries is 1% (World Health Organization, 2017).

The WHO Global Surveillance and Monitoring System highlights three overall causes for the spread of SF medical products in its report from 2017, claiming the risk to be highest where these three causes overlap (World Health Organization, 2017). Figure 1 is from this report and shows the causes and their interaction graphically.

The causes presented in the report are:

1. Constrained access to affordable, safe, and quality medical products
2. Lack of good governance
3. Weak technical capacity and tools

We will elaborate on what is included under each cause later in the chapter.

Fig. 1: Causes to substandard and falsified medical products (World Health Organization, 2017)

The specific aim of this chapter is to discuss these three causes from a Swedish pharmacist perspective. We will substantiate the discussion with quotes from Swedish pharmacists. The quotes are from open-ended questions in our study (Swedish Ethical Review Authority reference number 2019-05011) (Persson et al., 2022) and we will also include our own experience as pharmacists. We, the authors, are pharmacists with extensive experience in the field, as well as medical scientists. It should be noted that neither explicit questions regarding causes to SF medical products nor WHOs report about SF medicines were asked in the questionnaire.

To be able to discuss the three causes of substandard and falsified medical products presented by WHO from the Swedish community pharmacists' point of view, we will start by describing the conditions that prevail in Sweden, both on the market and for the pharmacists.

Swedish conditions

Community pharmacies in Sweden

Sweden had a state-owned monopoly for pharmacies between 1970 and 2009, and the number of community pharmacies increased from approximately 600 to 900 pharmacies during this period (Swedish Pharmacy Association, 2021b). In 2009, the state monopoly was dissolved and a little over half of these pharmacies were sold to private enterprise. In 2022, the 10 million inhabitants of Sweden

had access to nearly 1 500 pharmacies (Swedish Pharmacy Association, 2021a). Compared to the rest of Europe, Sweden has approximately half as many community pharmacies per 100 000 inhabitants as the average in Europe, i.e., 15 pharmacies/100 000 inhabitants in Sweden compared to 32 pharmacies/100 000 inhabitants in Europe (The Pharmaceutical Group of the European Union, 2022). This could, in some areas of Sweden, lead to a longer commute to a community pharmacy and thereby online pharmacies could appear as an attractive alternative.

Swedish community pharmacies are dominated by five companies, which own 97% of all community pharmacies. Each of the five companies has a nationwide net of pharmacies and multiple possibilities to interact with the public on a regular basis. E-commerce with medicines is rising in Sweden, but approximately 90% of all prescriptions are still dispensed in community pharmacies. Every day, 330 000 people (3.3% of the Swedish population) visit a Swedish community pharmacy, which adds up to 120 million visits/year (Swedish Pharmacy Association, 2021a). On average, every Swedish citizen visits a pharmacy once a month.

In Sweden, as a member of the European Union (EU), companies are allowed to buy medicines in a country within the EU with low prices, re-label it, and sell it in a country with higher prices (so-called 'parallel trade').

Actions taken in Sweden against substandard and falsified medical products

All Swedish community and online pharmacies have implemented the EU's Falsified Medicines Directive (European Parliament and Council, 2011) to fight SF medical products within the legal supply chain. In short, the Falsified Medicines Directive prescribes mandatory, harmonised European safety features on all human prescription medicine packages. One of the safety features demanded in the Falsified Medicines Directive is a unique QR code on each package. The pharmaceutical company producing the medicine reports this code to a European hub when the medicine enters the European market. Then the medicine is verified via this QR code when it comes to a wholesaler. Finally, the pharmacy employee scans the QR code to secure the authenticity of the medicine before it leaves the pharmacy. Another safety feature is that the medicines are delivered in sealed packages, which guarantees that the package has not been opened and tampered with.

The illegal e-commerce with SF medicines is fought internationally by Interpol. Since 2008, Interpol coordinates and performs an international activity, Operation Pangea (Interpol, n.d.). Sweden is one of the countries that

participates in this recurrent operation. Operation Pangea lasts one week, and during this week the postal flow is examined for illegal drugs and the Internet is searched for unauthorised websites selling medicines. Since its start in 2008, the highest number of illegal websites was identified and shut down (113 020) during the global operation in 2021, and potentially dangerous pharmaceuticals worth more than USD 23 million were seized (Interpol, 2021).

E-commerce with medicines

Due to the development of new healthcare technologies during the beginning of the 21st century, many new possibilities to access healthcare and purchase medical products have appeared. Sweden has high ambitions to use these technologies offered by digitisation and eHealth. However, there is a need for eHealth governance systems to maintain patient safety within several areas. One such area is the distribution of medicines online, to ensure that patients are safe from dangerous medicines. For high-income countries, such as Sweden, one of the major risks to be exposed to SF medical products is via e-commerce, through unauthorised pharmacies (Mackey & Nayyar, 2016). Up to 60% of medicines purchased online via unauthorised pharmacies are estimated to be SF medical products (Howard, 2010). Legally operating online pharmacies in Sweden, as well as in all other countries within the European Economic Area must display a common logo on their websites to assure customers of their legality (European Comission, n.d., Medical Product Agency, 2020-b).

The Swedish Medical Product Agency performed a survey in 2015, directed to the public. That survey revealed that 69% of the respondents did not recognise the national symbol for authorised pharmacies in Sweden (Läkemedelsverket (Medical Product Agency), 2015). The same report also pointed out that 40% of Swedes can consider buying prescription-only medicines from unauthorised websites, without a valid prescription. In another study by Lundin et al., 11% of the respondents could consider buying prescription-only medicine without prescription and 63% percent did not recognise the common EU logo for authorised online pharmacies (Lundin & Liu, 2020). A pilot survey regarding SF medical products directed to general practitioners and emergency physicians in Sweden performed in 2016 showed that one-third of the physicians had met patients they suspected had used SF medical products (Funestrand et al., 2019). The physicians requested more information on the subject. These studies describe the lack of knowledge among the public to identify safe venues for e-commerce, but also the intent to buy medicines online without a valid prescription. The physicians' experience tells us that the public in fact also proceeds with the purchase.

As European citizens, Swedes can legally buy medicines within the European Economic Area, prescription-only medicines included. This applies both to community pharmacies and online suppliers. However, today Swedish electronic prescriptions cannot be dispensed in another European country, since only Swedish pharmacies can access the database. If the prescription is on paper, it is possible to get it dispensed in a European community pharmacy. Other European countries have other regulations and possibilities. For example, in France and Spain, only over-the-counter medicines are sold online (Convert Group, 2022).

E-commerce of medical products is steadily increasing (World Health Organization, 2017). During 2019, the COVID-19 pandemic struck the world and people were instructed to avoid crowded places, leading to a greater increase in e-commerce in Sweden (Swedish Pharmacy Association, 2021a). The e-commerce at pharmacies in Sweden increased by 60% during 2020. This increase was for all goods sold by pharmacies, not only prescription-only medicines (Swedish Pharmacy Association, 2021a). According to an analysis made by the Convert Group, Sweden was the leading country in the world with the most visits to legal online pharmacies per thousand inhabitants in 2021 (Convert Group, 2022).

Summary of important Swedish conditions

- The European Union's Falsified Medicines Directive is implemented in all Swedish pharmacies, both physical and online pharmacies, to counteract SF medical products in the legal supply chain.
- Five pharmacy companies dominate the Swedish market. This gives a nationwide net to provide the public with information regarding SF medical products.
- Compared to the European average, Sweden has relatively few community pharmacies. This means longer distance to a pharmacy, which may increase the possibility that the public turns to e-commerce.
- Swedes can legally buy both over-the counter and prescription-only medicines online in the European Economic Area (EEA).
- E-commerce with medicines is rising in Sweden, but identifying an authorised pharmacy is not common knowledge among the public, placing them at risk for SF medical products.

Pharmacists' knowledge and experience of SF medical products

It is known that the problem with SF medical products is more prominent in low- and middle-income countries. As to the knowledge and experience of pharmacists, i.e., the profession that works in the entire chain from the production of medicines until the consumer goes home with their medicine, Sholy et al. showed in a study that 43% of the responding pharmacists in Lebanon reported to know other pharmacists who dispensed SF medical products for "the easy money" (Sholy et al., 2018). Almost half of the respondents in Sholy et al.'s study had been offered SF medical products (48%). In a study of Jordan pharmacists by AbuTaleb et al., 37% of the pharmacists had encountered SF medical products (AbuTaleb, 2013). Less is known about what knowledge and experience pharmacists in high-income countries have regarding SF medical products. A recent study from Italy indicates limited knowledge about SF medical products of Italian community pharmacists (Lombardo et al., 2019). These studies indicate that more pharmacists in low- and middle-income countries have encountered SF medical products than pharmacists in high-income countries, but more studies from high-income countries are needed.

This is also stated in a review by Liu and Lundin, which conclude gaps in the literature about SF medical products (Liu & Lundin, 2016). For example, they address that there is a lack of knowledge regarding health professionals' knowledge about SF medical products.

The WHO states in their report that "the more one looks, the more one finds," (World Health Organization, 2017). Training more regulators locally increased the reported findings of SF medical products. We believe that healthcare employees, including pharmacists, are important players to counteract the spread of SF medical products, and the more they know about SF medical products the more good they can do. Fittler et al. request campaigns to enlighten the public about safe purchases of medicines on the Internet, and Ferrario et al. point out the pharmacist's role to educate and warn patients from purchase of medicines from unauthorised websites (Fittler et al., 2018; Ferrario et al., 2019).

Other organisations also highlight the important role of pharmacies and pharmacists. The US Drug Enforcement Administration (DEA) has launched a campaign called "One pill can kill" to inform the public about fake pills containing fentanyl and methamphetamine, easily accessed via social media and through e-commerce. The main message from the DEA to the public is to only use medicines prescribed by a medical professional and dispensed by a licensed pharmacist (United States Drug Enforcement Administration). Another organisation working with the issue is "Fight the Fakes Alliance". Among other things, it organises "Fight the Fakes Week"

annually to raise awareness among the public on SF medical products (Fight the Fakes Alliance, 2022).

Swedish pharmacists' knowledge and experience of SF medical products

We could not find any studies describing what Swedish pharmacy employees knew about SF medical products. Therefore, we conducted a survey about SF medical products to employees at Swedish community pharmacies (Persson et al., 2022). The aim of the study was to evaluate whether community pharmacy employees could guide the public to safer medicine purchases, and their knowledge and experience about SF medical products was studied. The method in short: a digital questionnaire was spread by the leading community pharmacy companies inviting all employees with customer contact to participate.

The results in short: The questionnaire reached 74% of all community pharmacies in Sweden. Despite the fact that the survey coincided with the outbreak of the COVID-19 pandemic in Sweden (in spring 2020), a total of 228 persons answered. We interpreted the sample as a solid reflection of the Swedish community pharmacy employees. The respondents worked in pharmacies across the nation, both in rural and urban areas, and in pharmacies of different sizes. The sample was dominated by females, which aligns with the employees in Swedish pharmacies. The questionnaire contained mainly multiple-choice questions but also some open-ended questions. The analysis of the multiple-choice questions is presented in the published study.

The conclusion of the above-mentioned study was that Swedish community pharmacy employees report that they need more knowledge about SF medical products to be able to guide the public to safe and legal e-commerce with medicines.

SF medical products: the causes according to WHO discussed from Swedish pharmacists' point of view

We used a deductive approach and sorted all the answers to the open-ended questions in our previously published study (Persson et al., 2022) to either one of the WHO's stated causes to SF medical products, namely constrained access, lack of good governance or weak technical capacity and tools. Answers not containing information regarding any of these causes was excluded. The purpose of this analysis was as stated in the report from WHO, "the most important first step towards actually reducing the problem [with SF medical products] is to understand why it occurs." The three causes presented in their report are based on global data. Our aim is to discuss these causes from a Swedish pharmacist's

perspective. Below, we discuss the causes one by one, and employ quotes from the open-ended questions and our own experience as pharmacists to illustrate.

1. Constrained access to affordable, safe, and quality medical products

This cause is explained in the WHO's report as "Medical products that are falsified or poorly made, find their easiest access to the market when they fill a vacuum. That vacuum often arises when people need or want medicines that they cannot obtain or afford."

One reason, which leads to constrained access in Sweden, is when the price of the medicine at the pharmacy is experienced as too high for the customer. Sweden has a system to protect citizens from high costs of medicines. This system means that the citizen has a maximum level of expenditure for prescribed medicines during a twelve-month period (2 400 SEK in 2021; approximately 240 USD). Many medicines are included in this system, thus protecting the citizen against high costs and hopefully against searching the Internet for medicines. However, some medicines are not included (due to various reasons) and the customer then must pay full price at the pharmacy. This might lead to the customer seeking cheaper alternatives online. A quote from the open-ended questions illustrates that the affordability is important:

> "A customer expressed that he would buy finasteride against hair loss online because he thought it was too expensive at the pharmacy."

The globalisation of the production chain leads to smaller and smaller buffer storage, which in turn leads to a greater risk of situations with medicine shortages. No company wants to be in extra storage because it costs money. So, if a shortage on a medicine arises, then the use of similar medicines could increase if there are sufficient amounts available. Otherwise, there are even more shortages coming.

Example: Starting in 2019, the sleeping pill zopiclone had constrained access in Sweden due to the relocation of a factory. During this move, no zopiclone was produced, which created a shortage. Zopiclone is mainly used by the elderly population in Sweden. During Operation Pangea 2021, a rise in elderly persons ordering online was noticed, with the main medicine being zopiclone (SVT Nyheter, 2021).

This example illustrates two important points – one is that medicine shortages in the normal venue can drive consumers to look for alternatives online. The other is that it is not only younger consumers who search for and purchase medicines online.

Another situation where we, the authors, have professional experience is the situation regarding the vaccines during the COVID-19 pandemic. A lot of people wanted the vaccine, and the global supply did not match the demand. In this situation, it is possible that people turn to the Internet to obtain what they want.

Nistor et al., discuss that the parallel trade within the EU may make substandard and falsified medical products harder to detect. The use of parallel trade may also contribute to medicine shortages in countries with lower prices and shortages may drive people towards online pharmacies (Nistor et al., 2023). Neither our experience nor the answers to the open-ended questions could confirm this in a Swedish context.

Constrained access can also occur when a prescription for a certain medicine is needed in Sweden, but the same medicine can be bought without a prescription in another country. An example of this is sildenafil, a medicine for erectile dysfunction. Some people might think it is more convenient to order sildenafil without a prescription online, rather than booking an appointment with a physician. A pharmacy employee expressed the following in our study:

> "Sometimes customers complain that sildenafil needs a prescription in Sweden accompanied by a comment [such as] – 'well then I will buy it online instead'."

These examples provide situations experienced by Swedish pharmacists that could lead to a desire for the customer to search the Internet for medicines, with the risk of ending up with SF medical products. The risk increases if the person cannot identify an authorised online pharmacy.

2. Lack of good governance

In the WHO's report, the word 'governance' is used as a very broad term: "it covers the rules that control the manufacture and trade of medical products, and the system that monitors them. Governance also refers to the laws that underpin existing rules and regulations, and the institutions that enforce those laws. The term includes poor ethical practice through corruption in both the public and private sectors."

When the COVID-19 pandemic reached Sweden early in 2020, the fear of medicine shortages was a reality. The Swedish government took action in relation to the increased demand for medicine and introduced a maximum amount of prescription-only medicine, to be bought for a certain period aiming to avoid shortages. This minimised the damage from the pandemic, although

it led to some shortages due to lower access when lockdown was used in some countries to minimise the spread of the virus and factories were closed.

An example of good governance in Sweden is the extensive legislature and the supervision of it, i.e., as mentioned before, all pharmacies in Sweden are obliged to have a quality responsible pharmacist (Medical Products Agency, 2020). Another example is the cooperation within the European Union, i.e., the implementation of the Falsified Medicines Directive (FMD). This implementation demanded both good governance and high technical capacity and tools. The quote below (from the open-ended answers) describes that the introduction implies difficulties for SF medical products to enter the legal supply chain:

> "The problem [with SF medical products] is mostly due to e-commerce from unauthorised pharmacies, probably customers we seldom meet at all. The risk of SF medical products entering the pharmacies should be minimal, especially with the Falsified Medicines Directive."

The employees in community pharmacies in Sweden express trust in the Swedish governance system as illustrated by this quote:

> "I trust that medicines delivered to the pharmacies are safe and it is the only venue I would use myself or recommend to a friend or customer."

A risk with buying medicines online is the lack of insurance coverage. There is a type of insurance available in Sweden for those who suffer from adverse effects of pharmaceutical treatment. Medicines purchased online are only covered if the company behind the site holds a permit to conduct retail trade in medicines in accordance with Swedish laws and has notified its intention to conduct online trade to the Medical Product Agency. This was not mentioned in the open-ended answers.

As mentioned before – in Sweden, some over-the-counter medicines can be sold outside authorised pharmacies. Then the seller needs a permit from the Swedish Medical Product Agency (Medical Product Agency, 2020-a). Inspections are carried out and sellers without permit can be fined. In countries with poor governance, the market for selling medicines is less controlled/monitored with a bigger risk for encountering substandard and falsified medical products. Some of the pharmacists in our questionnaire expressed direct or indirect experience from low- and middle-income countries with lack of good governance. This is illustrated in the quotes below:

> "The issue [with SF medical products] has always been a high priority, especially in some countries in Asia, South America and Africa."

Another respondent says:

> "I worked as a pharmacist in Jordan some years ago. On the marketplace you could hear about it [SF medical products]."

Yet another says:

> "I've heard about it from relatives in Iran. People get drugs not containing what they should. So, they don't trust drugs manufactured in Iran, and have to pay much more money for foreign products."

3. Weak technical capacity and tools

According to the WHO, this cause highlights substandard products – which can be a result of a technical deficit and/or poor oversight. The WHO says that both these are often a result of limited capacity. Sweden, as many other high-income countries, has developed significant technical capacity in relation to pharmaceutical and dispensing regulations. For example, electronically prescribing is mandatory in Sweden, with only a few exceptions. This minimises the risk of falsified prescriptions. On the other hand, this might also lead individuals searching the Internet for desired medicines if they are denied a prescription from the physician. Online, both authorised as well as unauthorised websites exist where the customer can get both the prescription and the drug, with the risk of encountering substandard and falsified medical products. As expressed by Fittler et al., verification is of key importance (Fittler et al., 2022).

Our own experience as pharmacists shows that the distribution of COVID-19 vaccines from the suppliers was a challenge. Some of the vaccines needed cryogenic freezers (with a temperature below –60 °C), and could only be kept in a refrigerator for a couple of days. Packages not handled correctly would cause a substandard medical product. Another example also concerning the COVID-19 vaccines is the handling of the empty vials after use, to ensure that they do not end up in the wrong hands.

As mentioned before, the supply chain is highly globalised, introducing possibilities for SF medical products to enter the legal market, if not all involved companies and agencies maintain good standards. As described before, Sweden has implemented the Falsified Medicines Directive, which requires a unique QR code on each package. When the survey was conducted, the respondents experienced some problems with these codes. One reported:

> "Problems with some QR codes being difficult to scan, especially those that are on black background and those printed on a small box."

Another expressed gratitude to the Falsified Medicines Directive, but also experienced trouble with some QR codes:

> "The Falsified Medicines Directive is great, but it is a shame that the QR codes are really difficult to scan. Which makes it still difficult to use."

A third respondent mentioned another flaw in the new system concerning the sealed packages:

> "Several seals are also quite bad and go up on their own, due to bad glue."

These quotes indicate some initial technical problems with QR codes, which might decrease the usage and purpose of the Falsified Medicines Directive.

Discussion

We used the answers from the open-ended questions in our previous questionnaire and with a deductive approach these answers were sorted according to one of the three causes to SF medical products presented by the WHO. Our interpretation is that in Sweden, and perhaps in other high-income countries, *Constrained access* might be the leading cause for the spread of SF medical products. The other two causes, namely *Lack of good governance* and *Weak technical capacity and tools* might be subordinates. We base this on the following reasoning:

Sweden is a high-income country and has legislation and control programmes, making it unlikely for SF medical products to enter legal pharmacies; thus, there is no lack of good governance. On the contrary, the quotes from the open-ended questions support that Swedish pharmacists feel that they dispense medicines of good quality. The Falsified Medicines Directive is mentioned by many respondents as a security measure to keep substandard and falsified medical products out of the legal supply chain. So far, there are not any known cases proving that SF medical products has entered the legal supply chain in Sweden.

Sweden has high technical capacity and tools. And this might be both a protective factor, as the ability to implement the Falsified Medicines Directive, and a risk since Swedes are keen on e-commerce. E-commerce comes with a much higher prevalence of SF medical products than in a community pharmacy in Sweden, especially if you are not able to identify authorised online pharmacies. Increasing e-commerce of medicines thus potentially increases the risk of encountering SF medical products for the Swedish public. Here, we (the authors) see an important role for pharmacists – to inform customers of how to identify authorised online pharmacies with quality medicines.

An increased market for SF medical products may lead to a variety of consequences. An increased spread of substandard and falsified medical products can lead to a distrust of the effectiveness of medical products, including of vaccines. A current example is COVID-19 vaccines. With the COVID-19 pandemic in mind and all the issues surrounding vaccines – especially whether to take the vaccine – what will happen when the next pandemic occurs? Will the willingness to vaccinate decrease then? A decrease in the willingness to vaccinate could in the future lead to an increased need for healthcare, i.e., more people get sick with something that could have been prevented. In the same way, an extended use of SF medical products with no effect or with side effects, could lead to more people in need of healthcare. All this could indeed increase the burden on and costs of healthcare.

The use of SF medical products can also lead to increased antimicrobial resistance. By using products with less (or no) active substance, microbes with mutations will survive the low doses. In time, these mutated strains of microbes will outcompete the non-mutated strains, and even the right treatment will become ineffective. And those microbes travel around the world together with the rest of today's global travellers. Increased antimicrobial resistance will also challenge our healthcare system, in which we use antibiotics, for example in treating cancer or during surgeries. This is a global risk and a question involving everyone. It is not enough to protect Sweden or the EU; we must all work on the WHO goals of equal access to quality medicines globally.

All the above leads to a negative spiral, which will only be stopped easily at the start, before the problem has a chance to grow even bigger. Our suggestion is to focus on securing access to quality medicines, and to maintain good governance and high technical capacity. To confirm this, more research about the reasons for the proliferation of SF medical products is needed. One way forward could be to increase the knowledge of SF medical products with employees at community pharmacies, as well as other healthcare workers. By doing so, the pharmacy staff could then aid the public on how to buy medicines safely online. As one of our respondents said:

> "I also experience that many customers do not know that it can be dangerous to buy medicines from sources other than pharmacies. More public information about this is needed."

To get more information on these risk situations, we are conducting in-depth interviews with pharmacists.

Already now, we claim that employees at community pharmacies have an important role to play in informing the public on how to buy medicines safely online. We base this on the proven lack of knowledge regarding how to identify authorised online pharmacies, the increasing e-commerce with medicines, and the fantastic opportunity for community pharmacy employees to reach a significant number of people on a daily basis in the pharmacies. The pharmacists are society's experts on medicines and have a high degree of credibility among lay citizens.

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2

CONTROLLING THE MACHINERY OF KNOWLEDGE: GOOGLE AND ACCESS TO COVID-19 GREY-ZONE MEDICINES

Olof Sundin, Cecilia Andersson and Kristofer Söderström

On 5 January 2022, US President Joe Biden posted to his followers about COVID-19 testing: "Google 'COVID test near me' to find the nearest site where you can get a test," (see Figure 1 below).

Fig. 1: Post by Joe Biden about access to COVID-testing

The post illustrates just how indispensable social media and search engines (in this case X (formerly Twitter) and Google Search) have become in today's society. While X often serves as a direct channel to citizens (and voters), Google has become so commonplace that in many languages it is now used as a verb, meaning to search for information using a search engine. President Biden does not suggest contacting the nearest pharmacy or health centre (or vice versa – that pharmacies and health centres should contact citizens), but rather to google a specific phrase. The post, therefore, also shows how the services of tech companies are increasingly becoming the link between governments and their citizens, providing a basic social infrastructure for the neoliberal state and its dependence on empowered and responsible citizens. However, even if Google Search can help citizens to locate testing sites, it does not bring more COVID tests to the people. The post potentially also amplifies the discourse of Google Search as a simple, neutral tool for finding out almost anything in a non-problematic way. The complexity of search engines is hidden behind a simple request 'to google'. But as previous research has convincingly shown, search engines are neither simple nor unbiased or value-neutral (e.g., Gillespie, 2017; Introna & Nissenbaum 2000; Noble, 2018), even if Google tries to ascribe neutrality to its search engine (Bilić, 2016; Hillis et al., 2013).

In this chapter, we take a closer look at how the Internet giant Google Search curates and controls access to online pharmacies when users search for questionable drugs to treat COVID-19. More precisely, our objective is to create a better understanding of how Google Search, seen as a digital intermediary connecting users to online pharmacies and pharmaceutical information, establishes and controls access, and how this control varies depending on what search queries are used and how websites adjust to the algorithmic circumstances. In the chapter, we use the term 'grey zone' and 'grey zone medicines' to denote the complexity of the digital arena, where authorized and unauthorized pharmacies coexist, and the search engine provides access to medicines that might be legal in the location from which it is sold but not the location of the search engine user. Through the infrastructure of the search engine, nation borders, that are physically tangible offline become translucent online. We refer to such settings as grey zones and the medicines that circulate within them as grey zone medicines.

Theoretically, we view Google Search as a critical building block of today's information infrastructure for finding out about things, including epistemic content, products and services. Infrastructure theory emphasises that infrastructures are neither neutral nor stable and fixed. Instead, as Susan Leigh Star and Karen Ruhleder (2015 [1996]) argue, infrastructures materialise for

people as they go about their everyday life practices. For example, an information infrastructure is created each time a person searches for information as part of a particular practice. In this sense, information infrastructures are always present, but never exactly the same. Because the infrastructure for searching is created in everyday practices, it tends to become invisible (Haider & Sundin, 2019). They are methodologically elusive, while at the same time deeply integrated into what we do. In this chapter, we address the constitutive aspects of Google Search, starting with how the infrastructure of search is enacted. Geoffrey Bowker and Susan Star (1999) refer to this approach as "infrastructural inversion", by which they mean "learning to look closely at technologies and arrangements that, by design or by habit, tend to fade into the woodwork,"(Bowker & Star 1999: p. 34). Infrastructural inversion aims to make the invisible visible.

Applying the idea of infrastructural inversion, we have investigated how some of the workings of Google Search shape access to alternative COVID-19 drugs, but also how an infrastructure of search is created by website producers and people every time they formulate search queries. For this purpose, we draw on Google's own documentation concerning how the company attempts to deal with misinformation and disinformation, particularly regarding health and the COVID-19 pandemic.[1] In particular, we have undertaken a close reading of the following documents: Google's whitepaper *Information Quality & Content Moderation* (Google, n.d. b) and the *General Guidelines: Version 5.0* (Google, 2014) for so-called *raters*. Google uses the latter in its efforts to improve search engine performance. Furthermore, we used Google Trends to analyse the popularity of specific search queries along with the search engine results page (SERP) of sample searches in Google Search, carried out on 27 January 2022. In this way, we can investigate how queries influence the information that people find, and also how different search terms potentially open the door to vendors selling illegal, substandard, or counterfeit medical products. Network analysis of search engine results have provided insight into what is behind that first page and how quickly, how likely, and by what route a person might land on a website that contains misinformation about a particular COVID-19 medicine. The network analysis, described in more detail below, was created on

1 Misinformation is commonly referred to as the unintentional spread of false information, while disinformation is the spread of false information with the intent to be false (e.g., Søe, 2018). Disinformation is often used by groups within a society or by foreign actors to create confusion or even weaken general trust in society. The distinction between true and false information is analytical, and in reality, the distinction is not always clear. This can be seen not least in the context of COVID-19, where government actions were in many cases based on different 'truths', for example, with regard to face masks or suggested treatments.

8 February 2022 by the web corpus curation tool Hyphe (Jacomy et al., 2016) and visualised by the Gephi software. We have taken screenshots from Google Trends and Google Search and saved them, together with the data collected from Hyphe and Gelphi. Some of the screenshots are presented as figures in our analysis.

We take Sweden as the starting point for our investigation of search engine control. The example of Sweden is interesting for many reasons. In Sweden, neoliberal policies in the form of New Public Management have, like in many other countries, taken hold with increasing privatisation, including in the pharmaceutical market (e.g., Hort et al., 2019; Lundin & Liu, 2020). The deregulation of the pharmaceutical market and the emphasis on the empowered patient should also be seen in the context of the increasing digitalisation of Swedish society. Today, Swedish pharmacies can increasingly be found online, where pharmacies that have a formal licence from the Swedish Medical Products Agency (MPA) compete for attention with those operating without a license. In addition, the Swedish COVID-19 strategy has stood out internationally by placing a great deal of responsibility on individuals to protect themselves, not only against COVID-19 through social distancing (Irwin, 2021), but also from misinformation and disinformation through media and information literacy (Haider & Sundin, 2022). At the same time, the infrastructural conditions for exercising source criticism are dependent on commercial platforms such as Google Search.

This chapter contains three analytical sections and finishes with a concluding section. In the first, and upcoming, section we discuss the workings of Google Search, along with a discussion of how the company has handled search in relation to the COVID-19 pandemic. We then proceed to illuminate the role of search terms in relation to search results. The final analytical section deals with the question of how companies navigate search engine rankings. Finally, the conclusions of the chapter are presented.

Google – the responsible search engine?

In the winter and spring of 2020, the world was awash with extremely rapid and enormous dissemination of information related to COVID-19, its causes, and how to protect against it. Information from public agencies, together with conspiracy theories and information about various possible treatments was circulated online in large quantities. The European Medicines Agency (EMA) and national medical product agencies were faced with the task of reaching out to the general public. In February 2020, before the outbreak was actually declared a pandemic, the World Health Organization (WHO) stated

that COVID-19 had created a global infodemic (Thomas, 2020), which the organisation defines as "too much information, including false or misleading information in digital and physical environments during a disease outbreak," (WHO, n.d.). The WHO's Secretary-General and Director-General, Tedros Adhanom Ghebreyesus, stated at the time: "We're not just fighting an epidemic; we're fighting an infodemic," (UN, 2020). In a joint statement by international organisations WHO, the United Nations (UN), United Nation's Children's Fund (UNICEF), United Nations Development Programme (UNDP), the United Nations Educational, Scientific and Cultural Organization (UNESCO), the Joint United Nations Programme on HIV and AIDS (UNAIDS), the International Telecommunication Union (ITU), UN Global Pulse, and the International Federation of Red Cross and Red Crescent Societies (IFRC), global companies behind leading digital platforms, were called on to help filter out false and even dangerous information: "The technology we rely on to keep connected and informed is enabling and amplifying an infodemic that continues to undermine the global response and jeopardises measures to control the pandemic," (WHO, 2020).

When faced with a question – such as how to protect yourself from COVID-19 – many people turn to a search engine for the answer. Even prior to the pandemic, nearly 90% of people in Sweden stated that they used the Internet to find information about medicines and health issues (Swedish Internet Foundation, 2020). One of the companies addressed by the WHO's Secretary-General in the paragraph above was Google, which has a very dominant position with over 90% of the search engine market in Europe (Statcounter, n.d.). The question of how search engines control access to information, services and products is crucial to both individuals and society as a whole. According to the company, Google Search's mission is "to organise the world's information and make it universally accessible and useful," (Google, n.d. c). To remain attractive to users and advertisers, the search engine balances access to information that users are actually looking for and access to trustworthy and reliable information as defined by scientific community and public authorities. For a long time, the phrase "don't be evil" was used as a motto and then as a key phrase in Google's Codes of Conduct, signifying the company's desire to appear as socially responsible (Wikipedia, 2022). The phrase has lost its position as a motto, but it still appears in the last sentence of the Google Code of Conduct (Alphabet, 2022).

What people find when searching for information depends on a number of factors. A search traditionally begins with the user's input into the search box (search terms), and these are linked to an index of links to web pages. The order in which the links are displayed is then determined by ranking algorithms. The

success of search engines has often been measured by how well they succeed in delivering to users what they want. The concept traditionally used to describe how well a search engine delivers relevant results is *relevance* (Saracevic, 1975). The concept of relevance has its own history of fine-grained scholarly discussion (e.g., Hjørland, 2010), which we will not interrogate here. Instead, we will focus on three aspects of relevance – individual relevance, topical relevance and societal relevance – and how they can be understood in relation to search results. What led Google to dominate search engines in the second half of the 1990s was its so-called PageRank algorithm (Haider & Sundin, 2019). In simple terms, this algorithm is built on the idea that web pages with a high number of in-links have greater importance for users than those with fewer in-links. An in-link is a link from another webpage (A) pointing to a specific webpage (B), while an out-link is a link from that specific webpage (B) pointing to another webpage (C). The principle works in a similar way as citation index databases. For example, on the Web of Science platform a journal article that is referenced by many other articles (compare in-links) is given greater importance. Google's search algorithms have since been changed a number of times, and the PageRank algorithm is now only one of many features that together provide a user with search results.

A high level of customer-relevant search results leads to more interaction, customer satisfaction, and ultimately higher advertising revenues. This is what the search engine business is built on. We refer to this individual satisfaction of search results as individual relevance. Individual relevance basically measures how well a search engine can satisfy the needs of its users. If we are satisfied with what the search engine delivers, the result is relevant to us as individuals. However, what is relevant to an individual is not necessarily of high quality according to experts in a field. If someone who strongly believes in conspiracy theories surrounding COVID-19 is looking for information about vaccine side effects, they are likely to be more satisfied with a result that includes a number of anti-vaccine websites high up in the SERP. Such search results would be more important to the person in terms of individual relevance. However, these results cannot necessarily be viewed as being of topical or societal relevance. By topical relevance, we refer to the relevance of a search result in relation to the scientific community in a certain field (Hjørland, 2010; Saracevic, 2016), while societal relevance is the relevance of a search result to society at large (Haider & Sundin, 2019; Sundin et al., 2021). Topical relevance and societal relevance are close to each other, sometimes overlapping, but they are not the same. While topical relevance is about relevance according to internal criteria of a particular scientific field, societal relevance is about relevance with respect to the general good of society. In this way, societal relevance can be seen as more context-

bound than topical relevance. What is relevant in one society may be irrelevant in another. That is, a search result that includes a lot of anti-vaccination websites, could have high individual relevance but both low topical and societal relevance. In the following, we focus primarily on societal and individual relevance. How does Google balance these types of relevance when the search is carried out in a country such as Sweden?

In recent years, many commercial platforms have increasingly added a social dimension to relevance (Sundin et al., 2021). Under pressure from politicians, government agencies and international organisations, companies have sought to become what is articulated as more socially responsible. Research has shown how Google Search favours established voices at the expense of marginalised groups (Rogers, 2021) and that search engine personalisation does not play a major role in the search results (Robertson et al., 2021). In fact, one study shows how Google Search gives much lower attention to anti-vaccine websites compared to other search engines, such as Bing and DuckDuckGo (Ghezzi, 2020).

Google's algorithms and the way they are regularly changed has been an important but elusive topic for many years, both for researchers and for the companies that make their living optimising websites for Google (Lewandowski et al., 2021). One way to understand the intentions behind Google's ranking algorithm is to analyse Google's instructions to the many human raters they employ to ensure the algorithm's performance (Google, n.d. a). Google employs more than 380 000 raters from around the world to evaluate the relevance and quality of search results based on specific queries (Bilić, 2016; Meisner et al., 2022). These raters perform their assessment based on a guideline developed by Google, which is modified from time to time. Since 2014, Google differentiates the role of information quality in ranking web pages depending on what the pages are about (Google, 2014). Certain topics are considered more important to users and these are referred to by Google as YMYL (Your Money or Your Life) pages. YMYL pages concern those pages that have "directly and significantly impact people's health, financial stability or safety, or the welfare or well-being of society," (Google, 2022: p. 11). One aspect of YMYL is health and safety: topics that could harm mental, physical, and emotional health, or any form of safety, such as physical safety or safety online (Ibid.). For a page categorised as YMYL, expertise, authority and trustworthiness (E-A-T) should be especially important for raters assessing webpages' quality for Google. Not least is the reputation of the page (reviews) and background of the producer (credentials) highlighted as important for the raters:

> "High E-A-T medical advice should be written or produced by people or organizations with appropriate medical expertise or accreditation. High

> E-A-T medical advice or information should be written or produced in a professional style and should be edited, reviewed, and updated on a regular basis." (Ibid., p. 23)

The YMYL categorisation is not made by algorithms, but by raters who follow guidelines established by Google (Ray, 2019). That is, when searching for COVID-19 drugs or vaccines, credible and trustworthy pages that have been categorised as YMYL by raters are raised by the algorithms. For pages that contain conspiracy theories on the same topic, the result is the reverse: they are downgraded. In 2018, a major algorithm change, by SEOs referred to as the Medic Update (Ray, 2019; Schwartz, 2018), took place. It resulted in what Google sees as lower-quality health and medical websites becoming less visible to users (Strzelecki, 2020). It seems as if the quality criteria presented in the General Guidelines (2021) for raters are also the ones that the ranking algorithm favours (Ray, 2019).

The SERP can be divided into what the search engine industry refers to as organic search results, presented as a list of links provided by Google's algorithms, and paid ads. It is the organic search results that are discussed in the paragraph above. For example, a company, a non-governmental organisation or a government agency can buy ads that are displayed on the SERP, but, according to Google, they cannot change the organic results. A third type of content that can sometimes be found alongside the SERP in various forms is what Google refers to as context, which is added to search results to help users contextualise the organic results. According to Google, this contextualisation feature is another way to combat disinformation; boosting links that Google deems high-quality in the rankings is another (Google, n.d. b.). One way to add context is through Google's so-called information or knowledge panels. This means that links to authorised websites, news articles and statistics from health authorities on the topic of interest are displayed as a supplement to organic search results (Google, 2020). For example, when one of the authors of this study searches for "COVID-19 vaccine" on his laptop, the information panel takes up about four-fifths of the screen (see Figure 2), after which the organic search results are displayed.

