FORGING NEW PATHS IN ACCESS TO MEDICINES RESEARCH

Towards equitable access for all

Iris Rebecca Joosse

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Colofon

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TOWARDS EQUITABLE ACCESS FOR ALL

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"Of all the paths you take in life, make sure a few of them are dirt."

John Muir

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Bivatracin
BETADINE
Kaprofen
KETOLAC

CHAPTER 1

General introduction

General introduction

Medicines are widely acknowledged for their pivotal role in achieving the highest attainable level of health and saving lives. Despite their known importance, countries across the globe have struggled to improve access to medicines for long [1].

A first indication of the magnitude of this issue was provided in the 1988 World Drug Situation report [2]. In this baseline survey of (inter)national progress on access, it was estimated that less than half of the global population had regular access to essential medicines in 1975. By 1987, this had decreased to about 37% of the global population without access [2]. Alarming geographical inequities in access were evident at this time, with 75% of the global population residing in low- and middle-income countries (LMIC), yet consuming only 21% of the world's medicines. A subsequent review of the World Medicines Situation in 2004, offering updated data from 1999, revealed that approximately 30% of the global population still lacked access to essential medicines [3]. A staggering 80% of these individuals were living in low-income countries.

Recent reports continue to show the persistence of unmet targets and ongoing challenges in accessing medicines across therapeutic areas, such as essential medicines for cardiovascular diseases [4, 5], diabetes [6], epilepsy [7] and cancer [8], as well as for psychotropic medicines [9], sexual and reproductive health commodities [10] and snakebite commodities [11]. Access for specific vulnerable populations such as women and children remains particularly challenging [5, 12-16]. Former Director-General of the World Health Organization (WHO), Dr. Margaret Chan, emphasized in 2017 that access to medicines remained an enduring global challenge, with an estimated two billion people worldwide still lacking access [1]. While progress has been achieved compared to the earliest estimates, these recent reports underscore that urgent action is still required to bridge these persistent access gaps.

Defining and framing access to medicines

Access to medicines refers to the ability to acquire and utilize medicines in a timely, affordable, and equitable manner. It is a multi-dimensional concept that considers the availability, affordability, (geographical) accessibility and acceptability of medicines, with quality as a cross-cutting dimension (**Figure 1**) [17]. Each dimension covers both demand and supply aspects. Initially proposed by Penchansky and Thomas in 1981 [18], this definition was further refined in 2000 and culminated in the establishment of the first access to medicines framework [17].

To effectively tackle the major challenges impeding health systems from providing medicines that are available, affordable, accessible, acceptable, and of good quality, the World Health Organization introduced a different framework in 2004 [19]. This framework delineates four key dimensions for improved access: 1) rational selection and use of essential medicines, 2)

affordable prices, 3) sustainable financing, and 4) reliable health and supply systems. Affordability, encompassing considerations from both the demand and supply sides, stands as a cornerstone of access within this framework, with availability being given due consideration. The 2004 framework also encompasses elements required for the functionality and strengthening of health systems, such as treatment guidelines, essential medicines lists, procurement and supply mechanisms, regulation, and human resources.

Dimension	Decribes the relationship between
Availability	the type and quantity of the medicine needed by a user and the type and quantity available.
Affordability	the price of the medicine and a user's ability to pay, while protected from economic consequences.
Accessibility	the location of supply of a medicine and the location of a user.
Acceptability	a user's attitude towards a medicine and the medicine's actual characteristics.
Quality	a medicine's quality and the quality specifications set by national and international standards.

Figure 1 Five dimensions of access to medicines [17].

Bigdeli and colleagues further built upon this and considered access to medicines to be a holistic and intricate concept, also recognizing the role of various stakeholders in providing access and the relationships between medicines and other health system components [20]. Their significantly more complex framework integrates the previously mentioned five dimensions of access within six health system building blocks outlined by WHO [21] (**Figure 2**) and incorporates five adapted levels of access constraints: I) individuals, households and the community, II) service delivery, III) health sector level, IV) public policies cutting across sectors, V) and the regional and international level [22]. Constructed in 2013, this conceptual framework (**Figure 3**) continues to serve as a fundamental basis for understanding access to medicines over a decade later.

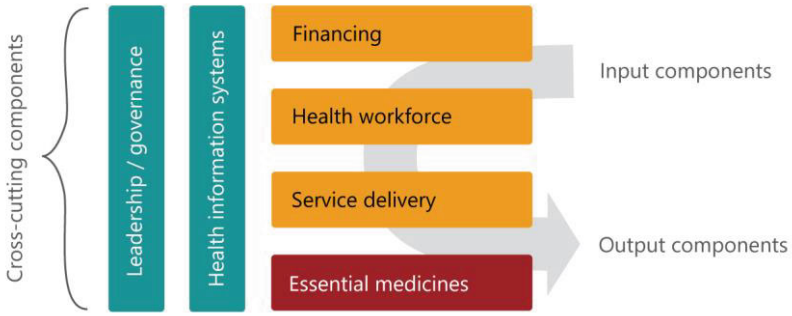

Figure 2 Health system building blocks [21].

Inextricably linked to the field of access to medicines is the concept of essential medicines. Essential medicines are those that satisfy the priority health care needs of the population [23], and are intended to be available at all times, in adequate amounts, in the appropriate dosage form, with assured quality, and at a price that is affordable to the individual and the health system. To guide the optimal use of limited financial resources, WHO was requested by the 28th World Health Assembly (WHA) in 1975 to provide assistance in selecting and procuring essential medicines [24]. This concept of selecting essential medicines originated within military medicine, tracing back to the Second World War [25].

In response to the WHA's request – and later described as a peaceful revolution in global public health [26] – the WHO developed the first Model List of Essential Medicines (EML) in 1977 [27]. The list has been revised every two years, with the 23rd list being published in 2023 [23].

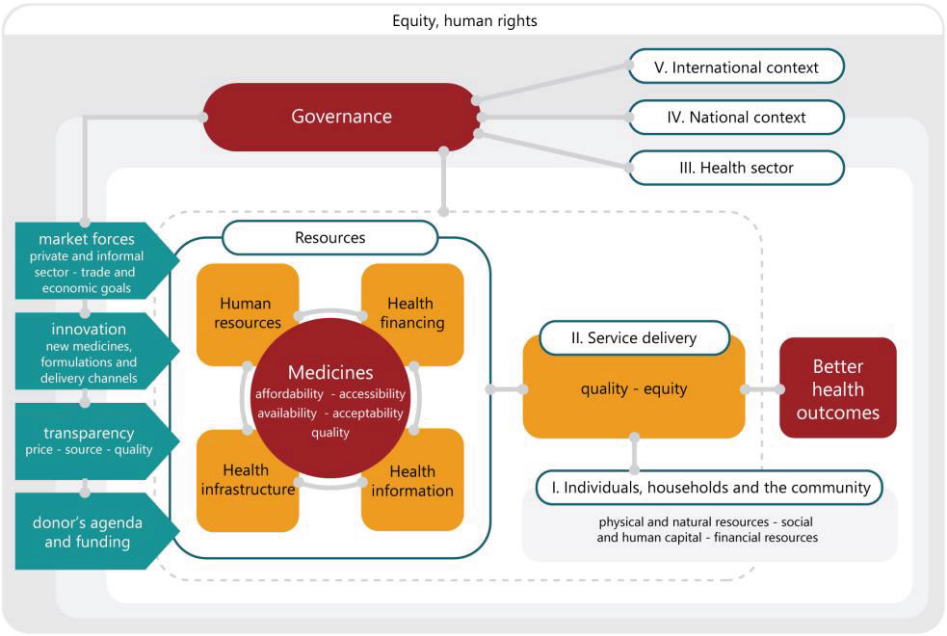

Figure 3 Access to medicines from a health system perspective: a conceptual framework [20].

A historical perspective on access to medicines

The pivotal role of medicines in health systems has gained increasing international recognition since the mid-twentieth century, to commence with the right to health formally acknowledged at the international level. This transpired in the wake of the second World War, when the right to health was formally recognized as a fundamental human right in the Universal Declaration of Human Rights by the United Nations (UN) in 1948 [28]. Nearly two decades later, the International Covenant on Economic, Social and Cultural Rights reaffirmed the right to health in 1966 and called on countries to establish the conditions required to ensure access to medical

services and attention for all in the event of illness [29]. Notably, no explicit reference was made to medicines in the full realization of this right. It is not until 1978 that medicines were given unequivocal attention: during the International Conference on Primary Health Care in Alma-Ata, essential medicines were advocated for as one of the key components in primary health care [30].