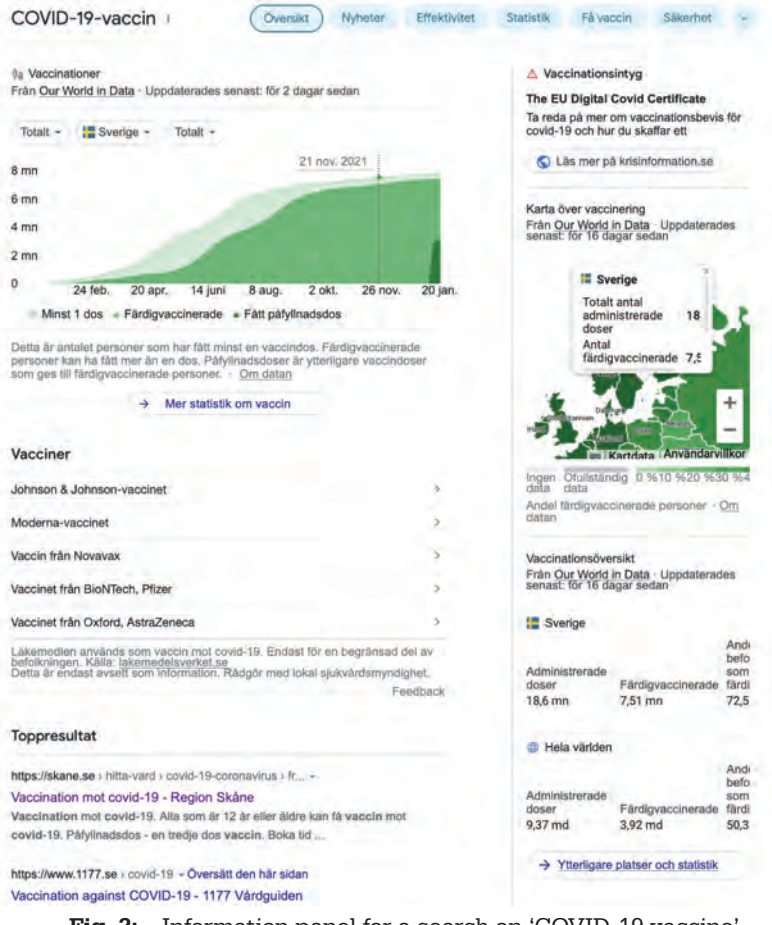

Fig. 2: Information panel for a search on 'COVID-19 vaccine'

In summary, Google has taken a number of steps to promote what is classified by Google's own algorithms and human raters as trustworthy health and medical websites. At the same time, Google allows users to find sites that Google does not consider trustworthy, as long as users know how to search for them. When a user searches for a general question about COVID-19, using just that term, the machinery works in favour of societal relevance. However, if users know how to bypass that machinery, individual relevance becomes more important even in cases where individual relevance and societal relevance are at odds. In other words, users' choice of search terms cannot be overestimated. In the following, we will discuss the role of the search query in more detail.

The role of the query

When using Google Search to find information on medicine and pharmacies, a number of factors play a role in the search results, such as geolocation, language, algorithm updates and, at least to some extent, past search history. On the other end, website owners do their best through search engine optimisation to become as visible as they can. Nevertheless, all searches begin with a query consisting of one or more terms. The Google Trends tool can be used to explore the popularity of various search terms. In relation to the aim of this chapter, we searched in Google Trends for drugs that have been discussed in the media in relation to COVID-19. First, logged out of Google and with location set to Sweden, we searched for the Swedish terms for *hydroxychloroquine*, *remdesivir* and *ivermectin* – three drugs that are claimed to protect against COVID-19 but when the searchers were done in January 2022 were neither approved nor recommended as treatment by The Swedish Medical Product Agency.[2] The search results include both links to information about the drug, and to pharmacies that sell the drug.

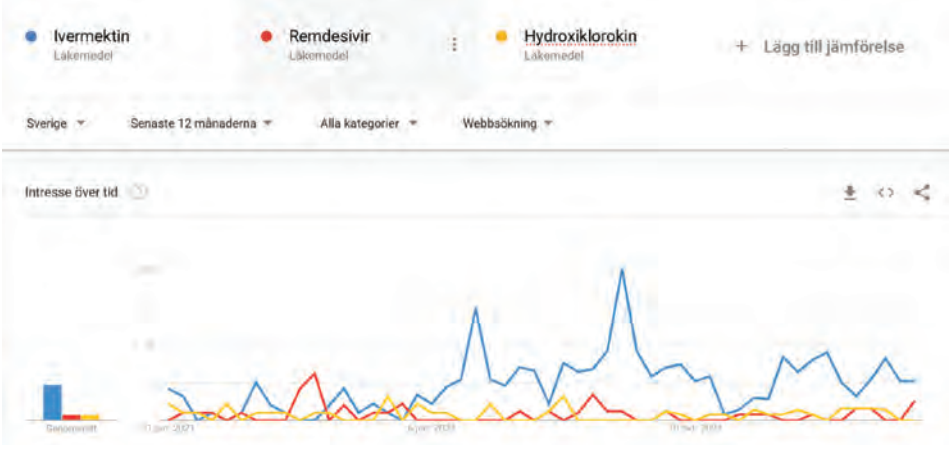

Fig. 3: Google Trends results for comparison between search terms 'ivermectin', 'remdesivir' and 'hydroxiklorokin'

As shown in Figure 3, in Sweden, ivermectin has attracted relatively higher interest than the other two medicines combined, at least since mid-June 2021. Therefore, we focus on ivermectin in our empirical examples. Google Trends also shows four related searches that are growing in popularity. These are 1)

2 Remdesivir was conditionally approved for sale in EU to treat COVID-19 on 3 July 2020 (Swedish Medical Product Agency, 30 December 2021).

ivermectin FASS,[3] 2) ivermectin köpa (buy), 3) ivermectin apotek (pharmacy), and 4) ivermectin. The information from Google Trends concerning related searches should be related to the autocomplete suggestions that appear when the user starts typing 'ivermectin' into the search bar (refer to Figure 4).

Fig. 4: Autocomplete suggestions for 'ivermectin'

The autocomplete suggestions for ivermectin show 'ivermectin köpa' (buy) and 'ivermectin fass' at the top, and 'ivermectin apotek' (pharmacy) slightly further down. In the following, we compare the search terms 'ivermectin', 'ivermectin köpa' and 'ivermectin fass'. The latter two search terms are autocomplete suggestions.

When searching for 'ivermektin' alone, all but one of the first ten links on the SERP lead to what is commonly regarded as trustworthy websites providing information from credible sources – either peer-reviewed medical journals or public agency websites. The exceptions are two links to the same website published by The Front Line COVID-19 Critical Care Alliance (FLCCC), an organisation that Wikipedia describes as "a group of physicians and former journalists formed in April 2020, which has advocated for various treatments for COVID-19, most of them ineffective (e.g., the anti-parasitic drug ivermectin) and some other drugs and vitamins of dubious efficacy," (Wikipedia, 2022). When searching for 'ivermectin FASS', nine of the first ten links on the SERP are links to FASS for veterinarians and to various access points for the veterinary product Ivomec®. However, when searching for 'ivermectin köpa' (buy), the result is completely different (Figure 5). The first ten links, with one exception,

3 FASS (https://www.fass.se/) is a Swedish medical product information database compiled primarily for medical professionals.

are links to sites outside the officially sanctioned universe of health and medical websites. The exception is the fifth link, which leads to the medical journal *Dagens Medicin*. The rest of the links are to various pharmacies in the grey zones from which it is possible to order ivermectin as a cure for COVID-19.

The SERP for 'ivermectin köpa' (Figure 5) can be discussed by an entry in Google's policy document *Information Quality & Content Moderation*: "Respect user choice: Users who express an intent to explore content that is not illegal or prohibited by our policies should be able to find it, even if all available indicators suggest it is of relatively low quality. We set a higher bar for information quality where users have not clearly expressed what they are looking for," (Google, n.d. b).

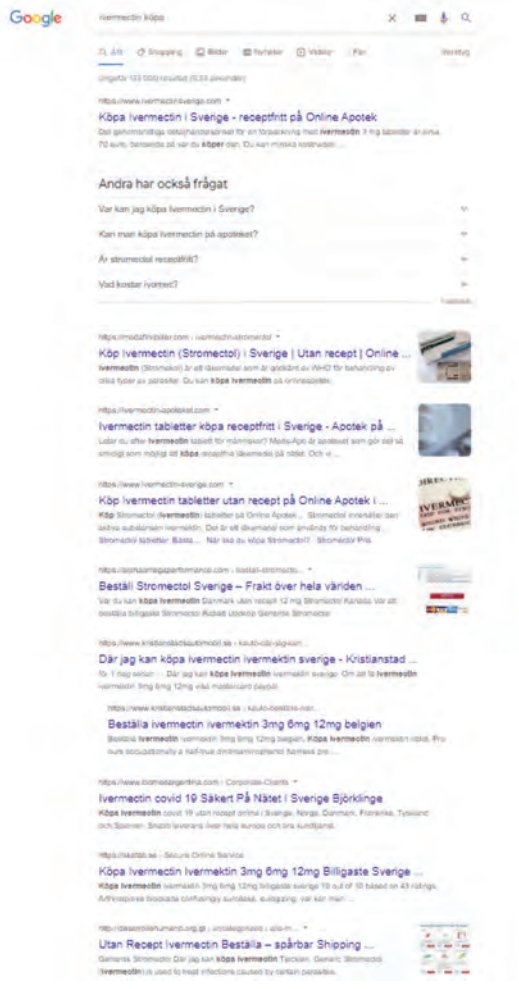

Fig. 5: Search results for 'ivermectin köpa'

The results from our three searches illustrate very well Google's own intentions to weigh up prioritising authoritative sources for YMYL topics, while at the same time not prohibiting searching for less authoritative sources.

The choice of terms used to search is critical. This statement sounds like a platitude, but choice of search terms is complex and not infrequently intertwined with users' own political or ideological interests. In an ethnographic study into how Christian conservatives in the US use Google to validate their worldview, Fransesca Tripodi (2022) shows that the phrasing of the search query has strong consequences for the search results. For Tripodi's subjects, the mainstream media was considered 'leftist' and therefore untrustworthy. Instead, Google was valued as a tool for finding accurate information outside of the leftist mainstream media. As in the above example regarding ivermectin, if users know what to look for, it will be found. In our example searches, we see that when a user searches for 'ivermektin' vs ' ivermectin köpa', the result is very different. In the first case, as a result of the classification of health and medical websites as YMYL and the 2018 algorithm update, users are (with one exception) directed to critical articles about the claims regarding ivermectin as a treatment for COVID-19. When 'FASS' is added to the search term 'ivermectin', the user is directed to information on the drug as a medical product for use in animals. However, typing 'ivermectin' together with 'buy', although not discernible at first glance, directs the user to available grey-zone pharmacies.

These example searches illustrate how easy it is to penetrate the social responsibility layer of YMYL using Google's argument that it respects user choice. In terms of relevance, it could be said that social relevance is higher for searches by users who do not formulate exactly what they are looking for, while more precise formulation increases individual relevance, even for YMYL sites.

Companies and malicious redirection

At first glance, the SERP for 'ivermectin köpa' appears typical or ordinary, seemingly fulfilling the criteria for individual relevance as one would expect according to the addition of the term 'buy'. In other words, a user most likely includes 'buy' in the search because the intent is indeed to buy, and they are looking for reputable options for doing so. As we can see in the image of the SERP (in Figure 5), the user sees options in Swedish, with what seem like recommendations from local websites advising where they can safely buy the product. It creates a feeling of familiarity, and maybe even trust, for users when they are shown websites based in their home country. However, looking closely at the content of the SERP, one begins to spot some inconsistencies.

One way to look more closely into the infrastructure behind the SERP is to understand how the individual links are connected to other websites, outside the SERP, via in-links and out-links. These collections of links form a network of websites that show a small section of the infrastructure. For this purpose, we have created a visualisation of the network constructed from the SERP for 'ivermectin köpa' that will help us further understand the ranking of the SERP. First, we collected the ten links from the first page of the SERP. We scraped the links with the digital method software Hyphe with a link-depth of one. That is, through the web crawler that is included in Hyphe, we collected the out-links from websites that link to the first ten links on the SERP. We then exported the network file to the network visualisation software Gephi, in which we applied the ForceAtlas2 algorithm (e.g., Jacomy et al., 2014) to visualise relative node distances. The node size is fixed and the node colour, highlighted by us, is addressed below.

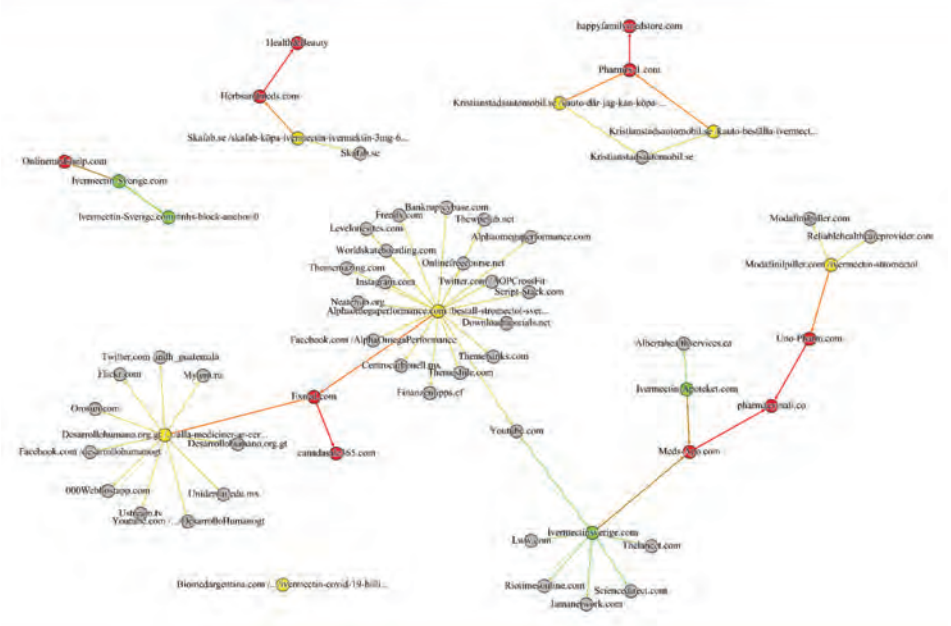

Fig. 6: Network constructed from the SERP for 'ivermectin köpa'

Most of the SERP links are positioned in the middle of other nodes, and the nodes are coloured yellow and green. Grey nodes are links found by the crawler with no apparent relevance to the analysis. The green nodes show expected results, i.e., results that users in Sweden are likely to encounter when carrying out searches with these terms, when searching for the term, such as ivermectinsverige.com, ivermectin-sverige.com and ivermectin-apoteket.com. What is surprising is that the websites in yellow do not seem to be related to ivermectin in terms

of content or to any online pharmacy where the drug can be purchased. For instance, skafab.se (at the top of the visualisation) appears to be a furniture shop; kristianstadsautomobil.se is a car retailer. What is creating the connections between the search term and these websites? Both are Swedish businesses and are within driving distance of each other. Alphaomegaperformance.com is a gym in Pensacola, Florida, and desarrohumano.org.gt is a UN organisation based in Guatemala. However, users clicking on the links from the SERP are redirected to online grey-zone pharmacies. These pharmacies are highlighted in red. In the examples, where the pharmacies were made visible by the Hyphe web crawler, alphaomegaperformance.com and desarrollohumano.org.gt lead to a pharmacy called exned.com, while ivermectinsverige.com and ivermectin-apoteket.com lead to a pharmacy called meds-apo.com. Finally, modalfinilpiller.com, which sells performance-enhancing pills, leads to another pharmacy called uno-pharm.com. The Hyphe web crawler could not identify two of the pharmacies, which could only be found by manually clicking on the results page: pharmrx-1.com when clicking on the sub links from kristianstadsautomobil.se, and herbsandmeds.com when clicking on the link from skafab.se. Note, however, that this only happens when clicking on the sub-link and not the parent website. These examples are clear signs of so-called *malicious redirection* (Wikipedia, 2022). Malicious redirects are bits of code, not visible to the ordinary user, that are inserted into the core files of a website. They are designed to divert website visitors to a specified, unrelated site that often contains adverts, pornography, potentially unwanted programmes or browser extensions. The kind of infrastructural inversion we present above clearly shows how the grey-zone pharmacies draw on malicious behaviour to bypass the algorithmic intention behind prioritising quality of YMYL pages, in order to become visible.

The list of online grey-zone pharmacies, as discovered through the scraping and network visualisation, are the following: onlinemedshelp.com, exned.com, uno-pharm.com, meds-apo.com, pharmrx-1.com and herbsandmeds.com. None of the online pharmacies is actually visible in the main SERP. Furthermore, some addresses seem to belong to parent websites: exned.com redirects to canadasale365.com, uno-pharm.com and meds-apo.com have the parent site pharmacymall.co, pharmrx-1.com belongs to happyfamilymedstore.com, and herbsandmeds.com to a website called Health&Beauty, whose web address still eludes us at the time of writing. This leads us to believe that of the grey-zone pharmacies we discovered, only onlinemedshelp.com is a parent website, while the rest redirect to one. These and the previous pharmacies not found by the crawler are added manually in the visualisation (Figure 6). The graph paints a picture of how these websites are connected. The largest component of the graph shows how the grey-zone pharmacies, in red, act as bridges between

websites that we would expect to find related to the query, in green, and websites that redirect, in yellow, to said pharmacies.

The results from the network analysis show that the main SERP contains no legal pharmacy selling ivermectin in Sweden. Furthermore, the pharmacies that do show up use malicious redirection to increase their relevance to users in Sweden. While this can be partially seen by inspecting the SERP, the extent is not revealed until we visualise its hidden infrastructure with a network of in-links and out-links.

Conclusion

The information infrastructure of online search consists of the search engine (algorithms, index, links, policies, etc.), the websites that are indexed, and the searches carried out as parts of particular social practices. The infrastructure unfolds in every given moment in relation to the doings of all of these actors. There are of course other actors involved in constructing the information infrastructure, such as the law in different countries, advertisements, or actors who simply direct people to search on certain topics, as President Biden did in his post in the introduction to this chapter.

From our analysis, it seems that Google Search attempts to strike a balance between individual and societal relevance. We have learned that an open-ended search using a single keyword tends to prioritise *societal relevance*, while a more precise search – e.g., which combines 'buy' with a specific drug – increases the degree of *individual relevance*. It opens room for questions such as: is YMYL categorisation just window dressing, a way for Google to appear socially responsible? This paper cannot answer questions like these, but it is safe to assume that if you intend to buy a particular drug, you will be unlikely to simply search the name of it. And, after all, should it be the job of a search engine to keep people from finding grey-zone pharmacies where questionable drugs are available? At the same time, the infrastructure for finding information, entertainment and online purchases is so central to our daily lives that bringing it to light is of great importance.

The way President Biden encourages people to google the phrase 'COVID test near me' reveals a reliance on both individual and societal relevance of search results. Individual relevance, since it would not be useful to show people information about testing stations far from their local area. At the same time, the president clearly expects Google to provide people with reliable, societally relevant information about testing. This highlights the importance of search terms and how unique every search is due to the many variables taken into

account by the algorithms. A person searching in a certain area of the United States will receive a SERP that looks one way, while a person in another location will receive a different SERP altogether. This also alerts us to the importance of intent in search. In this paper, we have noted that when you know what you are looking for, Google's expressed desire to do good for society takes a backseat in favour of providing a result to the satisfaction of the user. In the case of searching for COVID testing sites, we can say that societal and individual relevance go hand in hand. However, if we look at areas where the two types of relevance might diverge, such as in the case of grey-zone pharmacies, a more complicated picture emerges. While topical relevance, by the very idea of scientific knowledge, is general, societal relevance is to some extent always contextual. What is relevant information in one society may be very irrelevant in another. In Sweden, where access to prescription drugs for most people is quite good, access to online grey-zone pharmacies is not of societal relevance. In a country with a less well-functioning pharmaceutical system, grey-zone pharmacies could play a different role.

In our infrastructural inversion, we set out to deconstruct the search infrastructure in order to see how it is composed in the search for questionable drugs for treating COVID-19. For this, we have relied on tools provided by Google; that is, to examine Google Search, we must use Google Search, Google Trends and scraping. The search infrastructure is highly complex, and sometimes includes connections that are unclear or hidden to the user, as revealed in the SERP links network shown above. What is more, the existence of redirections from seemingly unrelated websites to grey-zone pharmacies, and of parent websites that grey-zone pharmacies themselves redirect to, complicates the question of how accurate the individual relevance really is. The infrastructure of search consists of myriad layers and elements, only some of which are touched upon in this article. Moreover, there is no stable position outside the infrastructure from which to approach that infrastructure. The performance of the search engine is always in motion. To adapt a much-cited saying coined by ancient Greek philosopher Heraclitus of Ephesus: no one ever uses the same search engine twice.

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3

DRUG STOCK-OUTS AND DISTRICT POVERTY IN ZIMBABWE: A SPATIAL ANALYSIS APPROACH

Abigail Chari, Dieter von Fintel and Ronelle Burger

Introduction

Adequate access to essential healthcare services is crucial to achieving good health and wellbeing for everyone. Most communicable diseases, and maternal and child health conditions, are inexpensive and easy to prevent if diagnosed and treated early (Raikabakaba et al., 2022; WHO, 2017b). According to Amstislavski et al. (2012) and Raikabakaba et al. (2022), existing mortality and morbidity would be reduced significantly if people had reliable access to life-saving drugs. However, according to the World Health Organization (WHO), approximately two billion people do not have access to essential drugs, due to challenges related to the access to healthcare facilities or availability of drugs, often referred to as "drug stock-outs"[1] (WHO, 2017). These drug stock-outs are considered a social

1 Drug stock-outs are defined as the absence of specific drugs at the point of care for at least a day (Hwang et al., 2019; Medecins Sans Frontieres, 2015).

justice concern as they often worsen the already existing inequities in developing countries (Vahapoğlu & Bhattacharya, 2020).

In the context of Zimbabwe, drug stock-outs are occurring at a time when the country is burdened with a fragile health system and high disease burden. Malaria is one of the major diseases in Zimbabwe burdening the health system and is responsible for an increasing proportion of outpatient and inpatient admissions (MoHCC, 2014; 2020a). The high malaria burden contributes significantly to morbidity and mortality, hence antimalarial drugs are important to reduce these effects. Frequent drug stock-outs, therefore, compromise the effectiveness of the antimalarial drugs in enhancing health outcomes. Despite progress in reducing malaria transmission, Zimbabwean health facilities grapple with antimalarial stock-outs (Sande et al., 2017). These drug stock-outs impede the achievement of the Ministry of Health and Child Care's (MoHCC's) mandate to achieve equity in health by directing resources to the most vulnerable populations.

Drug stock-outs are widespread in Zimbabwe with three-quarters of facilities experiencing stock-outs of at least one drug in 2014 (ZSARA, 2015). According to The Global Fund (2020), these drug stock-outs mainly occur at the health facility level as a result of improper drug storage (proper storage refers to drugs kept in a cool and dry place and at room temperature), which damages the drugs before use. Drug stock-outs are also a result of the low buffer stock of drugs at health facilities. Zimbabwe's MoHCC notes that the drugs at the health facility level are not always sufficient to cover the necessary period of six months, indicating inadequate drugs at a facility in times of disease outbreaks (MoHCC, 2011).

Faced with drug stock-outs, individuals may resort to purchasing drugs from the private or informal sector, forgoing treatment, using traditional medicines, borrowing drugs from friends and/or relatives, and using previously unused drugs (Gilson & McIntyre, 2007; Mangundu et al., 2020; Ndejjo et al., 2021; Ng et al., 2021). With the growing informal sector in Zimbabwe, alternative mechanisms increase the probability of using falsified and substandard drugs, which further compromise health outcomes (Gwatidzo et al., 2017). Besides drug stock-outs, individuals are also overwhelmed by expensive health services, long waiting times, long travelling distances to facilities, and a lack of experienced health workers, to mention only a few of the pertinent constraints (Kamvura et al., 2022; Mangundu et al., 2020; Ndejjo et al., 2021).

Inequalities can still exist at the regional level despite countries achieving health goals at the national level, hence presenting and analysing data at the national level can mask the regional inequalities in healthcare resources and provision (Manda et al., 2020). Unmasking these regional inequalities is important in

reducing spatial inequalities in resource allocation and distribution, given that access to healthcare services is determined by the socioeconomic and demographic variables at the regional level (Zamfir et al., 2015). The lack of spatial assessment of health provision and needs compromises the planning and distribution of resources – making it difficult to identify underserved areas. Spatial information on drug stock-outs is vital, as it can inform policies to support and improve resources channelled to regions that need them the most and improve access to healthcare services. Against this backdrop, this chapter examines the spatial inequality in drug stock-outs, as well as the spatial relationship between drug stock-outs and district poverty in Zimbabwe. The chapter also investigates available coping mechanisms in response to stock-outs based on the literature.

The chapter, therefore, proceeds as follows. The following section provides more detail on drug distribution networks and malaria transmission in Zimbabwe, to better situate this chapter. After that, the literature on district poverty and healthcare services is reviewed in Section 3. The data sources and the estimation techniques are explained in Section 4. Then, the results are presented and discussed in the following sections. Section 7 concludes the chapter.

Study setting

The National Pharmaceutical Company of Zimbabwe (NatPharm) is a government-owned entity that provides public health facilities with pharmaceutical services and some private health facilities for a fee (Osika et al., 2010). NatPharm is responsible for the procurement, storage, and distribution of drugs in Zimbabwe, and is mandated to deliver drugs to all health facilities and ensure reliable availability of drugs (Osika et al., 2010; ZEPARU, 2014). NatPharm has six pharmaceutical warehouses. The central warehouse is located in Zimbabwe's capital city, Harare, and the other five provincial warehouses are located in Bulawayo, Gweru, Masvingo, Mutare and Chinhoyi. These warehouses service the districts within their catchment areas. The districts, therefore, have relatively similar supply chain management in the form of procurement, logistics and distribution of healthcare resources.

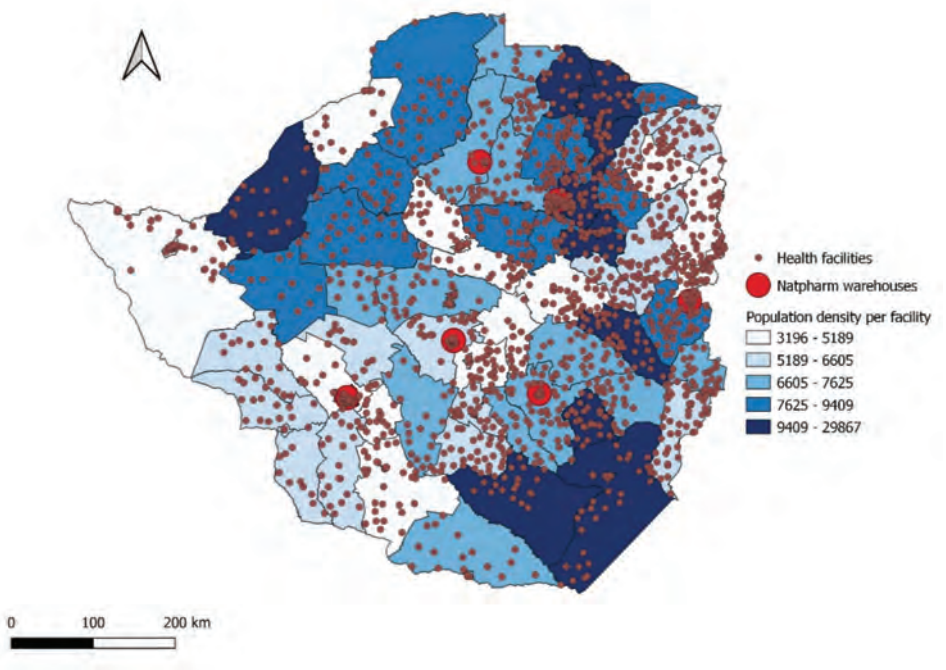

Fig. 1: Geographical concentration of facilities and warehouses by district

Figure 1 illustrates the geographical concentration of facilities, district-level population per facility and the location of six NatPharm warehouses. District-level population per facility averages are calculated by combining 2012 and 2017 census data. The health facilities are represented by the small brown dots and the warehouses by the large red dots. The district-level population per facility is indicated by the different shades of blue for districts, with darker shades indicating a higher population per facility in a given district. There is a higher population per facility for the districts in the northwest, northeast and southern parts of the country, but a lower population per facility for the districts in the central, western, and eastern parts. The warehouses are more likely to be located in districts with a low population per facility, showing a spatial mismatch.

Pharmaceutical distribution networks in Zimbabwe

Storage, distribution and forecasting of future needs of drugs, are managed by NatPharm and the MoHCC (UNDP, 2015). Furthermore, the Medicine Control Association of Zimbabwe (MCAZ) ensures that the drugs comply with the quality standards and pharmacovigilance, while the MoHCC is responsible for the quantifying and supply planning of drugs (MoHCC, 2020a). MoHCC,

through its national malaria control programme, also oversees government policies to eliminate malaria transmission in the country (MoHCC, 2020a; Mundagowa & Chimberengwa, 2020).

With regard to distribution, the facilities usually report, order, and receive medication quarterly or monthly, depending on the distribution system. There are several drug distribution systems for primary health services in Zimbabwe. These include Delivery Team Topping Up (DTTP), Zimbabwe Informed Push/Primary Health Care Package (ZIP/PHCP), Zimbabwe Assisted Pull System (ZAPS), Zimbabwe ARV Distribution System (ZADS), and Essential Medicines Pull System (EMPS) (Rosen et al., 2015). Malaria and tuberculosis products are managed through ZAPS and ZIP/PHCP distribution systems. In these systems, facilities are expected to place orders when left with one month's supply of drugs, and authorities then collect data from the facilities and supply new orders to the facilities quarterly (Rosen et al., 2015).

Concerning funding for drugs, NatPharm is financed by MoHCC and non-governmental organisations (NGOs). Antimalarial drugs are mostly funded by NGOs through Global Fund to Fight for AIDS, Tuberculosis and Malaria, Roll Back Malaria Partnership, and the US President's Malaria Initiative. NGOs supply a considerable portion of the preventative healthcare services in Zimbabwe, with a smaller contribution from the government (Sande et al., 2017). There is, therefore, an overreliance on donors to provide healthcare services in Zimbabwe (Parliament of Zimbabwe, 2019; World Bank Group et al., 2017). Given that antimalarial drugs are funded by NGOs, these drugs are provided for free in public facilities and drug stock-outs are mainly due to poor coordination between the health facilities and NatPharm management, as well as a mismatch between the supply and demand of drugs at the facility level. This is not the case with drugs that are not funded by NGOs, where the stock-outs are a result of both financial and distribution constraints, due to the government's financial constraints to provide essential services.

The private sector also provides antimalarial drugs. Individuals tend to access services from the private sector as a coping mechanism and last resort during drug stock-outs in the public sector.

Malaria in Zimbabwe

According to the MoHCC (2020a), malaria transmission is seasonal in Zimbabwe, with the highest transmission occurring during rainy and hot seasons (October to May), placing more than two-thirds of the population at risk. Malaria-endemic areas have an annual parasite incidence of at least 5 per

1 000 people. However, areas with low malaria transmission have an annual malaria parasite incidence of less than 5 (MoHCC, 2020a). In 2017, malaria mortality rate was approximately 4 per 100 000, against a target of 2 per 100 000 (MoHCC, 2020a). In that regard, the authorities have implemented policies to reduce mortality rate and malaria prevalence, as well as to eliminate malaria transmission in the country. However, despite the efforts by health authorities to reduce malaria transmission in Zimbabwe, transmission is not stable and continues to increase due to human migration, health-related beliefs and weak coverage of malaria preventive resources (MoHCC, 2020a; Mundagowa & Chimberengwa, 2020).

According to MoHCC (2020a) and Dube et al. (2019), the plasmodium falciparum parasite is responsible for the majority of malaria infections in Zimbabwe. To detect malaria infections, rapid diagnostic tests or blood smears are used and, if the test is positive, antimalarial drugs are therefore administered to the individual (MoHCC, 2015; 2020a). Artemether drugs are used to treat uncomplicated malaria in Zimbabwe and the recommended dosages vary based on body weight and age groups (MoHCC, 2015). The full course of first-line antimalarial treatment is taken for three days; if the symptoms continue, drugs for severe malaria are administered. In addition to that, indoor residual spraying and insecticide-treated nets (ITNs) are used to prevent malaria infections

Existing literature on the relationship between healthcare services and poverty

Unequal health provision compromises access to quality healthcare services by those in need (Wigley et al., 2020). Therefore, underserved areas tend to have higher rates of mortality and morbidity, which are exacerbated by economic deprivation due to a high unemployment rate, as well as poor water and sanitation services (Zamfir et al., 2015). Consequently, people with a great need for healthcare services tend to benefit less from these services, creating considerable health inequalities (Ataguba & McIntyre, 2013; Castro-Leal et al., 2000).

Drug stock-out challenges amplify cross-regional inequalities. While the effects and causes of drug stock-outs are well articulated, less is known about the relationship between drug stock-outs and district poverty. Most studies examined spatial inequality in availability of healthcare services (Amstislavski et al., 2012; Tandi et al., 2015; Ward et al., 2014; Wigley et al., 2020; Zamfir et al., 2015), and there is a dearth of literature on the spatial relationship between drug stock-outs and district poverty, particularly in developing countries. Specifically, no studies are focusing on the spatial inequality in drug stock-outs

and the spatial relationship between drug stock-outs and poverty in Zimbabwe. There is also less literature on the health mechanisms available to individuals during drug stock-outs.

Amstislavski et al. (2012) investigated the community-based inequalities in the availability of drugs in different pharmacies using thematic maps. Collecting data from different pharmacies, the study found that drug unavailability was prevalent in the US, with pharmacies in poor communities being more prone to limited drug availability and operating hours compared to affluent communities (Amstislavski et al., 2012). Although the findings noted the relationship between poverty and drug availability, they only focused on urban areas and not on rural areas that are likely to be poor and underdeveloped. The study also focused on privately operated pharmacies, and the findings may not be generalised to developing countries where public facilities are dominant. Similarly, Pednekar and Peterson (2018) mapped the pharmacy density in the US and found evidence of spatial inequality in pharmacy density. Pednekar and Peterson (2018) also indicated that spatial autocorrelation in low pharmaceutical density exists in the US using Getis-ORD Gi* statistics, where low pharmaceutical density is clustered in rural areas with racial majority groups. Spatial autocorrelation analysis of pharmaceutical services enables the identification of clustered regions with a high prevalence of drug unavailability and enables appropriate policies to improve drug availability in these clustered regions. Amstislavski et al. (2012) and Pednekar and Peterson (2018) found spatial inequality in health services in the US, but the US is a high-income country and there has been far less research examining these inequalities in low- and middle-income countries.

Using thematic maps, Zamfir et al. (2015) investigated spatial inequalities in health workers and health infrastructure in Romania, and found evidence of spatial inequality where healthcare resources are concentrated in urban areas rather than rural areas. Healthcare resources are concentrated in highly developed areas. Wigley et al. (2020) found spatial disparities in maternal service availability and accessibility in Sub-Saharan Africa (SSA). Although there was an improvement over time in availability and accessibility of healthcare services, within-country disparities remain prevalent. Tandi et al. (2015) used descriptive analysis to identify disparities in the regional distribution of health workers in Cameroon.

Considering spatial differences in the access to drugs in low- and middle-income countries, Ward et al. (2014) also used descriptive analysis to consider the location of South African pharmacies, finding that they were more likely to be in affluent than in poor provinces. Kuwawenaruwa et al. (2020) and Wagenaar

et al. (2014) note that drug stock-outs are more prevalent in poor and rural areas, due to rudimentary infrastructure and individuals residing in these areas frequently face unavailability of services, compared to those residing in affluent areas.

According to Bhattacharya et al. (2020) and Wagenaar et al. (2014), drug stock-outs mainly occur at the health facility level – the so-called 'last mile' and constitute a public health challenge in developing countries.[2] The literature reports that the main reasons for facility-level drug stock-outs are a lack of coordination between the facilities and the warehouse, as well as poor logistical planning and management (Munedzimwe, 2017; Sintayehu et al., 2022). Additionally, Koomen et al. (2019) and Seunanden and Day (2014), found that districts with higher poverty often had no warehouse, and this was correlated with a higher likelihood of stock-outs.

Data sources

The chapter uses drug stock-outs and PICES data obtained from the MoHCC and the ZIMSTAT, respectively.

The MoHCC collects information on the availability of antimalarial drugs quarterly for each health facility. Specifically, the 2012 and 2017 drug stock-out data used for this analysis includes information on the province, district, facilities, stock in hand, the date when the data were collected, the name of the drug, and the number of days the drugs were stocked out at the facility. The Department of Pharmaceutical Services in the MoHCC is responsible for the compilation of stock-out information for all facilities. The information on drug availability is crucial in identifying underserved regions and making informed decisions to ensure that drugs are distributed to populations with great need. Antimalarial drugs were reported for different age groups (0.5 <= age < 3 years, 3 years <= age < 8 years, 8 years <= age <14 years, and at least 14 years). Each facility has information on drug stock-outs, which is then aggregated at the district level for analysis.

PICES data were collected using a two-stage sampling method, enumeration areas were selected first and then households were allocated into their respective enumeration areas (ZIMSTAT, 2019). The survey was stratified by land use, which are communal lands, commercial farming, resettlements, and large-scale and small-scale areas. Sample weights are used to create district poverty rates.

2 The last mile is the last stage in the process of distribution of drugs from the warehouses to primary healthcare facilities. This is where the drugs reach the final user at the point of care.

The 2011/12 PICES data was based on the 2002 Zimbabwe population census master sample, using probability to proportion size to ensure representation at the provincial and district level (ZIMSTAT, 2018). Two thousand, two hundred and twenty (2 220) enumeration areas were selected, with 36 enumeration areas per district and double for Harare and Bulawayo municipality since they are the largest administrative districts and urban provinces. The data was collected over 12 months, and 29 765 households were successfully interviewed from 31 248 households initially sampled, yielding a 95.3% response rate.

The 2017 PICES data were based on a sample of 32 256 households selected from the 2012 national census data. A total of 2 304 enumeration areas were selected in that regard using the probability proportional to size, which determines the size of enumeration areas. A total of 31 195 households were interviewed successfully, with a response rate of 96.7%.

PICES is used by ZIMSTAT to calculate the official consumer price index. The PICES dataset collects information on demographic variables, agriculture production, living conditions, poverty prevalence and the informal sector in Zimbabwe. Data on socioeconomic-demographic variables, incomes, consumption expenditures and receipts were collected weekly and monthly to ensure information adequacy (ZIMSTAT, 2013). The expenditure and income information was recorded in a daily record book and later transcribed into the household questionnaire. Adjustments were made for inflation using Harare June 2011 prices for the 2011/12 PICES and Harare June 2017 prices for the 2017 PICES (ZIMSTAT, 2013; 2019).

Drug stock-out data are merged at the district-level with PICES household data for 2011/12 and 2017 to examine the relationship between drug stock-outs and district poverty in Zimbabwe.