Despite this milestone, the right to access medicines came under pressure during the global AIDS crisis in the late 1990s and marked a turning point [25]. Following initial underestimation of the gravity of the health issue, evidenced by inadequate and short-term responses to the diseases and marginalization of certain groups, international programs targeting the disease had gained considerable momentum by 1995 [31]. At this time, the first generation of HIV protease inhibitors became available on the market. These antiretrovirals represented a breakthrough, transforming AIDS from a death sentence to a chronic, non-progressive disease and redirecting attention for the first time from prevention to treatment [31].

However, the introduction of these novel antiretrovirals sparked a critical debate about the role of these medicines in LMIC. Several prominent players on the international stage – including the World Bank, the United States Agency for International Development (USAID) and the United Kingdom's Department for International Development (DFID) – were hesitant to provide AIDS treatment to developing countries, given that AIDS medicines were too costly, too difficult to administer, and too low a priority to afford access to people in these countries [31]. This denial of treatment for developing countries came at a time when the AIDS epidemic in Africa had reached catastrophic proportions, and AIDS-related deaths were undoing any advancements made in child health and survival.

The first developing country to redirect efforts from prevention to treatment was Brazil in 1996, enacting a law that made AIDS medicines – whether originators or generic – universally available in the country [31, 32]. Although this was considered an infringement of patent rights by pharmaceutical companies, other nations took similar steps and initiated comparable programs within their borders.

The South African initiative in particular gained significant attention. As one of the most affected countries globally, South Africa prepared legislation to enable parallel import and compulsory licensing of HIV/AIDS medicines in 1997 [33]. In response to this, 41 pharmaceutical companies sued the government of South Africa in early 1998, claiming that this was in violation of the Trade Related Intellectual Property Rights (TRIPS) agreement protecting drug patents [32]. The publicity surrounding this court case triggered international outcry, and the subsequent establishment of countless global access programs and non-government organizations in the following years, such as the Treatment Action Campaign (TAC), Health GAP (Global Access Project), Clinton Health Access Initiative, PEPFAR (President's Emergency Plan for AIDS Relief) and others [25, 31]. The case against the South African government was eventually dropped in 2001 [32].

Driven by the non-governmental sector, the 13th International AIDS Conference in 2000 marked a milestone, where activists, scientists and politicians denounced the global inequities in access to antiretrovirals [34]. By 2001, multilateral institutions previously denying treatment to developing countries had started changing their position, and pharmaceutical companies began reducing the prices of antiretrovirals following the game-changing Cipla Global Access (CGA) initiative that brought the cost of triple-combination therapy to less than 1 US dollar a day [31, 35]. Civil society also prompted the 2001 UN Special Session of the General Assembly (UNGASS), which declared AIDS a threat to global security and committed to facilitate access to medicines [36]. Later that year, during a Ministerial Conference of the World Trade Organization, the Doha Declaration on the TRIPS Agreement and Public Health was adopted, approving the use of so-called TRIPS flexibilities to waive patent laws and produce required medicines by compulsory licensing in emergencies [37].

Table 1 Millennium Development Goal and Sustainable Development Goal targets related to access to medicines and corresponding indicators.

Target	Description	Indicator
MDG target 6.B	Achieve, by 2010, universal **access to treatment** for HIV/AIDS for all those who need it.	-
MDG target 8.E	In cooperation with pharmaceutical companies, provide **access to affordable essential drugs** in developing countries.	46. Proportion of population with access to affordable, essential drugs on a sustainable basis.
SDG target 3.8	Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and **access to safe, effective, quality and affordable essential medicines** and vaccines for all.	3.b.3 Proportion of health facilities that have a core set of relevant essential medicines available and affordable on a sustainable basis.
SDG target 3.b	Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide **access to affordable essential medicines** and vaccines, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health, which affirms the right of developing countries to use to the full the provisions in the Agreement on Trade-Related Aspects of Intellectual Property Rights regarding flexibilities to protect public health, and, in particular, provide access to medicines for all.	

MDG = Millennium Development Goal; SDG = Sustainable Development Goal.

Following the difficulties of developing countries in accessing antiretrovirals, universal access to antiretrovirals was considered a top priority on the international agenda in the early 2000s. This was prominently reflected in the 2000 Millennium Development Goals (MDGs) committing to universal access to antiretrovirals and more affordable prices (**Table 1**) [38]. With that, the AIDS crisis has had major implications for access to medicines and health systems. In the following years, the Human Rights Council further emphasized the importance of access to medicines as one of the fundamental elements in achieving the full realization of the right to health, with the adoption of resolution 12/24 in 2009 [39]. Most recently, the goal of achieving access to medicines for all was reflected in its inclusion in two Sustainable Development Goal (SDG) targets in 2015 (**Table 1**) [40].

Monitoring and evaluation of performance, health systems and policies

Performance monitoring

The global emphasis on increasing access to essential medicines makes monitoring an imperative, for improvements cannot be tracked, nor progress realized, without measuring countries' performance in providing access to medicines [41]. This notion was highlighted for the first time at the 1985 Conference on the Rational Use of Medicines in Nairobi, at which time the need for more information on the medicine situation at global and national levels was acknowledged [42]. In response to this, and with the objective of evaluating and guiding national medicine policy-making, the 1988 World Drug Situation report provided a baseline survey of (inter)national progress [2].

The need for monitoring of access to medicines was reaffirmed at the turn of the millennium. With the global commitment to the MDGs in 2000, a corresponding monitoring and evaluation framework was agreed upon in 2003 with the intention to increase mutual accountability and improve decision-making [43]. Concurrently, the WHO was requested to develop a monitoring tool for medicine prices in 2001 [44], resulting in the now extensively used and validated WHO/Health Action International (HAI) methodology for 'Measuring medicine prices, availability, affordability and price components' in 2003 [45-47]. This methodology measures availability as a snapshot, binary variable: a medicine is considered available when a single pack is found in a health facility on the day of data collection. Affordability considers the wages of the lowest-paid unskilled governmental worker (LPGW) in addition to the price of a medicine.

A novel methodology to measure performance was introduced in 2018, when the UN agreed upon SDG indicator 3.b.3 for the monitoring of access to medicines [48]. Based on the principles of the WHO/HAI methodology for measuring access, this indicator integrated the dimensions of availability and affordability in a single metric: a medicine is only considered accessible when both criteria are met. Additionally, the methodology introduced a new metric in determining

affordability and integrates the LPGW wage with a National Poverty Line (NPL) – which represents daily living expenditures such as food and housing.

Health systems analysis

While performance monitoring can shed light on access gaps, its value in guiding national decision-making is limited. To identify root causes of access gaps and enable targeted policy-making health systems research can be of particular value, constituting a second key mechanism in access to medicines research. This type of analysis incorporates systems thinking, taking into account that medicines are one component of a broader health system (**Figure 2**) [49]. Here a health systems analysis (also referred to as health systems research or evaluation) of access to medicines refers to research examining the interactions between pharmaceutical processes and other health system components and the roles of different stakeholders therein (**Figure 3**) [20].

The 1990s marked a significant rise in attention toward health systems thinking, as reflected in the foundation of the Alliance for Health Policy and Systems Research in 1997 [50]. However, the role of health systems analyses in improving access to medicines specifically was first highlighted by Bigdeli and colleagues in 2013 [20]. This was further reinforced at the 67th WHA in 2014, with the adoption of resolution EB134.R16 on access to essential medicines that emphasized the role of health systems research therein, lateral to monitoring the performance of health systems in providing access to medicines [51].

Pharmaceutical policy analysis

Besides the monitoring of performance and health system analysis, pharmaceutical policy analysis constitutes a third core evaluation mechanism in access to medicines research. The term refers to research assessing whether or not an intervention achieved its intended goals and which elements contributed to its success or failure [49]. This may also include assessment of unintended effects of policies and interactions of existing pharmaceutical policies within the broader health system (combined health policy and systems research) [50, 52]. Pharmaceutical policy analysis specifically relates to evaluations of policies on objectives such as affordability, sustainability, efficiency and equitable access to medicines [53]. By evaluating pharmaceutical policy performance and gaining a deeper understanding of their content, context, and stakeholders involved, existing policies can be refined and new and effective strategies crafted and implemented [54-56].

Recognition of the potential of evidence from health policy research to inform policy-making has grown since the 1990s, largely parallel to increasing acknowledgement for health systems research [50, 54, 57]. In the early 2000s, this recognition culminated in evidence-based healthcare policy-making being widely accepted as the norm by intergovernmental institutions and the broader scientific community [58, 59]. Most prominently, the 58th WHA advocated for policy-making to be based on reliable evidence from policy research and called for these evaluations at national and international levels [60].

Evidence generated through these key monitoring and evaluation mechanisms thus has immense potential to shape pharmaceutical policy-making and inform the policy cycle (**Figure 4**) [58, 61]: performance monitoring and health systems analyses have the potential to steer the political agenda through problem identification; health system analyses also help identify root causes of problems and offer insight into the reasons for policy successes or failures; pharmaceutical policy analyses can inform which interventions to implement and how, and evaluate whether existing or future policies have achieved their objectives or whether further policies are required.

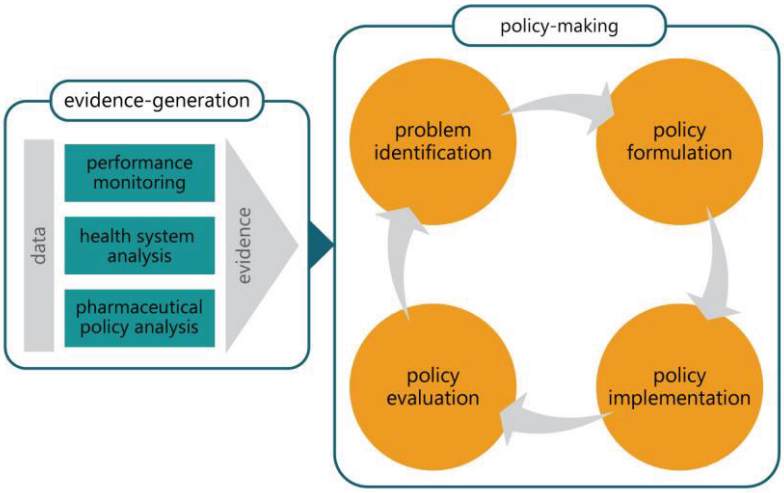

Figure 4 From evidence-generation to policy-making.
Evidence from performance monitoring, health system analyses and pharmaceutical policy analyses feed into the policy cycle.

A loss of momentum

After an epidemic peak in 2004, access to antiretroviral medicines increased, AIDS prevalence began to stabilize, and AIDS-related deaths significantly declined [31]. With that, the previous momentum in the international health community also subsided and support for universal access to medicines started wavering, despite progress needed in other therapeutic areas [32]. Equivalently, despite the reiterated importance of monitoring performance, studying health systems and evaluating pharmaceutical policies since the 1990s, limited progress has been achieved from a research perspective since the early 2000s.

An important example of the stagnation is observed in regard to the data required for tracking countries' performance in providing access to medicines. For even with the tools for monitoring access to medicines becoming available to countries in the early 2000s, the second review of the world medicines situation in 2004 already highlighted a lack of reliable data on some of the world's most populous regions (the People's Republic of China and India) [3]. This data

deficiency was readdressed in 2011; experts convening to discuss access to medicines as a human right – organized by the Human Rights Council in accordance with resolution 12/24 – repeated the importance of measuring access to medicines and again stressed the need to collect data [62]. The role of systematized and regular data collection was highlighted once more with the 2014 adoption of resolution EB134.R16 on access to essential medicines by the WHA [51]. Yet despite these reiterated calls to collect the data, MDG target 8E was not reported on in the 2015 final report due to a lack of available data [63].

A similar lack of evidence was noted in the area of pharmaceutical policy analysis – specifically pharmaceutical pricing policies. In an attempt to create guidance on policies that may be used to manage medicine prices and increase affordability, guideline developers not only highlighted a lack of evidence, but also the overall poor quality of the available evidence on this topic in 2015 [64]. This could be explained by a lack of explicit guidance that existed on the optimal research designs or methods to effectively inform quantitative health policy analyses and how to execute them [65-67]. This suggests that there is a need for tools or guidelines that support generation of the desired evidence.

Another illustration of the limited advancement in this field pertains to the methodologies used to measure performance. Specifically, the in 2003 developed WHO/HAI methodology for measuring medicine prices and availability has since gained international recognition as a gold standard for performance monitoring [68], yet it has several acknowledged limitations. These limitations particularly stem from the metrics availability and affordability [46, 47]. The methodology gauges availability solely based on the medicine's presence on the day of the survey, without considering factors such as volume, and duration and rate of recurrence of potential stock-outs [48, 69]. Affordability is determined based on the LPGW wage, overlooking that in many countries a significant portion of the population earns less than this threshold [46, 70]. Additionally, the methodology does not consider that multiple medicines may be needed simultaneously, potential insurance coverage, or the size of the household. Different metrics for measuring and expressing affordability have been proposed, but these have not been widely used [71]. Similarly, although some innovation was achieved with the approval of SDG indicator 3.b.3 in 2018, this novel indicator has not been used to monitor performance yet [48]. As a result, the WHO/HAI methodology continues to be extensively used and has remained largely unchanged for over 20 years with minimal innovation.

Not only has there been minimal innovation in monitoring performance, vulnerable groups such as children continue to face neglect. Specifically, SDG indicator 3.b.3 is unfit to monitor access to child-appropriate medicines, as it overlooks child-relevant active ingredients, age-appropriate formulations and their distinct dosing requirements in calculating access [48]. This presents a significant gap, considering that children under 15 make up approximately 42% of the population in low-income economies and 26% in middle-income countries, compared to 16% of the population in high-income countries [72]. Unfortunately, this group has historically been subject to neglect across various domains [73]. A telling example is the delayed

development of the first WHO Model List of Essential Medicines for Children (EMLc) in 2007, 30 years after the EML for adults was introduced [74]. Moreover, concerns have been raised about the systematic exclusion of children from the discussions on non-communicable diseases (NCDs) [75]. This exclusion is evident in the 2011 Moscow Declaration on NCDs and subsequent 64th WHA, which both failed to reference the needs of children [76].

Despite the recognized significance of health systems thinking in better understanding and driving access to medicines, evidence is often still generated through fragmented, vertical approaches concentrated on a singular data source or a single pharmaceutical process [77-82]. Without considering related elements and integration in the wider health system, pharmaceutical and other health system components continue to operate in silos. Although the framework as developed by Bigdeli and colleagues provides a fundamental basis for delineating the different contexts [20], its practical application is currently lacking. In fact, the few studies that do consider the health system in its entirety when studying access to medicines employed other, disease-specific frameworks to structure their analyses [83-86]. This suggests a need for practical guidance in performing such analyses. Additionally, the impact of evidence may be increased by triangulating data sources, to obtain a more comprehensive understanding of factors affecting access.

Objectives of this thesis

Despite the established value of medicines and the numerous national and international programs and initiatives to ensure access to them, significant disparities in equitable access to medicines persist with an estimated two billion people still lacking regular access to essential medicines. This reveals a pressing moral concern, for access to medicines is firmly acknowledged to be a cornerstone in the full realization of the right to health and as such a human right in itself.

In order to achieve progress, evidence from monitoring and evaluation is key in guiding effective policy development for access to medicines. However, a loss of momentum in recent years has resulted in diminished innovation in access to medicines research and limited evidence generation, constituting an evidence-to-policy gap in the field. Hence, this thesis aims to explore advancements to the three key evidence-generation mechanisms for formulating and evaluating pharmaceutical policies. It intends to do so by enhancing existing methodological instruments, introducing novel approaches in the monitoring and evaluation of access to medicines within existing health systems, and expanding their scope to typically understudied populations and health conditions:

Objective 1) To adjust and expand the scope of SDG indicator 3.b.3, as the most important performance monitoring tool for measuring access to medicines at this time, to include children.

Objective 2) To develop and apply adapted health systems analysis approaches to assess and understand access to medicines from a holistic perspective.

Objective 3) To review and identify gaps in the current landscape of pharmaceutical policy analysis and methodologies used.

With that, this thesis endeavors to bridge the gap between evidence-generation and policy-making.

Thesis outline

Following this introduction, **Chapter 2** focusses on performance monitoring for children by modifying Sustainable Development Goal indicator 3.b.3 to include this typically understudied population. **Chapter 2.1** addresses the current lack of performance data on child-appropriate medicines. In **Chapter 2.2**, we present a complementary indicator for children and provide proof-of-concept. The rigor of this complementary indicator is studied in **Chapter 2.3**, through the performance of sensitivity analyses. Finally, **Chapter 2.4** introduces a standardized set of age-appropriate medicines to facilitate performance monitoring of access to medicines for children.

Chapter 3 focusses on adapted approaches in health systems analyses, through a case study of access to childhood oncology medicines in South Africa. **Chapter 3.1** addresses the alignment of multiple pharmaceutical processes in South Africa, to identify sources of access constraint to pediatric cancer medicines. **Chapter 3.2** presents a novel analytical framework to facilitate the identification of barriers and enablers in access to medicines from a health systems perspective. This framework is applied to childhood cancer medicines in the South African context in **Chapter 3.3**, where we sought to identify drivers of access from the perspective of different stakeholders in the pharmaceutical value chain. The perspective and experiences of caregivers of children with cancer is presented in **Chapter 3.4**. In **Chapter 3.5**, the appropriateness of South Africa's National Cancer Strategic Framework in addressing barriers to childhood cancer medicines is examined through triangulation of findings from previous chapters.