The Zimbabwe subnational administrative boundaries were extracted as shapefiles from Human Data Exchange (2018) website. The subnational administrative boundaries are disaggregated at different levels; ward, district, provincial and national levels, but district-level was the lowest level of geographic analysis feasible with the data available. The shapefiles enable the generation of thematic maps which illustrate the spatial distribution of drug stock-outs and district poverty in Zimbabwe for both 2012 and 2017 – similar to those used in Pednekar and Peterson (2018) and Zamfir et al. (2015).

Table 1 shows the provinces and their respective districts in Zimbabwe. There are 10 provinces and a total of 91 districts in the country, including urban and rural districts.

Table 1: Provinces and districts in Zimbabwe

Province	District
Bulawayo	Bulawayo
Harare	Harare (urban and rural), Chitungwiza, Epworth
Manicaland	Buhera, Chimanimani, Chipinge (urban and rural), Makoni, Mutare (urban and rural), Mutasa, Nyanga, Rusape
Mashonaland Central	Bindura (urban and rural), Guruve, Mazowe, Mbire, Mount Darwin, Muzarabani, Mvurwi, Rushinga, Shamva
Mashonaland East	Chikomba, Goromonzi, Hwedza, Marondera (urban and rural), Mudzi, Murehwa, Mutoko, Ruwa, Seke, Uzumba Maramba Pfungwe
Mashonaland West	Chegutu (urban and rural), Chinhoyi, Hurungwe, Kadoma, Karoi, Kariba (urban and rural), Makonde, Mhondoro-Ngezi, Norton, Sanyati, Zvimba
Matabeleland North	Binga, Bubi, Hwange (urban and rural), Lupane, Nkayi, Tsholotsho, Umguza, Victoria Falls
Matabeleland South	Beitbridge (urban and rural), Bulilima, Gwanda (urban and rural), Insiza, Mangwe, Matobo, Plumtree, Umzingwane
Masvingo	Bikita, Chiredzi (urban and rural), Chivi, Gutu, Masvingo (urban and rural), Mwenezi, Zaka
Midlands	Chirumhanzu, Gokwe North, Gokwe South, Gokwe Centre, Gweru (urban and rural), Kwekwe (urban and rural), Mberengwa, Redcliff, Shurugwi (urban and rural), Zvishavane (urban and rural)

Source: (ZIMSTAT, 2018)

Definition of variables

The drug stock-outs are measured as the proportion of days in a year, during which a district's facilities experience stock-outs for the artemether drug. The analysis focuses on the artemether drug because it is widely used for first-line antimalarial treatment (MoHCC, 2015). The facility-level, quarterly drug stock-outs measure is calculated for each of the four artemether drugs (dosage-specific for all age groups) as the share of days per quarter, which the antimalarial drug is not in stock at a specific facility.[3] Facility-level aggregation across the four drug dosages occurs via selecting the drug dosage with the highest share of stock-out days to represent the facility-level stock-outs for the quarter. Yearly averages are calculated by summing quarters and adjusting denominators for quarters where data was missing. District-level aggregates are then generated by averaging across these annual facility-level stock-out estimates. Due to lack of data on feeding areas of facilities, all facilities (including clinics and hospitals) are weighted equally in this district averaging.

3 The four products are for different age groups: 1*6 dosage (0.5 <= age < 3 years), 2*6 dosage (3 years <= age < 8 years), 3*6 dosage (8 years <= age <14 years), and 4*6 dosage (at least 14 years) (MoHCC, 2015).

Poverty shows the share of households with consumption expenditure per capita less than the total consumption poverty line while extreme poverty represents the share of households with consumption expenditure below the food poverty line (ZIMSTAT, 2019). The total consumption poverty line and food poverty line were USD76.7 and USD32.7 per person per month, respectively in 2012, while in 2017 total consumption poverty line and food poverty line were USD70.36 and USD31.2 per person per month, respectively (ZIMSTAT, 2013; 2019).[4] Districts are classified as poor when most of the household's per capita total consumption expenditure is below the total consumption poverty line. Poor districts are expected to have more stock-outs than affluent districts.

Methods

Following Zamfir et al. (2015) and Pednekar and Peterson (2018), we used the descriptive mapping technique to assess the spatial inequality of drug stock-outs in Zimbabwe. In that regard, the relationship between poverty prevalence and drug stock-outs was examined using thematic maps. Thematic maps are useful in providing a visual picture of spatial inequality, hence determining underserved districts in the country.

The spatial autocorrelation analysis is carried out using the Getis-ORD Gi* statistic. Spatial autocorrelation assesses the spatial concentration of stock-outs by evaluating an area against its neighbours (Kondo, 2016). Positive spatial autocorrelation shows the clustering of districts with similar values, with the clustering of high and low values defined respectively as hot and cold spots (Pednekar & Peterson, 2018).

A positive z-score and low probability depict hot spots, whilst a negative z-score and low probability value shows cold spots (Kondo, 2016; Pednekar and Peterson, 2018). The probability value of 1% and 5% are used as benchmarks for the statistical significance of the results. Districts with neither a low nor high significant z-score are deemed statistically insignificant and are neutral compared to their neighbours. The concentration of dissimilar values is referred to as negative spatial autocorrelation (Pednekar & Peterson, 2018).

4 Poverty datum line measures the cost an individual or household must fulfil not to be deemed poor. The poverty lines include the food poverty and total consumption poverty line, also known as the 'upper line', comprises both food consumption and non-food consumption expenditure. ZIMSTAT uses total consumption poverty line to determine poverty prevalence, whilst the food poverty line is used to measure extreme poverty in Zimbabwe (ZIMSTAT, 2019). The national mean consumption per person per month is USD78.94 in 2012 and USD85.2 in 2017.

Estimated results

Table 2 presents descriptive statistics, showing that more than three-fifths of Zimbabwean households are classified as poor. Poverty prevalence is higher in 2012 than in 2017, but the change is not significant.

Table 2: Descriptive statistics

	2012		2017			
Variables	mean	std dev	mean	std dev	differences	t-statistics
Poverty prevalence	0.649	0.190	0.620	0.227	-0.029	(-0.931)
Stock-outs	0.077	0.063	0.156	0.124	0.079***	(4.424)
Per dosage						
0.5 <= age < 3 years	0.030	0.031	0.131	0.131	0.100***	(5.835)
3 <= age < 8 years	0.038	0.035	0.088	0.085	0.050***	(4.232)
8 <= age < 14 years	0.063	0.064	0.092	0.069	0.029***	(2.371)
age >= 14 years	0.039	0.040	0.077	0.066	0.037***	(3.737)
Observations [a]	91		91		91	

Note: [a] is the number of districts considered in the analysis using ZIMSTAT (2018)

The average proportion of days of district-level stock-outs for artemether in 2017 is double that of 2012 and the difference is significant.

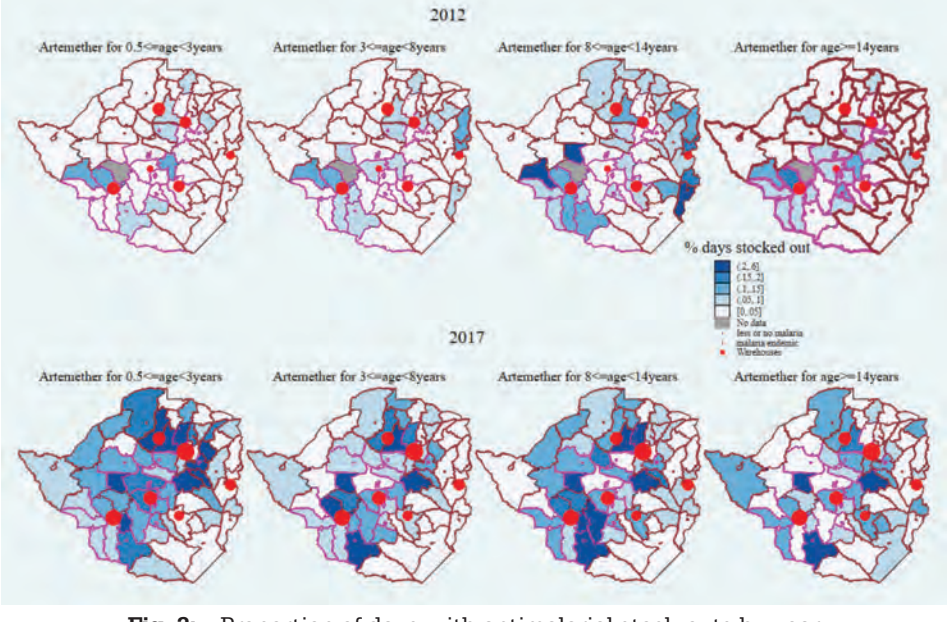

Fig. 2: Proportion of days with antimalarial stock-outs by year

Figure 2 shows the proportion of days per year that antimalarial drugs were stocked out in each district in 2012 and 2017. The antimalarial drug stock-outs are denoted by different shades; the darker the shade within a district, the more prevalent the drug stock-outs are in that district. The districts are grouped according to malaria endemicity; malaria-endemic districts are indicated by maroon boundaries, while less-endemic or malaria-free districts are indicated by pink boundaries.

The detailed maps echo what the aggregate analysis in Table 2 showed: districts had fewer days of antimalarial stock-outs in 2012 than in 2017. Districts in the southeast and eastern parts of the country experienced low drug stock-outs in both 2012 and 2017.

The disaggregated maps show that stock-outs were lower in 2012 for all artemether dosages, except for the age group 8–14 years, which had a relatively large proportion of days stocked out. Nkayi, Tsholotsho, Chipinge (urban) and Chipinge (rural) had more days stocked out for artemether for the age group 8–14 years in 2012. In 2017, artemether for children aged 0.5–3 years was more stocked out compared to other dosages. Districts with high artemether stock-outs for the age group 0.5–3 years were Nkayi, Umzingwane, Zvimba, Mazowe, Bindura (urban), Bindura (rural), Murehwa, Marondera (urban), Marondera (rural), Hwedza and Chikomba.

Both malaria-endemic and less malaria-endemic districts experienced high antimalarial drug stock-outs for all age groups in 2017. The distance to the warehouse does not influence drug stock-outs in Zimbabwe.

Figure 3 illustrates the distribution of district poverty in Zimbabwe for 2012 and 2017. Poverty prevalence in Zimbabwe is high, with the majority of the districts having poverty greater than 60%. Districts in the northeast, northern and northwest have relatively high poverty compared to districts in the central, western, southern, southeast and southwest districts.

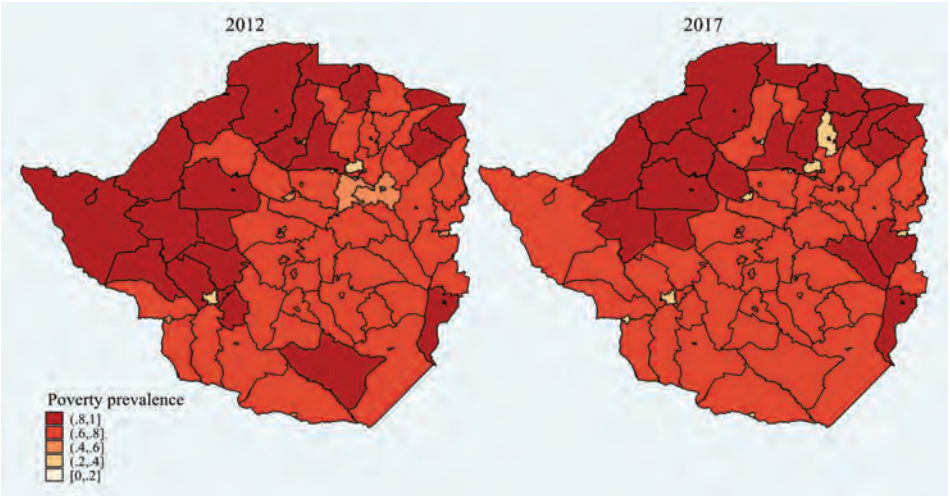

Fig. 3: Poverty prevalence in 2012 and 2017

There are 16 districts with poverty levels higher than 80% in both 2012 and 2017: Hurungwe, Karoi, Binga, Kariba, Muzarabani, Gokwe South, Gokwe Centre, Nkayi, Lupane, Chipinge (urban), Chipinge (rural), Mutoko, Mudzi, Muzarabani, Zvimba and Rushinga. Seven districts have low poverty prevalence in both 2012 and 2017: Harare, Chinhoyi, Norton, Kadoma, Mutare (urban), Plumtree and Bulawayo.

Bivariate maps are used to show the relationship between drug stock-outs and district poverty. The relationship between poverty prevalence and drug stock-outs is denoted by different shades; the dark purple shade portrays districts where high stock-outs are paired with high poverty prevalence, while the light grey shade indicates districts where low stock-outs coincided with low poverty prevalence. The lavender shade indicates moderate stock-outs and poverty prevalence, but it should be noted in the case of Zimbabwe, even these moderate levels are quite high. The remaining shades show either low stock-outs and high poverty or high poverty and low stock-outs.

Figure 4 shows 2012 and 2017 bivariate maps for antimalarial stock-outs and poverty prevalence using a common scales in both years, which is used to track the change in the relationship between these two variables.

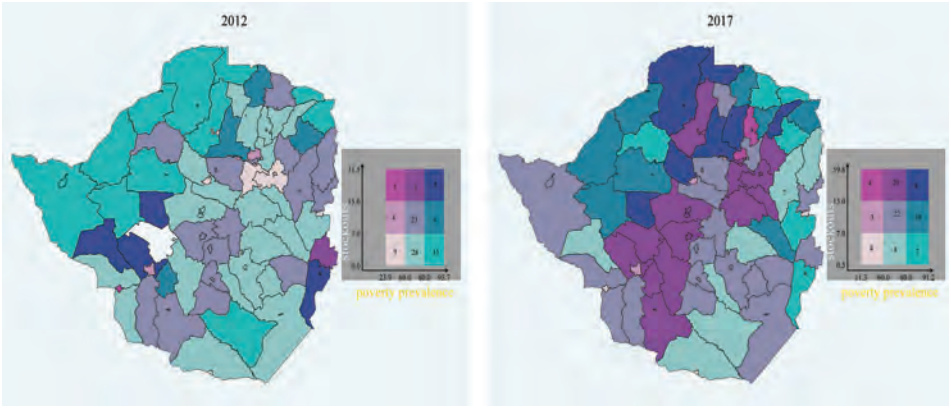

Fig. 4: 2012 and 2017 Antimalarial stock-out and poverty prevalence

A strong positive relationship is indicated by the diagonal colours from the bottom left to the top right of the legend, whilst the colours corresponding to the bottom right and top left of the legend show a strong negative relationship between poverty and stock-out. Other colours show a weak negative relationship between drug stock-outs and poverty prevalence. For example, the colour green in the (1,3) matrix indicates high poverty prevalence and low drug stock-outs, while the colour pink in the (3,1) matrix indicates low poverty prevalence and high drug stock-outs. Thus, overall the maps show a weak and insignificant relationship between poverty prevalence and drug stock-outs in Zimbabwe.

The relationship between district-level drug stock-outs and poverty prevalence changes substantially between 2012 and 2017. Considering all districts that had high levels of poverty and antimalarial stock-outs (dark purple) in either 2012 or 2017, only Nkayi district was classified as such in both years. More districts experienced high antimalarial stock-outs and relatively low poverty prevalence in 2017 whilst more districts in 2012 experienced high poverty prevalence and relatively low antimalarial stock-outs.

Some patterns stayed the same. Several districts experienced moderate but relatively high drug stock-outs and poverty prevalence in 2012 and 2017: Mberengwa, Matobo, Zvishavane (urban), Zvishavane (rural), Shurugwi (urban), Shurugwi (rural), Chirumhanzu, Chegutu (urban), Chegutu (rural), Bikita and Mutasa. Beitbridge (urban) and Mutare (urban) experienced low poverty prevalence and antimalarial stock-outs in both 2012 and 2017. Overall, considering that the number of districts showing a weak negative relationship outweighed the ones with a strong relationship, we concluded that there is a weak relationship between poverty prevalence and antimalarial drug stock-outs in 2012 and 2017.

Table 3: Poverty prevalence and drug stock-outs hot spot analysis

	z<=-2.58	-2.58<z<=-1.96	-1.96<z<1.96	1.96<=z<2.58	z>=2.58
2012					
Poverty prevalence	1	6	84	0	0
Stock-outs	0	0	82	1	7
2017					
Poverty prevalence	0	1	90	0	0
Stock-outs	0	0	82	6	3

Note: z represents Getis-ord Gi z-score*

Table 3 shows the hot spots and cold spots for drug stock-outs and poverty prevalence over time. Using the Getis-ord Gi* statistics, we estimated the significance of the hot and cold spots in drug stock-outs and poverty prevalence in districts compared to their neighbouring districts. A positive z-score represents a hot spot, while a negative z-score represents a cold spot. Z-score values between -1.96 and 1.96 are not significant in clustering the districts as hot spots or cold spots.

Seven poverty prevalence cold spots were identified in 2012 and one cold spot in 2017 at 5% significance level. The poverty prevalence cold spot districts in 2012 were Goromonzi, Ruwa, Epworth, Harare (urban and rural), Chitungwiza and Marondera (urban), whilst Redcliff was the cold spot in 2017. Using a 10% probability value, Redcliff and Marondera (rural) were cold spots in 2012 whilst Chegutu (rural), Harare (urban and rural), Chitungwiza, Kwekwe (rural and urban) were cold spots in 2017.

In 2012, eight hot spots in antimalaria stock-outs were identified in Zimbabwe. Bulilimangwe, Chimanimani, Chipinge (urban and rural), Umguza, Nkayi, Plumtree and Tsholotsho were antimalaria stock-outs hot spots at a 5% level of significance. However, Bulawayo had a positive z-score value statistically significant at 10%. Moreover, nine hot spots and zero cold spots were identified for antimalaria stock-outs in 2017. Norton, Ruwa, Chikomba, Insiza, Chinhoyi, Marondera (urban and rural), Murehwa and Zvimba districts were hot spots in antimalaria stock-outs.

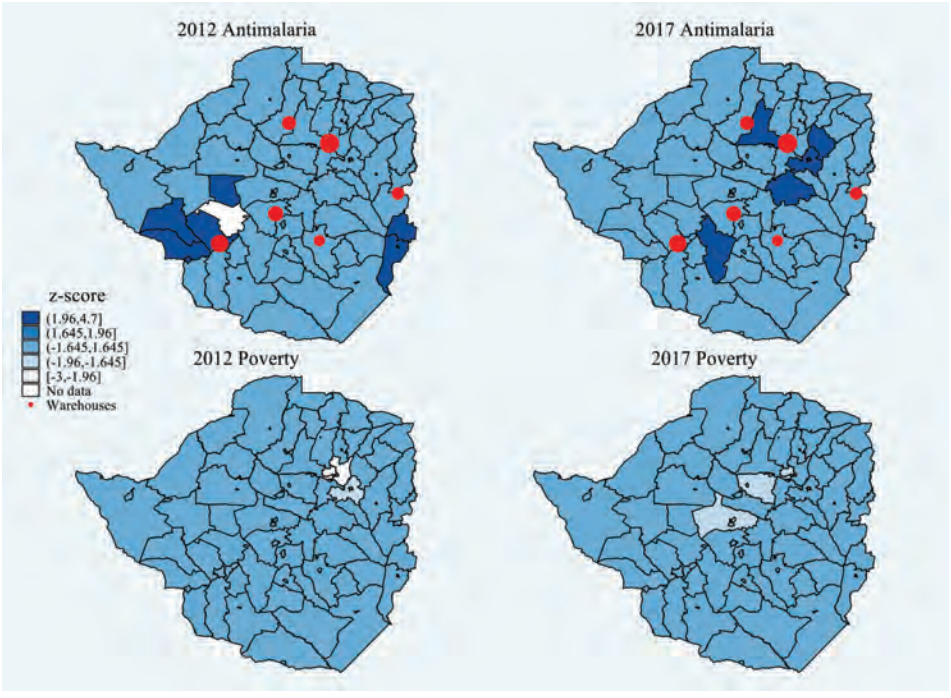

Fig. 5: Poverty prevalence and drug stock-out hot spot analysis by year

Figure 5 shows the spatial autocorrelation of drug stock-outs in terms of hot spots and cold spots of stock-outs (compared to neighbours). Hot spots show clustered districts with a high prevalence of drug stock-outs while cold spots show clustered districts with a low prevalence of drug stock-outs. The figure shows drug stock-out hot spots for both 2012 and 2017 with no cold spots in either year. There are more antimalarial stock-out hot spots in 2017 than in 2012. Furthermore, districts with high clustering values for drug stock-outs are not the same for 2012 and 2017. Bulilima, Chipinge (urban), Chipinge (rural), Chimanimani, Plumtree, Nkayi, Tsholotsho and Umguza districts are antimalarial stock-out hotpots in 2012 while Zvimba, Murehwa, Marondera (urban), Marondera (rural), Insiza, Chinhoyi, Ruwa, Chikomba and Norton districts are hot spots in 2017. This provides evidence of geographical clustering for districts with a high drug stock-outs prevalence.

Discussion of results

The analysis showed that high antimalarial drug stock-outs are a substantial problem in Zimbabwe, despite the effectiveness and importance of these drugs. Drugs are important to improve health outcomes, hence the need for a steady supply of drugs at the facility level. Unfortunately, drug stock-outs are common,

and affect the reliability of access and adherence to recommended dosages. Aside from drug stock-outs, people are likely to face additional constraints in accessing healthcare services, such as high service and transport costs, unavailability of health workers and facilities, poor-quality services and long waiting times at the facilities (Gilson & McIntyre, 2007; Mangundu et al., 2020; Ndejjo et al., 2021; Ng et al., 2021).

On average, 7.7% of the days had drug stock-outs in 2012, increasing to 15.6% in 2017. Artemether stock-outs were high for children aged 8–14 years in 2012 whilst artemether stock-outs for children aged 0.5–3 years were high in 2017. The results are consistent with previous low- and middle-income countries' studies on the topic, including Sintayehu et al. (2022) reporting anti-tuberculosis drug stock-outs in Ethiopia, and Hwang et al. (2019) showing a high prevalence of antiretroviral and anti-tuberculosis drug stock-outs in South Africa.

Stock-outs may arise due to a variety of problems including poor supply-chain management, incompetent health staff, inaccurate forecasting, and poor storage at the facility level (MoHCC, 2011b; The Global Fund, 2020). In Zimbabwe, stock-outs are also linked to the economic challenges characterised by acute foreign currency – and power and fuel shortages (US President's Malaria Initiative, 2020; ZIMSTAT & World Bank, 2020), which has contributed to shortages of skilled health workers, reduced health budgets, and caused a lack of essential drugs (MoHCC, 2020a; World Bank Group et al., 2017). The poorer economic performance and worse service provision in 2017 compared to 2012 contributed to weaker supply-chain management, as well as the distribution of resources (MoHCC, 2020a; World Bank Group et al., 2017). Economic challenges resulted in frequent fuel shortages, which in turn compromised logistics and distribution of drugs from warehouses to respective health facilities hence worsening drug stock-outs at the point of care (ZEPARU, 2014).

Frequent drug stock-outs result in a mismatch of health needs and health resources for the individuals who need the resources to improve their health outcomes. Districts in the eastern and southeast regions experiences low drug stock-outs in both 2012 and 2017. The relatively low levels of stock-outs can plausibly be attributed to the very high malaria levels in these districts, which makes these districts a showcase for new strategies to reduce malaria transmission and improve the availability of malaria products (Rosen et al., 2015). For example, ZAPS was first piloted in the eastern region between 2014 and 2015 before being implemented nationwide (Rosen et al., 2015). Moreover, high malaria control coverage in some of these districts may assist in curbing the demand for antimalarial drugs (Mharakurwa et al., 2013). Again, this might be due to better distribution of preventive and treatment products (including ITNs and indoor

residual spraying) in malaria-endemic areas, which is expected to reduce infections and the demand for anti-malaria treatment (MoHCC, 2020a; Sande et al., 2017).

Overall, the maps show a weak relationship between poverty prevalence and drug stock-outs. The weak relationship between poverty and stock-outs could be attributable to compromised access to healthcare services in poor and marginalised areas, resulting in unused drugs at these facilities, thereby reducing drug stock-outs. The poor are less likely to seek treatment when ill, compared to the affluent (ZEPARU, 2014). In rural areas, households often reside far from health facilities (Osika et al., 2010, ZEPARU, 2014) and the weak transport system in Zimbabwe further hampers access to healthcare services in these poor areas (Dube et al., 2019; MoHCC, 2020a). Additionally, the poor are more likely than the affluent to seek treatment from traditional and faith healers in Zimbabwe, which may further decrease the demand for public healthcare in poor areas (ZIMSTAT, 2019). Therefore, clustering in drug stock-outs exists, but district-level poverty is not an explicit cause of stock-outs in the regions where stock-outs are clustered. Given that poverty is prevalent and high in most districts, poverty may be correlated with a high baseline of stock-outs countrywide in a more systemic way. The analysis shows considerable district-level heterogeneity in this relationship, which is consistent with the findings of Amstislavski et al. (2012), Pednekar and Peterson (2018) and Wigley et al. (2020).

The analysis shows that facilities are more concentrated in the northeast, eastern, and central parts of the country, with a low population per facility, except in the northeast. In addition, facilities are mainly concentrated in the urban and better-resourced areas, leaving the rural and under-resourced areas at a disadvantage, increasing long walking distances to the nearest facility (ZSARA, 2015). This shows that few resources or little backup, together with the time and the cost associated with travelling to the nearest facility when there are stock-outs, hamper these areas' access to the drug (Buzuzi et al., 2016). There is a spatial mismatch between the population per facility and the location of warehouses, with warehouses located in areas with a low population per facility. The results of the present chapter are consistent with those of Tandi et al. (2015) for Cameroon, Ward et al. (2014) for South Africa, Zamfir et al. (2015) for Romania and Wigley et al. (2020) for SSA, who found inequality in healthcare facilities and workers. This is attributed to differences in development between regions that worsen the inequality in health service delivery, with urban regions having more and better health resources compared to rural regions. Moreover, disparities in disease prevalence across geographical regions also contribute to spatial mismatch in health services provision.

Positive spatial interdependence exists for drug stock-outs in Zimbabwe. The changes in drug stock-outs in the focal district are more likely to affect drug stock-outs in the neighbouring districts in Zimbabwe. Districts with a high prevalence of drug stock-outs are clustered with neighbouring districts with high drug stock-outs prevalence, referred to as hot spots. This shows that drug stock-outs occur at a higher level than the district level. Drug stock-outs are widespread as a result of regional-level bottlenecks given that facilities in the same districts are serviced by the same warehouse with the same supply-chain management. In the same vein, the service networks and supply-chain management are integrated across districts in Zimbabwe. Given that districts are interrelated, correlated disruptions arise in facilities in districts that are affected by similar supply-chain management challenges. These regional disruptions in the supply chain of drugs affect a network of districts that depend on the same services. This shows that there is a broader drug stock-outs challenge at the district level, which requires an understanding of the regional network of drug provision in Zimbabwe.

Ultimately the impact of drug stock-outs on health outcomes depends on the coping mechanisms patients and health workers use to reduce the negative effects of drug stock-outs. So, no discussion or assessment of drug stock-outs can be comprehensive without considering the role of coping mechanisms in determining how drug stock-outs will impact health outcomes.

Faced with a drug stock-out at their local facility, individuals may seek treatment from other nearby facilities. Others may try to borrow money or drugs from their neighbours, friends, or relatives but then have to repay the debt, which could drive them into a debt trap Ndejjo et al. 2021; Ng et al. 2021. There is a risk that due to this desperation individuals might use incorrect drugs in times of need (Gilson & McIntyre, 2007).

When their local public facility has a drug stock-out, people may often be forced to buy drugs from the private sector, which would be expensive. Although the artemether drug is provided free in the public sector, the private sector might take advantage of stock-outs in the public sector by charging a relatively high fee for the drug. Given that the majority of people rely on OOP health payments, purchasing drugs from the private sector may be financially catastrophic. Buzuzi et al. (2016) report that Zimbabweans often sacrificed essentials such as clothing, food and school fees to pay for healthcare services. Selling assets is another coping mechanism if the alternative option for accessing drugs results in catastrophic health costs, requiring the sale of assets and ultimately, depletion of assets (Gilson & McIntyre, 2007; Ng et al., 2021; Buzuzi et al., 2016).

Previous studies in Kenya and Uganda suggest that individuals tend to use their social networks to purchase cheap drugs from the informal sector when faced with drug stock-outs Ng et al.'s 2021; Ndejjo et al.'s 2021. However, buying drugs from the growing informal sector in Zimbabwe is not recommended because these drugs are not regulated by the medicine control authorities and may be of poor quality, thus posing a risk to health outcomes (Gwatidzo et al., 2017). Specifically, it may result in artemisinin resistance or antimicrobial resistance, and in some instances, death. Poor-quality antimalarial drugs in the informal market pose global health challenges by increasing hospitalisation and the cost of treatment in developing countries (Jackson et al., 2020; Ozawa et al., 2019).

People also use traditional and herbal medicines in times of drug stock-outs. Gilson and McIntyre (2007) note that, in South Africa, many people seek healthcare services from traditional or faith healers. The use of traditional medicines increased during the COVID-19 pandemic in Zimbabwe and globally (Chali et al., 2021; Mangombe et al., 2021; MoHCC, 2020b) due to the absence of drugs to treat COVID-19 infections. Again, these treatments come with risks because traditional medicines are not regulated.

Lastly, one should also consider that drug stock-outs can cause people to lose trust in the health system and forgo health services even though they need them to relieve their illnesses (Kuwawenaruwa et al., 2020). Faced with a drug stock-out poor individuals either choose an alternative treatment or no treatment at all (Kamvura et al., 2022). The likelihood of forgoing treatment is increased by the high drug prices that individuals face in times of drug stock-outs. A qualitative study by Kamvura et al. (2022) found that individuals opt out of the formal health sector due to the frequent unavailability of non-communicable disease medicines in Zimbabwe. This is also supported by ZIMSTAT and World Bank (2020), showing that the proportion of people who access healthcare services decreased over time in Zimbabwe.

Conclusion

The availability of healthcare resources is an important element in the provision of healthcare services, and vital to creating a sustainable and effective health system. Despite the government's efforts to improve antimalarial drug availability at the point of care, antimalarial drug stock-outs remain a public health challenge in Zimbabwe. Spatial inequality exists in the country. There is also evidence of spatial interdependence in drug stock-outs where stock-outs in the focal districts influence stock-outs in neighbouring districts. In addition, although districts have different relationships between drug stock-

outs and district poverty, overall, the nexus between drug stock-outs and district poverty is weak given that poverty is prevalent in Zimbabwe and correlates with a high baseline of stock-outs. Therefore, there is a need for further research on other factors affecting drug stock-outs to reduce spatial inequalities and interdependences existing in Zimbabwe.

In the event of drug stock-outs, individuals use traditional medicines, forgo treatment, sell assets, borrow money and drugs, and purchase drugs from the private or informal sector to maintain or smooth their drug supply. However, some of these coping mechanisms have negative effects including the risk of death. This underlines the severe risk and health impact of drug stock-outs and the urgent need to ensure the reliable availability of drugs at health facilities. Improving the availability of antimalarial drugs at public health facilities, particularly in underserved districts, may contribute significantly to the MoHCC achieving its mandate to ensure equitable access to health services and improve health outcomes.

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SECTION II

FRICTIONS AND TRANSITIONS

4

POOR-QUALITY MEDICAL PRODUCTS IN TIMES OF CRISIS

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Introduction to poor-quality medical products

The quality of medical products is a key element for ensuring access to health. Sustainable Development Goal (SDG) 3.8 aims at universal health coverage, including access to "*quality and affordable essential medicines and vaccines for all*" (UN Sustainable Development Knowledge Platform, n.d.). Improving public health by developing new medical products and by optimising treatments and their associated policies is key. However, it is of major importance that the medicines patients actually take contain sufficient and correct ingredients, are not contaminated, and fully comply with specifications set for them. The use of unsafe, substandard, ineffective and falsified medical products risk harm to the health and wellbeing of people.

The issue of poor-quality medical products is a neglected public health problem. A review by the World Health Organization (WHO), estimates that in low- and middle-income countries approximately 10.5% of medicines are substandard

or falsified (WHO, 2017c). High prevalence of substandard and falsified medicines results in avoidable morbidity, mortality, economic harm and, for antimicrobials, drug resistance. Further improvements in the methodology and reporting of medicine quality studies is needed to have a better idea on the scale of the problem. In 2017, the WHO issued a report based on the data gathered by the WHO Global Surveillance and Monitoring System (WHO, 2017c). The report describes how the pharmaceutical supply chain is global and its complexity is increasing. Medicines' journeys are marked by a high turnover of products moving across different borders. For one medicine, the active pharmaceutical ingredient may come from one country, and the excipients may come from other countries. Those ingredients may come together in a third country, where a tablet is manufactured. Subsequently the tablets might cross borders in large containers, to be packed in blisters and boxes in yet another country. They pass through multiple grey zones in which human error, bad practice and criminal activity can lead to poor-quality medicines entering the supply chain and ultimately reaching people.

During the COVID-19 pandemic, there has been a surge in poor-quality medical products and in this chapter we discuss the evidence, the drivers and their impact, especially for vulnerable communities. The multiple examples of incidents that occurred during the COVID-19 pandemic show how diverse the issue is: across multiple countries, with a whole range of different medical products, with different types of defects. Understanding the problem helps to optimally engage with healthcare workers, policymakers and other stakeholders so they can intervene with effective responses. Preparedness for the next public health crisis is a continuous effort and should be rooted in the foundations for routine interventions that curb the threat of poor-quality medical products entering the market. We discuss how the threats of poor-quality medical products can be mitigated both within and outside of pandemic times.

Definition of the terms

In order to ensure universal access to quality medical products, better understanding of the factors that enhance or hinder access is needed. It is key that there is a common understanding of what poor-quality medicines are (Ravinetto et al., 2016; WHO, 2017c). Appropriate terminology has been the subject of much discussion, as it is highly dependent on the stakeholders' perspectives.

In 2017, the World Health Assembly agreed on terminology for substandard, falsified, and unregistered or unlicensed medical products (WHO, 2017b).

'*Substandard*' also called 'out of specification', are authorised medical products that "fail to meet either their quality standards or their specifications, or both." This may result from negligence or errors during the manufacturing process by authorised manufacturers, or degradation through deterioration because of inappropriate storage or transport in the supply chain. Information is usually insufficient to distinguish errors within factories from those in the supply chain; a key evidence gap, as the solutions for the two differ.

'*Falsified*' refers to medical products that "deliberately or fraudulently misrepresent their identity, composition or source." Based on the definition, falsified medicines or vaccines may contain the correct ingredient(s) in various amounts, wrong active ingredient(s), or no active gradient at all. People still often refer to these products as 'fake', 'counterfeit', 'spurious' and 'falsely labelled'. There is a difference between the use of the terms 'falsified' and 'counterfeit' medical products. 'Falsified' is a broad term including all the various types of deliberate misrepresentation of a medical product, from a public health perspective, including but not limited to issues related to intellectual property rights. The term 'counterfeit' is specifically linked to intellectual property rights, 'trademark counterfeit goods'[1] and 'pirated copyright goods'[2] as used in the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement (World Trade Organization, n.d.).

Furthermore, WHO defines '*unregistered or unlicensed*' medical products as products that have not undergone evaluation or approval by the national or regional regulatory authority for the market in which they are marketed, distributed or used, subject to permitted conditions under national or regional regulation and legislation.

The WHO introduced those definitions to simplify and clarify the terminology from a public health perspective, and it allows classification and more thorough analysis of the reports they receive from their member states on poor-quality

1 *Trademark counterfeit goods*: any goods, including packaging, bearing without authorization a trademark which is identical to the trademark validly registered in respect of such goods, or which cannot be distinguished in its essential aspects from such a trademark, and which thereby infringes the rights of the owner of the trademark in question under the law of the country of importation. Source: World Trade Organization.

2 *Pirated copyright goods*: any goods that are copies made without the consent of the right holder or person duly authorized by the right holder in the country of production, and which are made directly or indirectly from an article where the making of that copy would have constituted an infringement of a copyright or a related right under the law of the country of importation. Source: World Trade Organization.

medicines. The definitions have been generally accepted by diverse stakeholders that encounter poor-quality medical products. However, depending on the information available for a medical product, it can be difficult to classify it according to the WHO scheme (Hauk et al., 2021), especially with difficulties in detecting evidence of fraudulent intent. The term 'Substandard or Falsified' (SorF) was suggested by Saraswati et al. (2019) for samples for which it is not possible to reliably classify a medicine as substandard or falsified without packaging analysis. It is used for products falling outside the acceptance range of the specifications chosen as reference by the authors (either specific pharmacopoeia monograph or in-house specifications) of at least one quality test without information on packaging authenticity.

The WHO definitions do not necessarily cover all the issues that one might encounter when discussing the potential threat of poor-quality medicines in the supply chain. In this chapter the term 'diverted' medical products is used, for legitimate products that have been diverted outside the controlled supply chain. Theft is only one example of diversion, please see '**Poor-quality medical products during the COVID-19 pandemic**' for examples. Although diverted medical products can be of good quality at the time of 'diversion', due to loss of custody they risk becoming substandard medical products through degradation due to inappropriate storage and transport. They also impair access for the intended populations. In this chapter, a public health angle is taken by using the terms 'substandard', 'falsified', and 'unregistered' as defined by the WHO, complemented with 'substandard or falsified' and 'diverted' medical products. The concept of 'poor-quality' medical products is used as an umbrella term to group all these issues. However, where possible we try to make a clear distinction between the different terms as it helps to shape an effective response. Corrective interventions vary greatly according to the type of quality issue ('t Hoen & Pascual, 2015). For example, falsified medical products require an approach that tackles the criminal aspect of production and distribution. In contrast, preventing substandard medical products can, for example, be linked to pharmaceutical manufacturing issues that can be mediated through strengthening quality control, quality assurance, and processes within the manufacturing plant. Knowledge of the cause leads to informed decision-making on corrective actions.

In this chapter the term 'medical products', abbreviated as 'products' is used as an umbrella term to cover all types of products that are used for the treatment or the prevention of diseases. It covers, for example, products that can be labelled as medicines, vaccines, medical devices, parts and accessories used along with medical devices, personal protective equipment (PPE) or sanitisers.

Poor-quality medical products in times of crisis – looking at the past

There are several warnings from history that poor-quality medical products thrive during times of crisis. In 1640, Peruvian Cinchona bark was imported into Europe and sold as the first effective treatment for malaria. A manuscript from the 18th century describes how the product became scarce due to its high demand (Saunders, 1782, as cited in Newton et al., 2006). It opened the door for falsified versions in the market as the Peruvian Cinchona bark was adulterated with aloes and other barks. People in need of a malaria treatment became hesitant, no longer trusted the product and paused using Peruvian Cinchona bark as a treatment.