Chapter 4 examines the landscape of pharmaceutical policy analysis through the lens of pharmaceutical pricing policies. **Chapter 4.1** presents systematically collected and assessed evidence on policies promoting price transparency. Existing literature on policies regulating mark-ups in the pharmaceutical supply and distribution chain is reviewed in **Chapter 4.2**. In **Chapter 4.3**, common weaknesses in studies of pharmaceutical pricing policies are identified and methodologies used are critically reviewed for their value in providing robust evidence.

In **Chapter 5**, we discuss themes that transcend the different chapters, provide recommendations to advance access to medicines research further.

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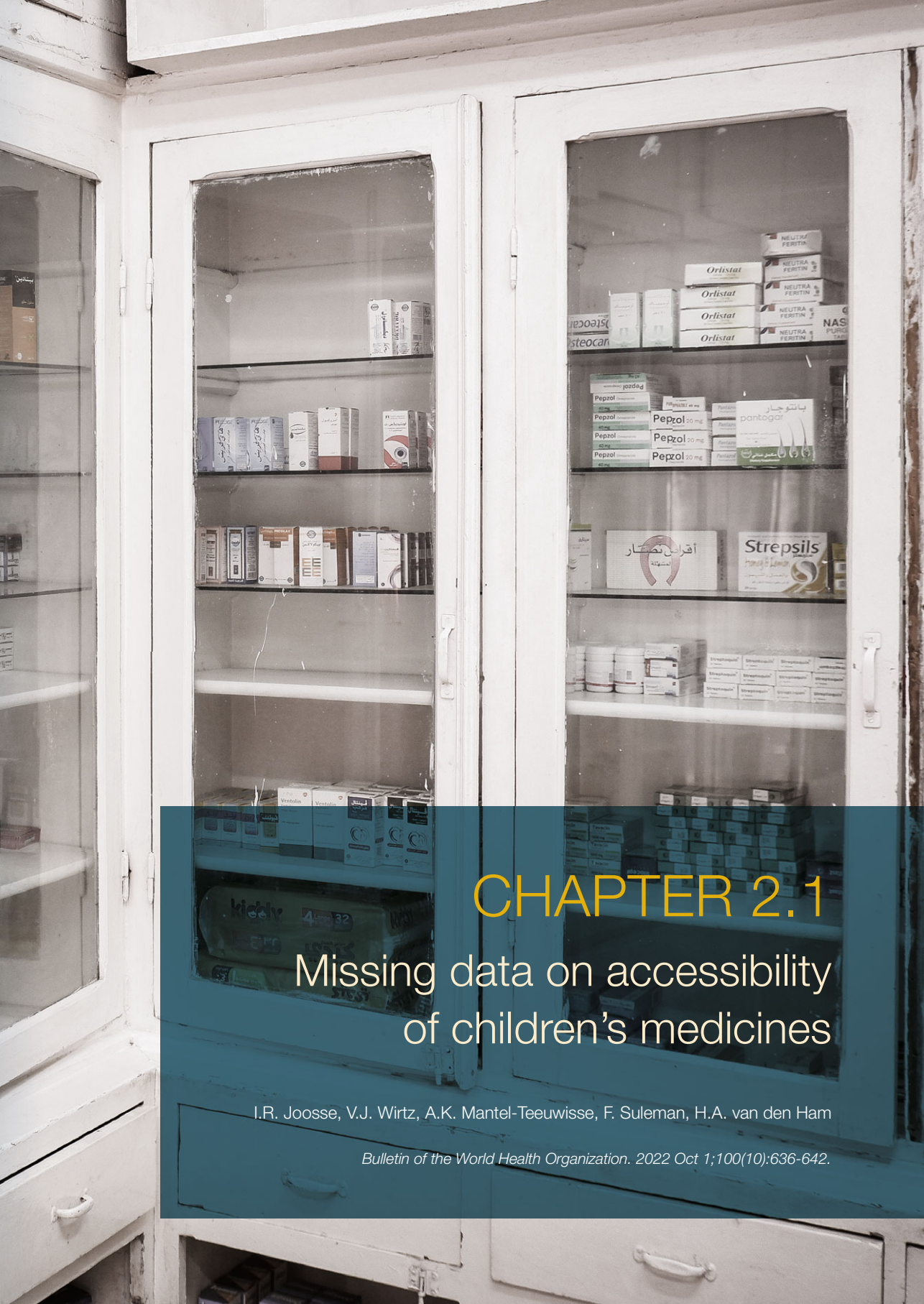
CHAPTER 2

Monitoring access to medicines for children


Bivatracin
BETADINE
Kaprofen
KETOLAC



CHAPTER 2.1

Missing data on accessibility of children's medicines

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Abstract

Child-appropriate medicines are essential for the safe and effective treatment of children, yet we have observed a large gap in the data required to adequately monitor access to these medicines. We have examined data on the availability and pricing of child- appropriate medicines across 50 surveys. Child-appropriate medicines for nine out of 12 priority diseases in children were infrequently surveyed or not at all. A similar data deficit on age-appropriate medicines is detectable in the broader scientific literature. We also note that existing instruments for collecting data on the availability or prices of medicines are limited in their ability to generate the required data for children. We have identified four priorities as key for improved monitoring of access to medicines for children: (i) dedicated child medicine surveys are needed on availability and prices of child-appropriate medicines; (ii) standardized survey instruments should include age-appropriate medicines and dosages; (iii) health facility service readiness survey tools should include the collection of data on the price of child-appropriate medicines in addition to the availability of medicines; and (iv) sustainable development goal indicator 3.b.3 should be modified to enable the monitoring of access to medicines for children. These deficiencies need to be addressed to ensure the monitoring of access to child medicines as part of the sustainable development goal agenda for 2030 and to implement appropriate interventions for improving access for this vulnerable population.

Introduction

The importance of access to available and affordable essential medicines for all is embodied in targets 3.8 and 3.b of the sustainable development goals (SDGs) and remains a priority on the international agenda [1]. Data on the availability and prices of medicines are considered pivotal for measuring progress on these SDGs. The key indicator to assess country progress on target 3.b (indicator 3.b.3) requires both availability and price as inputs (**Figure 1**) [2]. The outcomes of the indicators are meant to guide national and international efforts to improve people's access to medicines [3].

However, research efforts have traditionally focused on measuring access to medicines for the general population, without particular consideration for medicines for children. As a result, we note that there is a major gap in our understanding of accessibility of medicines for children. The gap is manifested in two ways: first, validated surveys dedicated to medicines for children is lacking; second, surveys whose results are made available in the public domain have not sufficiently covered child-appropriate medicines. In addition to this data gap, the main indicator

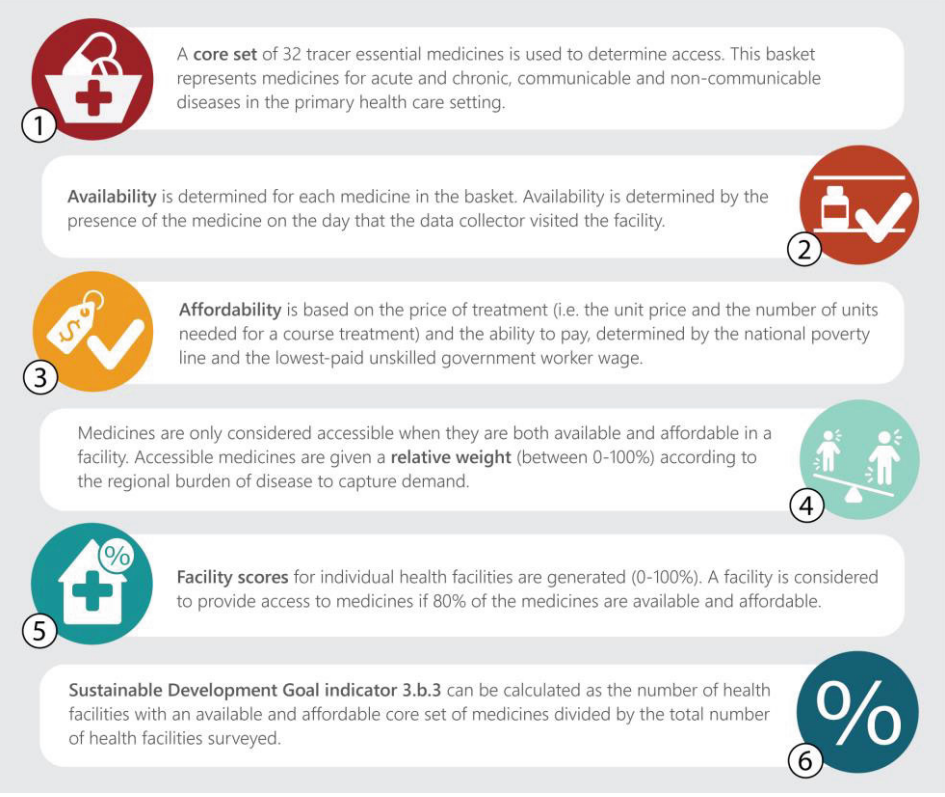

Figure 1 How Sustainable Development Goal indicator 3.b.3 is used for measuring access to medicines. Note: adapted from United Nations, 2019 [2].

to measure access to medicines (SDG indicator 3.b.3) is primarily aimed at adults. These deficiencies impede the monitoring and understanding of accessibility of pediatric medicines and thereby the possibility for policy-makers to implement appropriate interventions. We discuss here the extent of the data gaps and propose ways to address the gaps.