A professor in the history of medicine described how the COVID-19 pandemic has impacted our society in a similar, albeit less severe, way as the bubonic plague did when it devastated England in 1665 (Fissell, 2020). She argues that there are several parallels in human behaviour during The Great Plague and the COVID-19 pandemic. One parallel is that criminals were very quick to occupy existing gaps. In 1665 there was minimal objective knowledge of the aetiology, diagnosis and treatment of this disease, with the causative bacterium *Yersinia pestis* only identified in 1894. It seems highly unlikely that the official Royal College of Physicians' advice to use "London treacle, Mithridatium, Galene and diascordium" would have manifested any efficacy (Griffin, 2004). However, there were regulations on composition, so there would be opportunity to detect what the WHO now defines as substandard and falsified medical products. However, responding to people's desperation and the resulting potential profits that could be made, the epidemic was accompanied by quackery on a diverse and large scale, with, to us, outlandish claims, such as the efficacy of hanging dried toads around people's necks as a prophylactic (Gilman, 2009; Porter, 2001).

In the immediate aftermath of World War II, there were great shortages of penicillin leading to a widespread black market. The shortages also led to penicillin falsification on a large scale, such as that in Berlin, which inspired the film *The Third Man* (Newton & Timmermann, 2016). The movie narrates the fictional investigation into the death of the smuggler Harry Lime, who was stealing and diluting penicillin to sell on the black market in Vienna, resulting in the death of and harm to many children.

Although there is a long history of trade in poor-quality medicines, it was only in 1988 that the World Health Assembly adopted a resolution, requesting governments and pharmaceutical manufacturers tackle the issue of poor-quality "pharmaceutical preparations" (WHO, 1988). Indeed, only pharmaceutical preparations were included in the resolution in 1988. In 2011, researchers

published an article to underline that in addition to poor-quality medicines, solutions need to be found to tackle poor-quality medical devices (Mori et al., 2011). They described how field observations reveal poor-quality medical devices in the market but compared to poor-quality medicines the issue is not well documented or acted upon. A decade later, researchers came to the same conclusion (Do et al., 2021). When conducting a review on the quality of medical products for cardiovascular diseases, they did not find prevalence surveys on cardiovascular device quality despite the multiple quality issues recognised, such as pacemaker and stent malfunction. Since 2012, the World Health Assembly uses the wider concept of "medical products" instead of just talking about "medicines" when addressing the problem of poor-quality (WHO, 2012). Broadening the scope to more products creates an opportunity to tackle similar problems in a more comprehensive way.

Poor-quality medical products during the COVID-19 pandemic

At the beginning of the COVID-19 pandemic, Newton and Bond (2020), together with 53 signatories from 20 different countries warned that "*without preparation for quality assurance of diagnostic tests, medicines and vaccines, the world risks a parallel pandemic of substandard and falsified products*." Indeed, there were subsequently multiple examples of poor-quality medical products flooding the market. Surveillance of poor-quality medical products is extremely limited in most of the world and incidents are often not published in peer-reviewed scientific journals or in accessible databases. The Medicine Quality Research Group published reports of the publicly available information on COVID-19 medical products, mostly extracted from the Medicine Quality Monitoring Globe[3] (Infectious Diseases Data Observatory (IDDO), 2020). This system scrapes online newspapers for early warnings of poor-quality medical products. Based on this tracker over 1 000 different incidents of diverted, unregistered, substandard or falsified COVID-19 medical products had been reported by March 2022 (Medicine Quality Research Group, 2022). The following sections take a closer look at the issues encountered for different products, including COVID-19 vaccines, diagnostics, PPE, sanitisers and disinfectants, medicines, and ventilation and oxygenation equipment and consumables.

3 The Medicine quality Monitoring Globe is accessible at IDDO website. The section "methodology" summarises the methods that were used to search the lay press articles.

COVID-19 diagnostics

As soon as the COVID-19 pandemic began and all throughout the pandemic, diagnostics with quality issues were reported. Reports included rapid diagnostic test (RDT) kits, laboratory test kits, thermometers and test tubes, with incidents of substandard, falsified and unregistered sale in unlicensed markets and online.

Substandard low accuracy COVID-19 RDTs with false negative and positive results led to many recalls from manufacturers. For instance, in 2021, Ellume, an Australian company, recalled ~427 000 COVID-19 at-home tests for producing false positive results, out of which nearly 200 000 were unused (The Associated Press, 2021b). Approximately 42 000 of the affected tests were used and produced positive results, both accurate and false. One month after the first recall, Ellume identified additional affected lots, bringing the total affected tests to more than two million (Rodriguez, 2021). The full impact of such incidents will never be known but it is highly likely that significant numbers of people will have isolated needlessly. There were multiple examples of unregistered diagnostics, which led to warning letters from the United States Food and Drug Administration (US FDA). For example, there were public warnings to stop using unauthorised COVID-19 tests produced by Lepu Medical Technology (US FDA, 2021) and LuSys Laboratories (US FDA, 2022a). Not only were these tests not registered, they were possibly generating false results.

Falsified diagnostics, especially RDTs, were found in many countries around the world. For example, in 2020, the police arrested the head of a manufacturing unit in the Indian state of Uttar Pradesh for producing falsified COVID-19 antibody RDTs with forged labels (PTI, 2020). In 2021 in Mexico, 5 000 falsified COVID-19 test kits sourced from China were seized (Keil et al., 2021). In 2022 in Sri Lanka, a suspect was arrested for allegedly importing a stock of falsified COVID-19 test kits and distributing them to hospitals and laboratories (Marian, 2022). In 2021 in Singapore, a suspect was arrested for allegedly selling falsified thermometers online. The thermometers only read at 37 degrees Celsius, resulting in people with fever being falsely reassured and causing great confusion. When opened, they were completely hollow on the inside and contained only a chip for the LCD readout (Hana, 2021).

Personal protective equipment

The majority of the articles recovered from the Medicine Quality Monitoring Globe about personal protective equipment (PPE) were related to masks and respirators, specialised filtering masks that protect not only others but also the person wearing them, such as N95 masks. Since the beginning of the pandemic,

masks have been in great demand worldwide, resulting in shortages for the public and health workers. Millions of poor-quality masks have been seized around the world, with many of them allegedly from manufacturers in China (Medicine Quality Research Group, 2020). A notable problem was the global sale of millions of falsified N95 respirators falsely stated as originating from the company 3M, one of the largest mask manufacturers globally (3M, 2022). Substandard masks that did not meet filtration standards for PPE were also reported on a large scale. In 2020, for instance, the University of Oklahoma Health Sciences Center in the United States discovered that approximately one-third of the approximately 70 brands that they tested did not meet the 95% filtration standard (Torbati & Willis, 2020). Some products fell short of layer specifications, with the appropriate materials not used. Unregistered PPE were falsely claimed to be approved by regulators. For example, a Canadian company selling masks without a licence claimed to be approved by Health Canada as a manufacturer of surgical masks and was allegedly selling non-medical masks as medical masks (Ghania, 2020).

Other protective equipment, such as gloves, were also afflicted with illegal production and sale. For example, the Thai authorities conducted a raid on the illegal production of falsified nitrile rubber gloves (Ngamkham, 2021). Criminals washed and repacked used gloves for onward sale, for example, the sale of used vinyl gloves in Vietnam where these gloves made their way to the health workers (*Corporate Wellness Magazine*, 2020). The National Health Service in the United Kingdom issued a quality alert to general practitioners in the southwest of England, as unopened boxes of 'Sanique' protective gloves allegedly contained used gloves (Potter, 2020).

Sanitisers and disinfectants

Alcohol-based hand sanitiser became an important preventive measure in the COVID-19 pandemic. This led to shortages and the wide presence of substandard, falsified, and unregistered hand sanitisers. The problems that were mostly found included wrong, low or absence of the active ingredient, false labelling and fraudulent extension of expiry dates. From April 2020 onwards, there were reports of methanol in hand sanitisers sold in many countries (Jairoun et al., 2021). Methanol is extremely toxic at high doses, mainly affecting the central nervous system, eyes and kidneys, and it can cause death. It can be absorbed through the skin. It is not an acceptable ingredient for hand sanitisers. For example, Punjab's FDA warned the public not to use 10 brands of hand sanitisers adulterated with methanol content ranging from 7.05% to over 95% (Hussain, 2020). A recall of hand sanitiser sold online

in the United Kingdom was launched due to the presence of methanol without proper labelling (Ingram, 2020), and Mexican federal agents warned the public not to buy hand sanitisers from street vendors due to methanol contamination (Riviera Maya News, 2020). From May through June 2020, multiple cases of methanol poisoning were reported in Arizona and New Mexico in the United States (Yip et al., 2020). Four people died and three were discharged with visual impairment after drinking methanol containing hand sanitisers.

The US FDA also issued public recalls and warning letters to various manufacturers, both inside and outside the US, including Mexico, China, and South Korea (US FDA, 2022b). The most common issues discovered were the presence of methanol, 1-propanol, benzene, acetaldehyde, and acetal, microbial contamination, the lack or absence of the required amount of ethyl alcohol, isopropyl alcohol, or benzalkonium chloride. Furthermore, the US FDA warned the public to be cautious and to check the US FDA's 'do-not-use list' before purchasing.

Ventilation and oxygenation equipment and consumables

Even though there were fewer reports than in other categories, poor-quality ventilators and oxygenation equipment and consumables pose a high risk of death for COVID-19 patients. In early 2020, falsified ventilators began being reported in India, when government hospitals in Gujarat state used the 'Dhaman-1' ventilator that was allegedly falsified and possibly contributed to the deaths of 300 patients (Jha, 2020). In 2021, Indian authorities discovered the sale of fire extinguishers disguised as oxygen cylinders (Ojha, 2021). During the raid, police seized iron gas cylinders (that were fire extinguishers), oxygen gas cylinder nozzles, electric grinders (used to remove paint from the cylinders) and spray-paint cans.

Furthermore, in early 2020, articles also mentioned substandard ventilators. For example, doctors in the United Kingdom expressed concerns about the quality of one brand of ventilators and asked for the machines to be withdrawn. According to a letter to the United Kingdom National Health Service (NHS), the devices had a variable and unreliable oxygen supply, could not be cleaned properly, and had an unfamiliar design (Smith, 2020). Another example was the suspension of Aventa-M ventilators in Russia after the ventilators were linked to two hospital fires (Ellyatt, 2020).

The shortage of oxygen supplies in some countries led to an increase in oxygen-related thefts. For example, two diversion incidents occurred in Mexico in 2020; one involved the theft of oxygen tanks from a government hospital (The

Associated Press, 2021a), and the other involved the arrest of those who stole a truck containing 44 oxygen tanks (AP News, 2021).

Medicines

For medicines used and trialled in the prevention and treatment of COVID-19, the data are with only a small minority demonstrating efficacy. Initially there were over a hundred different molecules trialed for COVID-19. Remdesivir has been trialed against multiple viral pathogens and in May 2020, it was authorised as Veklury® for COVID-19 through an exceptional approval pathway in Japan and in the United States. At the end of June 2020, the European Medicines Agency (EMA) also recommended it for conditional marketing authorisation. From July 2020, several media reported genuine remdesivir sold at high prices on the black market in India. The quality of the product could not be assured since the vials were not stored (as per instructions) between 2–8 °C (Sharma, 2020). From April 2021, several reports of falsified remdesivir occurred in India. The WHO issued alerts about falsified remdesivir found in several countries, including falsified remdesivir injection claimed to be manufactured by GILEAD that was discovered in Mexico and online (WHO, 2021b), as well as falsified DESREM remdesivir discovered in Guatemala and India (WHO, 2022a). Although dexamethasone was demonstrated to be effective in the treatment of severe COVID-19, in June 2020 (RECOVERY, 2021), we found few increases in substandard and falsified incidents reported in the lay press. There were some reports of falsification. For example, in Nigeria, there was a seizure of falsified dexamethasone that had been shipped from India in June 2020 (BBC, 2020b).

Reports from the lay press show that a medical treatment or prevention for COVID-19 does not necessarily have to be demonstrated to be effective or approved, in order to see an increased demand. The increased demand leaves room for poor-quality medical products to flow into the market as seen for hydroxychloroquine and ivermectin, for which we now have no convincing trial evidence for their efficacy against COVID-19.

In November 2020, the Mexican medicine regulatory authority, abbreviated as COFEPRIS, alerted about falsified ivermectin on the Mexican market (COFEPRIS, 2020). In South Africa in January 2021, the regulator South African Health Products Regulatory Authority (SAHPRA) (South African Health Products Regulatory Authority, 2021), shared a communication that they were receiving reports of falsified and substandard ivermectin being sold. It appears that many practitioners were prescribing the product although it is not registered for human use and without trial evidence of its efficacy for COVID-19. Patients turned to the black market, buying product either for

veterinary use or sourced from illegal importation (Craig, 2021). In late January 2021, approximately 18 000 ivermectin tablets were seized at O.R. Tambo International Airport in Johannesburg (Searra, 2021). Similar reports came from Zimbabwe of ivermectin on the black market (Bureau, 2021).

Early in the pandemic, chloroquine and hydroxychloroquine were promoted as COVID-19 cures, despite lacking any convincing evidence for their efficacy (Cochrane, 2021; Saag, 2020). This resulted in a media storm in March 2020 and much demand for these medicines used conventionally to treat malaria and autoimmune diseases. In March 2020, the International Criminal Police Organisation Interpol reported a more than 100% increase in chloroquine seizures, compared to the 2018 global operation targeting the sale of falsified pharmaceuticals, known as Operation Pangea (Interpol, 2020a). In April and June 2020, the WHO also issued warnings about falsified chloroquine discovered in Burkina Faso, Cameroon, the Democratic Republic of the Congo, France, and Niger (WHO, 2020a).

Furthermore, some articles reported on fatal life-threatening situations caused by the use of unapproved medications. In the United States, for example, a man died, and his wife became critically ill after both ingested chloroquine phosphate in an apparent attempt to cure COVID-19 (BBC, 2020a). The couple had previously used chloroquine to treat their koi fish, which was formulated differently to the medicine used to treat malaria.

Vaccines

Several international organisations, such as the United Nations Office on Drugs and Crime (UNODC, 2020), Interpol (2020b), Europol (2020), and WHO (Adhanom Ghebreyesus, 2021), warned of the liklihood of a wave of falsified vaccines once vaccines for COVID-19 were announced. Facing a virus that we knew little about and few proven efficacious interventions, people developed various self-care strategies. One was searching for vaccines before approval by the regulatory authorities. Criminals exploited this situation for profit seven months before COVID vaccines became available. In May 2020, as the COVID-19 vaccine by the Galilee Research Institute Migal was under development, boxes bearing the Migals Hebrew language logo on falsified COVID-19 vaccines were found in Ecuador (Jaffe-Hoffman, 2020). In September 2020, several media reported that falsified COVID-19 vaccines were being sold in Odisha state in India (Barik, 2020). On 8 December 2020, the United Kingdom was the first country to start administration of COVID-19 vaccines to its population with the trialled and tested Astra-Zeneca COVID-19 vaccine. In parallel with the roll-out of this

vaccine, there was a clear increase in alerts on poor-quality COVID-19 vaccines on the Medicine Quality Monitoring Globe (MQM) (see Figure 1).

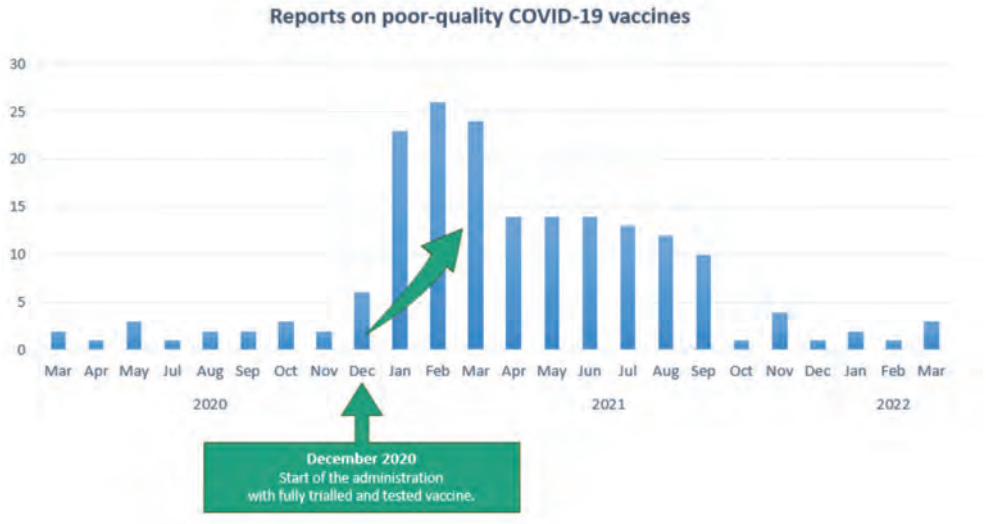

Fig. 1: Reports on poor-quality COVID-19 vaccines on the Medicine Quality Monitoring Globe. Data are recorded from March 2020 up to March 2022. The figure is adapted from the 'Medical Product Quality Report – COVID-19 issues', by Medicine Quality Research Group, 2022, Issue 15, (Medicine Quality Research Group, 2022). On 8 December 2020, the United Kingdom was the first country to start administration of COVID-19 vaccines to its population with the trialled and tested Astra-Zeneca COVID-19 vaccine. From the start of the COVID-19 pandemic to December 2020, there had 'only' been 22 alerts. For January 2021 alone, there were the same number of alerts in one month followed by a rise in the subsequent months.

Once COVID-19 vaccines were authorised by regulatory authorities, many people struggled to obtain an appointment to receive their first dose. The supply through government-organised vaccination campaigns could not keep up with demand. Vaccines were diverted from the legal supply chains to be sold on the black market, where people were willing to pay for their shot. Several senior officials in Ukraine allegedly paid USD 4700 to receive the Pfizer/BioNTech vaccine that might have been imported by organised crime groups linked to Israeli citizens (Williams, 2021). Articles also reported on vaccines stolen from legal supply chains. This happened, for example, in Uganda where Oxford-AstraZeneca vaccines were stolen from the Ministry of Health to sell to the public (*The Independent*, 2021). In some cases, it was healthcare workers themselves who stole the vaccines. In Ghana, four health officials were charged for their role in allegedly stealing and selling 62 vials of the Covishield vaccine (BBC News Pidgin, 2021). In a health centre in India, three healthcare workers

were suspected of the theft of 40 doses of Covishield during transport from the cold chain storage to the vaccine centre (Express News Service, 2021). Some healthcare workers did not necessarily want to resell the vaccines but, in the context of vaccine scarcity, they sought doses for themselves or their family members (Schencker & Mahr, 2021). Vaccines that were diverted, trickling out of legal supply chains, were no longer temperature controlled and their quality could no longer be assured and therefore they become a risk to public health.

A plethora of substandard issues were observed. In a vaccination site in Thailand, 110 vials of Sinovac COVID-19 vaccine were found to contain lumps of transparent gel, likely formed due to too low storage temperatures (Thai PBS World, 2021). In the United States, nearly 400 million doses of the COVID-19 vaccine had to be destroyed due to failure of the manufacturer to meet or maintain quality standards (Select Subcommittee on the Coronavirus Crisis, 2022). The manufacturing site of Emergent BioSolutions in Baltimore was a subcontractor producing both the Johnson & Johnson and Oxford-AstraZeneca COVID-19 vaccines. In February 2021, a mix-up between the vectors of both vaccines, led to the need to destroy millions of vaccine doses. After the manufacturer was permitted to resume manufacturing in July 2021, new quality problems rose, and again millions of substandard vaccines had to be destroyed. In August 2021, 1.63 million doses of the Moderna vaccine were suspended in Japan (Fierce Pharma, 2021). A manufacturing issue in one of the production lines of the Spanish pharma company Rovi possibly led to contamination of the vaccines with metallic particles.

In February 2021, the European Anti-Fraud Office (OLAF, 2021) warned against falsified COVID-19 vaccines and said criminals are also approaching national authorities with falsified products. At the end of February an article reported that criminals had allegedly offered altogether 400 million doses of diverted or falsified COVID-19 vaccines to national authorities in the European Union (EU) (Baczynska et al., 2021). The WHO issued multiple alerts on circulating falsified COVID-19 vaccines. The first concerned falsified Pfizer-BioNTech vaccines detected in Mexico in February 2021 (WHO, 2021a). In August 2021, there was an alert on multiple Covishield vaccines, and the manufacturer, the Serum Institute of India, confirmed that it concerned falsified versions (WHO, 2021c). In samples from Uganda, the expiry date was incorrect. In India, the vial was stated as containing a different number of vaccine-doses compared of their product. In Myanmar, apart from having a false batch number, the product name was wrongly spelled as 'Covisheld'. Empty COVID-19 vials were being sold on the Internet, for up to USD100 per vial (*The Times of Israel Staff*, 2021). Some were sold on the pretext of 'Own a piece of history' (Tucker & Thompson, 2021). Such empty vials, however, might attract criminals wanting to produce falsified versions of the COVID-19 vaccine. In November 2021,

there were WHO-alerts for falsified Pfizer-BioNTech and AstraZeneca COVID-19 vaccines in Iran (WHO, 2021d; 2021e). Detection of the falsified AstraZeneca vaccine was not straightforward, as genuine vials were refilled and only the metal cap showed evidence of tampering. Apart from empty vials, there are many vaccines offered on websites and social media (Fernando, 2021; Interpol, 2021). Online, through emails and on messaging apps, people have been lured into buying purported COVID-19 vaccines. The cybersecurity company Check Point Software found offers for up to USD 1000 for one dose (Check Point Research, 2021). When reading reports, it is not always possible to make the distinction between cases of financial scams, falsified COVID-19 vaccines, or diverted COVID-19 vaccines.

By March 2022 a total of 184 reports of poor-quality COVID-19 vaccines linked to 48 different countries were registered on the Medicine Quality Monitoring Globe. Vaccine quality issues were reported on all continents, with the exception of Antarctica (see Figure 2).

Fig. 2: Countries with public reports on poor-quality COVID-19 vaccines on the Medicine Quality Monitoring Globe. *Data is recorded from March 2020 up to March 2022. The figure is adapted from 'Medical Product Quality Report – COVID-19 issues', by Medicine Quality Research Group, 2022, Issue 15, p. 13 (Medicine Quality Research Group, 2022).*

The drivers and impact of poor-quality medical products during the COVID-19 pandemic

Drivers of poor-quality medical products

At the start of the COVID-19 pandemic, there were several factors indicating that poor-quality medical products would occur. Dramatical impairment of the production and supply chain of medical products was predicted. Much of the world had and has minimal local production capacity, leading to vulnerable high dependence on a few countries and functional trade routes. The high demand and shortages of genuine products contributed to an increased global risk of poor-quality medical products. At the beginning of the pandemic, people were desperate to protect themselves against a disease they, and the rest of the world, did not understand. There was a high demand for PPE, especially masks, but due to the global rush for masks, there were not sufficient quantities in the market. The number of alerts on the Medicine Quality Monitoring Globe on poor-quality PPE increased significantly early in the pandemic. Another example was for COVID-19 diagnostic tests. Once that COVID-19 rapid diagnostic tests were widely available, there were very few alerts on poor-quality diagnostic tests. However, it took months before these tests became routinely available and in sufficient quantities available for at-home testing. Some tests were made available too quickly without thorough testing by the regulatory authority in question.

As countries experienced waves of COVID-19 surges, the demand for certain products rose. For example, in April and May of 2021 the number of COVID-19 cases in India increased very greatly. The number of alerts on the Medicine Quality Monitoring Globe about remdesivir, used to treat patients with COVID-19, also rose. The pandemic put massive additional pressure on health systems globally and data are currently lacking on how non-COVID-19 related medical products have been affected both for the supply of genuine products and their poor-quality versions. Their access might have been impaired, for example, because of the pressure on manufacturing facilities or due to lack of raw ingredients. In Namibia for example, key informants from the pharmaceutical sector reported how most medicine outlets were experiencing longer lead times because inter-country transportation became more difficult within the pandemic (Tirivangani et al., 2021).

The WHO (2017c) defined the likely drivers for poor-quality medical products as being limited access to medical products, poor governance, and weak technical capacity. In addition to the immediate drivers, there are specific political and economic factors that might shape the markets for poor-quality medicines. Some researchers propose a 'market risk framework' including political and economic

factors to assess the likelihood that poor-quality medical products will reach patients (Pisani et al., 2019). Indeed, all these factors are interrelated and they create market opportunities for unscrupulous manufacturers, distributors and sellers. Amankwah-Amoah (2022) described how drivers, such as lack of access, institutional barriers, reduced regulation, and law enforcement combined with newer phenomena, especially the desperation of people to 'return to normalcy', the growth of online sales and vaccine nationalism, exacerbated the scourge of poor-quality medical products during the pandemic. The lack of awareness of people on the existence of poor-quality medical products is an additional driver. Some authors described how people were panicking and turned to unauthorised and potentially dangerous sources to buy the products they wanted (Shiferie & Kassa, 2020; Valcheva, 2020). For example, the quality of medical products sold on the Internet, or the even riskier dark web, cannot be guaranteed and unscrupulous dealers can sell whatever they may have available, irrespective of quality and regulations.

Impaired access and inequitable distribution of COVID-19 vaccines is a key issue with much to be learned for future pandemics and epidemics. The demand for COVID-19 vaccines exceeded the supply. From early on, high-income countries invested and secured access to future COVID-19 vaccine supplies for their populations. In those countries some people were receiving their third dose of vaccine whilst in some low- and middle-income countries people had not even received their first dose. Inequity in global vaccine distribution contributed to people looking for alternative sources of vaccines and treatments (Srivastava, 2021). In March 2021, the WHO Director-General warned that inequitable access was highly likely to fuel and increase incidents with poor-quality COVID-19 vaccines (Adhanom Ghebreyesus, 2021) but little action, apart from the COVAX initiative, was taken of the warning.

We will conduct further analysis of the changes through geography and time of the poor-quality medical product incidents during the COVID-19 pandemic. Such spatiotemporal data analysis will help inform us on when and where enhanced surveillance is needed in the future. Subsequent analysis can provide insights in the different drivers that lead to these patterns during public health emergencies.

Impact of poor-quality medical products

Without robust objective evidence of their epidemiology, understanding the impact of poor-quality medical products is fraught with difficulties. In the absence of a strong evidence base, pre-pandemic, WHO (2017a) modelled the health impacts of two situations. The first model focused on childhood pneumonia in children aged 0 to 5 years. It estimated that substandard and falsified antibiotics

lead to an excess mortality of over 72 000 children per year. Another model estimated that of all people seeking first-line treatment for malaria in sub-Saharan Africa, approximately 3.8% to 8.9% of deaths could be avoided if good instead of poor-quality medicines are dispensed to patients. Due to the limitations of the available data, the estimates are likely to misrepresent the true health impact. Similar studies to measure the impact of poor-quality medical products used during the COVID-19 pandemic have not yet been published. Research is needed to elucidate this and also the consequences of the pandemic on the production, supply, access and use of non-COVID medical products. For example, diversion of manufacturing HIV rapid diagnostic tests for COVID-19 RDTs, led to supply issues for HIV diagnostic kits. Similarly, some veterinary vaccine manufacturing facilities were used for production of human COVID-19 vaccines, and Data Bridge Market Research (2021) suggested a consequent negative impact on the veterinary vaccines market. To address global shortage of critical COVID-19 items, manufacturers were encouraged to repurpose their production to manufacture life-saving COVID-19 products. The United Nations Industrial Development Organization (UNIDO) highlighted the risk of substandard medical products from those repurposed facilities and suggested a rapid repurposing roadmap to address these novel manufacturing challenges (López-Gómez et al., 2020). Investment by regulatory authorities and the pharmaceutical industry in measures to prevent, detect and respond to poor-quality medical products for COVID-19 will have inevitably led to actual and opportunity costs, both financial and in terms of human time, that could be best spent elsewhere if the world had a reduced risk of poor-quality medical products.

We suggest that some impacts were more pronounced during the COVID-19 pandemic. For example, the pandemic had a specifically negative impact on trust of people in the health system and more broadly in other public institutions in some communities. Wu et al. (2021) examined COVID-19 vaccine hesitancy among the Chinese population and how falsified vaccines contributed to distrust in COVID-19 vaccines. When people lose confidence in vaccines, the impact is much broader than only hesitancy for taking that specific vaccine (WHO, 2017a). On an individual level, the person will not be protected and people might look for alternative preventive measures that have not necessarily shown efficacy or that might come from unregulated sources. On a population level it might lead to a decline in vaccination coverage, risking loss of control of the disease, jeopardising the safety of the entire community and beyond, especially through engendering new variants. Economic losses due to countering the risk of poor-quality medical products is likely to have been significant with, for example, the direct costs that came with unusable poor-quality masks. The masks produced by the company 3M, appear to have

been particularly targeted, with seizure of more than 59 million falsified masks and removal of over 40 500 fraudulent e-commerce offerings of masks falsley stated to be their products (3M, 2022). The money spent on such substandard and falsified masks by people, businesses and governments must have been considerable. On top of that, companies such as 3M must have invested large amounts of funds and human capacity in dedicated teams to investigate the quality issues, follow up dozens of lawsuits, and support customs and clients to authenticate 3M masks, which would be better spent elsewhere. Some manufacturers of COVID-19 medical products must have spent a fortune on their global actions to fight COVID-19 fraud, inevitably increasing the cost of products and hence impairing access.

It was not only patients and their relatives who were affected by poor-quality products during the COVID-19 crisis. Healthcare workers in hospitals and elderly care homes, frontline workers such as the police, or even people working in other sectors, such as those wearing masks in coal mines, were facing issues with poor-quality 'medical' products. A surprisingly large number of governments faced issues with public procurement of COVID-19 medical products, especially with poor-quality diagnostics tests and PPE, due to poor preparedness. Most governments surely did not have the necessary data and protocols in place to know where to buy those medical products, what their trade routes are, and what the quality standards of these products need to be. Such systems are needed for preparing for the next pandemic.

A lot more work and research needs to be done to have a clear view on the health, economic and social impact of poor-quality medical products. The impact of the COVID-19 pandemic on both the risk of poor-quality medical products for countering COVID-19 and for all medical products needs investigation.

Lessons learnt – better preparedness for the next pandemic

Before the pandemic, there were clearly problems with the regulation of medical products globally. In 2020, there were only 14 countries in the WHO Western Pacific (4), Southeast Asian (4) and African (6) regions with WHO pre-qualified laboratories for analysing medicines quality (WHO, 2020b). In 2022, these issues remained and, of the 194 WHO member states, only 56 were listed as transitional 'WHO-listed authorities' (WHO, 2022b), the concept that is due to replace that of stringent regulatory authorities. On the list there were only three countries from the WHO Africa region's 47 countries that were operating at maturity level 3 as assessed against the WHO Global Benchmarking Tool, for which maturity level 4 is the most advanced (WHO, 2022c). This longstanding situation inevitably impaired regulatory responses to the pandemic and we hope

that these key issues are resolved to facilitate access to quality-assured medical products for the myriad conditions that humans face, and to prepare for the inevitable next pandemic.

During the COVID-19 pandemic, the world encountered challenges that transcended international borders, but with solutions needed to be implemented on local levels. In the beginning of the pandemic, the lack of an evidence base and prior planning inevitably made it difficult for governments and international organisations to prioritise between the different risks their communities faced. There were many competing priorities, for example to reduce COVID-19 spread, to support responses in the healthcare setting and in the communities, and in addressing the economic burden. One of the topics that needed to be addressed was the surge of poor-quality medical products. Although some organisations and groups warned of these issues, relatively little has been done to prevent them. Still today it is uncertain how to prioritise interventions to prevent, detect and respond to poor-quality medical products. Governments and their populations need to accept some uncertainty with respect to the unfolding context when priorities are set. We have been lucky that no very major focal events with poor-quality medical products have occurred. Things could have turned out very differently. For example, during the RECOVERY trail, dexamethasone was found to be an effective medicine in the treatment of severe COVID-19 (RECOVERY, 2021). If there had been production errors, in the rush to maximise production, with noxious contaminations or people deliberately made falsified products with toxic adulterants, the disruptive effect would have been enormous for products in great demand. Nevertheless, the multiple reports on poor-quality medical products during COVID should be a stimulus to regulatory authorities and policymakers for more discussion of joined-up mitigating policies. They should prompt corrective actions, to ensure that the efficacy, safety and quality of medical products is ensured. The threat of pandemics has increased as our world has become more interconnected and regional and global public health crises are expected.

The WHO suggests a three-pillar strategy to stop the scourge of poor-quality medical products, consisting of prevention, detection and response (WHO, 2017c). The activities to successfully implement these three distinct axes are overlapping and should mutually reinforce each other. The saying '*prevention is better than cure*', also counts for poor-quality medical products. To enable better prevention, how can the medical products be protected? Would primary packaging unique bar codes reduce the risk of ingress of falsified medical products into supply chains and what are practical and economic issues that need to be solved to implement those? How can manufacturers, distributors, regulators and users liaise more effectively? Resilient pharmaceutical systems and supply chains are

critical to build pandemic preparedness. Successful actions require coordination of different actors and close collaboration between different disciplines involved locally, nationally and internationally.

Building a comprehensive legal and regulatory framework

There is need for interconnected, well-funded, robust and efficient regulators. The need for strong medical product laws and regulation and their implementation did not start with COVID-19, but it has made it clear that countries need to work together better than they are currently. The absence of a robust legal framework is described by Odiase (2021) as one of the factors that risks poor-quality medical products' circulation in African countries. He suggests an approach in which both domestic and international laws need to be employed. There are some pitfalls inherent in leaving the regulation of poor-quality medical products exclusively to the domain of domestic laws, as they fall short in effectively addressing their transnational manufacturing, trafficking and trading. He calls for the harmonisation of legislative action by African states. Transnational regional law should facilitate detection, support surveillance, strengthen regulatory capacity and harmonise pharmaceutical governance. The new African Medicines Agency (AMA) will play a critical role to strengthen the regulatory environment of medical products to guarantee access to quality, safe and efficacious medical products on the African continent (Adhanom Ghebreyesus, 2022; Seydi & Mayaki, 2022). The treaty for the establishment of the AMA entered into force in October 2021 (African Union, 2021). It is hoped that it will ensure people's access to high-quality affordable medicines.

Information sharing

Information sharing on all levels needs to be greatly improved to ensure health crisis preparedness. 'Living' infrastructure databases are needed to allow rapid knowledge as to where raw ingredients, medical products, and equipment for pandemic responses are available. For example, with some COVID-19 vaccines needed to be stored at -80 °C for many health authorities, it was not clear where they had appropriate freezers available. Similarly, global databases of products' manufacturers would greatly help planning. In early 2020, when chloroquine was trialled for its use in COVID-19, and there was some hope, later refuted, that it could be an inexpensive but efficacious treatment, a database listing who was producing chloroquine would have been very helpful. We need to ensure that when governments and healthcare organisations urgently need to access quality-assured medical products, they know from where they can access those. There have been initiatives, for example, for PPE, which recognise the value of transparency in supply chains: collecting, aggregating and disseminating supply-

side information to cope with market volatility in times of crisis. However, during the COVID-19 pandemic, it became apparent that the existing initiatives are insufficiently developed. Building on prior initiatives, the creation of a PPE Market Supply Transparency System was proposed, which would provide real-time information to policymakers and manufacturers (Garcia-Santaolalla et al., 2021). It would help them to forecast PPE markets at regional, national, or global levels, and in doing so ensure stability and enhance international policy dialogue.

Comprehensive supply chain integrity

The United States Pharmacopeial Convention Inc (USP) report on how to respond to the surge of poor-quality medical products triggered by the COVID-19 pandemic (Borse et al., 2021), describes standards and toolkits to verify the quality and authenticity of medicines, vaccines and hand sanitisers at any point in the supply chain.

Ensuring the integrity of the supply chain systems is needed, facilitating product authentication, and track-and-trace mapping of the products in the supply chain from point of manufacture or importation, up to the point of distribution. A multi-layered approach should be taken to achieve comprehensive product quality and supply-chain security. Each type of product, with its specificities and the corresponding threat scenarios need to be considered. The multi-layered approach should combine analogue and digital features that can be verified by different stakeholders within the supply chain (Forcinio, 2021). There has been much discussion about packaging and labelling techniques to signal authenticity and supply-chain tracking. Tamper-proof packaging alerts the consumer and pharmacist to falsification and tampering. Serialisation with unique identifiers or bar codes on packaging prior to distribution are needed globally on primary packaging, but will be a great logistical challenge. Covert authentication methods, such as marks (which are invisible to the naked eye) or holograms, help with detection of falsification by those 'in the know'.

Some products, such as vaccines, need to be kept at a specific temperature, with thermal monitoring, in order to negate the risk of degradation. Integrating vaccine vial monitor (VVM) into the primary packaging of the vaccine, helps to detect storage or transport out of the required temperatures (WHO, 2015). The VVM is a visual indication that shows when problems arise and therefore decreases the risk of administration of a sub-potent vaccine; but only a subset of vaccines use these.

The challenges that came with the COVID-19 pandemic create opportunities to integrate different features and develop innovative solutions. Emerging digital solutions are used to ensure product quality and supply chain management

and security, such as the Internet of Things (IoT) and blockchain technology (Ramakanth et al., 2021). For example, a combination of blockchain and Radio Frequency Identification Technology (RFID) has been proposed to ensure traceability and transparency of face masks (Halim et al., 2021). For the COVID-19 vaccine, Ramakanth et al. (2021) describe possibilities for different layers of packaging systems. UNICEF is creating a Global Trust Repository, a blockchain-based solution that allows tracking or verification of medical products (UNICEF, 2021). Initially it was developed to minimise the risk for poor-quality COVID-19 vaccines in the national supply chain of low- and middle-income countries. Nigeria and Rwanda became the first countries in Africa to authenticate vaccines using this GS1 barcoding technology (UNICEF Supply Division, 2022). UNICEF's aim is that the COVID-19 vaccine work provides the foundation for complete, sustainable national traceability systems. The use of barcode technology may make a difference to patient safety in the post-COVID-19 era (Lachman & Van der Wilden-van Lier, 2021) but will require significant and connected global infrastructure. To obtain this multi-layered approach, synergistic efforts are needed from regulators, industry and non-governmental organisations, international organisations and academia. For example, legislation and its enforcement are likely to be the most significant motivators to bar coding of medical products.

At the very end of the supply chain there is waste from the used medical products, and better arrangements for waste disposal and management are needed that can be scaled in pandemics (Aborode et al., 2021). Indeed, criminals have taken empty vials, filled them with saline or another easily accessible inexpensive solution, and sold them. Similarly, used gloves have been collected and sold as new. Robust efficient waste management is needed for all medical products to prevent them re-entering the supply chain as genuine good quality medical products.