Age-appropriate medicines

Children require medicines that are age-appropriate. Differences in the pharmacokinetic and pharmacodynamic profile of children and adults mean that children require different dosage strengths. There is also a need for preparations that are easy to administer, contain excipients that are safe for children, are better accepted by children, and enable flexible dosing [4]. In recent years there has been a shift away from liquid formulations to solid oral dosage forms [5]. However, most traditional solid oral preparations are unsuitable for children younger than 6 years due to the risk of choking and difficulties with swallowing [6]. Additionally, manipulation of existing dosage forms (such as breaking, crushing or diluting) may cause harmful dosing errors [7]. Child-appropriate medicines – such as orodispersible or chewable tablets and possibly oral liquids or rectal formulations – are thus required to achieve effective and safe treatment and often cannot be replaced by medicines for adults. Accordingly, it is essential that child-appropriate medicines are monitored for their availability and affordability.

Data deficit

In our attempts to assess the accessibility of medicines for children we observed that there is a large deficiency in data on the availability and price of child-appropriate medicines. To illustrate the extensiveness of the data gap on child medicines, we screened surveys using the standardized World Health Organization (WHO)/Health Action International (HAI) method on the availability and prices of child-appropriate medicines used in treating diseases with the highest burden in children. These survey methods are regarded as a gold standard when studying the availability and price of medicines, and the survey results have been widely used to assess progress towards the millennium development goals [8, 9].

We screened surveys on child-appropriate medicines for 12 priority diseases in children. We selected 10 diseases that are associated with the highest absolute burden of dis- ease expressed in disability-adjusted life years for children aged 0–14 years according to the Global Health Estimates [10] and treatable with medicines from the WHO essential medicines list for children [11]. We also selected two other diseases – pain and palliative care, and vitamin K-associated bleeding – which are not included in the Global Health Estimates, but nevertheless represent priority diseases. We defined appropriate medicines as first-choice medicines in primary care according to the uses described in the essential medicines list for children [11]. Dosage forms that we considered child-appropriate included inhalers, oral liquids, injections, powders for dissolving, suppositories and chewable or dispersible tablets. If none of the dosage forms above were listed in the essential medicines list for children, we also considered tablets or capsules as

appropriate. We screened surveys that were conducted according to the WHO/HAI method for child-appropriate medicines and were published on the initiative's website [12]. We started screening at the most recent surveys.

In total, we screened 50 surveys, conducted between 2001 and 2015 and across 43 countries in all six WHO regions (**Box 1**). A single survey was specifically dedicated to child medicines, whereas no specific age group was targeted in the other 49 surveys. **Table 1** shows the number and percentage of surveys that included at least one child-appropriate medicine for each of the 12 priority diseases in children. Our findings show that child-appropriate medicines for nine out of 12 diseases were only sporadically surveyed or not at all, including medicines for treatment of tuberculosis and iron deficiency anemia. The better results for asthma medication and antibiotics are probably because the formulations of these medicines (such as inhalers and injections) are used by adults as well. Noteworthy, however, (child) spacers for inhaled medications were not part of our screening. Additionally, these results may not be applied to individual medicines, as the results in **Table 1** are grouped by indication. To illustrate, ampicillin was included in only eight of 50 surveys, and even a key antibiotic such as amoxicillin (or amoxicillin plus clavulanic acid) was surveyed as a child-appropriate formulation in just half of the surveys (26 of 50).

Box 1 WHO/HAI surveys screened for child-appropriate medicine(s) for treatment of common childhood diseases, by country and year.

African region		**European region**		**Eastern Mediterranean region**	
Burkina Faso	2009	Armenia	2001	Afghanistan	2011
Burundi	2013	Kazakhstan	2004	Egypt	2013
Ethiopia	2013	Kyrgyzstan	2005	Iran	2007
Tanzania	2012	Kyrgyzstan	2010	Jordan	2004
Uganda	2015	Kyrgyzstan	2015	Kuwait	2004
Western Pacific region		Moldova	2011	Lebanon	2004
China[a]	2012	Russia	2011	Lebanon	2013
Laos	2013	Tajikistan	2005	Morocco	2004
Malaysia	2004	Tajikistan	2013	Oman	2007
Mongolia	2012	Ukraine	2007	Pakistan	2004
Philippines	2008	Ukraine	2012	Saudi Arabia	2015
Region of the Americas		Uzbekistan	2004	Sudan	2012
Bolivia	2008	**South East Asia region**		Sudan	2013
Brazil	2008	India	2005	Syria	2003
Colombia	2008	India	2011	Tunesia	2004
Haiti	2011	Indonesia	2010	United Arab Emirates	2006
Mexico	2009	Sri Lanka	2001	Yemen	2006
United States	2015	Thailand	2006		

[a] Survey dedicated to pediatric medicines

A similar data deficit and lack of attention to age-appropriate formulations is detectable in the broader scientific literature. A recent systematic review on accessibility of child medicines identified only 18 surveys that included data on the availability, price or affordability of pediatric medicines, out of 4732 records screened [13]. There were only 11 studies that reported both the availability and price of medicines. Of note, one of these surveys was also recorded in the HAI database and included in our own sample of surveys screened (China, 2012). The surveys identified in the systematic review were conducted from 2009 to 2019 and included studies from eight different countries [13]. We judged that seven of 18 studies included surveys of limited significance for measuring accessibility of medicines in a country, as they (i) focused on one disease area only (such as cardiovascular medicine or cancer medicine), (ii) were studies of formulations that were often not age-appropriate (such as traditional solid oral dosage forms versus oral liquids or flexible oral dosage forms), or (iii) solely looked at active ingredients and not formulations.

Limitations of tools

Despite being considered the gold standard, the WHO/HAI survey type has been less used since 2015. WHO has instead been looking at other means to collect data on the availability and pricing of medicines, partly to promote leaner data collection and analysis methods. The WHO Essential Medicines and Health Products Price and Availability Monitoring mobile application (MedMon) is such an instrument [14]. This tool was developed for rapid and flexible data collection and analysis, and should facilitate more routine monitoring. Nonetheless, wide-spread implementation of this promising tool has been delayed, despite several successful pilot studies.

A WHO-recommended instrument for assessing health facility performance is the Service Availability and Readiness Assessment (SARA) survey, a tool designed through collaboration between WHO and the United States Agency for International Development (USAID) [15]. Although essential medicines are only a small part of this tool's scope, it has been suggested that these surveys could nevertheless be an important data source for monitoring access to medicines. However, the relevance of data from these surveys for children is very limited because this survey type does not specify which formulations should be surveyed, or which formulations are age-appropriate. More importantly, collection of price data is not part of this tool. With affordability being a core component of accessibility to medicines, the applicability of this tool in monitoring accessibility of child medicines is limited.

Another tool for collecting data on essential medicines, and a predecessor of the Service Availability and Readiness Assessment, is the Service Provision Assessment (SPA) within the Demographic and Health Surveys programme, funded by USAID and other partners [16]. SPA was designed to gather data on a range of health facility services and their quality, with child and maternal health being one of the key topics assessed in these surveys. Although the dosage

Table 1 World Health Organization/Health Action International surveys that covered child-appropriate medicines for treatment of common childhood diseases.

Disease area	Screened surveys to cover child-appropriate medicine(s)		Associated disease burden (ranked)[a]	Age group most affected
	number	% (n=50)		
Asthma	49	98	8	5-14 years
Bacterial infectious diseases[b]	45	90	1	All ages
Pain and palliative care	24	48	-[c]	All ages
Diarrheal diseases	13	26	2	All ages
Malaria	7	14	3	1 month-14 years
Epilepsy	7	14	9	1 month-14 year
Measles	3	6	5	1 month-5 years
Migraine	1	2	10	5-14 years
Tuberculosis	0	0	4	1 month-14 years
Iron deficiency anemia	0	0	6	1 month-14 years
HIV/AIDS	0	0	7	All ages
Vitamin K deficiency bleeding	0	0	-[c]	Neonates

0-33% 33-67% 67-100%

AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus infection.

[a] We selected diseases with the highest burden of disease in children (in disability-adjusted life years) from the Global Health Estimates [10].

[b] Bacterial infectious diseases is an aggregated term for several prevalent infectious diseases with bacterial origin (such as lower respiratory infections, neonatal sepsis, meningitis, pertussis and syphilis).

[c] Dashes indicate that these diseases are not associated with a burden in the Global Health Estimates, so no rank can be assigned.

Note: Dosage forms considered child-appropriate were: inhalers, injections, oral liquids, powders for dissolving, suppositories, and chewable or (oro)dispersible tablets. If none of the dosage forms above were listed in the WHO essential medicines list for children [11], tablets or capsules were also considered appropriate.

form of medicines for surveys is specified, the number of medicines that are relevant for children is sparse. Similar to SARA surveys, SPA does not include collection of data on medicine prices.

Apart from original data collection, secondary data to benchmark affordability are also lacking. A widely used standard reference to benchmark medicines prices, the Management Sciences for Health International Medical Products Price Guide, has not been updated since 2015 [17]. In addition, commercial data sets such as those provided by IQVIA® (IQVIA Inc., Durham, United States of America) may include meaningful data in terms of medicines' sales and utilization, but these data sets are generally not publicly available, although some countries may have purchased a license for access. An overview of data collection tools and sources can be found in **Table 2**.

Table 2 Characteristics and limitations of data collection tools

Tool	Main characteristics	Limitations
Primary data collection tools		
Standardized WHO/HAI surveys [8]	Designed to collect and analyze data on availability and prices of medicines.	A paper-based tool; labor intensive. Little use in recent years.
WHO Essential Medicines and Health Products Price and Availability Monitoring Mobile Application (MedMon) [14]	Electronic tool designed to collect and analyze data on availability and prices of medicines.	Tool currently unavailable to the public due to modifications being implemented.
Service Availability and Readiness Assessment survey (SARA) [15]	Designed to collect data on availability of medicines at facility level, among other facility services.	Data on medicine prices not collected. No data on private sector outlets. Tool does not collect data on age-appropriate medicines.
Service Provision Assessment (SPA) [16]	Designed to collect data on availability of medicines at facility level, among other facility services.	Data on medicine prices not collected. No data on private sector outlets. Number of age-appropriate medicines limited.
Secondary data sources		
International Medical Products Price Guide	Includes international comparative price data on medicines.	Not updated since 2015.
Electronic medical records/claims data/hospital data (e.g. IQVIA® datasets[a]).	Real World Data on medicines' sales and utilization, among other health data.	Available on purchase.

WHO = World Health Organization.

[a] IQVIA Inc., Durham, United States of America.

Closing the gap

In an effort to close the gap in accessibility between adult and child medicines, a landmark resolution called Better medicines for children was adopted by the World Health Assembly in 2007 [18]. This resolution identified several areas that needed to be addressed to close the gap and requested WHO to intensify their efforts in making safe and effective medicines as widely available for children as for adults. Since this resolution, WHO has invested in comprehensive activities to improve access for children, including establishing the first WHO model list of essential medicines for children in 2007 [11, 19]. This initiative was 30 years after the first essential medicines list, which included some medicines for children but failed to systematically consider medicines for this

vulnerable population at the time. Other milestones since the resolution included the Make Medicines Child Size campaign (2007), the development of a model formulary for children (2010), the establishing of a priority list of essential medicines for women and children (2011), and up- dated treatment guidelines (2013) [20–23].

Despite the increased attention on child-appropriate medicines globally, data collection on the subject still lags behind that for adult medicines. In fact, the SDG indicator that was designed in 2017 to measure access to medicines fails to address the needs of children [2]. This current lack of a method and an indicator that combine availability and affordability of medicines for children in a single measure is an important gap that needs to be filled. For the indicator to be appropriate for measuring access to medicines for children, the method should include a basket of medicines with a broader selection of medicines that are relevant to children, including age-appropriate dosage forms and strengths (**Figure 1**, step 1). Additionally, a novel measure should be developed for the number of units that are needed for a course of treatment for children (**Figure 1**, step 3), to substitute the defined daily dosage that is currently used in the calculations but is applicable to adults only. Without such adjustment, measurement for children would not be possible. Furthermore, for this prospective child indicator to be of real value, the corresponding data on availability and prices of child medicines are required. This necessity is highlighted in the tier classification for global SDG indicators, which requires that – for a so-called tier 1 indicator – both a method is established, and the data are produced regularly by countries [24].

We have identified the following four priorities for adequate monitoring of access to medicines for children. First, we call for urgent action to fill the current data gap, as countries have to report each year on their progress towards the 2030 SDGs. Surveys that are conducted for the general population should stratify results by child and adult medicines. Second, standardized survey types for collecting data on the availability and prices of medicines – such as the surveys using the WHO/HAI method – should provide guidance and the tools for collecting the required data on child-appropriate medicines. These survey instruments should include a broad range of priority medicines for children of different ages, alongside those for adults. Special attention

should be paid to the inclusion of flexible oral solid-dosage forms and other child-appropriate dosage forms. New technologies such as the WHO MedMon application may provide opportunities for gathering the appropriate data and should be implemented without further delay [14]. Third, any routine assessment of facility readiness such as SARA and SPA surveys should include assessment of the affordability of essential medicines for adults and children as well as their availability [15,16]. Fourth, the SDG 3.b.3 indicator for measuring access to medicines as a combination of availability and affordability needs to be adjusted to make it appropriate for child medication [2].

Implications

Because of the unique requirements of children, data on adult medicines do not provide an insight into access to medicines for children. We believe that swift action is needed to include child medicines in national surveys. If this is not done soon, an important window of opportunity will be missed to improve accountability and transparency in progress towards access to medicines – for both adults and children – as part of the 2030 SDGs agenda. If medicines were to be dropped from the overall progress report on SDGs, it would be the second time that the global public health community has failed to report on access to medicines [25].

We observed that child-appropriate medicines are neglected when measuring accessibility to medicines. Although the data deficit we discuss above may not provide a complete overview of the available data on children's medicines, it nonetheless highlights the gaps in these types of data. This situation is concerning; without sufficient and appropriate data to inform us, we cannot identify potential barriers to access to medicines and to accomplish real change. Children have no voice to advocate for themselves. Who will advocate on their behalf for adequate data to improve and trace access to child-appropriate medicines?

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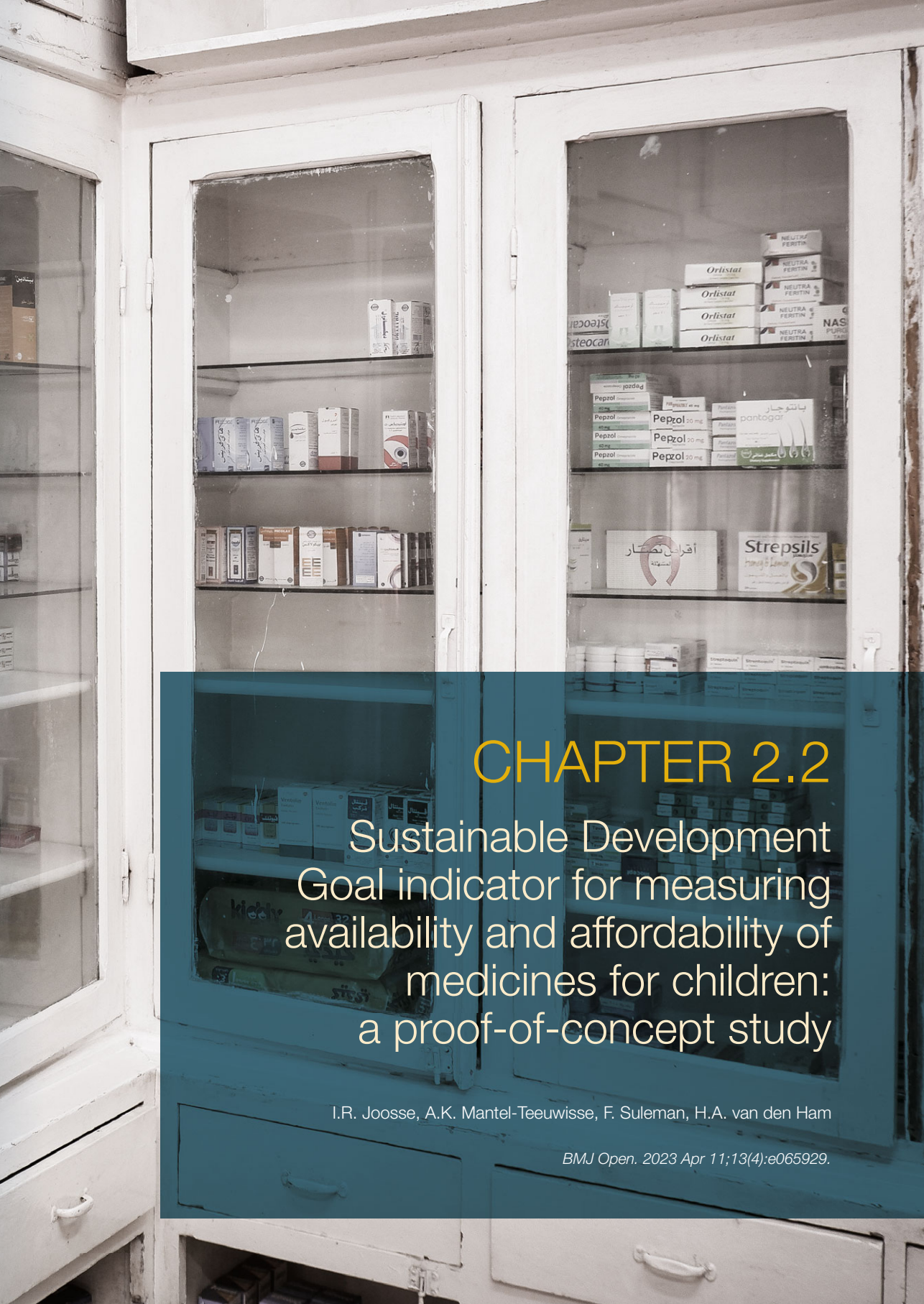
Bivatracin
BETADINE
Kaprofen
KETOLAC