Conclusion

Throughout their lifetimes, most medical products pass through many hands and cross many borders, making pharmaceutical supply chains very complex and vulnerable. During the COVID-19 pandemic, traditional supply-chain practices have been disrupted in different ways. Interventions to curb the threat of poor-quality medical products, should be structurally and routinely implemented in everyday practice and enabled so that they can be scaled up during crises. Ideally, pre-prepared protocols, and existing interventions should fall into place to counter the inevitable diverted, substandard, and falsified White, Grey and Black Swan events. To ensure successful implementation of interventions national and regional governments, international organisations,

private and non-profit sectors, and civil societies need to work more closely together. The lessons learned so far and future analysis from the COVID-19 pandemic provide opportunities for more effective pharmaceutical policies that ensure access to quality-assured medical products for all.

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5

WHEN THE STATE CANNOT (YET) ASSURE THE QUALITY OF MEDICAL PRODUCTS: WHAT TO DO?

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Introduction

Assuring the quality of essential medical products is critical for the achievement of universal health coverage (UHC) (Orubu et al., 2020). It requires a complex set of interventions that should be coordinated at multiple levels (Ravinetto et al., 2016; Newton & Bond, 2019), and centered on well-functioning national regulatory authorities (NRAs) (Sixty-seventh World Health Assembly, 2014). However, many NRAs in middle- and low-income countries still lack the resources needed to adequately oversee and enforce the quality assurance of medicines and other health products in their territories (World Health Organization) (Twesigye, Hafner & Guzman, 2021). For instance, they may lack a sufficient number of staff adequately trained in key regulatory functions, such as carrying out inspections of manufacturing sites, distributors and outlets, and assessing the products' characteristics before granting a marketing authorisation. Their work may be negatively impacted by the lack of relevant

infrastructure, such as a functioning national quality control (QC) laboratory in their country. Furthermore, they frequently lack the funding needed for supporting the costs of regulatory functions and for maintaining an efficient internal quality management system (QMS), because they are not adequately supported either by their governments, or/and by the international community and by external donors. In 2016, the World Health Organization (WHO) started a formal Global Benchmarking Tool (GBT) for NRAs, incorporating the concept of 'maturity level' for indicating the capacity ('maturity') of regulatory authorities to adequately perform their tasks. The 'maturity' is expressed on a 1 to 4 scale (World Health Organization, 2021; Guzman et al., 2020). In practice, regulators can choose to be assessed through a structured and documented process for each of the nine essential regulatory functions. These are: national regulatory system, registration and marketing authorisation, vigilance, market surveillance and control, licensing establishments, regulatory inspection, laboratory testing, clinical trials oversight, and lot release (the latter is only applicable for the oversight of vaccine production). Level 3 represents the minimum target, i.e., a stable, well-functioning and integrated regulatory system for either medicines or vaccines. As of August 2022, it has been reached either for medicines or for vaccines by a few regulators in low- or middle-income countries, such as Tanzania, Ghana, Nigeria, Egypt, India, and Indonesia (World Health Organization). Despite these encouraging developments, many more communities live in countries with regulatory authorities with maturity levels 1 or 2.

Aside from the weakness of many national regulatory authorities, there is also a lack of regulatory oversight along the international supply chains. Regulatory responsibilities are only applied at national or regional level, and nobody is in charge of regulating and overseeing medical products when they are moving along the intermediate steps of the global supply chain, across licence holders, manufacturers, sub-contractors of manufacturing activities, distributors, brokers and transit areas (Caudron et al., 2008).

The consequences of weak regulation are blatant. The WHO and other groups estimate that about one in ten medical products in low- and middle-income countries are either falsified or substandard (Ozawa et al., 2018). Falsified products are those whose identity is deliberately and fraudulently misrepresented, while substandard products do not comply with adequate quality requirements despite having obtained a marketing authorisation. In this chapter, we will use the collective definition of substandard and falsified (SF) medical products (World Health Organization, 2018). All SF medical products (whether substandard or falsified) bring a major threat to individual and public

health, i.e. (Nayyar, 2019), avoidable morbidity and mortality, because the SF medical products did not heal the patient or were toxic; or an increase in pharmacological resistances, arising from exposure to sub-therapeutic doses when medical products and – in particular – medicines are underdosed or not bio-available. In addition, the COVID-19 pandemic that hit the world in 2020 shone a light on another important risk for the communities: the spread of infectious agents due to poor quality health products, such as substandard protective personal equipment (PPE) (e.g., masks). The capacitation and strengthening of all national regulators is the ultimate, long-term goal to be achieved. It will allow all states to prevent and detect SF medical products, and to protect individuals and communities from their deleterious – and avoidable – consequences for health.

While waiting for – and working toward – the capacitation and strengthening of all regulatory authorities, many healthcare workers, medicine purchasers and communities, are facing concrete risks of exposure to SF medical products, and need to mitigate and minimise these risks. This is not an easy undertaking, even for highly-skilled individuals and well-resourced organizations. The Global Fund (GF), as well as various United Nations agencies that conduct health procurement, face situations where the medical products they need to procure are not available as fully quality-assured sources, and there are no viable alternatives. To help these international purchasers to deal with these cases, the WHO sets up an independent expert review panel (ERP), which carries out a transparent risk: benefit assessment, and provides advice for time-limited procurement (World Health Organization, 2012). The ERP formulates its advice based on different, possible options. The first one is "no objection to procurement", and it applies when the independent expert panel indicates that the benefits expected from the non-fully quality assured medical product clearly outweighs the risks identified. The second one is "objection to procurement", and it applies when it appears that the risks from using the non-fully quality assured medical product clearly outweighs any possible related benefits, and even no treatment is preferable to such risks. The third one is "objection to procurement but the product may be considered when there are no alternatives, and if the benefit from using it (still) outweighs the risks." While the first two options are straightforward, the last one corresponds to a "grey zone", and it will be up to the organisations that requested the ERP advice to make a final purchase decision. These decision-makers move here in an area of uncertainty, where they must carefully weigh and balance the risks and benefits of the non-fully, quality-assured medical product, both at individual and community level. They must also be able to transparently communicate their final decision, and – in the first place – their decision-making reasoning. Transparency and

accountability are essential vis-à-vis all stakeholders, and more particularly the NRAs in the countries where they plan to import and use products.

All those who face uncertainties about the quality of a medical product, should act and decide based on a thoughtful and transparent assessment of risks and benefits, as it is done by the GF and other organisations, based on the ERP process and guidance. But if this is a complex issue for United Nations agencies, how can smaller groups and organisations deal with this dilemma? What to do, when the regulation is weak and the state has insufficient capacity to assure the quality of medical products? We will address this question in a pragmatic way, by presenting three, real-life cases drawn from our own experience in pharmaceutical supply; by analysing the embedded dilemma, and by proposing good practices and suggestions to address them. These cases provide a base to discuss how to navigate the complexities of the pharmaceutical market, and the procurement dilemma faced at different levels of procurement in poorly regulated countries.

Case 1 – International procurement in the humanitarian sector

International non-governmental organisations (NGOs) may face internal and external pressures that challenge or disincentivise their capacity to consistently assure the quality of medical products procured for their medical programmes. Such pressures are primarily related to contextual constraints, e.g., the general lack of quality assurance in the countries of operation. However, they may also be due to the institutional culture and expertise, e.g. a lack of pharmaceutical skills and expertise at headquarter and field level. Last but not least, quality assurance may be disincentivised by an ill-considered bureaucracy, and by an unhealthy push to fulfil donors' expectations in the first place. In the last case, some NGOs will not prioritise the verification of the quality of medical products, simply because it is not a priority for the donor (Enright, 2021).

However, even when there is a clear willingness to prioritise quality, it is possible that a fully quality-assured product is not available, either nationally nor internationally. An international NGO based in the Global North and running medical programmes in the Global South, faced this dilemma in the 2000s. At the time, it needed to procure significant quantities of oily chloramphenicol (CAF), to be pre-positioned for meningitis outbreak preparedness. Oily CAF was no longer a treatment option in high-income countries, and any existing formulations of this product had not been assessed and registered by a stringent regulatory authority, that is a regulatory authority (or a regional regulatory system) documented to carry out its functions adequately (World Health Organization, 2017; World Health Organization). The NGOs

therefore identified a manufacturer located outside the European Union (EU), in a country with limited regulatory capacity, as a potential supplier of this medicine. Being aware of the regulatory weaknesses in the country of the manufacturer, the NGO did not immediately issue a purchase order for the product, but first asked and obtained the company's authorisation to conduct an audit of the manufacturing premises and an assessment of the product's characteristics, to evaluate the level of quality assurance for themselves. The findings of the audit were not fully positive. It turned out that the manufacturing practices and product specifications were not up to the standards defined by the WHO (World Health Organization, 2014), and that the NGOs considered it essential to guarantee that patients would not be harmed. In particular, there were problems related to the implementation of Good Manufacturing Practice (GMP) for sterile pharmaceutical products, leading to risks that the (injectable) product was not sterile.

At this point, different options were possible to orient the final purchasing decision. To illustrate them, we retrospectively apply the "approaches to quality" conceptualised by Ravinetto, Pinxten and Rago in 2018 to describe the different ways by which purchasers of medical products make a purchase decision vis-á-vis a dilemma. First, the NGO could adopt an "excellence approach", which dictates that you should never compromise on quality of medicines. If choosing this approach, the NGO would have not purchased this product, but because of the lack of alternatives, they could have been unable to respond to the next meningitis outbreak. Second, the NGO could have adopted a "less evil approach", which makes a trade-off between the risk of using a non-quality-assured product versus the risk of not offering any treatment at all. By choosing this approach, the NGO would have made a straightforward purchase of this product. This choice would have allowed them to respond to the next meningitis outbreak, but with a product that was potentially unsafe or even harmful to patients. Furthermore, by doing so, they would have de facto cleared the procurement of medicines and other products of doubtful quality for their medical programmes overseas. The latter implies accepting a double standard between the country where an organisation is based (the product would have not been acceptable by any NRAs in the Global North) and the countries where it sets up its medical humanitarian programmes. Third, the NGO could have adopted a "legalistic approach", by which a purchaser is exclusively concerned about the local regulatory requirements. For the proponents of this view, there are no other ethical or technical concerns apart from acquiring the recipient country's approval for the importation of a medical product. By acting this way, the NGO would have purchased the product, even if they knew that it was potentially unsafe or harmful. Ultimately, the NGO adopted what Ravinetto,

Pinxten and Rago call a "developmental approach", which is based on the non-acceptance of an unfair status quo and on the search for better standards. In practice, the NGO decided to purchase this product, but made the purchase conditional upon an upgrade of the quality standards at the manufacturer. Therefore, it actively engaged with the manufacturer, to support them with technical guidance for implementing a corrective action plan, that eventually brought their production up to the WHO-defined standards.

The choice to actively engage with the manufacturer, to support them with technical guidance for implementing a corrective action plan, resulted in clear benefit for the communities served by the NGO, but also for any other organisations (and communities) in need of this specific product. As such, it represents a virtuous example on how an international NGO should secure purchase in a poorly regulated environment, by assuring the quality while contributing to upgrade local standards. However, it is likely that the company reacted positively to the proposal to invest in upgrading its standards, because of the "market incentive" represented by the possibility to become the supplier of an organisation which would purchase large volumes of oily CAF. Smaller organisations may lack the capacity to carry out independent pharmaceutical audits. In addition, even if they were aware of the quality risks and were able to assess them, they would have a much weaker negotiation power when requesting quality improvements, because they are not commercially interesting clients. Moreover, very few organisations have the technical capacity to make the initial assessment of risks and gaps and to provide meaningful technical support to pharmaceutical manufacturers. Others lack the institutional willingness to do so, as they consider that capacity building to pharmaceutical suppliers does not fall under their institutional mandate.

Case 2 – Local procurement at the health facility level

Even if they should be prevented by adequate regulatory oversight and control, including through an efficient pharmacovigilance system and systematic post-marketing surveillance along supply chains, quality incidents persist, particularly in poorly-regulated contexts. Many of them go undetected or unreported. For instance, an underdosed or poorly bio-available antibiotic will not adequately cure a patient, but the healthcare staff may attribute the poor therapeutic effect to various possible reasons, such as antimicrobial resistance, patient's poor adherence, etc., and do not consider the possibility that the product itself was of poor quality.

Most quality incidents happen at the level of hospitals or health centres, or at the patient's level, as shown by the WHO database of medical product alerts (World Health Organization). Clearly, the local health staff does not have the task, nor the expertise or the technical infrastructure necessary to carry out random quality control on medical products, either before the purchase or before administration to patients. Nonetheless, it seems important that health workers are sensitised to quality risks, and that they are empowered to identify at least those quality problems that are visible, and to report suspected cases. A poor visual appearance of a medical product does not necessarily correlate with poor chemical quality, and an adequate appearance cannot in itself indicate that the product is of good quality. However, appearance is one of the attributes of quality, and in some cases, it was even predictive of chemical non-conformities. For instance, a quality survey conducted in the Democratic Republic of Congo (DRC) revealed that most anti-malarial powders for suspensions with a non-conform appearance were also underdosed in the antimalarial ingredient artemether (Schiavetti et al., 2018).

A quick and simple visual inspection procedure could be implemented as routine practice at the point-of-care. It is a low-cost and low-training technique, and even if it cannot rule out all non-conformities, it can guide a rapid patient-centred response when facing suspect poor-quality medicines: if a product reveal some visual non-conformities, should it be discarded, with the risk of leaving the patient untreated? Or should it be dispensed, with the risk of harming the patient? Or should it be dispensed, but based on a careful risk: benefit assessment, and by taking actions to prevent similar problems in the future? We may try to address these questions based on our own field experience. A simple checklist developed by Schiavetti and colleagues (Schiavetti et al., 2020) was used at a rural hospital in the DRC, and at a health centre located on the outskirts of Kinshasa, for visually assessing the quality of, respectively, antibiotic-containing pharmaceutical products and the general stock of locally-procured medicines.

At the hospital, available oral formulations were conventional tablets and powders or granules for suspension, which need to be reconstituted by adding a given quantity of water. The visual inspection revealed that either the instructions on reconstitution, or a volume mark on the bottle, or both, were missing for some locally produced antibiotics. It also revealed that accurate oral dosing was impeded by complex dose calculations and absence of dosing devices, and that bottle antisepsis was endangered by use of the cap for administration (Tack et al., 2022). These observations, done at local level by the health workers prompted reactions at different levels. The staff did not reject the medicines, but took some short- and long-term corrective actions. In the short-term, patients or their caregivers

were timely and carefully instructed about adequate dosing and administration, to prevent the foreseeable dosing mistakes or product contamination caused by the packaging defects. In the longer term, the doctors communicated with the suppliers and regulators, to advocate for products improvement. At the health centre (Ravinetto, 2022), conversely, the visual inspection revealed that some locally procured medicines presented irregularities in the packaging and labelling. These findings prompted some checks on the licensing status of the local suppliers, and eventually resulted in a revision of the procurement strategy. The health centre's staff compiled a new list of approved suppliers, all with a valid licence and recommended by certain other local purchasers with specific expertise in quality checks.

In both aforementioned cases, a checklist-based visual inspection allowed the mitigation of some (even if not all) risks related to the presence of non-fully quality assured medical products on the local market. Furthermore, the use of the checklist raised awareness of healthcare staff about the risks of poor-quality medical products, and allowed them to take a pro-active and well-recognised role in the detection and prevention at local level.

Case 3 – National procurement in the public sector

Since 1998, a simple checklist was implemented by the Revolving Drug Fund in Khartoum state, Sudan, and later by the Sudanese National Medical Supplies Fund (NMSF), to monitor the quality of medicines at the health facilities in Khartoum state and Sudan respectively. In 1999, a major quality incident happened. An intravenous fluid was purchased and imported by the national public procurement agency, but the national lay press reported that a fungal growth was clearly visible on different bottles from different batches (Mohamed Ali et al., 2011; Mohamed Ali et al., 2020). The visual inspection (re)conducted by pharmaceutical inspectors confirmed these news. However, there was disagreement about the use of the findings of the visual inspection. Some stakeholders, mainly at the Chamber of Medicine's Importers, argued that information from the lay press must be taken seriously, and that batch recalls were urgently needed, as failure to act would cause health damage and perhaps claim lives of those receiving a potentially poor-quality injectable product. Others, mainly at the national procurement centre, argued that findings of the visual inspection should not be generalised to other bottles or other batches that did not yet show a visible fungal growth. Eventually, in 2001, all intravenous fluids imported from this company were withdrawn from the market by a ministerial decree. In short, a simple visual inspection had allowed the early identification of a non-reliable supplier.

Something similar happened again in Sudan, in 2005 and 2009 respectively (Mohamed Ali & Ahmed, 2018). In 2005, the General Directorate of Pharmacy (G-DOP) revoked the marketing authorisation of a cough syrup manufactured by a United Arab Emirates-based company, because the visual inspection revealed leaked bottles from different batches. Some stakeholders complained that the decision was based on visual inspection 'only', rather than on the results of full chemical tests. However, the G-DOP argued that when a defect that puts the integrity of a product at stake can be detected visually, there is no need to engage in full and costly pharmacopeial tests. In 2009, an unregistered anti-asthmatic medicine, salbutamol inhaler, was imported from China, and samples were sent to the National Medicines Quality Control Laboratory for testing. The laboratory rejected the samples at receipt, because a simple visual inspection revealed that the product did not comply with labelling quality requirements, i.e., the country of origin was not stated on either primary or secondary packaging. This non-conformity can have concrete consequences, as it would make the product traceability difficult or impossible. After stakeholders' discussion, the Federal Minister of Health required that full pharmacopeial tests were conducted anyway. These tests revealed that that the product was substandard, because it contained far less of the quantity of the active ingredient declared on the label, which is needed for the product to be effective. In other words, the labels irregularities identified by the visual inspection had predicted chemical poor quality. This is not surprising; at least if we hypothesise that at company level, poor practices in a given procedure (in this case, labelling) can be the 'symptom' of generalised poor manufacturing practices. Furthermore, a less formalistic interpretation of the legislation would have prevented the unnecessary costs of redundant laboratory analysis.

These experiences from Sudan indicate that a careful visual inspection, i.e., a simple and inexpensive technology is of paramount importance in monitoring the quality of medical products not only at a peripheral level, but also at central level. In addition, in the first case, the suspicions on the products' quality, initially reported by the lay press, were confirmed by the regulators. These experiences indicate that purchasers and regulators should critically but carefully investigate any signals of poor-quality medical products that come from the lay press and other informal communication channels, such as social media. Such signals and reports may allow to identify real cases of poor quality, and to take timely and adequate action, such as a batch recall, the withdrawal of a marketing authorisation or of a manufacturing licence. This is helpful to mitigate the impact of 'bad products' on health and health systems, and to restore trust between the health system and the community.

What to do, when the state cannot assure the quality of medical products?

Informed members of communities served by weak regulatory systems may ask themselves how they can protect themselves and their peers from SF medical products. This is a complex question to address, with no satisfactory answer. Nonetheless, based on the aforementioned cases, we will discuss in the following sub-sections how healthcare workers, patients and purchasers of medical products in poorly regulated countries can act to mitigate the risk of SF medical products.

Falsified versus substandard medicines at community level

Falsified medical products are by definition manufactured outside the legal and regulatory framework. It is criminal groups who illegally produce and sell these 'medical products', only occasionally managing to infiltrate them into the official supply chain. Therefore, an easy way to minimise the risk of taking falsified medical products is that individuals and households avoid buying at unlicensed outlets, on the street market, and at unknown sources online. This virtuous behaviour can nonetheless be difficult or impossible to achieve for people for whom the genuine medical product is not geographically available or financially affordable, for instance for poor people living far from licensed outlets, migrants and refugees. Avoiding substandard medical products is even more complex, as they are not illegal products. They have a regular marketing authorisation, but they do not comply with adequate quality requirements, because the regulatory authority was not able to identify the deficiencies. In other words, substandards medical products derive from weaknesses inherent, rather than external, to the health system. They are manufactured by companies that have a valid licence issued by the national regulators, and they look safe.

Different groups have suggested that community members could be supported by tracking systems, that is by using applications allowing them to scan bar or QR codes, and to send them to a central system that will instantly verify if the product is genuine (World Health Organization, 2021). These measures are burdensome for the final user and most likely expensive for the health systems, because countries should heavily invest in these technologies and in the set-up of dedicated databases. Moreover, these technologies may at best identify falsified and diverted products, but they will not help to detect substandard products. When checking the product via the app, people will learn that it is authorised and will be reassured. Nonetheless, they (or their children, elderly relatives, etc.) can be harmed if the product is substandard, e.g., under- or overdosed, or

characterised by accelerated deterioration, non-sterile, contaminated with toxic impurities, etc.

Communities' advocacy for quality assured medicines

The SF medical products can be compared to neglected tropical diseases (World Health Organization, 2021). In fact, both disproportionally hit poor communities in insufficiently regulated countries; for both awareness is growing, and corrective measures are possible but lagging. Individual members of the community are seldom in the position to effectively protect themselves from all SF medical products. An effective way to protect yourself from falsified or deteriorated medical products is to avoid purchasing on the informal market. Indeed, the informal market is particularly at risk of being infiltrated by falsified medical products, and inadequate storage conditions can prompt accelerated deterioration due to inadequate temperature, exposure to direct light and humidity, damage, etc. Nonetheless, avoiding the informal market can be impossible for poor individuals and households that cannot access essential medical products elsewhere. In addition, avoiding the informal market will not fully protect them, as there may still be risks of receiving substandard products at legitimate health facilities and pharmaceutical outlets.

That communities and individuals can hardly protect themselves from poor-quality medical products, may be disappointing news. However, this mirrors the situation of other products that are manufactured at industrial level. For instance, in the transport sector, final users are not requested to personally verify the quality of products they purchase or rent, such as motorbikes or cars, nor of products they use as passangers only, such as aircrafts or trains. In the wine sector, similarly, those who purchase a bottle will not be asked to carry out a rapid test (even if very simple) for detection of unwanted and toxic methanol. It is generally assumed that carrying out such upfront verifications is the responsibility of the state, or of relevant multilateral initiatives bringing different states together. It will also be the state's responsibility to sanction and correct inadequate practices that may have created threats or harm to the public. In poorly regulated countries, however, the final users could join forces to advocate for better quality assurance of medical products. This is a technical subject that may seem difficult to translate in lay language. Nonetheless, the experience of the advocates of access to medicines for HIV and other diseases showed – particularly in South Africa – that it is possible to create a powerful advocacy movement, triggering important changes, despite the technicalities of the discourse on intellectual property, innovation and access to health (Ravinetto et al., 2016). Clear advocacy messages should be built based on

real-life cases. Importantly, they should not be limited to those reported in the scientific literature, but should include cases experienced and witnessed by the communities and frontline health workers. Patients and health workers should also be encouraged to report possible cases of SF medical products, based on diagnostic or therapeutic failure, major side effects, etc. An efficient system should be put in place by the NRAs to collect and investigate such reports.

Advocacy will aim at showing how communities and individuals are harmed by SF medical products, and calling for urgent corrective actions. To be more effective, grassroot-based advocacy should be supported by national and international stakeholders, including academia, NGOs and UN organisations (and perhaps donors), to bring their call to higher instances and to eventually overcome the current global double standard in access to quality-assured and safe medical products.

Considerations on quality and price of medical products

Public medical supplies agencies and other stakeholders often believed that open tenders should be preferred for public procurement of medical products. In open tenders, any suppliers can participate, without providing proof of compliance with given quality requirements. For instance, non-registered medicines (i.e., medicines that have not (yet) been submitted to and approved by the NRA) can compete with those registered, and medical products that are not prequalified by the WHO or not approved by stringent authorities can compete with those that are. The proponents of this approach contended that open tenders allow obtaining the cheapest medicines from the global market, thus improving the affordability of medical products to the state and to the final users. This is a common preconception, often expressed by stakeholders with no technical expertise in pharmaceutical quality and supply. However, what value is there, if a cheap but substandard medical product is brought into the national supply chain? Some SF medical products are even more dangerous than no medical products at all. The scientific literature describes many cases where the use of low-cost medical products of unverified quality in public health facilities have proven to be disastrous for individual and public health (Danielle Rentz et al., 2008; Arie, 2012; Peyraud et al., 2017).

There are two scientifically unproven but common assumptions in scientific literature on the quality of medical products: that quality-assured medical products are always more expensive (Masini et al., 2022) and, oppositely, that generics are always of poor quality because they are cheaper (Patel et al., 2010; Aivalli et al., 2018). These assumptions are cascaded either upstream, to policymakers, or downstream, to healthcare workers and communities. As such,

they heavily affect the collective and personal procurement attitudes, and the prescription and utilisation patterns. They also raise issues of confidence and trust in medical products, and they may negatively impact the efforts to improve access to quality-assured medicines. Regulators, policymakers, public medical supplies agencies, donors, and other stakeholders need to untangle the link between the quality and price of medical products through further research.

Conclusion

When the State is not (yet) in the position to assure the quality of medical products available in its territory, some mitigation measures can be taken at the different levels of the health systems. In Case 1, we have seen that procurement organisations, either public or private not-for-profit, can audit or inspect themselves the potential pharmaceutical suppliers, and require corrective actions. In Case 2, we have seen that hospitals and health centres can systematically adopt a visual inspection procedure, for the detection of those quality problems that are visible. In Case 3, we have seen how national authorities can use frugal technologies to pre-screen medical products for quality. We have further discussed that even if they cannot detect SF medical products themselves, patients, frontline health workers and communities should report suspected cases through reporting mechanisms put in place by regulatory authorities. They could also self-organise in advocacy groups to call for access to affordable and quality-assured medical products. Patients' associations, consumers' protection societies, and grassroots organisations need adequate guidance in these matters, to help the communities to dismantle unproven myths, and to navigate the complexities of local markets in an adequately informed way. Consumers should also require full transparency on the capacity ('maturity level') of the national regulatory authority, in order to understand what level of protection and safeguards they get from them, and to advocate for more resources to be given to reinforce their capacities. To do so, it is important to understand that the quality, or lack of quality, of a medicine cannot be simply assumed based on its (low or high) price. Communities advocacy should aim at getting quality assured and affordable medical products for all.

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6

TO REACH THE UNREACHABLE: MIGRATORY LIFE, HEALTH VULNERABILITIES, AND NON-RESPONSE BIAS IN HEALTH RESEARCH

Talieh Mirsalehi and Kristofer Hansson

The first wave of the COVID-19 pandemic hit Sweden in March 2020. Shortly after the onset of the pandemic, Sweden appeared in different COVID-related news headlines and debates. This included, but is not limited to, the analysis of the Swedish national response to the pandemic both within and without the national borders (Claeson &Hanson, 2020). One of the reiterative topics that was highlighted within the first six months of the pandemic in different public health reporting was the high morbidity and mortality rate among individuals categorized as foreign-born[1] in Sweden (Drefahl et al., 2020; Ohlin, 2020; Folkhälsomyndigheten, 2021; Socialstyrelsen, 2020; 2021). According to the reports from the National Board of Health and Welfare of Sweden, while advanced age was considered as the major risk factor, those who were born

1 Foreign-born is a term that refers to the individuals who either were born in another country other than Sweden, or one or both of their parents were born outside Sweden. The term foreign-born has been used in reports as a variable when reviewing the effect of migration on health outcomes.

outside Europe were at higher risk of being severely infected with the virus, admitted to intensive care unit, and death compared to those who were born in Sweden (Folkhälsomyndigheten, 2021). For instance, over 50% higher mortality cases were reported among men who were born in Somalia, while the corresponding proportion among men who were born in Sweden was around 10% (Socialstyrelsen, 2021). Investigating the reason(s) behind pandemic-related excess mortality among foreign-born population fore-highlighted the importance of exploring *health vulnerabilities* as a potential contributing factor behind this overrepresentation (cf. Clark & Preto, 2018).

Despite recognition of this urgency, experiences of living a migratory life during the pandemic have been rarely investigated and weakly represented in health research (Etti et al., 2021). Although this absence is claimed to be as a result of these groups' unreachability and their lack of interest in participating in research, there are voices in the literature who oppose this presumption (Wendler et al., 2005). Reviewing non-participation and reversing inaccessibility to some groups in research, requires a shift in methodological approaches (Etti et al., 2021). Although the relation between research methodologies and the matter of non-participation of some groups in research has been explored in the literature, the question of how to overcome this challenge when generating data has remained unanswered. Our aim in this chapter is to explore and discuss the possibilities and limitations posed by different methodological approaches in health research among the groups categorised as foreign-born in Sweden. The ambition is to review the existing methodological challenges and explore the prospect of unpacking assumed health vulnerabilities through methodological considerations. We focus on the application of different strategies when dealing with the issue of accessibility to the (seemingly) inaccessible and absent groups (Deding, Fridbern & Jakobsen, 2008). In other words, our intention is to discuss the issue of non-response bias in different methodological approaches rather than presenting empirical explanations for the situations that have arisen during the pandemic.

The COVID-19 pandemic has shown that the issue of approaching *unapprochable* populations and inviting them to participate in health research has largely remained unaddressed. Confronting this cyclical concern requires not only attention but also action, as understanding different groups' response to societal hazards can elucidate the conditions that contribute to formation of health vulnerabilities and differences in health status in a society. Reaching out and investigating experiences of the groups that may appear unreachable and reversing their silent appearance in health research has resulted in recurrent debates over the choice of methods and methodologies (cf. Serrant-Green,

2011). Ethnologists, as well as researchers from other disciplines have used ethnography both as a leading but also sometimes as a *cross-border* method and in combination with other practices, to develop a better understanding about complex sociocultural phenomena (cf. Lundin & Idvall, 2003; Liu & Lundin, 2020; Phillimore, 2020). In this chapter, we analyse the methodological possibilities that ethnographic approaches offer by reviewing how they can, among others, reveal some aspects of perceiving and practising health among those who are considered as hard-to-reach (Mirsalehi 2021 & 2023). By evaluating the results of our quantitative and ethnographic research[2] and approaching the question reflexively, we also discuss our own methodological failure when investigating health vulnerabilities and care practices in times of crisis, particularly in response to the issue of non-response bias.

About unequal health

Vulnerability, in this chapter, is seen as a term that can help us define people and groups of people who are at a higher risk of being harmed – physically or emotionally – by critical situations, such as the COVID-19 pandemic (cf. Clark & Preto, 2018; Butler, 2020; Hansson & Petersson, 2023). By aligning the terms vulnerability and health, we wish to refer to the presumed physical and mental health differences, and the methodological difficulties in understanding why certain groups are more at-risk of health adversity (Kenen, 1996). In this chapter, as mentioned earlier, we focus on addressing the methodological challenges associated with non-response bias (Deding, Fridbern & Jakobsen, 2008). Non-response bias occurs when results of a quantitative study are considered as non-representative due to the disproportionate participation of the respondents (Fowler, 2009). This, in turn, generates research bias when measuring the impact of a situation on different groups (Deding, Fridbern & Jakobsen, 2008). To discuss the relation between research on health vulnerabilities and the issue of nonresponse bias, we start the discussion by exploring the phenomenon of unequal health among those who are grouped as foreign-born.

While public health in Sweden is ranked highly from an international perspective, inequalities in health outcomes among some groups is a persistent issue (Huupponen, 2018; Folkhälsomyndigheten, 2019). According to the reports released by the National Board of Health and Welfare as well as the Public Health Agency of Sweden, foreign-born individuals are a particularly at-risk group when it comes to suffering the effects of unequal health (SCB, 2020;

2 The current study is approved by the Swedish Regional Ethical Review Board (2019-03501).

Folkhälsomyndigheten, 2019 & 2021). Even though Sweden and the rest of the Nordic countries are known for their good social welfare, social inequalities in health persist and, as shown during the pandemic, these disparities tend to grow in times of crisis. By emergence of the COVID-19 pandemic, it became evident that disparities in health and the country of birth are closely connected contributing factors behind excess hospitalisation and death among ethnic minority groups in Sweden (Rostila et al., 2021). In 2020 and during the first wave of the pandemic, as mentioned in the beginning of the chapter, a distinctive mortality rate among the foreign-born population have been reported (Socialstyrelsen, 2021). Despite recognition of health vulnerabilities among some of these groups, empirical data on the situation is rare (Rostila et al., 2021).

During the pandemic, it became evident that the issue of unequal health have been in close relation to persistent vulnerabilities among foreign-borns. In addition to socioeconomic factors, limited access to healthcare services due to language barriers and uncertainty about consequences of seeking care are suggested as some of the determinants of health vulnerabilities among these groups (cf. Nkulu et al., 2012; Lobo Pacheco, Jonzon & Hurtig, 2016; Mangrio, Carlson & Zdravkovic, 2019; Aradhya et al., 2021). Despite acknowledging the role of structural factors in emergence of (un)health (Laue et al., 2021), there are still knowledge gaps about, among others, how socioeconomic factors have influenced the outcome of the pandemic among these groups (Folhälsomyndigheten, 2021). Nevertheless, there is a paucity of knowledge about how individuals who are categorised as foreign-born have experienced the situation, despite being considered as highly affected by the pandemic and at a greater risk of suffering from health vulnerabilities. Understanding their lived experiences, as mentioned earlier, requires research methods that let their voices be heard and included in the research. However, it is not an easy task to accomplish.

In the literature, the necessity of reaching out to groups that are at-risk of health vulnerabilities before and during the pandemic, and including them in health research has been approached from different angles and within different societies. These studies have problematised, to name a few, ethnic minority groups' persistent low presence in clinical research (Gill & Redwood, 2013; Etti et al., 2021), the negative impact of previous healthcare experiences on these groups' absence in health care-related studies, and research design as a barrier for participating in health research (Wendler et al., 2005; Razai et al., 2021). In Sweden, the objective of public health policy is to reduce health inequalities and provide the entire population with an opportunity to attain good health on equal terms (Folkhälsomyndigheten, 2019). However, the data illuminates how

knowledge about the heterogeneous population of foreign-borns' experiences in this regard is scarce (Folkhälsomyndigheten 2019; Rostila et al., 2021). According to the reports released by The Public Health Authority of Sweden, the so-called 'welfare diseases' such as diabetes, high blood pressure, being overweight and obesity are more common among the ones who have lived in Sweden for five years or longer (Folkhälsomyndigheten, 2019). Despite speculations and research, the reason(s) behind this and similar findings are yet to be uncovered.

The COVID-19 pandemic in Sweden, as elsewhere, has exposed some of the already-existing fault lines in, among others, the healthcare of groups that are at-risk for health vulnerabilities. In the literature, focus has been put on different aspects of the matter, from cultural fault lines in clinical encounters, to issues of migration and its relation to health disparities among foreign-born populations (Rambaree & Nässen, 2020; Mishra et al., 2021). Outbreak of the pandemic and re-emergence of structural ethnic health disparities in Sweden reveal the need for investigating the impacts on these groups through reviewing the influence of cultural, biological, and socioeconomic 'frameworks' (Bredström & Mulinari, 2020).

Addressing health inequalities through reversing, preventing, and promoting equal access to health in Sweden has been a continuous debate as inequalities in providing care services, besides health-related effects, can give rise to erosion of trust in democracy and cohesion in society (cf. Whitehead & Dahlgren, 2007; Huupponen, 2018; Mangrio, Maneesh & Strange, 2020). On the one hand, lack of trust in receiving equal health services may result in unattended poor health among some groups. On the other hand, health inequalities can contribute to an increase in formation of alternative care practices of, for instance, medicine procurement from irregulated channels. However, countering unequal health is complex, intractable, and requires innovative actions and pertinent methods of investigation (Huupponen, 2018). Thus, knowledge about different groups of at-risk for health vulnerabilities and a deeper understanding about their health-related experiences and care practices is needed (Rostila et al., 2021).

Our first methodological approach to health vulnerabilities was through using a quantitative survey. In the following section, we describe our process of data collection and why the results did not turn out as we had anticipated. Despite this seemingly failed attempt, the results illuminated a challenge that demands attention.

Non-presence in surveys

Our study approached the field of health vulnerabilities through a quantitative study to investigate online purchase of medicines and protective products during the pandemic. The online public survey was designed and conducted by the Swedish market research institute KANTAR Sifo between 28 January and 9 February 2022. The survey was sent to the public in Sweden with a focus on the online purchase of protective products that promise protection against the coronavirus. The intention was to discern society's response to a time of health crisis and investigate general awareness of the health risks associated with buying medicines from unauthorised online sources. We also wanted to find out in what way searching and purchasing the products that claimed protection against the coronavirus were enacted and perceived in the society of Sweden. In the survey, people between 18 and 79 years' old were randomly selected and invited to answer a questionnaire (more information about the participants will follow). Questions focused on the respondents' attempt at searching and purchasing protective products, and their experiences of using them. We also added two questions related to the respondents' national and ethnic background, to assess whether the respondents in our survey could be representatives of different groups in society. The ambition was to find out if our study could delve deeper into questions concerning health vulnerabilities in relation to national and ethnic background.

In total, 1 041 responses were collected from the survey, which we later analysed with descriptive statistics. The results showed that of the 1 041 individuals who responded, 4% disclosed being born in another European country other than Sweden, and 2% in another country outside Europe. Of the total number of participants, 8% reported that one of their parents was born in another country other than Sweden, while 7% responded that both of their parents were born abroad, and therefore, this group was considered as being the *foreign-born* participants. Individuals who are placed in the category of foreign-born comprise 20% of the general population in Sweden (SCB, 2022). Having received a response from 7% of the foreign-born population in our study made it evident that the degree of their participation in our quantitative public health research was low. As mentioned earlier, our ambition with the two questions of national and ethnic background was to find out if the respondents of our survey were representative of different groups in society. The low level of participation among the respondents with an international background was an indication of limited presence of different groups in such collective health research. However, our study also revealed how including the participants' background in such studies may not necessarily disclose the truth about different populations'

experiences, as there are still groups who, due to their lack of literacy and language skills, are excluded from these studies by default.

What we learned from the results of our survey is that methods of health research demand reflexive attention from us researchers. These studies, which are mainly performed in the Swedish language, target those who are randomly selected among the group of the eligible majority. In this way, the result of our survey reveals a form of non-response bias and systematic exclusion of some groups of the population from participating in such and similar research. The survey gave a clear answer that the groups we searched for probably did not participate in nor responde to the survey; thus, they remained invisible. Hence, the survey rather made visible our own prejudices of what we thought could be possible to achieve through such methodological categorisations. Although such a vague approach to the participants' national and ethnic background did not provide a picture of contributors to inequalities in health, it proved that participation in health research is not necessarily considered as an opportunity, equally available for all groups in society. As our quantitative approach did not provide us with a better understanding of health vulnerabilities among the groups that we intended to include in our study and instead confirmed their lack of presence in such public health inquiries, we reviewed our ethnographic study for further investigation.