CHAPTER 2.2

Sustainable Development Goal indicator for measuring availability and affordability of medicines for children: a proof-of-concept study

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Abstract

Objectives

To complement Sustainable Development Goal (SDG) indicator 3.b.3 that monitors access to medicines for all, a corresponding child-specific methodology was developed tailored to the health needs of children. This methodology could aid countries in monitoring accessibility to pediatric medicines in a validated manner and on a longitudinal basis. We aimed to provide proof-of concept of this adapted methodology by applying the method to historical datasets.

Method

A core set of child-appropriate medicines was selected for two groups of children: children aged 1 to 59 months and children aged 5 to 12 years. To enable calculation of affordability of medicines for children, the number of units needed for treatment (NUNT) was created, incorporating the recommended dosage and duration of treatment for the specific age group. The adapted methodology was applied to data from Burundi (2013), China (2012) and Haiti (2011) for one age group. SDG indicator 3.b.3 scores and (mean) individual facility scores were calculated per country and sector.

Results

We were able to calculate SDG indicator 3.b.3 based on historical data from Burundi, China and Haiti with the adapted methodology. In this case study, all individual facilities failed to reach the 80% benchmark of accessible medicines, resulting in SDG indicator 3.b.3 scores of 0% for all three countries. Mean facility scores ranged from 22.2% in Haiti to 40.3% in Burundi for lowest-price generic medicines. Mean facility scores for originator brands were 0%, 16.5% and 9.9%, for Burundi, China and Haiti respectively. The low scores seemed to stem from the low availability of medicines.

Conclusion

The child-specific methodology was successfully applied to historical data from Burundi, China and Haiti, providing proof-of-concept of this methodology. The proposed validation steps and sensitivity analyses will help determine its robustness and could lead to further improvements.

Introduction

Despite considerable progress in recent decades, unacceptably high numbers of preventable child deaths remain an important challenge in resource-limited countries. The number of child deaths is unevenly distributed: in 2020, over 80% of the 5.0 million under-five deaths occurred in just two regions – Sub-Saharan Africa and South Asia [1]. A similar geographic disparity is visible in children and youth over 5 years of age, although mortality rates are somewhat lower in this group [1]. The large population of children in these regions put a further strain on often fragile health systems [1]. A key element in reducing the number of children suffering and dying from preventable and treatable diseases is improving access to medicines, as outlined in targets 3.8 and 3.b of the United Nations (UN) Sustainable Development Goals (SDGs) [2].

In order to promote access to essential medicines, countries' current performance and their progress need to be assessed and monitored [3]. This will help program managers and policy-makers in planning their activities and developing targeted policies. Although SDG indicator 3.b.3 has been developed precisely for this purpose [4], it predominantly targets adult medicines. As to not exclude children from access to medicines research there is a need for an assessment method tailored to children.

SDG indicator 3.b.3 is a multidimensional index of medicines' access, reported as the proportion of health facilities that have a core set of essential medicines available with affordable prices relative to the total number of surveyed health facilities (at a national level) [4]. Indicator 3.b.3 thus allows for a combined evaluation of two important dimensions of access to medicines - availability and affordability - while also permitting separate analysis of these dimensions if overall performance is poor. However, the core set of medicines used for this indicator targets diseases such as cardiovascular diseases and diabetes mellitus type 2, which are typically not prevalent among children. Moreover, age-appropriate formulations are not considered as part of this core set of medicines [5]. Yet, manipulation of adult formulations to obtain an appropriate dose for children risks administrating toxic or sub-therapeutic doses through inaccurate dosing, as well as dosing errors [6]. Availability of age-appropriate formulations is thus required for safe and effective treatment of infants and young children. Finally, affordability of medicines in indicator 3.b.3 is based on Defined Daily Dosages (DDDs), which are only applicable to adults. Hence, the current indicator fails to provide critical insight into access to pediatric medicines.

At present, there is no methodology for measuring accessibility of essential medicines specifically for children, but a number of studies have reported on the availability or price of medicines, or both [7-35]. The methodologies for measuring these two important dimensions of access varied greatly between studies, as did the medicines surveyed, covering different age groups of children (e.g. children under five, children under twelve, or all children and adolescents), priority diseases (anticancer medicines, cardiovascular medicines or a range of

diseases) and number of surveyed medicines. Results are therefore difficult to compare and may not reflect overall access to medicines for children in a country. This emphasizes the need for a standardized and validated methodology for measuring access to medicines for children that will enable global comparison and eventually benchmarking of indicators.

In the present study, we propose a conceptual methodology for adapting the SDG indicator 3.b.3 that can be used to assess access to essential medicines for children. We apply the methodology to three case study countries (Burundi, China, Haiti) as proof-of concept.

Methodology

SDG indicator 3.b.3 is a composite bidimensional indicator of access, that can be calculated as follows [4]:

$$SDG_{3.b.3.} = \frac{Facilities\ with\ available\ and\ affordable\ basket\ of\ medicines\ (n)}{Surveyed\ Facilities\ (n)} \quad (1)$$

The indicator includes three core concepts used to calculate access to medicines:

1) A core set of globally relevant (quality-assured) essential medicines – weighted for the regional burden of disease.
2) Availability of medicines.
3) Affordability of medicines – based on the price of a medicine, the daily dose of the medicine needed for treatment, the national poverty line (NPL) and the lowest-paid unskilled government worker (LPGW) wage.

As both availability and affordability are important dimensions of access, the combination of these core concepts into a single measure allows evaluation of overall access to medicines. As SDG indicator 3.b.3 was formally approved by the UN Statistics Division, we aimed for an adapted indicator 3.b.3 for children to resemble the original indicator as closely as possible. In this section, we discuss the critical steps of the original framework and describe how the core concepts have been adapted to allow calculation of access to pediatric medicines.

A core set of globally relevant essential medicines

The core set of medicines consists of tracer essential medicines, together indicative of overall access to medicines in primary health care. Over the years, several baskets of pediatric medicines have already been proposed. However, the list of medicines defined for the 2007 'Better medicines for children' project is not only dated, but also purposely excludes antiretroviral therapies (ART) for HIV [3]. Since HIV/AIDS is still prevalent among pediatric populations in low- and middle-income countries, this selection of medicines is not suitable for the current purpose. In 2012, the World Health Organization (WHO) published a list of thirteen 'Priority life-saving

medicines' for children under the age of five, intended to help countries in prioritizing those medicines that will have the biggest impact on reducing child morbidity and mortality [36]. We believe that an access indicator should serve a broader age group, especially since children aged 5 to 12 years may have different treatment requirements than the youngest. Additionally, the priority list only targets seven prevalent diseases, and is thus limited in its scope. With that, no existing basket of pediatric medicines was deemed suitable for the current purpose.

A new core set of medicines for children with ages 1 month to 12 years for treating acute and chronic, communicable and non-communicable diseases in the primary health care setting and including child-appropriate formulations was thus established. To cater to the unique needs of children with different ages, separate baskets for two age groups were created: young children (infants, toddlers and pre-school children) aged 1 month to 59 months, and school-aged children 5 to 12 years of age. These groups will allow stakeholders to differentiate between health needs in terms of disease prevalence, required dosage strengths and preferred dosage forms. Children above the age of 12 often do not require pediatric formulations [37] and their health needs may already be adequately covered in the original SDG indicator 3.b.3 methodology.