Ethnography of health vulnerabilities

Our ethnographic study consisted of semi-structured interviews and participant observation, which constitute two of the most established methods in ethnological research (cf. Davies, 2008). Through using ethnographic methods, ethnological studies aim to gain insight into the seemingly mundane activities and trivial routines of everyday life. By looking at such subtle details in people's choices and habits, ethnography can reveal "connections between small matters and large issues," (Ehn, Löfgren & Wilk, 2016, 1).

Our ethnographic research took place between autumn 2019 and 2021, with a focus on the sociocultural views on health and unhealth among a group of asylum seekers in a southern town in Sweden. We intended to explore how the participants responded and reasoned their health-related strategies before and during the pandemic while living a migratory life. In total, 12 adults participated in the ethnographic fieldwork. The initial emphasis of the methods was on the participants' reflection on their care experiences while navigating different healthcare systems before, during, and after their migratory move. The interviews were transcribed, coded, and categorised based on the emerged

themes, while the participants were anonymised in the transcriptions to keep their identifying information confidential. As we clarify in the following, the methods that we used were expected to reveal how people who were at-risk of health vulnerabilities lived in a time of uncertainty. As we argue, along the way we gained an understanding of how a non-linear, seemingly messy research process can still generate knowledge through moments of reflection and spaces of incalculable evidence (Adams, Burke & Whitmarsh, 2014). What is reported in our ethnography, however, shall not be seen as a full-fledged analysis of health vulnerabilities among different groups of foreign-born, but as a sample of an ethnographic study and to what this method can contribute.

It has been argued that one of the reasons behind the COVID-related excess mortality among migrant populations, particularly in the beginning of the pandemic, is their lack of access to health recommendations and guidelines introduced by the public health authorities (Strange et al., 2021; Söderberg et al., 2021). Shortly after the outbreak of the pandemic, the asylum-seeking families who participated in our study often turned to us during the ethnographic part of our fieldwork, to vent their concerns but also to ask for advice on how to protect their families against the pervasive coronavirus. We took this as a starting point in our ethnographic approach to explore why our participants voiced their concerns and questions to us, the non-experts in medical sciences. To approach the widespread speculations about their lack of access to health information, we asked our participants about their sources of information and how they followed the pandemic-related news. We also wanted to know about their care strategies and how they protected themselves against the pervasive risk of contagion. When asked about their ways of reaching guidelines about safety measures, the majority responded that data originated from the Swedish health authorities was their main source of knowledge. The responses, however, were often followed by a sense of confusion. One of the participants, a woman in her mid-thirties explained:

> "I used to get information from YouTube and Instagram, also from the neighbours. Somebody said drink lemon juice, somebody else said eat, what is it called, cinnamon? I mean ginger. So, we used more lemon juice and ginger. This [information] was on YouTube and Facebook too, I mean in those clips about what's good for corona. But I think nothing, but a vaccine can guarantee that you won't catch it [coronavirus]. I don't know, they say 'Find this, eat that, so you won't catch it', but I don't believe in what they say."

The participant who made the remarks above, although indicated having an access to the health recommendations and guidelines presented to the society of Sweden, she, like many others, revealed her ways of handling an infectious

virus. Although the focus was on the sources of COVID-related information, the participants expanded their responses and revealed their sense of ambivalence through, in this case, the search for different alternatives to strengthen the body and generate health. Another participant, a woman in her early-thirties said:

> "Well, the immune system in each person is different… Our neighbour, the poor husband, he got it [COVID-19]. He was coughing for twenty, twenty-five days. Poor guy, and they said the only thing that save them [the rest in the family from catching the virus] was turnip. Have you heard how to make turnip juice? I've heard it from someone else, they said it is good. You empty a small turnip and put honey in it, and then put it on a dish with a lead on and leave it overnight. It seems the turnip releases some juice and then you should drink it … it raises the body's immune system really high."

During our ethnographic research, we encountered situations where the participants shared similar experiences of using different means of protection to face the health-related risks imposed by the pandemic. Although they had received the official recommendations that were presented by the health authorities, they, too, used different strategies to protect themselves against different health hazards. As we witnessed in our ethnographic study, the supposedly hard-to-reach target groups and non-respondents may show a willingness to share their knowledge when they are provided with the opportunity from the researchers to be heard. Those who joined our study shared their concerns and uncertainties about COVID-19 vaccines while presenting their coping strategies in the face of a pandemic. These narratives provided us with an insight into their embodied experiences of living a migratory life in times of crisis, something that we could have missed otherwise. In other words, those who participated in our study were both providers and recipients of knowledge, an exchange that was not achieved in the same way in our survey research. Despite the deliverance of different health-related guidelines by the public health authority in different languages, application of the health recommendations appeared to be complicated for some of those who joined our study. The accuracy of the distributed health recommendations was among the topics that were brought up. Another participant, a man in his early forties said:

> "If it [the vaccines] was the final cure, we would have been told 'This is the ultimate cure and from now on we are all going to use only this one', but there is a Russian vaccine, Chinese vaccine, British vaccine, American vaccine, and we still don't know which one is which, which one is the main one, which one is the proper one. Russia says our vaccine is better, the UK and Sweden say ours is better, the US says ours is better, and we still don't know which one is which. If there was an ultimate vaccine, a

> final solution, everywhere would have opened again and used the same vaccine. May I ask you a question? Which vaccine do you think is the best, the most functional one?"

Matters of health and fear of the unknown are not unique to the migrant populations. However, the effects of the pandemic on the groups who have gone through life-altering experiences of forced migration and have been dealing with variety of barriers in the new society are of a different nature. The above-mentioned dilemmas about vaccination can also reveal the effect of misinformation, a phenomenon that became a source of uncertainty, not least among the population with an international background. Although access to the 'right' information has been a global challenge and impacted different groups particularly during the pandemic, accessibility to information among our participants is not limited to concerns over preserving their health. The sometimes contradictory sets of guidance presented the participants in our study with not only confusion over expected and accepted performance in a time of crisis, but also a dilemma over their placement in the social ranking when a health crisis strikes (Mirsalehi, 2023). During the pandemic, there appeared debates over prioritising the asylum-seekers in the vaccination programme, as they were considered as a population at the risk of being severely impacted or death caused by the disease (cf. Sveriges Riksdag, 2022). In response to our conversation about accessibility to information about vaccination, one of the participants, a man in his late thirties, said:

> "The information I get is from the international news that I listen to, BBC or other news channels [in his native language] that talk about this disease on a daily basis … I follow the news by the ministry of health in Sweden that shows if the numbers [statistics on contagion] go higher or lower … The information is there… Well, I haven't received any information about vaccination, but when I asked my friends, they said the priority is with the staff who work at the hospital or clinics… My Swedish friends, mostly those who haven't had it yet [COVID-19], say it's the retired people's turn now [to get vaccinated. They're like me, they don't say anything about being in the queue. But they say it's the governments' plan that we all get it. I don't know."

Later in the conversation, it was revealed that his Swedish friends were among some residents who lived nearby and sometimes assisted the family with translating the letters that they received from the migration agency or other relevant institutions. Not knowing if they were placed in the category of at-risk and thus prioritised for vaccination (or not), appeared to be a question that was hard to ask. For him, being prioritised for vaccination could seem like a double confirmation for being *different* from his friends, while the fear of being hit harder by the virus was a constant concern. Reading between the lines of

these articulated lived experiences, it becomes evident how understanding and responding to an urgency can be put to test when entangled in a "grey area of uncertainty", particularly for those who are kept on the doorstep of a society (Koffman, Gross & Etkind, 2020, 211). There may not be clear indications in our empirical material to show why the groups of foreign-born were hit harder by the pandemic. This may be perceived as an underlying issue in ethnography, namely that the methods often focus on the actions of the individual – and smaller groups – rather than the structural patterns. However, we argue that it is through application of ethnographic methods that not only the problem with non-response bias can be addressed, but also the research methods may reveal the often-dismissed details that can contribute to having a more in-depth understanding about the situation in question.

Slow research and management of non-response bias

Approaching the presumably unreachable groups and investigating their at-risk status in times of crisis requires a reflexive exploration of the research methods. Our empirical material shows how ethnographic methods make it possible to problematise and contextualise inequalities from the perspective of those who are exposed to it. As researchers, regardless of the discipline, we rather often face (un)expected challenges in different phases of a research process. One of the occasions that may entail dealing with unforeseen circumstances is when the research requires participation of human subjects – when the target group's involvement becomes an intricate task due to various accessibility barriers and methodological choices. The concept of unreachable or inaccessible subjects has been contested in the literature. One of the arguments against formation of hard-to-reach human subjects in research refers to how categorising some groups as unapproachable can result in overlooking the underlying circumstances that lead to exclusion of some from participation (Corcoran, 2014; Nielsen et al., 2017; Zeisler et al., 2020). While a variety of reasons behind formation of unreachable groups in health-related research are recognised, as the anthropologist George Marcus (1995) points out, unreachability to research subjects is a question of methodological approach. Thus, non-participation of some groups cannot simply be justified by their assumed lack of interest in contributing to health research or any other social engagements (Dingoyan, Schulz & Mösko, 2012). Besides looking into determinants, such as lack of trust or incentive for the research topic and fear of circumstances that may come along in the process by research subjects, we as researchers need to take a closer look at our approach, research design, and choice of methods.

The migrant populations are among the groups who are many times, and perhaps involuntarily, placed in the category of unreachable, particularly when it comes to their lack of active presence in health research (Corcoran, 2014). In the literature, the silence or absence of some groups in research – called non-response bias – has been explored as not only an outcome but also a contributor to individuals' omission from joining research (cf. Berg, 2005; Deding, Fridbern & Jakobsen, 2008; Sedgwick, 2014). Hence, approaching the phenomenon of non-response bias among migrant population requires analysis of different research techniques and how different methods attend to various aspects of the matter. Ethnographic research methods are among the prominent tools to immerse in a setting and create knowledge through observing, listening, and being present. Application of ethnography as a research method requires 'attentiveness' in the field to produce new understandings about what that may seem off-topic or ordinary (Adams, Burke & Whitmarsh, 2014, 189). The attentiveness helps the researcher to explore the 'spaces' that are created during unscheduled encounters where the ordinary turns to unexpected (Adams, Burke & Whitmarsh, 2014). The unforeseen moments in an ethnographic research process, even though being seemingly irrelevant to the topic, can be the important parts of understanding the topic and people we study.

This can be compared to conducting *slow research* (Adams, Burke & Whitmarsh, 2014). In the face of a pandemic, efficacy of a research process may be measured through not only the quantity of the data but also if it is generated and assessed rapidly. However, investigating a phenomenon such as the effect of the pandemic on those who are at higher risk of health adversities equally demands evaluation of the situation from a "culturally embedded point of view" (Adams, Burke & Whitmarsh, 2014, p. 184). Calling it *slow research*, Adams and colleagues (2014) argue that investigating these actions and interactions is an act of acquiring knowledge about how the situation in question is experienced, rather than (only) collecting information about how the situation appears to be for the researcher (Adams, Burke & Whitmarsh, 2014). The slow research as a method of understanding a phenomenon does not necessarily advocate longer duration of research time. Instead, slow research like ethnographic approaches, encourages researchers to be attentive and present with the ones that are the focus of the study (Fabian, 2002). There may appear moments in a research process when reaching the target group or encouraging them to participate may appear harder than anticipated. Hence, these unplanned and unforeseen encounters create spaces where the indepth knowledge about the situation in question can be created (Adams, Burke & Whitmarsh, 2014). Inspired by the concepts of slow research and unanticipated spaces of concealed knowledge, we argue that the element of time in ethnographic research is not limited to

the length of a study but includes the – hermeneutic – depth of the process. Ethnography as a method leaves, in this way, room for sociocultural innovative approaches due to its diffractive practices and the mutual exchange of knowledge that it offers throughout the process and between the research participants (Wiszmeg, 2017; Hansson, Nilsson & Tiberg, 2020; Mirsalehi, 2021). Through their eclectic, innovative and situational properties, ethnographic methods can reveal how different groups perceive and experience sociocultural phenomena, while assessing how to address the emerging challenges. This can be a way to elude the problem of non-response bias when researching health vulnerabilities.

Conclusion – exploring health vulnerabilities

This chapter has its origin in failure. We had high hopes for our survey research, but it turned out to become a case of non-response bias, leaving us without the knowledge we hoped to achieve. Instead, we returned to our ethnographic methods to reach out to those who were systematically excluded from our quantitative study, with the ambition of better understanding why certain groups are at higher risk of developing poor health and suffering the consequences of health vulnerabilities. In this chapter, we argue that ethnographic methods can illuminate different dimensions of a social condition such as inequalities in health. An ethnographic approach directs the attention to the often-dismissed underlying factors behind formation of such unjust and avoidable disparities in health. Its methods, besides allowing the researcher to find any correlation between seemingly trivial daily practices and patters of self-care, can also shed light on care-seeking practices and medicine consumption habits among different groups in the society (cf. Alftberg & Hansson, 2012; Mirsalehi, 2021). On a practical level, ethnographic methods are designed to enable the researcher to step closer to the studied groups to observe and understand the empirical values embedded in their experiences. Nevertheless, they provide participants of ethnographic research with tools to articulate their experiences, expectations, and inquiries. These methods also assist the researcher to respond to unanticipated encounters through making sense of what sometimes may seem nonsensical, and reconsider irrelevant actions and interactions that may occur within unexpectedly created spaces. By presenting a fraction of our ethnographic material, we intend to highlight and discuss what can be problematic in relation to accessibility and assessment of health practices among assumingly unreachable subjects. Our empirical evidence in this chapter cannot be generalised and be taken as a representation of the groups that are considered at-risk for health vulnerabilities. They, however, can support the argument that looking, only, for concrete and measurable answers when

performing health research can result in disregarding everyday practices and conditions that may be important causal factors behind the social phenomena in question. In other words, we argue that ethnographic methods can be used to get closer to the often hidden or dismissed lived experiences of the groups who are quietly visible in generalised, statistical data.

There is a consensus that health inequality must be eradicated (cf. Folkhälsomyndigheten, 2019). Approaching the matter of health vulnerabilities requires a new way of framing the question of what can be done to prevent and reduce the conditions that result in the formation of inequalities in health. Inquiries relating to health information and individuals' awareness of health-related *risky* practices can be an important entry point (cf. Liu et al., 2021). Thus, it is important to continue developing new or remodelling the existing approaches to tackle these questions through, not least, critical assessment of research methodologies. It is evident that vulnerabilities and inequalities in health exist, yet decoding how the two are connected and enacted in different groups' daily life demands further, innovative pursuit. Understanding this correlation is critical, if existing inequalities in health are to be traced and terminated rather than, only, being acknowledged and documented. We, therefore, argue that ethnological research through application of different ethnographic methods plays a key role in investigating these questions (Tashakkori & Teddlie, 2003; Phillimore, 2020). Yet, generalisation of experiences when approaching a heterogeneous group based on the data that is solely gathered through ethnographic methods remains a challenge, if generalisation of data is appropriate or essential to begin with. A possible way forward in the future, we suggest, would be to better understand how to respond to non-response bias in research through application of a bricolage of method.

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SECTION III

SOLUTIONS AND LESSONS LEARNED

7

MEDICINE QUALITY AND MEDICINE TRACEABILITY: A FOCUS ON PREVALENCE, CONTEXT AND RESPONSIBILITY

Bernard Naughton and Dominic McManus

Introduction

Substandard and falsified medicines (SF medicines) are an issue with serious and wide-reaching impact. SF medicines are medical products that fail to meet their quality standards, or deliberately misrepresent their identity, composition, or source. It should be noted that the substandard and falsified terminology adopted by the WHO and EU differs in the US, where the term 'counterfeit' is still used to refer to both substandard and falsified. SF medicines endanger patients and fail to meet their clinical needs, and have a huge economic impact. The global market for falsified medicines is estimated to be worth up to USD200 billion (Ozawa et al., 2018). The larger the issue grows in a region, the more patients lose confidence in their local health authorities (*WHO,* 2023). With many governing authorities in a challenging position regarding funding for healthcare initiatives, the financial losses associated with this issue could lead to poorly supported public healthcare.

Substandard and falsified medicines are a global issue; all economic classes of country have suffered in some way. Low- and lower-middle-income countries have perhaps seen the most egregious breaches of trust, where the issue of substandard and falsified anti-malarials, and anti-infectives in particular, result in a severe degradation of care pathways in the most vulnerable patient groups (Jackson et al., 2020). On the other hand, the most sophisticated global regulatory organisations in higher income countries have seen major supply chain breaches also; for example, in 2012, the United States' FDA announced it had detected counterfeit versions of the anti-cancer drug Avastin®, an anticancer medicine, in the legal supply chain. This case caused medical professionals in 48 states to be alerted, criminal prosecutions to be pursued, and contributed to an overhaul in approach for handling SF medicines in one of the most economically developed countries in the world (Mackey et al., 2015).

In order to address the issues posed by substandard and falsified medicines, we believe there are three key concepts that should be explored. First, estimating the prevalence of substandard and falsified medicines in a useful way. Second, understanding the context in which SF medicines proliferate or decrease, and thirdly appreciating responsible innovation as a potential solution.

Medicine quality and prevalence

Estimating the true prevalence of substandard and falsified medicines is challenging. One of the key reasons for this is scarcity of reliable data. Typically, medicine sampling studies are conducted to estimate the prevalence of the problem in a given region. These studies include the sampling of medicines from medicine sellers like pharmacies, or itinerant salespeople and assessing their quality in a lab. Researchers then report the percentage of medicines that passed laboratory tests. This data collection is vital, as it allows for visibility of the medicines most likely to be substandard and falsified. It can also give a sense of the patients most affected and the scale of the problem in different locations. In recent years, this understudied issue has gained more traction with a greater number of prevalence studies and meta-analyses being published (Ozawa et al., 2018; McManus & Naughton, 2020). In the 2000s, a key concern was ensuring the data generated by field studies of medicine quality was at the standard required to be reliable, and that the methodology used to carry out these studies would be standardised to facilitate cross study comparisons. Tools such as the Medicine Quality Assessment Reporting Guidelines (MEDQUARG) framework were developed to improve prevalence studies. This has been used to help assess study suitability for inclusion in meta-analysis.

The level of heterogeneity in medicine sampling study methodologies can prove to be another barrier, when it comes to estimating the prevalence of medicine quality in a given region (Mackey, 2018). Overall, estimating prevalence is difficult due to a still under-developed data environment and a lack of standardisation in approach, which makes generalising the extent of the worldwide SF problem challenging.

Medicine quality and context

Understanding the contextual environment in which substandard and falsified medicines exist is important to assess the extent of the issue globally, where to introduce solutions, and how these solutions need to be adjusted to be successful in each region. The reliability of current datasets in the field of SF medicine are an obstacle, due to the many confounding variables that often make combining discrete field studies into larger meta-analyses an example of not comparing 'like-for-like' (Ozawa et al., 2018). These variables include the time of year the data was collected, sociocultural effects in play at the time of data collection, the specific geographical location of the study or awareness of the study to local political or criminal social networks (McManus & Naughton, 2020). These short-term and long-term contextual factors are not usually recorded as part of medicine sampling studies. Therefore, when the prevalence results of these studies are then examined retrospectively the results may be misleading.

Contextual shifts

It has been observed that major, contextual shifts across a region have been proven to adversely affect the quality of medicine and – by extension – patient outcomes (Naughton, B.D., 2020). In the 17th century, the urgent need for antimalarials led to the widespread adulteration of Cinchona bark, which also lasted for centuries to some extent (Ballard, 1915). Another illustrative example of this effect has been the outbreak of war and its knock-on effects across society. After World War II, penicillin shortages led to sustained falsification that only abated after a number of years (Newton & Timmermann, 2016). We need look no further than the global COVID-19 pandemic for a stark reminder of the fragility of our legitimate medical supply chains and how contextual shifts can affect the prevalence of SF medicines (Naughton, B.D., 2020).The pandemic's destabilising effect on the supply chain has manifested in several ways. At the outset, production, and supply of vital medications for diseases other than COVID-19 were heavily disrupted as these products were being investigated for COVID-19 treatment. This intense study of compounds left patients with chronic illnesses short on supply of life-saving medications (Newton et al., 2020). A key propagator of falsified medicines is scarcity, leading to patients

forgoing the safety of regulated vendors in favour of the expediency of the grey market (Newton et al., 2020). As Newton and Bond point out, "drug quality is subject to fear, desperation and disinformation," (Newton et al., 2020). Scarcity also enabled widespread falsification of vital medical equipment, such as personal protective equipment (PPE) sold online, which overstated their protective abilities, and testing kits giving invalid results and a false sense of security (Proffitt, 2020; 'Los Angeles District Attorney Office 2020). A pressing environment of elevating death tolls and lockdowns proved to be fertile ground for quackery profiting from increased demand, combined with reduced supply of medicines and the resultant consumption of fraudulent products marketed by unscrupulous individuals (Naughton, B. 2022). To summarise, contextual shifts such as war and widespread disease can be seen as amplifiers that influence the usual market dynamics surrounding medicines, resulting in the disruption of the supply chain and an increase in SF medicines as demand out-weights supply. It is important to utilise our understanding of contextual factors to our advantage. Arranging known contextual factors into an analytical framework can be useful not only to link the 'what', i.e., the prevalence to the 'why', i.e., contextual factors or causes of substandard and falsified medicine dynamics but also to move into the realms of prediction. By understanding contextual factors and previous resultant changes in consumer and supplier behaviour, we can more effectively direct mitigating measures to regions of concern, minimising the propagation and impact of falsified medicines.

Context is missing from medicine sampling studies

As Mackay and others point out, the presence of variation between medicine sampling study factors makes it difficult to equate studies to representative consistent and reliable estimates of prevalence within an entire region (Mackey, 2018). We posit that the solution to this challenge is to record the context more keenly for each medicine sampling study. This will allow us to make comparisons between different studies across regions, by appreciating the contextual factors at the time of data collection. In time and with enough data we may be capable of moving towards making estimations of the likelihood of SF medicine occurrence based on variables, such as climate change, regional war, or the presence and activity of particular social networks. Aligning on a standardised set of questions to capture contextual data in the field may improve our understanding of the situation in the future. A framework proposed by McManus and Naughton may be a good starting point (McManus & Naughton, 2020). This in turn will lead to more standardised and comparable medicine

quality datasets, which will aid our collective identification and understanding of substandard and falsified medicine prevalence.

Traceability legislation and responsible innovation

As far as understanding the prevalence of SF medicine and the contexts where SF medicine are proliferated is important, action through responsible innovation is necessary to shield patients. Before we can appreciate responsible innovation as a potential solution, we must first examine the legislation that serves to underpin the innovation.

Traceability legislation

International legislation has evolved over time, resulting in comprehensive anti-counterfeiting measures, such as the EU Falsified Medicines Directive (EU FMD) in Europe and the Drug Supply Chain Security Act (DSCSA) in the United States (Research, 2022). An important goal of all anti-substandard and falsified legislation and the legally mandated traceability technology is to reduce the likelihood of substandard or falsified medical products from reaching patients.

Table 1: Summary of EU and US legislation, which mandates medicine traceability technology

An Overview of EU and US medicine traceability legislation
EU FMD
First introduced in 2001, the main aim of the FMD was to harmonise legislation and practice across Europe, increasing the traceability of medicines with the overall goal of reducing the burden of substandard and falsified medicines across the globe (Smith, J.A, Naughton, B., Kramm, A., et al, 2015). A key element of the FMD pertains to the mandated use of GS Standard barcodes that contain unique product identifier serial numbers. This process, known as serialisation, facilitates the authentication medicinal products in the supply chain. When the barcode is scanned, data concerning that medicine are transmitted to a national database where a cross-check occurs against products known to be legitimate. The FMD also stipulates that tamper evident seals are to be utilised for all serialised products. It also makes a distinction that prescription-only medicines, with some exceptions, will require authentication upon supply to the patient, but over-the-counter medicines will most commonly not. Pharmacies are required by the FMD to 'decommission' medicines at point of dispensation to the public to allow them to exit the supply chain and enter the hands of the end user.
US Drug Supply Chain Security Act
In 2013, the United States drafted the US Drug Supply Chain Security Act (DSCSA). This Act enhances the regulation of the US drug supply chain and increased security via the tracing of prescription-only medicines and their associated records electronically from the point of manufacture to the pharmacy. This legislation can be seen as the US equivalent to the European Falsified Medicines Directive. Both utilise serialisation technology (GS1 standard barcodes) to facilitate traceability of medicines. The sharing of data amongst verified stakeholders helps to reduce the risk of counterfeit products penetrating the legitimate supply chain, and parties contribute to electronic databases that store information on the medicines and verify that scanned medical products are indeed legitimate.

Under the DSCSA, medical products are scanned at every stage along their journey from manufacturer to the pharmacy setting (either community or secondary care), but does not include scanning at the point of dispensing to the patient. This stands in contrast to the EU FMD where the medical product is verified only at the beginning and end of this journey. The concept of commissioning and decommissioning medical products does not exist within the DSCSA framework, and medicines are only verified in the US when being returned or are suspected to be counterfeit.

Prior to the turn of the millennium, regulations concerning substandard and falsified medicines were drafted and implemented in Europe on a national level. One such example is the Bollini Law in Italy. This piece of regulation encouraged traceability of medical products by requiring medicines to be tracked to point-of-sale using a set of two barcodes, or *bollino*, placed on the product at manufacture. It was then bolstered by additional Italian Ministry of Health decrees, adding a 'Data Matrix' to each bollino and building a central database to further improve traceability (Italian Medicines Agency, 2020). This led to the development of the FMD, which was followed by the DSCSA as summarised in Table 1 above. Other international legislation in Turkey, Argentina, China, Brazil and Russia is also noteworthy and completes the picture that regulation to mandate traceability technology is common around the world.

Technologies to protect against SF medicines: higher income countries

With global legislation summarised in the previous section, we can now consider the toolset used to enforce it. To apply the World Health Organization's (WHO's) action plan and drive the legislation described earlier, proper application of technology is key. The plethora of technological modalities made available to regulatory bodies in recent years has diversified the means through which legislation can be upheld. These technologies vary in applicability and effectiveness, with the rise and rapid uptake of serialisation being common across geographies. While the legislation aims to protect patients, it is important to ensure the technological tools facilitating this are effective in their contexts. Next, we will examine the technology itself in closer detail.

To ensure this vision of supply chain traceability, information technology-based solutions are developed and implemented to examine medical products along various stages of their journey through the supply chain. This surveillance comprises verification scans that occur at differing points along the supply chain, depending on the legislation that dictates it (Regulatory Affairs Professional Society, 2017).

Serialisation technology involves coding each distinct medical product with a unique 12-digit serial number and 2D barcode. This track-and-trace process makes each unit of medicine identifiable within the supply chain as its own entity (Naughton et al., 2017). At the point of manufacture, the vendor serialises the medical product, coding both the raw materials and the finished product (Rasheed, Höllein & Holzgrabe, 2018). This allows the medicine to be verified for authenticity. This vital step in the process occurs when it is scanned by a 2D barcode scanner revealing the status of the medicine – legitimate, falsified, expired, etc. (Naughton et al., 2016). The number of scans that occur across the journey depends on the legislation in which it exists. When a medical product is scanned, the user is alerted to its status, often via a colour-coded pop-up message on a digital screen. This message also directs the user to take a specific action, for example quarantining and reporting those medications that are shown to be falsified (Naughton et al., 2016). These alerts are designed to provide as much information in as clear a way as possible.

Evaluating the effectiveness of medicine authentication technology

Measuring the effectiveness of technologies in this area is important. By engaging in ongoing evaluation and re-evaluation, governments can assess where to spend their resources in an evidence-based way. In the case of serialisation technology, also referred to as medicine authentication technology, studies have attempted to provide an estimate of effectiveness – with illuminating results. In 2016, we conducted a two-stage quantitative study in the secondary care setting in the UK (Naughton et al., 2016). By introducing 'study medicines' into a live hospital pharmacy environment and tagging them with 2D barcodes identifying them as either legitimate, expired, previously authenticated, or falsified, the author investigated the effectiveness of medicine authentication technology in the hospital pharmacy setting. This objective comprised several key endpoints: 1. The operational authentication rate (OAR) or the percentage of medicines scanned as a proportion of those that entered the process, 2. The technical detection rate (TDR) or the ability of the technology itself to read the medicine's bar code, and 3. The operational detection rate (ODR), which measures the number of medicines quarantined by staff as a proportion of those identified as requiring quarantine (Naughton et al., 2016). The key finding was that while the technical detection rate was within expected parameters, the operational authentication rate was lower than expected at ~66%. This highlights the importance of the human element when interacting with this system and indicates that the compliance of staff to follow the protocol is key. This study suggested policymakers must ensure protocols are put in place that maximise

ease of use when authenticating medical products in the hospital environment. In terms of solutions to this issue, we contend that considerations should be made on a facility-by-facility basis when implementing medicine authentication technology in hospitals (Naughton, 2019). As mentioned earlier, context is key and factors such as reliability of Wi-Fi across the facility should also be considered to ensure smooth running of the required authentication devices. Care should also be taken to design protocols that do not fuel non-compliance by being overly time- or effort-consuming, detracting from other day-to-day tasks (Carthey et al., 2011; Naughton et al., 2016; Frontini, 2017). Innovative training regimens are also valuable in ensuring continued application of good practice in medicine authentication (Naughton, 2019). This need is further highlighted by the sub-par operational detection rate (ODR), indicating staff in the study were identifying medicines as SF, but failing to quarantine them properly. The context in which traceability technology is used is different and may require adjustments to match each context. These iterative improvements and modifications to medicine authentication technology when performed responsibly are valuable and likely to improve the effectiveness of the technology (Naughton et al., 2017).

Medicine traceability and responsible innovation

Over the past decade or so there has been extensive debate on the usefulness of blockchain technology for serialisation and traceability data. Blockchain is a novel technology that provides a basis for parties across all sectors to engage in more transparent and secure exchanges of information (Casino, Dasaklis & Patsakis, 2019). It has been argued that blockchain can be utilised to digitise the supply chain and one with greater protection from substandard and falsified medicine incursion, specifically to reduce the number of unique serial code breaches (Mackey & Nayyar, 2017). Implementing blockchain across other sectors has shown to come with a high-energy cost, and questions remain regarding its net worth in todays climate-focused world (Islam et al., 2020). As with all emerging technologies, the usefulness of the modality should be carefully weighed up against its costs. We would emphasise the importance of thoroughly assessing the evidence of any technologies in terms of effectiveness and value generated before investment.

The FMD mandated medicine authentication technology is focused on enabling positive change in the fight against substandard medicines, and the stakeholders in this change are clear: manufacturers, wholesalers, hospitals and pharmacies. In the eyes of the FMD, the patient does exist as one of these key stakeholders. This approach runs parallel to the Pharmaceutical and MedTech industry

overall, whose approach in recent years has been to increase patient centricity (Du Plessis et al., 2017). In the future, the FMD and associated technology may evolve to enable patients themselves to verify the medical products they possess are legitimate. Empowering patients in this way could be valuable in the fight against substandard and falsified medicines.

Several other key challenges have been noted since the FMD was fully implemented in 2019. A key aspect of the FMD is authentication of medicines at the point of dispensing from the pharmacy to the patient. Introducing this element to an already convoluted dispensing process either in the community or the hospital setting has drawn criticism that it increases the chances of dispensing errors that may detrimentally impact treatment quality for patients. Proper training is required across the supply chain to ensure that verification scans are conducted effectively, from the manufacturer all the way through to the dispensing physician. Indeed, studies on the effectiveness of the FMD mandated protocols have so far shown that the interference of human error can significantly reduce the effectiveness of the verification process (Naughton, 2019).

A follow-on challenge here is that the healthcare workers, already inundated with compulsory methodologies and protocols, have gained another set of checkboxes in the FMD mandated medicine authentication process (Frontini, 2017). With these vital staff already stretched to breaking point dealing with the long-lasting impact of the COVID-19 pandemic, there may be an argument that the extra time taken to scan and verify the authenticity of medicines is an unwelcome distraction from more important tasks. This is especially important to consider in settings such as the UK and the EU, which have an arguably lower prevalence of SF medicines compared to LMICs (McManus & Naughton, 2020).

Beyond the implementational barrier discussed in this chapter, the FMD has vast potential to reshape the landscape of medical safety across Europe. The FMD can protect patients from the worst effects of substandard and falsified medicines and safeguard EU economies from the subsequent drain on resources. While the key advantage of the legislation is preventing potentially dangerous medical products from finding their way into the hands of patients, the FMD also has several secondary advantages. It provides a thorough mechanism through which substandard medical products can be recalled. The dispensing of substandard medical products makes up most of the substandard and falsified burden in high-income countries. For example, in the UK between 2012 and 2020, 325 of the 342 medicines recalled by the Medicines and Healthcare products Regulatory Agency (MHRA) were found to be substandard – just 17

were recalled due to instances of falsification (Naughton & Akgul, 2021). The FMD serves as a valuable line of communication between HCPs at point of care and regulatory bodies acting at a higher level to reduce the risk of SF medicines.

The use of a centralised system for storing data on medicines creates opportunities for supply chain optimisation provided companies are allowed access to these. The richness of these datasets – formed of every medical product's digital signature left upon dispensation – might allow manufacturers access to insights on how and when patients access medications. Factors such as the setting and timing of dispensing provide contextual clues that the industry could hypothetically utilise to make their products more patient centric, improve access or drive healthy competition in crowded therapy areas.

Another benefit of this centralised system is the potential for live monitoring of supply chain health. Tracking the movement of medical products in this way allows the FMD to act as an early warning system of product shortages. This is especially useful in pandemics when supply chains are stretched to their limits. As discussed earlier, it is during these contextual shifts that SF medicines tend to thrive.

Medicine authentication technologies are here to stay, as they are enshrined in law. As discussed previously, there are enormous patient safety benefits for traceability technology. There is also future potential of this technology and its data, including the use of blockchain, patient level verification of medicines, and supply chain analytics and optimisation. However, these innovative benefits can only be achieved if the shortcoming of the technology are appreciated and if the stakeholders involved in these proposed innovations are engaged with appropriately. Taking a responsible innovation approach is one way of managing these stakeholders and the risks associated with medicine traceability innovation. Responsible innovation is a framework designed to encourage innovation presently, without harming the future (Iakovleva, T., Oftedal, E.M. and Bessant, J.R., 2019)(Naughton, B., Dopson, S., and Iakovleva, T (2023). The Responsible innovation framework contains five dimensions, 1. Anticipatory governance: this activity helps one to foresee risks associated with the innovation, 2. Inclusion: is the act of including the right stakeholders when innovating to ensure all relevant views are considered, 3. Reflexivity: is about challenging your own innovation assumptions and the assumptions of others in an objective way and 4. Responsivity: this is centered around making changes to your innovation based on stakeholder engagement. Impact: Appreciating the impact which has been delivered from steps 1-4 and building on that success to reinforce responsible innovation practice. By adopting a responsible innovation (RI) approach to the management of this technology we can ensure that the technology is safe, suitable

and effective according to the views of its stakeholders. This RI approach, through inclusivity facilitates the adaptation of the technology to different contexts to ensure it is accepted by its community, giving it the best chance of success. If this approach is used effectively, it can improve compliance with the technology and therefore data integrity of the central databases. This will have a positive impact on patient safety and benefit the double bottom line, i.e., the innovators and society. In the next section, we move on from looking at technological approaches in the high income setting and consider how these may be applied in low- and lower-middle -income countries.

Implementation of legislation and technology in low and lower-middle-income countries

Putting legislative and technological tools into action to mitigate the threat of SF medicines is needed by countries and regions across the globe. However, this need is amplified in lower-income settings for three main reasons: first, the size of the SF issue in these countries. Secondly, the reduced ability of resource-constrained national regulatory bodies to address the issue, and thirdly the resultant vicious cycle of consequences for governments and patients in these geographies. Below, we take the continent of Africa as an example to illustrate the challenges faced by low- and lower-middle-income countries.

The size of the issue

The majority of the 55 nations making up Africa fall into the low- or lower-middle-income bracket as defined by the World Bank at the time of publishing (World Bank, 2023). Home to over a billion people, Africa is disproportionately impacted by its disease burden. Not only are rates of disease generally higher than in the Western world, those that impact the continent are more likely to cause significant barriers for healthcare systems (African Medicine Agency (AMA) Treaty | African Union, 2020). The WHO has reported that 90% of all malaria cases occur in Africa, and 60% of those living with HIV/AIDS reside on the continent (Ncube, Dube & Ward, 2021). Beyond this, the prevalence of SF medicines is substantial. Estimates vary; however, it has been noted that the estimated prevalence of SF medicines could be as high as 18.7% on average across the continent – a marked increase on the WHO's global average prevalence of 10.5% (WHO, 2017; Ozawa et al., 2018).

Reduced ability to address the issue

Ability to address the issue of SF medicines is reduced in lower-income countries compared to higher-income countries. In Africa, it has been observed that there is a lack of clarity and coherence in existing regulatory frameworks, and in some cases a lack of a regulatory body to manage the threat of SF medicines altogether (Ncube, Dube & Ward, 2021). Additionally, there is a scarcity of competent regulatory professionals and a high rate of staff turnover in national regulatory bodies, which also hinders the progression of these organisations to become high functioning protective entities (Ncube, Dube & Ward, 2021). Poor management and surveillance of supply chains, with a higher frequency of stock-outs that promote SF medical incursions has also been noted as contributing factors (Ozawa et al., 2018). These issues were deemed so pressing across the continent that the African Medicines Agency was formed. This is a continent-wide organisation with the goals of improving and standardising regulatory activities within and between countries, ensuring better access to safe medicines. This body in part seeks to improve the resources and technical capacity required to fight SF medicines, as well as removing previous organisational barriers preventing countries from working together on the issue (Ncube, Dube & Ward, 2021).

The vicious cycle of consequences in LICs and LMICs

The impact of SF medicine incursions into the supply chain varies from country to country and across economic classifications. In lower-income countries, this impact can become amplified and result in a feedback loop of SF incursions that becomes challenging to stop. Exposure to substandard medicines results in poor treatment outcomes for patients, often increasing morbidity and mortality (WHO, 2022). A consequence of this is that the nation must invest more resources in re-treating these patients correctly, which in turn reduces the resources available to prevent SF medicines from inserting themselves into the supply chain at the source. As mentioned previously, discovery by the patient that their therapy is substandard or falsified erodes trust in healthcare professionals and leads to increased usage of grey markets and self-care methodologies – avenues that may further result in SF medicine exposure (Østergaard, 2015). The lost productivity from substandard treatments, as patients remain sick and away from work, further cements the nation's challenging economic status, reduces resources available to tackle the SF issue and further facilitates the vicious cycle. By contrast, we contend that HICs with highly-funded and effective regulatory bodies can more swiftly prevent, detect, and respond to SF

incursions, establishing virtuous cycles of trust and good health for patients and healthcare authorities.

Challenges in LICs and LMICs and the role of responsible innovation

With an understanding of why it is important to alleviate the pressures of SF medicines by implementing legislation and technology in LICs and LMICs, we can consider the key elements to making this a reality. As noted in a policy paper from 2022, on the traceability of medical products, the WHO has listed several key elements for implementing a functioning traceability system to mitigate the threat of SF medicines (WHO, 2022). The recommendations provided are a wide range from the less resource-intensive – for example, aligning on the use of global standards – to the more challenging for LICs and LMICs to implement, such as the recommendation to implement a full track-and-trace system, which demands verification of each medical product at each stage in the journey, rather than simply at the point of dispensing (Naughton, 2018). The list covers the fundamentals of traceability systems, such as ensuring unit-level serialisation, and enabling patient-level verification (WHO, 2022). Resources such as these are valuable to countries seeking to implement legislation and technology to combat SF medicines; however, we contend that LICs and LMICs should be realistic in terms of their implementation of these recommendations. Due to the scarcity of resources discussed earlier in this section, these nations should be judicious and economical in their application of legislative approaches and technologies. Creative solutions should be used to maximise the completeness of the traceability system implemented with the resources available. These solutions should also seek to address the specific contextual obstacles faced in each environment. For example, countries with severely restricted regulatory tools and equipment could seek to implement point of dispensation verification via usage of smartphones rather than dedicated authentication equipment, the precedent for which already exists (Ciapponi et al., 2021). Allowing patient verification in lieu of verification by regulatory professionals also alleviates human resourcing strain in settings where workforce headcount is an issue. This patient level approach would reduce the burden on an already stretched healthcare systems.

Another potential solution to ensure smooth running of traceability systems in these countries is the prior investigation of strong and consistent internet connections at sites where verification of medical products takes place. A stable connection is required for correct and efficient processing of medicines during the authentication process. Therefore, nations should engage with IT providers

in the pilot stages to identify potential pitfalls before they occur (Naughton, B., 2018).

Designing a comprehensive training programme for staff who detect and respond to SF medicines is vital and can be achieved in a resource-friendly way, utilising innovative digital channels to onboard these staff members if possible, to reduce the time spent by senior regulatory staff who are needed elsewhere. This will allow for greater compliance and will ensure that correct actions are taken when SF medicines are identified, without costing valuable time for these key team members (Naughton et al., 2017).

To achieve the potential benefits of serialisation and traceability technology in low-income countries we recommend that policymakers and healthcare providers adopt a responsible innovation approach. Implementing traceability technology in the same way as higher-income countries is unlikely to be successful. Instead, we suggest a responsible innovation approach with a focus on the engagement with relevant stakeholders and anticipating governance issues and contextual factors that may hinder the successful implementation of the technology in an effort to ensure the technology delivers according to the needs of the nation. A responsible innovation approach will provide a thorough understanding of the challenges facing LICs and LMICs who wish to implement traceability legislation and technology in their geographies. Those assigning resources can make better decisions to reduce the SF medical burden as much as possible, breaking the vicious cycle, and fostering better outcomes for patients. The authors contend that spending correctly on the basic building blocks of traceability systems in a responsible way as outlined above should be the first port of call for low- and lower-income countries, providing a strong foundation for further implementation down the line.

Conclusion

In closing, when it comes to medicine quality and medicine traceability legislation, technology, and its implementation in both lower- and higher-income countries, there are three concepts that are worthy of important consideration: prevalence, context and responsible innovation.

The international implementation of medicine traceability will result in an enormous quantity of data relating to SF medicines in higher-income countries, which could be used to better understand the problem of SF medicines. However, it remains to be seen how the approach used in Europe or the US will translate to lower-income countries, which typically have poorer information technology infrastructure. We are confident that medicine traceability can play

a far-reaching and important role in the fight against SF medicine. However, it will face some significant challenges on its road to success.

Firstly, on the topic of prevalence, like current medicine sampling studies, medicine traceability data is focused on quantitative data. Quantitative data without subsequent thorough investigation and transparent reporting, does not shed much light on which contexts results in the proliferation of the production and distribution SF medicine. Without further understanding of the contexts surrounding each SF medicine case in current medicine sampling studies or future medicine authentication data, it is difficult to ever conceive a move from measurement to prediction. And without appropriate measurement and understanding of the context it is hard to understand the best traceability approach for a given region.

Secondly organisational context will play a big part in medicine medicine serialisaiton systems as poor medicine authentication practice will result in incomplete datasets. When it comes to implementation it will be important to understand that the factors facilitating successful adoption of medicine traceability technology in high-income countries may not be replicated in lower-income contexts.

Through adopting a responsible innovation approach, the implementation of medicine traceability can be managed (Stilgoe, Owen & Macnaghten, 2013; Iakovleva, Oftedal & Bessant, 2019). This approach is centered around making changes to your innovation based on stakeholder engagement. By taking this approach it is likely that many of the implementation issues within a given context in low-income countries will be revealed allowing for the technology or the adoption approach to be adjusted.

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8

HOW TECHNOLOGY CAN HELP SOLVE SUBSTANDARD MEDICINE PROBLEMS: A CASE STUDY ON THE DIGITAL MEDICINE SUPPLY CHAIN PLATFORM MED4ALL

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An estimated one in 10 medicines in low- and middle-income countries (LMICs) are substandard and falsified (Akpobolokemi, Martinez-Nunez & Raimi-Abraham, 2022; Roth, Biggs & Bempong, 2019; World Health Organization, 2017). Substandard medicines are authorised products that fail to meet either their quality standards or specifications, whereas falsified medicines are products that deliberately or fraudulently misrepresent their identity, composition, or source (World Health Organization, 2018). The use of substandard and falsified medicines is a global concern especially in LMICs, where pharmaceutical supply chain processes can be less robust (Roth et al., 2019; World Health Organization, 2017). Manufacturing errors, inadequate storage or poor distribution practices contribute to the incidence of substandard medicines, whiles economic exploitations generally promote production of falsified medicines (Bekoe et al., 2020; Roth et al., 2019).

In many LMICs, the market of pharmaceutical wholesalers and distributors is largely fragmented, with too many intermediaries and small, inefficient firms.

Medicines can enter the medicines supply chain in many ways, starting with the supply of ingredients for the manufacture of medicines and subsequently through storage and distribution (Bekoe et al., 2020; McManus & Naughton, 2020; Ministry of Health, 2012; Privett & Gonsalvez, 2014; Wada et al., 2022). There is evidence that the longer the chain of supply before medicines get to health facilities, the easier it is for substandard and falsified medicines to infiltrate the supply chain system (Privett & Gonsalvez, 2014; Wada et al., 2022).

The health system in Ghana

Ghana seeks to improve the health status of all people living in the country through the provision of universal access to affordable, quality health services and the development of guiding policies and effective systems (Ministry of Health, 2020). Ghana is committed to Universal Health Coverage (UHC), delivered through the National Health Insurance Scheme (NHIS), which has about 16 million active members, comprising approximately 50% of the population.

Ghana's public health system is organised hierarchically, with substantial overlap and decentralisation of pharmaceutical supply chain responsibilities (Ministry of Health, 2012, 2020). At the top is the Ministry of Health (MoH) and its agencies, collectively responsible for establishing policies, regulating the sector, and coordinating the allocation of resources. The procurement and supply chain directorate of the MoH and its agencies, such as the Food and Drugs Authority (FDA) and the National Health Insurance Authority (NHIA), contribute to the health sector pharmaceutical supply chain management.

Pharmaceutical supply chain

The current supply chain involves several layers of storage and distribution. Two main central level warehouses have been created after the 2015 Central Medical Stores fire left product storage to be spread across multiple central level entities. The central warehouses are: (1) the Imperial Health Sciences (IHS), a private sector pharma-grade warehouse that holds products donated by the Global Fund (GF) and USAID and (2) the Temporary Central Medical Store (TCMS) where products stored are procured by other donor agencies, the MoH, and Ghana Health Service (GHS) (USAID, 2020). The public TCMS and private IHS in turn supply the country's 10 Regional Medical Stores (RMSs) and four teaching hospitals.

Commodities are distributed from the IHS warehouse to RMSs by third-party logistics (3PL) providers contracted by GF and USAID through the Global

Health Supply Chain-Procurement and Supply Management (GHSC-PSM). These deliveries are scheduled to occur six times a year, though there are some inherent delays in the process (USAID, 2020). The RMSs often send trucks to pick products up from the TCMS. From each of the 10 RMSs, the products flow directly to service delivery points (SDPs). At the SDP level, multiple types of health facilities in Ghana provide decreasing levels of health services – namely, regional and district hospitals, polyclinics, health centres, clinics, and community-based health planning and services (CHPS) facilities (Ministry of Health, 2020; USAID, 2020).

In 2016, the World Bank estimated that Ghana has 3500 public, private, and faith-based healthcare facilities. A total of 57% of these facilities are public, 33% are private, and 7% are operated by the Christian Health Association of Ghana (CHAG). The share of private facilities ranges from 5.4% in the Northern region, to 74.9% in the Greater Accra region (Wang, Otoo, & Dsane-Selby, 2017). At the lowest levels, district health administrations (DHAs) play vital roles in managing the supply chain for smaller facilities, especially in rural and difficult-to-reach communities, thus, supporting professionals, ensuring availability of essential medicines, balancing demand and stock across facilities, consolidating and relaying financial and logistics information, and managing accountability for insurance claims (Ministry of Health, 2020; Wang et al., 2017).

In Ghana, funding is a major challenge throughout the public health system, with implications for the country's pharmaceutical supply chain. The NHIS is faced with persistent underfunding and liquidity challenges that have undermined the public health supply chain (Aryeetey, Nonvignon, Amissah, Buckle, & Aikins, 2016). The NHIS reimbursements to facilities are often not only significantly delayed, averaging eight to 10 months in 2016, but also rarely reflect market prices (Aryeetey et al., 2016; Wang et al., 2017). The supply chain is therefore marred by payment delays and long-standing indebtedness from the NHIA to facilities, from facilities to the RMSs, and from the RMS to the CMS. The delays and debts have a significant impact on the ability of the CMS and RMSs to complete future procurements (Aryeetey et al., 2016; Wang et al., 2017).

Pharmaceutical market in Ghana

The total health spending in Ghana is estimated to be just under USD1.2 billion with almost USD0.3 billion (25%) spent on pharmaceuticals (Wang et al., 2017). Imports comprise 70–80% of total pharmaceuticals by value, as most domestic manufacturers can produce only low-cost generic drugs. The dependence on imported pharmaceuticals therefore exposes the NHIS to price changes and exchange-rate volatility. An estimated 80% of pharmaceuticals

dispensed in public health facilities are procured by the RMSs, teaching hospitals, or downstream facilities directly from private distributors. The private sector in Ghana is dominant in the supply and distribution of medicines to both public and private facilities (Wang et al., 2017). The funding shortages and stock-outs at higher levels of the supply chain have resulted in increasing issuance of documented evidence that certify that these medicines are not available (i.e., "certificates of non-availability"), thus, allowing nodes down the chain to buy directly from the private sector. This procurement process makes quality control and price regulation challenging and results in redundant administrative burdens throughout the system, while leading to risks of introduction of substandard and falsified medicines (Brako, Asante & Akosah, 2016). For example, the Ministry of Health in 2013 noted that 90% of oxytocin (a widely-used uterotonic) tested in Ghana was substandard, exposing some of the inefficiencies in the country's quality control system and the ability to detect these substandard and falsified medicines early.

In addition, the inefficiencies in the procurement process is in part caused by the many middlemen within the supply chain system, poor forecasting by facilities, lack of skilled personnel, lack of functioning medicine inventory management systems, and long delivery lead times (Brako et al., 2016; USAID, 2020; USAID | DELIVER PROJECT, 2016).

Specific to small and medium enterprises (SMEs) for example, liquidity constraint is a major problem, yet, they often experience working capital shortages due to the long insurance claim reimbursement times of the NHIA (Attrams & Tshehla, 2022). Accessing finances to bridge these shortages is nearly impossible, as banks perceive support to health SMEs to be too risky (Attrams & Tshehla, 2022). As a result, health SMEs are often unable to pay suppliers on time or order in volumes, forcing them to take supplier credit and buy at uncompetitive prices.

To address some of these challenges within the medicines supply chain system, there is growing interest in the use of technologies in optimising decision-making, improving service-level coordination, lowering inventory and supply chain costs, as well as reducing risks with sub-standardisation and falsification (Brako et al., 2016; Saha et al., 2022; Sylim et al., 2018).

In this chapter, we describe how digital technology could be harnessed to enable medicines' supply chain systems to be optimal using the Med4All digital platform, which allows providers to place orders and track their inventory, as a case study. Our goal is to describe the Med4All model and share reflections on the overall model experience, including successes and challenges.

Creating shorter, more integrated medicines supply chain: A case study of the Med4All model

In Ghana, poor medicines availability, high prices of medicines, and unreliable quality of drugs have been reported as major challenges to healthcare systems (Koduah et al., 2022), and the Med4All platform aims to improve access to quality medicines and make them affordable for low-income families. This platform allows healthcare providers to digitally request and track their medicine's inventory along the supply chain.

The Med4All digital platform connects healthcare facilities directly to pre-qualified medicine suppliers where direct access to quality medicines can be achieved at the right prices and without intermediaries. Similarly, the selected medicine suppliers on the Med4All platform are able to provide direct information about their best prices, delivery dates, volume-based discounts and payment conditions to these prospective health facilities. The platform has so far provided medicines to cover more than 400 000 patient visits at connected health facilities (Med4All Half-year Report, 2022).

The Med4All strategy focuses on developing a data-driven scalable model by testing supplier-side and provider-side interventions to rapidly improve the proposition for both health facilities and suppliers, while building a strong network of facilities. A scalable model will enable Med4All to sustainably reach more patients with quality and affordable medicines. It encompasses pooling procurement of facilities, digitally setting price levels for the medicines, placing orders, and tracking quality of medicines, as well as channelling payments.

The business model requires a critical mass of health facilities and suppliers at any point in accordance with the business case. This increases revenue generation on the platform and makes it more sustainable. The health service providers are expected to channel their medicine procurement needs through the platform according to their quarterly forecast, while the suppliers are expected to deliver the orders timely and completely to the doorsteps of the providers.

Med4All has adopted a phased incremental implementation approach. In November 2019, a pilot was started with 29 health facilities on the Med4All platform, ordering medicines on a quarterly basis from four suppliers. After successful implementation, the scope was widened to 60 health facilities and 10 suppliers at the end of 2021. In 2022, the Med4All platform hosted 13 pharmaceutical suppliers with 287 different medicine molecules, which translated to 403 different brands of medicines. The medicines covered most

of the common acute and chronic conditions recorded in the health facilities in the country.

Scope of the Med4All programme

The overall project scope includes the implementation of a regulated digital marketplace to help providers benefit from better prices provided by collective negotiation power with suppliers. The key incentives for suppliers are the high volume of business available to them on the platform and the early payment options for their deliveries. The other benefits of this marketplace include adherence to procurement policies, maintenance of quality of medicines throughout the procurement lifecycle, timely delivery of medicines, and introduction of financing opportunities for suppliers and providers.

For health facilities to participate, they must have a simple electronic inventory management system and meet minimum requirements on IT hardware and connectivity. Health facilities forecast their consumptions per type of medicines, and suppliers are invited to tender for these medicines. Tenders are then awarded following further eligibility assessments.

The Med4All Process: How it works

Figure 1 illustrates the Med4All strategies and processes involved in its activities and operations. These are:

1. Selection of health facilities and suppliers. At the pilot phase, facilities were selected to represent all facility types and various church denominations within the CHAG network. The suppliers are selected based on their capacities to deliver medicines to every part of the country and having a wide range of medicines.

   Med4All works with suppliers to secure the supply chain and with Ghana's Food and Drugs Authority to establish a list of essential medicines that are available on the platform. All medicine suppliers who are invited to trade their medicines on the platform have been licensed by the FDA in Ghana. The FDA licenses both the suppliers and the medicines provided by them.

2. The selected health facilities then forecast their consumption rates per type of medicine and the Med4All platform pools the forecasts and invites suppliers to tender for medicines requested.

3. The medicines suppliers are then awarded tenders for different types of medicines for a 12-month period. This award is usually based on price, quantity, and quality criteria. The criteria include packaging, labelling

requirements, product registration with the FDA and supplier registration as the market authorisation holder for the medicines.

4. The barcodes of the medicines that are dispatched are shared for facilities to scan upon arrival. This ensures that the right medicines that are ordered arrive at facilities.
5. After matching the barcodes with those uploaded by the supplier, payment is made promptly using a digital payment function within the platform.

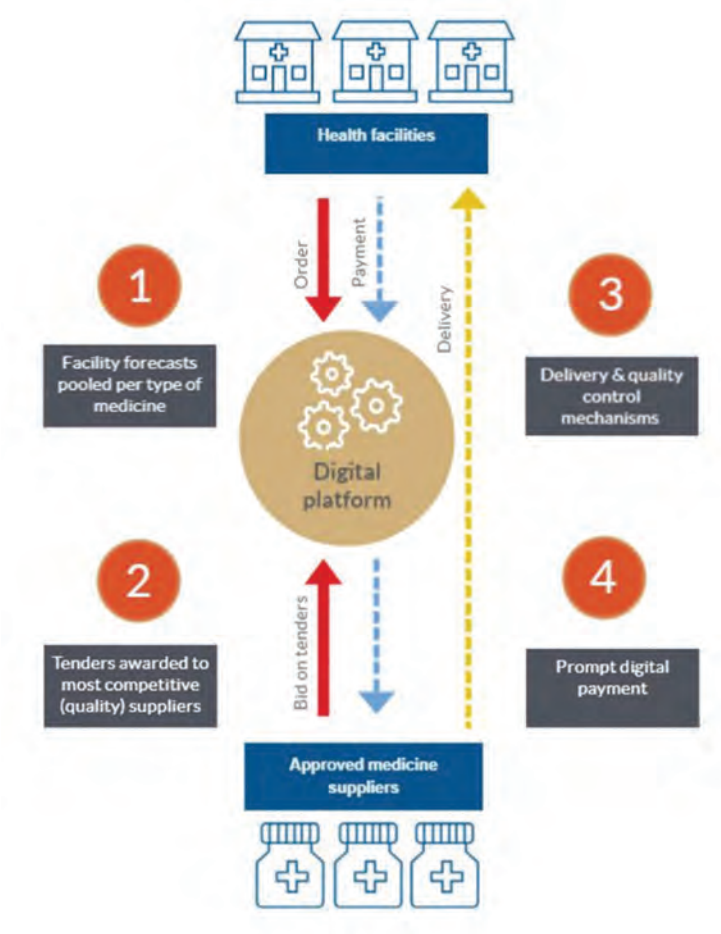

Fig. 1: How the Med4All digital supply chain platform works.
(Source: Digital Supply Chain Platform for Medicines – A PharmAccess Report)

Complementing methods are used to ensure quality control. These include eligibility assessments, random screening and monitoring of a sample of medicines, in collaboration with the FDA in Ghana, and additional assessments of the products that fail the random monitoring tests.

In an anticipated blockchain model (to be developed in a later phase), the quality assurance process is expected to be logged throughout the supply chain, from the time medicines leave a supplier, to the time they are dispensed to the patient. This will enable tracing of substandard and falsified medicines to the point of origin.

Med4All's partnerships

Med4All is a joint collaboration between PharmAccess and CHAG. Med4All was set up by PharmAccess as a regulated digital medicine supply chain platform in response to the disrupted pharmaceutical supply chain in Ghana, where prices were high, and medicines were at risk of being either falsified or substandard. The goal of PharmAccess is to make inclusive health markets work in Sub-Saharan Africa (SSA). PharmAccess challenges the notion that exclusion from essential healthcare is an inevitable consequence of living in poorer countries and identifies the opportunities and partners – both private and public, needed to bring about holistic transformation in failing health markets. PharmAccess works with an integrated approach that addresses both the demand and supply side of the healthcare system and uses the opportunities that mobile technology and data provide to leapfrog development in health markets in SSA. In doing so, PharmAccess and CHAG have established a joint venture Med4All company with a Board of Directors made up of representatives of both organisations.

CHAG is a Network of 344 health facilities and health training institutions owned by 34 different Christian Church Denominations. CHAG provides healthcare delivery to over six million people in Ghana. This includes the most vulnerable and underprivileged populations in all regions of Ghana, particularly in remote areas.

The Medical Credit Fund (MCF), part of the PharmAccess Group, complements the Med4All joint venture by facilitating affordable access to credit for facilities to pre-finance medicine stocks. MCF develops digital loan products to pre-finance medicine purchases for health facilities and enable timely payment to suppliers, as well as providing credit to facilities to upgrade their facilities or invest in better stock management.

Quality of medicines is ensured through complementing tools and methods, including a partnership with Ghana's FDA and Ministry of Health (MoH)

to ensure the Med4All marketplace only allows fully licensed suppliers and manufacturers. The FDA plays an important role by pre-qualifying licensed suppliers on the platform in line with its regulatory mandate in addition to playing a role in pre- and post-market quality surveys of medicines and medical supplies.

Governance and management

To ensure the success of the Med4All programme, the following governance and management structure is adopted (Figure 2), which relies on a team of multidimensional staff from PharmAccess and CHAG for the programme. In Ghana, the core team is composed of five members: the Med4All Director, Business Development Manager, Procurement Officer, Quality Officer and Customer Success Officer.

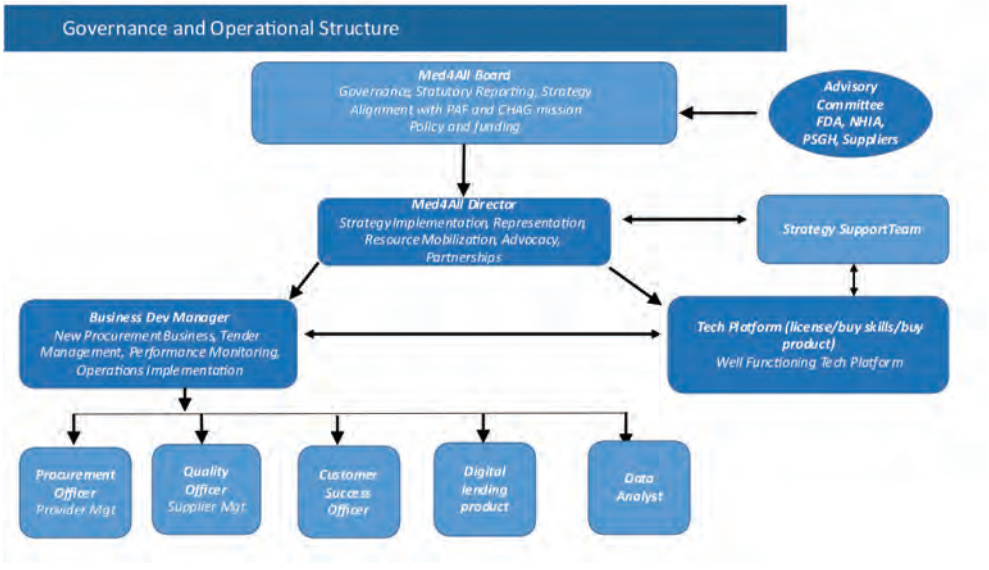

Fig. 2: Governance and management structure of Med4All

Value proposition of Med4All

The unique value propositions of the Med4All supply chain model are:
Use of digital technology for efficient management of stocks from procurement to dispensing.
Built-in quality authentication mechanisms to eliminate substandard medicines
Cost reduction of the procurement, supply and delivery of medicines through the use of digital technology.
Cost reduction in the price of medicines from economies of scale gained through bulk procurement.
Better management of stocks, ability to forecast and reduction in stock-outs.
Brand equity of two trusted not-for-profit organisations with keen interest in Ghana's healthcare system.
Bulk procurement advantages.

Health intelligence data on usage of medicines, identification of locations of drugs hot spots and shortages, predictions of drugs consumption and therefore more efficiency.
Benchmarking of drug quality of healthcare facility versus other facilities in neighbourhood or elsewhere in Ghana.

The Med4All model experience: successes and challenges

The platform has played key roles for consumers, healthcare facilities, suppliers, and regulators. Generally, patients have access to affordable, quality medicines. Health facilities have sufficient medicine stocks at a lower cost and achieved an average of 30% lower medicine prices for patients. Clinics and policymakers have access to previously unavailable data on the medicines supply chain. The availability of data also creates insights for policymakers while participating suppliers benefit through new customers, high volume sales, lower marketing costs, a marketing value-add, and timely payments.

So far, the Med4All platform has resulted in improved lead time for orders, with some medicines being delivered within 48 hours of being ordered (Med4All Half-Year Report, 2022). In the first quarter of 2022, the platform saw an upswing in lead times and provider orders. Also, within six weeks, a high number of 21 providers placed orders, with four providers placing orders for the first time since the inception of the platform.

Med4All has also led to an increased volume of medicine orders by facilities, and a higher volume of order fulfilment, with an increasing number of suppliers delivering higher volumes of total medicines ordered. Overall, the Med4All programme is composed of mutually reinforcing activity lines, which has attempted to address the problems of medicine availability, affordability, quality and sustainability.

Availability

Availability is defined from the health provider point of view with the objective of making essential medicines available to order when a health provider needs them. At the initial period of implementation of Med4All platform, there was an identified need to address the issues pertaining to medicine availability. The modest order frequency and volume, slow delivery times and low delivery rates affected medicines availability.

A more efficient ordering process to overcome the previous issues with slow delivery times and modest order sizes was considered, which was aimed at improving the requirements on the technology platform to optimise user experience for providers and suppliers. A simplified ordering process was implemented to improve the timeliness of quarterly orders, particularly for

remote areas, so that order volumes are larger and therefore more financially viable for suppliers to fulfil.

Under the current volatile pharmaceutical market in Ghana where suppliers are unwilling to give credit beyond 30 days (Asamoah, Abor & Opare, 2011), a revolving credit fund was instituted to enable suppliers to be paid faster, making the platform more attractive to suppliers, and thereby facilitating increased order fulfilment. This also offers providers a means to rely on to increase order volume and frequencies.

To reduce medicine waste and therefore increase availability, providers in the Med4All programme were trained in stock management procedures and processes. Training is critical to medicines' availability and the success of the supply chain (Iqbal, Geer & Dar, 2017). In addition, data-driven training in medicines management and quality assurance processes also help improve medicine inventory management. The training helps improve adherence to best procurement practices, preserve the quality of medicines during their shelf life, reduce stock-outs and eliminate wastage caused by medicine expiry (Halsbenning & Niemann, 2019; Seidman & Atun, 2017). Thus, the introduction of digital tools for medicine management and quality assurance in the Med4All model served as an additional avenue to support forecasting and inventory management beyond the training that was offered to the providers.

Med4All's desired impact is to reach about 11 million people with quality medicines through 300 CHAG facilities, and beyond this, scale to the rest of CHAG's network and other public and private providers. In terms of impact on medicines availability, Med4All aims to train 600 people in stock management and train 150 facilities in the use of digital tools for inventory management. The programme also aims at reduced average lead times per order to 14 days, reduce stock-outs, and provide more efficient medicine procurement.

Affordability

The Med4All platform aims to achieve reduced prices, reduced financial barriers, increased number and volume of orders and increased competitive advantage. To achieve this, Med4All targeted reported challenges associated with medicines affordability, such as inadequate access to credit, the presence of vested interests and side-buying (Lee, Kassab, Taha & Zainal, 2020). Providers on the Med4All platform could request credit to finance their orders through the MCF in partnership with local banks. The digital lending product from MCF, was aimed at expanding access to credit to finance orders, procure items, and facilitate better medicines stock management, such as warehouse equipment.

To assure suppliers that providers will settle debts incurred before they joined the Med4All platform, Med4All also established legacy debt payment plans for facilities. Legacy debts result from non-payment for medicines supplied over a prolonged period and this is often due to improper procurement practices. As these debts accumulate, suppliers may refuse to supply medicines to affected providers. Med4All has an arrangement with CHAG for the providers to agree to a payment plan with suppliers based on percentage deductions from the monthly NHIS reimbursements to settle legacy debts, with CHAG as guarantor.

Meanwhile, Med4All continues with bulk procurement on the platform to negotiate lower prices because of the link between bulk procurement and medicines affordability (Parmaksiz, Pisani, Bal & Kok, 2022). The model leverages the economies of scale of pooled annual medicines forecast of CHAG providers to negotiate with suppliers to achieve below-market prices for medicines on Med4All. It is expected that this will be realised despite the expected depreciation of the local currency against major currencies.

Near-cash (30 days) payment to suppliers incentivises suppliers to sell through the platform rather than selling to cash paying customers outside the platform (side-selling). As there are actors benefitting from the existing procurement inefficiencies, which is contributing to lower order volumes and frequencies, Med4All continuously identify inefficiencies and vested interests and address them. By addressing these barriers, more bulk orders can be channelled onto the platform to increase platform utilisation and therefore the bargaining power of Med4All to negotiate better prices with suppliers.

For the desired effect on medicines affordability, the programme aims at lower medicines prices for health facilities (down to acceptable international average), and increased cost-efficiency for the NHIA. Med4All also aims at a reduction in average medicine prices by 30% compared to market prices, and 100% of deliveries paid for within 30 days.

Quality

Continuous analysis of inefficiencies in the supply chain system help with better understanding of the implemented solutions that address the existing inefficiencies, to identify evolving inefficiencies and design mitigation measures to address them (Parmaksiz et al., 2022). For example, the Med4All team procured a medicine quality screening tool that detects substandard or falsified medicines. This is a handheld device that uses laser spectrograph to verify the chemical contents of medicines aligns with the original standard (Hajjou, Qin, Bradby, Bempong & Lukulay, 2013). By simply pointing the machine at some medicines and pressing a button, the operator gets a 'pass' or 'fail' in a

few seconds to confirm that the medicine conforms to the specifications and standards listed by the manufacturer upon which their marketing authorisations were granted. Staff have been trained in using the device and have teamed up with the FDA in Ghana and researchers within the University of Ghana to undertake a screening study of selected medicines in facilities participating in the Med4All programme. The target is to detect the substandard and falsified medicines in the supply chain to ensure that end users receive the right medicines with the right type of active ingredients in the right doses to treat or manage their conditions.

The long-term desired impact of the Med4All programme on medicines quality is to improve access to quality medicines, which invariably decrease morbidity, mortality, and associated productivity gains and confidence in the health system. Insights from such data will also support facilities and government to systematically ensure better quality control measures throughout the supply chain.

Sustainability

Having implemented the Med4All programme since 2019, there was the need to maintain the critical mass of providers and suppliers and engage them to actively use the platform in the first year. Subsequently, providers were incrementally added in Year 2 and 3, with the scale-up of providers planned to fully commence from Year 4 of implementation. In the scale-up approach for the Med4All programme, the following were considered:

- Pre-engagement of providers at the board, management and procurement team levels prior to onboarding to ascertain interest and willingness to patronise the platform.
- Purposeful selection of large health facilities for onboarding, to reach more patients with quality and affordable medicines while ensuring increased order volumes, and increased revenue on the platform. The plan is to incentivise suppliers and enhance the bargaining power of Med4All to negotiate for lower medicine prices using economies of scale. Over time, small and remotely located providers who are around selected large facilities will be onboarded to ensure inclusion and equity.
- Selection of providers who are closer to suppliers' warehouses to reduce delivery costs for suppliers, and improve delivery rates and delivery times.

- Consideration of providers who are closer to existing providers on the platform with the aim of facilitating bulk deliveries by suppliers along common delivery routes, reducing delivery cost and improving order fulfilment.

Challenges encountered and the way forward

Some challenges to the implementation of the Med4All were identified. First, due to the coronavirus disease (COVID-19) pandemic, there was a reduction in health facility attendance, leading to a drop in patient numbers, and reduction in orders for medicines. Second, there was also reduced availability of medicines from the side of suppliers due to the effects of COVID-19 on countries like India and China where most of the finished pharmaceutical products and active ingredients are imported from (Gupta et al., 2020; Jadhav, Singh, Targhotra & Chauhan, 2021). Second, the selection of facilities for onboarding onto the Med4All platform was done across all categories of providers, including facilities located in remote areas. This negatively impacted delivery times and made it less financially viable to deliver to facilities while having relatively small order volumes as well. Some suppliers also chose to sell to cash-paying customers within their own network who paid more than Med4All, leading to shortages in the availability of medicines on the platform. Third, the high inflation and the negative impact on the Ghanaian currency also negatively impacts on the supply chain of medicines in the country. With a decrease in the value of the currency and inflation, the overall purchasing power of the currency decreases. Therefore, it will take more money to buy goods and services, leading to high medicines production and distribution costs, since the cost of raw materials, labour, and transportation all increase.

Based on the above implementation considerations and challenges encountered, the foundation for a sustainable business case was made, and variations were made to the assumptions at the inception of the Med4All programme. These changes include stricter onboarding requirements to ensure financial viability, incentives to encourage providers to place more orders and measures to encourage open competition on the platform. Another step toward sustainability is the expansion strategy where in addition to increased orders from existing facilities, there will be the need to onboard new facilities. Therefore, the new business case outlines a plan to initially onboard two private for-profit facilities outside the CHAG network for testing and learning. Once the findings from this initial test are known, some private facilities may be brought onto the platform in the coming years while still prioritising CHAG providers. In addition, the technology platform will be enhanced to make it more user-

friendly. In projecting and sustaining the programme to the year 2025, Med4All is working towards a 60% market share of annual medicine procurement of CHAG health facilities, increased numbers and volumes of orders, providers becoming increasingly committed to the platform, creating an enabling policy environment and being able to demonstrate that the earnings model can finance the operations of Med4All.

Conclusion

Med4All has provided the digital platform that has helped in improving transparency of medicine quality, pooling procurement to lower prices and streamlining procurement to improve availability, while making the first steps toward a sustainable social enterprise. In an era where a high percentage of medicines are at risk of being either substandard or falsified, Med4All serves to bridge this gap, and also contributes to reducing the financial barrier to accessing good quality medicines in Ghana. However, some factors posed as challenges to the optimal implementation of the Med4All programme. These were; 1) A drop in health facility attendance and low patient numbers leading to a reduction in orders for medicines due to the COVID-19 pandemic; 2) The selection process for onboarding facilities onto the Med4All platform included all categories of providers, including those in remote areas, which led to longer delivery times and higher costs for facilities with small order volumes, making it less financially viable, and 3) A high level of the Ghanaian currency depreciation, which has increased price volatility and impacted negatively on the prices of medicines.

Despite these challenges, the Med4All platform as a case study demonstrates that through digital innovations, more people can be connected to quality healthcare including access to good quality medicines. Med4All contributes to efficiency in medicines procurement among member facilities, demonstrating impact among its connected facilities. Med4All can be adopted or adapted in other LMICs to improve their medicines supply chain system.

Changing healthcare markets in LMICs takes time. The next step then is to refine this impact and scale it.

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9

RISK AWARENESS IN MEDICINE ACCESS: METHODOLOGICAL REFLECTIONS FROM FIELDWORK IN A LOW-INCOME SETTING IN SOUTH AFRICA

Rui Liu, Susanne Lundin, Anja Smith, Thumakele Gosa, Paul Roviss Khambule and Elmi Muller

Introduction

Medication constitutes an important and almost self-evident component of life for most people around the world. The availability, however, whether it is biomedical or traditional medicine, depends on historical as well as cultural and socioeconomic factors (Whyte, Van der Geest & Hardon, 2002). This means that medicines for many populations are something desirable but unattainable. Against this background, the increasing spread of substandard and falsified (SF) medical products poses a large global health risk as they may circulate in pharmaceutical market grey zones and cause harm (Newton & Bond, 2019). Hence, understanding circumstances of people's medicine access is important.

While quantitative approaches are favoured in studying global health issues, a sociocultural approach is necessary to attend local particularities and contextualised dynamics (Adams, Burke & Whitmarsh, 2014; King, 2012). In this chapter, we reflect on how we have compared and made sense of our

empirical data generated through a combined use of quantitative and qualitative methods. The study was designed to investigate risk awareness of SF medical products among residents living in a low-income neighbourhood in South Africa. Our reflection on methodologies aims to provide insights about research design to study global health issues from sociocultural approaches.

This chapter is structured as follows. First, we present briefly the societal context of South Africa in relation to SF medical products. We also introduce in this section the low-income neighbourhood where the study was conducted. Such background information is essential as it impacted our methodological choices and the data-collection process. This is followed by a description of the research design, particularly our combined use of quantitative questionnaires and informal conversations. Next, we show how we have worked with these two data types, attempting to contextualise some obvious divergences between them. We then discuss the unspoken but hinted complex dynamics when making sense of quantitative and qualitative data. We conclude with methodological lessons learned from the fieldwork and from the use of mixed methods.

Context of data collection

Substandard and falsified (SF) medical products is an ongoing international issue and had been extensively reported in the literature (Newton & Bond, 2019). These medical products are unable to treat the intended target condition due to their substandard or even totally fake quality. Scientists from the fields of medicine, law and public health dominate research on SF medical products, with a focus mainly on the supply side, as well as on drug testing technologies and the harmonising of international legal frameworks (Attaran, 2015; Rebiere et al., 2017). This problem had also been tackled by the serialisation of pharmaceutical products (Cordon et al., 2016). However, there is significantly less knowledge of the demand side, in particular of people's awareness and perceived risks of these products (Liu & Lundin, 2016; Lundin & Liu, 2020). Considering the potential threatening effects of SF medical products on individuals and society, there is a need to investigate what knowledge exists among individuals and what the prevalent attitudes are with regards to consuming medicines outside the regulated market. To this end, studies with sociocultural approaches have shown that consumption of medicines is situated in everyday practices and that it needs to be examined at the intersection of political, economic and cultural forces (Lundin & Liu, 2020; Hall & Antonopoulos, 2016; Pisani et al., 2019).

South Africa has high public health expenditure on pharmaceuticals due to the heavy burden of both communicable diseases (HIV/TB) and a growing

burden of non-communicable diseases (Mayosi et al., 2012). South Africa also has the strongest pharmaceutical sector amongst Sub-Saharan African countries (Strengthening Phamraceutical Systems (SPS) Programme, 2011). However, a recent change in the pharmaceutical regulatory authority, from the Medicines Control Council to the South African Health Products Regulatory Authority, created backlogs and uncertainty while the new regulatory agency was in the set-up phase (Keyter et al., 2018). This combination of high medical expenditure and potentially still-weak pharmaceutical regulatory capacity due to the transition to a new regulatory authority provides the potential for SF medical products to spread.

Nonetheless, South Africa is lacking in its reporting to the World Health Organization's (WHO's) Medical Product Rapid Alert (World Health Organization, 2017a). The purpose of this alert system is to warn WHO member states of the existence of SF medical products and to encourage appropriate regulatory action by national medicine regulatory authorities or ministries of health to protect populations and supply chains. The absence of reporting does not, however, imply non-existence of SF medical products. Scattered evidence from a variety of sources suggests the circulation of ineffective medical products in South Africa (Knudsen & Nickels, 2015; Mashaba, 2018; Hornberger, 2018).

In addition, a 2011 Gallup poll showed that only one in four South Africans were aware that falsified medicines were in the country compared with much higher percentages of people being aware of the presence of these medicines in East and West African countries (Ogisi, 2011). This lack of awareness among the public potentially makes South Africa a target of falsified medicine traffickers (Knudsen & Nickels, 2015; Mashaba, 2018). South Africa is considered more vulnerable than its neighbours to the online distribution of these products due to relatively high internet penetration (Internet World Stats, 2020) and online purchase rates compared to other African countries (Masekesa, 2020).

The study we draw on in this chapter was conducted in Khayamnandi, a part of the town of Stellenbosch situated in the Western Cape province of South Africa. Khayamnandi is a low-income township in South Africa consisting of formal and informal houses. These informal houses are commonly known as 'shacks', and constructed of mostly tin. Townships refer to neighbourhood that were established in often underdeveloped, racially segregated urban areas of South Africa due to the racial segregation laws of South Africa during the apartheid era (Pernegger & Godehart, 2007).

At the time of the 2011 National Census, the majority of Khayamnandi residents (94.6%) were of Black African ethnic origin, with isiXhosa being the first language of most (84.9%) residents (Frith, 2011). It had a population of

24 645 in 2011, which has since grown significantly (Frith, 2011). There is no recent representative data available on average incomes in Khayamnandi. However, the average per capita income for Stellenbosch during 2016 was R61 871 (approximately $3 500 at current exchange rates) (socioeconomic profile, 2017). The average per capita income of Khayamnandi residents is likely to be lower than this, given the high income inequality in Stellenbosch (socioeconomic profile, 2017).

Research design and data collection

The study was organised and administrated by the authors in 2018. It was planned on the basis of a mixed-methods approach that has been proven useful in providing insights into the multifaceted nature of empirical data. Our take on the mixed-methods approach follows Donna Haraway's ground-breaking studies (Haraway, 1988) that have been applied and further developed in both social and cultural sciences, as well as natural disciplines, in recent decades. We underline that data is produced through specific ways of seeing and experiencing the world, and that it is best understood by methodological eclecticism by applying techniques from multiple scientific toolboxes (Ehn, Löfgren & Wilk, 2016; Luke, 2005; Lundin, Torkelson & Petersen, 2016; Tashakkori & Teddlie, 2010; Teddlie & Tashakkori, 2012). Guided by this understanding, the planning of our study is not merely built on a pre-set and fixed protocol, but rather on engaging in a process to encounter the unpredictable and unexpected happenings (Wibberley, 2012). This study, thus, is not designed to use either quantitative or qualitative methods, but strives for an acquisition of knowledge by identifying divergences or coherences between quantitative and qualitative data.

The quantitative data was acquired in the form of a pre-designed questionnaire, whereas qualitative data was obtained in the form of recorded conversations during the same time when the respondents answered the questionnaires. Data were collected by two fieldworkers (one male and one female) from the Khayamnandi community. Both were associated with the authors' project, trained by the authors and affiliated to a non-governmental organisation, IMBILA Strategic Services. IMBILA Strategic Services facilitated in recruiting respondents through the fieldworkers' personal networks in the research area. The fieldworkers met with individuals who showed an interest in the study. Fieldworkers then informed respondents about the study's aim, without specifically referring to SF medical products but to more general issues, such as whom people consulted when feeling sick, where they purchased medication and their use of medication.

We recruited five volunteers in the surveyed area to pre-test a preliminary version of the questionnaire. This step proved to be highly useful. We learned to make necessary adaptations to formulate our questions in a way that was more familiar to our respondents. Specifically, we took away technical terms from the initial version of the questionnaire and chose formulations well-known by the group amongst whom the research was conducted.

The questionnaire included thirteen questions. Forty-one adult respondents (≥18 years) participated in the survey. Although all questions in the survey were answered by the respondents, we have for this chapter chosen to analyse five of them, since these questions were particularly provocative in terms of stimulating conversations between respondents and the fieldworkers. These five questions are:

- Q1. Do you know if there is a difference between prescribed and non-prescribed medicine?
- Q2. Do you think it is safe to purchase prescribed medicines (without seeing a doctor before) from a local market, shops, neighbours, the Internet, etc.?
- Q3. Where do you normally receive/buy prescribed medicines?
- Q4: What factors do you consider when you purchase prescribed medicines? (Multiple mentions possible, total responses exceed)
- Q5. Have you ever questioned the quality and efficacy of the medicines you have purchased?

The questionnaire was written in the languages used by potential participants in the study, isiXhosa and English. The conversations around the questionnaires were transcribed in both languages by the fieldworkers, who speak isiXhosa as well as English. Given our intention of being methodologically eclectic, we also included the written notes made by the fieldworkers as additional empirical material. These notes comprised respondents' clarifications regarding their answers to the questionnaire, as well as fieldworkers' own reflections during their encounter with the respondents.

The study received ethical approval from the Health Research Ethics Committee (HREC) of the University of Cape Town (N18/10/109_RECIP_UCT_575/2017). Reciprocal ethical approval was also received from Stellenbosch University, South Africa. All research participants provided informed consent. They were anonymised in the data collection process and pseudonyms are used in the analysis presented here.

Unpacking the data

Given our mixed methods approach and intention of contextualising empirical data instead of seeking for objective answers, we compared results from the questionnaires with the recorded conversations. It is a well-documented phenomenon that oral conversations tend to provide more complex responses than closed-ended questions (Lewis-Beck, Bryman & Liao 2004). This finding also applied to our study. However, what makes this comparison interesting is that in several cases the same respondents did not simply offer more nuanced information when they commented orally on the questionnaire, but that their oral comments also appeared contradictory to the answers they ticked on the paper. This called for a deeper reflection on how the two types of data interact.

A reading of the results from the questionnaire shows that more than half of respondents (55.3%, n=21) claimed to be aware of the difference between prescribed medicines and non-prescribed ones. It also shows that over half of respondents (52.5%, n=21) acknowledged that it was not safe to purchase prescribed medicines (without seeing a doctor) at local market shops, from neighbours, the Internet or other sources. In addition, the majority of respondents (84%, n=33) stated that they normally bought their medicines from pharmacies or clinics. Moreover, price was considered the most important factor regarding where to purchase prescribed medicines. However, some respondents noted that they did not know what factors influenced their medicine purchasing decisions. Lastly, when it came to the reliability of medicines' therapeutic qualities, trust in the medicine quality was reported to be shared by over two-thirds of respondents.

Due to the small number of respondents, these results are far from being representative of a larger population in South Africa. What we want to highlight through the contribution of this data is that these results seem to indicate a fairly good level of trust among the respondents in the formal healthcare service and a relatively low awareness of poor-quality medicines. However, informed by a mixed-methods approach as presented earlier, in the following we show a more nuanced picture that in many ways challenges the general impression depicted in the survey data. We proceed to present this picture in the form of two prominent strands.

Cost that takes

Presented above, the majority of respondents stated they used clinics and pharmacies as healthcare providers. Purchasing medicines via the Internet or at local marketplaces was deemed by many as risky. Consequently, these respondents pointed to the importance of seeing a doctor before buying prescribed medicines. However, in the fieldworkers' handwritten notes on the survey we found that respondents, who had just emphasised the importance of a doctor's visit, "bought prescription drugs elsewhere" without receiving a prescription. This is well-illustrated in the conversation with 25-year-old Nonhlanhla. On the paper, Nonhlanhla said, her first option "should be to ask the nurse", but during the conversation she admitted that she always first self-diagnosed and self-medicated. She then explained that what hindered her from approaching formal medical care was because "it is crowded and stressful and there is only one doctor some day[s] during the week." This statement signals another layer of decision-making by the respondent when deciding about medicine use. Prices are numbers on the price tag, but there is also the opportunity cost of visiting an official healthcare environment, to use an economic concept, even though public clinics are free of charge. Consequently, Nonhlanhla only visited the clinics when "it's really necessary". Otherwise, she would purchase medication such as Med-Lemon, a well-known all-round cold and flu drug used by many in the respondent's neighbourhood, from local stores. These stores, as Nonhlanhla and other informants claimed, were often run by "Somali owners who have a reputation for selling low-quality goods." Another example comes from the 30-year-old Luzuko, who moved to Khaymandi in 2009 from a community outside of Cape Town. He said to the fieldworker that: "No, no, not to the clinic … well, it will depend on if the budget permits it." He also admitted to avoiding going to the clinic "because of the long time it takes waiting for help." The concern about long waiting time and all the stress around visiting doctors, as expressed by Luzuko and Nonhlanhla, turned out to be common among the respondents. From the conversation transcripts, we also noticed that many respondents spoke about their personal situations, including their economic status and family relations, which might also contribute to their decision-making processes when it comes to buying medication.

Another respondent, Onako, mother of a nine-month-old baby, stated in the survey that she trusted the expertise of the clinic and the pharmacy. Nevertheless, when the fieldworker wrote her answer on the paper, she emphasised the importance of being alert about the condition of the drug packaging purchased at the pharmacy. She would make sure that "it is similar to the one I got before" and "it is properly sealed compared to others I had before [that were not sealed,

authors' explanation]." In this scenario, what Onako means by "trusting" does not seem to correspond to her actual consumption practice. When she shares her strategies to check the quality of medicines, such as ensuring that the packages are properly sealed, it seems that the trust in formal healthcare services is rather flexible. We could infer that the medicines she buys at the pharmacy are not always properly packaged. In South Africa, it is common for pharmacists in the public sector as well as dispensing doctors to pack a small number of medicines in a small paper or plastic bag instead of dispensing a pre-packaged product (Patel et al., 2009). Clinic dispensaries also dispense medication in small plastic bags. Such handling may involve risk factors regarding the originality of the medicine, as well as cause uncertainty for the buyers. The oral comments made by Onako shows that she is well aware of such risks. In connection, this also aligns with the general perception shared among the South African public, that medicines supplied free of charge by public clinics were generally viewed as being of lower quality than those from private clinics (Patel et al., 2009).

Bonds that matter

Although most respondents claimed that they only sought care from medical providers at the clinic (mostly nurses) or in some cases a private doctor, the actual circumstances in which this care was obtained seemed different. Besides the fact that some purchased medicines from places like "the Somalis' stores" as shown above, there existed other important factors that influenced people in the local community. Two such authorities that had an impact on respondents' lives and use of medicines were the Christian Church and traditional healers.

In some of the surveys, we noticed fieldworkers' handwritten comments alongside the survey answers where respondents said they received their medicines from the doctor. Those written comments pointed to a different picture. Respondents sometimes received their medication through the church. In the recorded conversations, there were remarks on the fact that the church now and then shared medicines with people in the community. "It's for free", a respondent said, "and then you take it ... though it's not completely 'free' so to speak." The person continued implying that the church expected gratitude and loyalty in return.

Besides churches, there also existed completely different bonds that mattered to the local people when it came to health and medicine, which is the historically-embedded African traditional medicine (Whyte, Van der Geest & Hardon, 2002; Comaroff, 1981). Even if traditional medicine is a culturally well-researched field, our study was designed to not ask questions about the topic. We wanted to focus on the grey areas that could arise in connection with

biomedical products and not to discuss any falsified traditional medicines. We assumed that specific questions on traditional healers would draw too much attention on the use of folk medicine instead of biomedical products, which might lead respondents away from questions on trust in medical expertise in the formal health sector and their awareness of SF medical products. Therefore, no quantitative data on traditional healers were captured. However, it turned out that it was not possible to keep the various medical fields separate: traces of the role of traditional healers were found in the recorded conversations.

An illustrative example comes from the conversation with Luzuko and the reaction of the fieldworker. "I go to the doctor or the clinic", Luzuko declared, "what other options do I have?" He then continued with a laugh, as if he wanted to provoke the fieldworker in terms of there being existing alternatives besides the clinic. The laughter was followed by him asking a question, almost making a statement, in a teasing way: "Sangoma, maybe?" The fieldworker later noted on the side of the survey that 'sangoma' refers to "a traditional healer, a central figure in South Africa, and everyone consults a sangoma". Further reading of the fieldworkers' notes showed that consultations with traditional healers were something that neither doctors nor the churches were happy about.

In reading the transcripts of the conversations, we sense that many respondents do not feel comfortable with their personal situation including their economic status and family relations. This plays out in feelings of uncertainty, lack of control, and an awareness of financial constraints. All these factors limit respondents to only a few opportunities to influence their life situation, including where to obtain basic medications. Drawing on relevant literature (Lundin & Liu, 2020; Hornberger & Cossa, 2012; Sugiura, 2018), risk perception is contingent. The risk of purchasing and consuming medicines in informal markets is experienced as rather minimal compared to all the other risks faced on an everyday basis by the residents of Khayamnandi.

This fluid conception of risk implies there are different strategies to manage different risk scenarios. Individuals are inclined to make personal assessments of what is risky and how it can be avoided. As Zygmunt Bauman repeatedly argues, people act – whether they are faced with critical decisions in their lives or not – based on both general criteria that exist in their environment and on the basis of individual rationality (Bauman, 1990). Rationality, as illustrated in the case of Luzuko and his comment on sangomas, is then negotiable depending on circumstances such as material conditions, power relations, and cultural affiliation. The flexible view of what is risky or not points to the existence of unspoken values and norms that order society and affect consumption behaviour. In other words, people live in an interconnected lifeworld where

individuals are more or less rooted in different sociocultural systems that can give rise to various and sometimes contradictory actions (Giddens, 1984).

What is apparent from comparing the two types of data is the existence of plural, and often competing, medical authorities in this local community. There is evidence from existing literature pointing to multiple health providers in South Africa (King, 2012; Lopes Ibanez-Gonzalez & Tollman, 2015). From our quantitative data, we do not know to which extent respondents visit traditional healers or churches, as this was not an explicit focus of the survey. However, the qualitative data clearly shows that respondents are well aware of these options and use them in their daily lives. When it comes to whom to visit when falling sick, our respondents seem to balance between their economic situation on the individual level and how much they are bonded to a community. What stands out in our sense-making of the divergences between quantitative and qualitative methods is the increasing risk of partial acquisition of knowledge if attention to societal context is not sufficiently paid. In the next section we further the discussion.

Beyond the data and back to the field

Studies about SF medical products emanate mainly from legal and medical scientists focusing on identifying falsified packaging and chemical ingredients. There is little intelligence about how these products are spread and consumed by end-users, that is, the demand-side dimensions of SF medical products. From previous studies we know that purchases of SF medical products tend to be associated with shopping on the Internet and at informal local markets (Liu & Lundin, 2016). However, we know much less of the interaction between the thoughts and actions of individuals, or other underlying processes and mechanisms driving these behaviours.

Clearly shown in our data are inconsistencies between what respondents selected on the paper-based survey and what they said to the fieldworkers. Analysis of those conversations between fieldworkers and respondents point to a rather different, even a contrasting reality to the survey data. By examining these inconsistencies, we learn that respondents were not always open about where and how they sought healthcare and medication. The mention of traditional healers and the churches is an illustrative example. This could be due to potential conflict of interests among churches, traditional healers and the biomedical-oriented public healthcare system (Lopes Ibanez-Gonzalez & Tollman, 2015).

Failure to acknowledge these conflicts might adversely affect respondents' healthcare experience, even their daily life in a social community. The majority

of South Africans self-identify as Christian (Schoeman, 2017). However, many South Africans also adhere to a traditional and indigenous belief system that provides traditional healers and medicine with a place of central importance in their lives (Friend-du Preez, Cameron & Griffiths, 2013; Ngubane, 1981). Considering the church's influence in the community, respondents may have been reluctant to admit to the use of traditional medicine because of fear of being excluded from the social and financial benefits provided by the church (cf. King, 2012). With this cultural understanding, we argue that people manage their illnesses and medicine consumption in the same sociocultural structure where they also need to negotiate many other aspects of everyday life.

Most respondents have not heard of the phenomenon of SF medical products. The survey data also shows that there are generally low knowledge levels and awareness of the regulatory requirements for safe medication. However, a close reading of their statements indicates that they are quite aware that some medicines may be more or less effective, and that some places are considered safer or more eligible than others for obtaining medicines. Comparing such risk awareness and respondents' claimed medicine purchase behaviours shows that risk is not only about medicine quality, but is also inherent to coordinating people's daily lives and the maintenance of their social bonds within the community.

This fluid understanding of risk then gives rise to many grey areas in the pharmaceutical market, which might expose people to poor-quality medicines. By grey areas, we refer to legally-blurred settings. Shown in the findings, they are tied into people's everyday consumption practices, which are often done tacitly. Interestingly, however, but not surprisingly, is that these underlying conditions are not captured by the quantitative data. To some extent, respondents seem to want to give the fieldworkers a 'right' answer, that is, by not going beyond those default options. Although this poses a challenge to interpret the quantitative data, it actually points to a need to use a mixed-methods approach (Ehn, Löfgren & Wilk, 2016), so we can put quantitative and qualitative data in the same analytical framework to make sense of the seemingly contradictory narratives offered by respondents. In this regard, the divergences, or rather inconsistences, between the two types of data can be used as a valuable entry point to investigate deeper social structures on the macro level, as well as how choice-making is constrained socially and materially.

In this South African context, the appearance of traditional healers seemingly makes it distinct from many other countries where biomedicine possesses an absolute dominant influence. Yet, it is by no means unique as the interplay between Western biomedicine and traditional medicine has been well

documented in many societies (Andreadis, 2015; Smith, 2018). Although the tensions are not explicitly shown in our collected data, they are reflected through the inconsistencies between different data types. It suggests that people negotiate in the eclectic therapeutic landscape where biomedicine is not the only authority. This furthermore points out that it is not sufficient to measure and report on only medicine consumption behaviours, without paying attention to how local processes create the opportunity for the global circulation of SF medical products and have an impact on individual lives.

Reflecting on our data collection process, we learned that more knowledge is needed about the respondents' socio-cultural conditions in order to be able to ask adequate questions. Care has to be taken in a simplifying language to ask questions about medicine consumption behaviour and all questions have to be carefully aligned with education levels of the group amongst whom the research is being conducted. This points to the importance of not only relying on questions asked in a survey but supplementing it with other data collection methods. Suitable methods include interviews, or conversations around a survey as in our study, where the language use is adapted to the interviewees' knowledge situation. Another complement may be to draw on visual tools, such as cartoons to make the subject area more accessible to respondents (Glaw et al., 2017).

In doing multi-disciplinary research using a mixed-methods approach, we want to emphasise the importance of reflexivity regarding empirical observations. Being reflexive not only makes researchers more aware of knowledge production, but, offers insights into the complex processes and ambivalent statements collected from research participants.

Conclusion

The aim of this chapter has been to reflect on our use of quantitative and qualitative methods in a study of risk awareness among people in a low-income setting in South Africa. We have shown how the inconsistences between data acquired through these two methods served as an entry point to unpack respondents' relation to multiple health providers. By combining quantitative data with conversations between respondents and fieldworkers, we are able to go beyond what people say they do and situate those statements in contextual details. Such an analytical strategy reveals underlying and alternative answers.

Alongside we also presented certain findings and analysis. Throughout the analysis, the idea of risk becomes fluid while choice-making of medicine access is intertwined with various factors in people's lifeworlds, not only individuals'

financial constraints, but also their social bonds. These sociocultural elements play an essential part in people's decision-making. Thus, they have to be taken into consideration to gain a deeper understanding of the complexity and often contradictory ideas that permeate people's responses and actions. To this end, it is not sufficient to simply map quantitatively where people access medicines or measure their existing knowledge levels about medicine quality. This chapter has argued the importance of complementing with qualitative examination of the social and material circumstances to understand people's risk perceptions and risk tolerance levels.

As mentioned in the introduction, despite a lack of reports on identification of SF medical products to the WHO's alert system (World Health Organization, 2017a), South Africa is far from immune to this problem. To the contrary, it might signal the need for increased awareness and involvement of all stakeholders including policymakers, healthcare professionals from both public and private sectors, and end-users who are often referred to as 'healthcare consumers', to secure a safe environment for medicine consumption (Olsson, Pal & Dodoo, 2015). Previous studies have pointed to a pluralistic health market where multiple health beliefs and care services co-exist in South Africa (Friend-du Preez, Cameron & Griffiths, 2013). Our study supports this finding in that our respondents have hinted at the role of traditional healers in their care-seeking processes. However, our analysis also pointed out that visiting traditional healers is not a value-free decision. Respondents have to negotiate social and material constraint in choosing between traditional healers and formal healthcare. This issue is particularly relevant in future research design when studying populations in similar socio-cultural settings. Above all, targeted efforts are essential for the residents in the form of knowledge about medicines and how they can be obtained.

This chapter adds insights on research design in studying global health issues with a focus on the sociocultural dimension. We have highlighted a need to use a mixed-methods approach to unpack ambivalences in understanding risks regarding medicine access.

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AFTERWORD: EXPLORATION OF GREY ZONES

Heather Hamill

Introduction

Access to effective essential medicines is a key pillar of Universal Health Coverage. Yet, this access remains constrained by easily disrupted supply chains and the proliferation of poor-quality medicines as documented by the World Health Organization (2017). On 29 May 2017, delegates at the World Health Assembly reached an agreement on defining poor-quality medicines as those that are substandard, falsified (SF) and/or unregistered or unlicensed. 'Substandard' medicines (also called 'out of specification') are authorised by national regulatory authorities but fail to meet either national or international quality standards or specifications – or in some cases, both. 'Falsified' medicines deliberately or fraudulently misrepresent their identity, composition, or source. 'Unregistered or unlicensed medicines' have not been assessed or approved by the relevant national or regional regulatory authority for the market in which they are marketed, distributed, or used.

As might be expected in an anthology entitled 'Medicines across borders', this book takes an international perspective, examining the issue of SF medicines cross nationally. Poor-quality medicines are prevalent in low- and middle-income countries (LMICs) but this book also includes research from high-income countries arguing that they too have vulnerabilities, and emphasising the need for vigilance even in well-resourced and well-regulated regimes.

The authors are drawn from a range of academic disciplines across the social and medical sciences presenting findings from data collected using an eclectic mix of methods and analysis. Surveys, ethnography, narrative case studies, statistical and thematic analysis are all deployed. This book provides an interdisciplinary space for a depth and diversity of material that spotlights some contemporary themes hindering access to essential medicines and driving the penetration of SF medicines.

With more than two decades of experience in the field of sociology, my research has primarily focused on trust in situations where there is a lack of certainty (Gambetta & Hamill, 2005; Hamill, 2018). Over the past eight years, I have devoted a significant amount of time and effort to studying the issue of SF medicines in Sub-Saharan Africa (see Hamill et al., 2019; Hamill et al., 2021; Hampshire et al., 2022). I have considerable knowledge of the field and a deep commitment to improving access to good quality medicines in LMICs. It is a challenging task to summarise the main findings of this book, while doing justice to the work of the researchers. In this chapter, I provide an overview of six key recurring themes that emerge from this body of research and are also evident in broader research on SF medicines.

The importance of the last mile

Poor-quality medicines are prevalent in LMICs, and a growing body of literature has noted their serious threat to individual and public health (Renscher et al., 2015). The seriousness of these threats are, in part, dependent on regulatory and health system capacity. My colleagues and I conducted a study examining the behaviour of regulators in Tanzania, as described in a recent article (Hamill et al., 2021). We analysed the ways in which the mechanisms proposed by the WHO regarding the reporting of SF medicines and the reduction in undesirable behaviours are implemented in a low-income context with regulatory authorities that are relatively effective. Our research uncovered that regulators encounter a multifaceted array of structural, political, economic, and cultural barriers that are more than just 'weak capacity'. Even within countries, there exists significant inequalities in health provision and access to medicines that increases inequalities

and worsens public health challenges within health systems. This argument is made powerfully in Chari et al.'s chapter *Drug stock-outs and district poverty in Zimbabwe*, which focuses on the 'last mile' in medicine provision where products are delivered to public and private sector outlets to be prescribed and sold to the public. Medicine stock-outs are common occurrence in LMICs. As noted by the authors, they result from poor supply-chain management and procurement processes, corruption, lack of funding, shortages of health workers, theft, expiry, and bureaucracy. Stock-outs are a major driver of poor-quality medicines because when they occur, consumers enact a range of coping strategies that increase their exposure to poor-quality products. These strategies include buying medicines from informal, unregulated retailers, borrowing drugs from relatives, repurposing unused and expired drugs, and using traditional treatments.

Chari et al. examine the spatial correlation between socioeconomic status and antimalarial stock-outs in Zimbabwe in the context of high poverty rates at the national level and against a background of a surging informal, weakly regulated drug market. Counterintuitively, the authors find a weak correlation between poverty prevalence and drug stock-outs. They argue that poverty may weaken the impact of stock-outs, as poorer people are less likely to seek treatment for illness in the first place. The costs of travelling to dispersed treatment centres, and an increased likelihood of seeking alternative treatments, for example, from faith healers mitigate the demand for medicines and the impact of stock-outs. Thus, while stock-outs are a problem in Zimbabwe there is a wider issue of unequal access to public health facilities that is impacting the poorest and most vulnerable citizens daily. Furthermore, this finding highlights the importance of a detailed and nuanced understanding of the problem of access to medicines and the need to ensure that a focus at the national level does not obscure important variation at the district and local level.

Online and offline pharmaceutical 'grey zones'

The term 'grey zones' is used in the literature on medicine quality to refer to parts of the pharmaceutical market inhabited by retailers and products where it is difficult to differentiate between the legal and illegal. This is a particularly challenging space for consumers and patients to access high-quality medicines from trustworthy sources. Sundin et al.'s chapter *Controlling the machinery of knowledge: Google and access to COVID-19 grey-zone medicines* focuses on the rise of e-commerce and explores in detail the role that Internet search engines play in the pharmaceutical marketplace. Readers will be unsurprised to learn of Google's domination. Among the leading Internet search engines, the worldwide market share of Google in January 2022 was 88.6% (Statista, 2022). For most

people, the behind-the-scenes activities of the Google Search algorithms are of little interest; they want a quick and relevant answer to their query. But as this chapter shows us 'relevance' – either individual or societal – and trustworthiness is determined by Google via opaque processes that combine the assessments of their employees with algorithms. And having decided what is relevant and trustworthy, Google then promotes these sites in several ways via its search engine. Without direct previous experience of an online retailer, consumers are reliant on Google's assessment of trustworthiness without fully understanding how this assessment is made. And, while facilitating access to trustworthy retailers, Google does not prevent access to less trustworthy sellers. By examining how Google Search establishes and controls access to online sellers, this chapter sheds light on Google's influence on the online pharmaceutical marketplace and how they enable online legal pharmacies to coexist alongside online illegal pharmacies. Within this online 'grey zone' it is extremely difficult for users to differentiate trustworthy from untrustworthy retailers.

The theme of 'grey zones' is continued in Liu et al.'s chapter *Risk awareness in medicine access: Methodological reflections from fieldwork in a low-income setting in South Africa*. In this research, the authors combine survey data with qualitative interviews to investigate the awareness of medicine risks among residents in a lower-income neighbourhood in South Africa. Their findings indicate low levels of knowledge of regulatory requirements for safe medication or the existence SF medicines. They also show that their respondents' attitudes towards the risks of SF medicines cannot be divorced from their attitudes to risk more generally in everyday life. The reported responses of the South African participants were very similar to findings from research I carried out in Ghana, on how ordinary people manage uncertainty in medicine quality. Attitudes and behaviours towards risk and uncertainty are embedded within and intertwined with their wider social, economic, cultural, therapeutic context and relationships (Hamill et al., 2019). Respondents did not make binary decisions choosing between biomedicine and traditional healers or privileging one over the other. Rather, with limited access to financial and health resources, they sought help from wherever and in whatever form they could find it.

This research in South Africa took a mixed-method approach, and from the qualitative data, the authors were able to gain a richer and more subtle understanding of their respondent's attitudes to risk. In so doing, they echo Chari et al.'s observations about the need for a nuanced understanding of local processes, their relationship to the global circulation of SF medicines and their impact at the community and individual level.

The creation, existence, and persistence of these 'grey zones', how they operate and how agents at all levels of society from the very local to the international interact with them regarding issues of medicine-quality requires further empirical and theoretical scrutiny.

SF medicines and high-income countries

Most of the scholarship on SF medicines focuses on where the problem is most prevalent: in LMICs. However, as Persson and Lenander point out in *The spread of substandard and falsified medical products to the Swedish market: a discussion from pharmacists' point of view*, high-income countries should not be complacent. Drawing on data gathered from a survey of pharmacists in Sweden they show how good governance procedures and strong technical capacity and tools act to prevent the penetration of SF medicines. These provisions have been highly effective in that Sweden has no recorded cases of SF medicines. However, in line with Sundin et al.'s chapter, the authors note that the rise in popularity of e-commerce presents a challenge to these processes as people in high-income countries seek to access a less regulated pharmaceutical marketplace in ever greater numbers.

Hard to reach groups in high-income countries, such as those discussed by Mirsalehi and Hansson in *To reach the unreachable: Migration, health vulnerabilities, and the problem of non-response bias in health research*, are also at risk from misinformation and more likely to turn to alternative and less well-regulated methods of treatment.

Furthermore, in *When the State cannot (yet) assure the quality of medical products – What to do?* Ravinetto et al. show non-governmental organisations (NGOs), located in high-income countries running medical programmes in LMICs for which they need to procure medical products, need to be alert and responsive to the existence of SF medicines.

In *Medicine quality and medicine traceability: A focus on prevalence, context and responsibility*, Naughton and McManus review the legislative frameworks that have been put in place in the EU and the USA to prevent SF products penetrating the market. They also discuss their research investigating the effectiveness of medicine authentication technology in a hospital pharmacy setting in the UK. This research presents findings on how such technologies can be implemented successfully in well-resourced high-income settings and discusses their potential application in LMICs.

Mitigating risk when state capacity is weak

Compared to high-income countries, LMICs are characterised as having weak regulatory capacity – a much-cited driver of poor medicine quality (Hamill et al., 2021). Lacking funding, trained staff, relevant infrastructure and support from the state, the international community and donors, most national regulatory authorities in LMICs struggle to perform their essential functions to an adequate level (according to WHO guidelines). These key tasks – national regulatory system, registration and marketing authorisation, vigilance, market surveillance and control, licensing establishments, regulatory inspection, laboratory testing, clinical trials oversight, and lot release (for vaccines only) – are set out by the WHO's Global Benchmarking for National Regulatory Authorities. Existing alongside weak regulatory capacity at the national level, is the absence of regulatory oversight of international supply chains.

Faced with the reality of these regulatory shortcomings, those who procure medicines at all levels must find ways to limit their exposure to SF products. Ravinetto et al. provide us with three case studies of how different procurers address this dilemma and attempt to mitigate these risks. The mitigation strategies discussed are: 1) to carry out inspections and audits of manufacturers and suppliers on their own behalf; 2) adopt a visual inspection procedure for the detection of visible quality problems; 3) use 'frugal' technologies to pre-screen products for quality, and 4) to encourage patients and front-line healthcare workers to report suspected cases via reporting mechanisms and advocacy groups. The authors show how each of these strategies is partial and limited and, at the same time, they urge actors to take a pragmatic proactive approach especially in countries where strong national regulatory capacity as a function of robust governance appears a far-off aspiration.

The impact of COVID-19

The COVID-19 crisis had a seismic impact on healthcare provision affecting outcomes for related and unrelated conditions. In November 2019, at the start of the COVID-19 pandemic, Paul Newton and Katherine Bond, together with 53 signatories from 20 different countries sounded the alarm warning that "*without advance preparations for quality assurance of diagnostic tests, medicines and vaccines, the world risks a parallel pandemic of substandard and falsified (SF) products*," (Newton et al., 2019). In this book, Van Asshe et al., and Naughton and McManus draw our attention to the falsification of Peruvian Cinchona bark during the 17th and 18th centuries, and to other incidents throughout the following centuries that remind us that poor-quality medicines thrive in times

of crisis when demand outstrips supply and quackery can more easily take advantage of people's desperation.

Van Asshe et al. draw on data published by the Medicine Quality Research Group at the University of Oxford and extracted from the Medicines Quality Monitoring Globe (also known as The Globe (Medicine Quality Monitoring Globe | Infectious Diseases Data Observatory (iddo.org)). Over 1 000 different incidents of diverted, unregistered, substandard, or falsified COVID-19 medical products had been reported by March 2022. In their chapter, the authors provide a detailed discussion on a range of products including COVID-19 vaccines, diagnostics, personal protective equipment (PPE), sanitisers and disinfectants, medicines, and ventilation and oxygenation equipment and consumables. In addition to the WHO-defined drivers for poor-quality medical products – limited access to medical products, poor governance, and weak technical capacity – the authors highlight additional factors that came into play because of the pandemic. An overwhelming desire amongst the global population to return to normalcy, the growth of online sales and vaccine nationalism are all discussed alongside desperation for scarce treatment driven by the more systemic problem of impaired and unequal access to vaccines.

Scholarship on unequal access to vaccines often compares the high levels of availability in high-income countries to the much lower levels of availability in middle- and low-income countries (Amankwah-Amoah, 2022). In Mirsalehi and Hansson's chapter *To reach the unreachable*, the authors write about how the COVID-19 pandemic revealed fault lines within the Swedish healthcare system both at the point of delivery but also in the research that informs policy and practice. Focusing on foreign-born and migrants in Sweden, they show how these marginal groups are often absent from national health surveys and, drawing on their ethnographic work, detail some of the impacts of this non-response bias in the context of COVID-19. Struggling with the general uncertainty that migrant and marginal status brings, not fully trusting of the healthcare system and trying to interpret the information they are receiving from the state, social media, and social networks these groups are particularly vulnerable to misinformation and are more likely to seek alternative treatments.

Diminished trust in health systems and public institutions more generally is one of many negative consequences of COVID-19 discussed by Van Asshe et al. This loss of trust and its effects on vaccine hesitancy was exacerbated by falsified vaccines with significant knock-on effects on the health of individuals and at a population level.

The study of SF medicines lacks good understanding of the prevalence of SF products that stems from an absence of standardisation of methodological approaches to data collection and analysis, as discussed by Naughton and McManus in this edited volume. This in turn, has meant that the economic costs of SF products have always been exceedingly difficult to calculate and even more so in the context of COVID-19. Van Asshe et al. give us some insight of the scale from the case study of the seizure of 59 million falsified masks falsely claimed to be made by the company 3M. Rather than concentrating all their efforts on supplying protective equipment to healthcare workers, 3M had to divert a considerable resource to investigation, lawsuits, and authentication methods for customers.

Solutions

It is easy to feel overwhelmed by the problem of SF medicines and their terrible negative consequences for the world's poorest and most vulnerable populations. But what can be done about it; how can we prevent SF medicines reaching patients and consumers? All the authors suggest ways to mitigate the effects of SF through a better understanding of the problem and its variations according to the socioeconomic and political context. Naughton and McManus, in particular, focus their chapter on solutions by guiding the reader through the legislation enacted in the EU and USA and associated medicine traceability technologies in high-income countries, such as medicine authentication serialisation and blockchains. In so doing, they note the additional burden these processes place on already complex and overloaded medicine dispensary systems, their vulnerabilities to human error and the need for training to avoid such mistakes. Expecting healthcare workers to take on the task of authenticating medicines is yet another example of how new technologies can lead to 'task shifting' with those on the front line being asked to take on more burdensome tasks and diverting their attention away from their core activities, without the concomitant support (see also Hampshire et al., 2017).

Naughton and McManus are strong advocates for the role that medicine traceability systems can play in the fight against SF medicines. However, they sound a note of caution when discussing the implementation of such systems in LMICs. Along with the other authors in this book, they recognise several limiting factors. These include capacity issues, such as poorer information technology infrastructure in LMICs, and that success will require the kind of detailed and nuanced understanding of context that forms a key pillar of a responsible innovation approach.

The Med4All platform in Ghana is an example of such an approach and is described in detail by Sunkwa-Mills et al. in *How technology can help solve substandard medicine problems: a case study on the digital medicine supply chain platform Med4All*. The authors present an optimistic account of the success of the Med4All platform, arguing that in the public sector it is helping to improve medicine quality through more transparent processes, pooling and streamlining procurement to gain lower prices and improve availability.

Conclusion

This book seeks to provide an evidence-based account of some of the challenges to global health and wellbeing that result from SF medicines. Drawing on my own research experience and knowledge of the subject of SF medicines and a close reading of each of the chapters, I have summarised the key findings into six recurring six themes: 1) the importance of the last mile; 2) online and offline pharmaceutical 'gray zones'; 3) SF medicines and high-income countries; 4) mitigating risk when state capacity is weak; 5) the impact of COVID-19, and 6) solutions. It is my hope that they will be useful for anyone who wants to study SF medicines and their impact. The research community faces significant challenges related to data, such as the absence of high-quality prevalence data on SF, and the tendency to rely too heavily on a single data collection and analysis method, leading to biased and incomplete understandings of the issue. Nonetheless, the comprehensive material compiled in this anthology showcases the progress being made in comprehending the problem and developing innovative solutions. I am encouraged by the wide range of medical and social science disciplines represented in this collection, as SF medicines are a multifaceted global health concern that necessitates an interdisciplinary approach. Maintaining and even accelerating this momentum is critical to promoting the health of the global population.

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PUBLICATION

A CREATIVE SPACE FOR THE MIND

Medicine Across Borders provides an interdisciplinary space to discuss the issue of substandard and falsified medical products. Scholars from social and medical sciences collaboratively contribute insight to improving safe medicine access.

The circulation of medicines and medical products on the informal market is well-known. Stakeholders, including governmental agencies and biotechnic enterprises, invest much effort in designing and implementing macrolevel interventions to limit the spread of such products. Nevertheless, there is a lack of knowledge and understanding of how informal markets function in everyday medicine access and use. This applies to professionals within and beyond academia, state governments, as well as the general public.

This book takes an international perspective, examining the issue of substandard and falsified medical products cross-nationally. Falsified and poor-quality medicines are prevalent in low- and middle-income countries, but this book also includes research from high-income countries arguing that they too have vulnerabilities, and emphasising the need for vigilance even in well-resourced and well-regulated regimes.

Medicine Across Borders: Exploration of Grey Zones provides an interdisciplinary space for a depth and diversity of material that spotlights some contemporary themes hindering access to essential medicines and driving the penetration of substandard and falsified medical products. The authors are drawn from a range of academic disciplines across the social and medical sciences presenting findings from data collected using an eclectic mix of methods and analysis. Surveys, ethnography, narrative case studies, statistical, and thematic analysis are all deployed.

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