To enable use of this methodology in a global context, medicines used for treating diseases with a high global prevalence were selected. Starting point for establishing a universal set of pediatric medicines were the 2019 global burden of disease estimates in children (Global Health Estimates, GHEs) [38]. We selected ten priority conditions causing the most mortality and morbidity in DALYs per age group, which were treatable with medicines from the 2019 WHO Essential Medicines List for Children (EMLc) [39]. This excluded for example congenital defects and malnutrition. And although not separately represented in the GHEs, pain and palliative care was included in the selection of diseases for each age group as these are considered essential in supportive care of many conditions.

Priority conditions were linked to first-choice medicines in primary health care using WHO and South African treatment guidelines [40-44]. Multiple medicines from the same therapeutic class of medicines could be selected and can be considered interchangeable (including antiepileptics, anthelminthics, antimalarials). Medicines requiring cold-chain management were excluded, as these may not be widely available in primary health facilities. Additionally, although vaccines are a key component in health care, vaccination coverage is already included within indicator 3.b.1 of the SDGs and will therefore not be covered in indicator 3.b.3 as well. To ensure that the proposed basket of medicines sufficiently addresses priority health needs in clinical practice, expert validation of the core set of essential medicines has taken place through an online survey (see Appendix 1 for details). The provisional basket of medicines for children aged 1 month to 5 years can be found in **Table 1**. Child-appropriate medicine formulations were selected

pragmatically, based on formulations present on the WHO EMLc and the required dosage strengths in young children.

Availability of medicines

The second core concept in the SDG indicator 3.b.3 is the availability of medicines. Availability is a snapshot, binary variable: a medicine is considered available in a facility when found in the facility by the interviewer on the day of data collection [4]. The definition and analysis of availability in the original framework were deemed compatible with pediatric medicines and was applied without revisions.

Table 1 Proposed core set of essential medicines for children 1-59 months.

Disease area (GHE code)	Medicine name	Acceptable formulations
Diarrhoeal diseases (110)	Oral rehydration salts	*Powder sachet 200 ml, 500 ml or 1L*
	Zinc sulphate	*Cap/tab 20 mg*
Epilepsy (970)	Carbamazapine	*Cap/tab 100 mg; oral liquid 100 mg/5 ml*
	OR Phenobarbital	*Cap/tab 30 mg or 100 mg; injection 100 mg/ml or 200 mg/ml; oral liquid 15 mg/5 ml*
	OR Phenytoin	*Cap/tab 25 mg, 50 mg or 100 mg; injection 50 mg/ml; oral liquid 25 or 30 mg/5 ml*
	OR Lamotrigine	*Cap/tab 25 mg, 50 mg or 100 mg*
	Valproic acid	*Cap/tab 100 mg, 150 mg, 200 mg or 500 mg; oral liquid 200 mg/5 ml*
	Diazepam	*Rectal solution 5 mg/ml; injection 5 mg/ml*
	OR Lorazepam	*Parenteral solution 2 mg/ml or 4 mg/ml*
	OR Midazolam	*Oromucosal solution 5 mg/ml or 10 mg/ml; ampoule 10 mg/ml*
HIV/AIDS (100)	Abacavir + lamivudine + dolutegravir	*Cap/tab 120/60 mg (abacavir/lamivudine)* ***AND*** *cap/tab 10 mg (dolutegravir)*
	OR Abacavir + lamivudine + lopinavir/ritonavir	*Cap/tab 120/60 mg (abacavir/lamivudine)* ***AND*** *cap/tab 40/10 mg or 100/25 mg (lopinavir/ritonavir)*
Iron-deficiency anemia (580)	Ferrous salt	*Cap/tab 60 mg or 200 mg; oral liquid 25 mg/ml*
	Albendazole	*Cap/tab 200 mg or 400 mg*
	OR Mebendazole	*Cap/tab 100 mg*
Malaria (220)	Artemether + lumefantrine	*Cap/tab 20/120 mg*
	OR Artesunate + amodiaquine	*Cap/tab 25/67.5 mg or 50/135 mg*
	OR Artesunate + mefloquine	*Cap/tab 25/55 mg*
	OR Dihydroartemisinin + piperaquine	*Cap/tab 20/160 mg or 20/320 mg*
	OR Artesunate + Sulfadoxine-pyrimethamine	*Cap/tab 50/500/25 mg or cap/tab 50 mg (artesunate)* ***AND*** *cap/tab 500/25 mg (sulfadoxine-pyrimethamine)*
	OR Chloroquine	*Cap/tab 100 mg; oral liquid 50 mg/5 ml*
	Artesunate	*Cap/tab 50 mg; suppository 50 mg*
Measles (150)	Retinol	*Cap/tab 25,000 IU, 100,000 IU or 200,000 IU*

Vitamin A deficiency (570)		
Pain and palliative care (weight = 1/T[a])	Paracetamol	*Cap/tab 100 mg; suppository 100 mg; suspension 120 or 125 mg/5 ml*
	Morphine	*Cap/tab (slow release) 10 mg; injection 10 mg/ampoule; oral liquid 10 mg/5 ml*
	Ibuprofen	*Cap/tab 200 mg; oral liquid 200 mg/5 ml*
Tuberculosis (30)	Ethambutol + isoniazid + pyrazinamide + rifampicin	*Cap/tab 100 mg or 400 mg or oral liquid 25 mg/ml (ethambutol)* ***AND*** *cap/tab 50/150/75 mg (isoniazid + pyrazinamide + rifampicin)*
Lower respiratory infections (390) Other infectious diseases (370)	Amoxicillin	*Cap/tab 250 mg or 500 mg; powder for injection 250 mg/vial, 500 mg/vial or 1 g/vial; suspension 125 mg/5 ml or 250 mg/5 ml*
	OR Amoxicillin + clavulanic acid	*Cap/tab 100/125 mg, 250/125 mg or 500/125 mg; powder for injection 500/100 mg/vial; oral liquid 125/53.25 mg/5 ml or 250/62.5 mg/5 ml*
	Ampicillin	*Cap/tab 250 mg or 500 mg; injection 500 mg/vial or 1 g/vial*
	Benzylpenicillin	*Injection 1 MIU/vial*
	Gentamicin	*Injection 10 mg/ml or 40 mg/ml*
Other infectious diseases (370) Meningitis (170)	Ceftriaxone	*Injection 250 mg/vial, 500 mg/vial or 1 g/vial*
	Cefotaxime	*Injection 1 g/vial*
Syphilis (50)	Procaine benzylpenicillin	*Injection 1 MIU/vial*

Cap/tab = capsule/tablet; GHE = Global Health Estimates; MIU = milli-International Units.
[a] T is the total number of surveyed medicines.

Affordability of medicines

A medicine is considered affordable in SDG indicator 3.b.3 when no extra daily wages (EDW) are needed for the LPGW to purchase a monthly dose treatment of this medicine after fulfilling basic needs, represented by the NPL (formula 2):

$$Extra\ daily\ wages\ (EDW) = \frac{NPL + price\ per\ treatment}{daily\ wage\ of\ LPGW} \quad (2)$$

In which: $$price\ per\ treatment = \frac{unit\ price * number\ of\ units\ needed\ per\ treatment}{365/12} \quad (3)$$

This measure indicates whether the LPGW wage is enough to cover the costs of daily expenditures for food and non-food items plus the cost of a medicine. The EDW is again transformed into a binary variable: a medicine is considered affordable when no EDW are required to purchase it (formula 4).

$$\begin{cases} if\ EDW \leq 1, & affordability = 1, \\ otherwise, & affordability = 0 \end{cases} \quad (4)$$

Number of units needed for treatment

The price per monthly treatment of a medicine is calculated from 1) the price of a medicine unit (e.g. tablet, milliliter, etc.) and 2) the number of units needed for treatment (NUNT). In the original framework, the latter is based on DDDs that are not applicable to children. Hence, in order to calculate affordability for children, the NUNT was determined through the elements below.

1) The recommended dosing per age or weight group;
2) If applicable, the transformation of weight-based dosing (or based on body surface area (BSA)) to age-based dosing;
3) The duration of treatment.

Recommended (maintenance) doses per day in children – used for its main indication – were determined based on international treatment guidelines [40-44]. As many dosing regimens are based on the body weight of a child, weight-based dosing regimens were converted to age-based regimens using weight-for-age charts [45-47]. Median weights of boys and girls within an age group were averaged to obtain a single measure per group. Medicines dosed based on BSA were converted through an extra calculation step, using the Meeh type equation [48]. Of note, each of the two age groups represents a range of ages. In order to calculate a single outcome for each group, the NUNT is based on the average age and weight of a child within a group (i.e. a 30 month old child of 11 kg and an 8 year old with a weight of 25 kg). Some examples of how the NUNT was calculated are provided in **Box 1**. The NUNT was predetermined for all medicines in the core set of pediatric medicines (Appendix 2).

Box 1 Two example calculations of the number of units needed for treatment (NUNT).

Paracetamol 100 mg cap/tab
The recommended dosage for a child below five is 10-15 mg/kg 4-6 times daily. Assuming pain treatment is continuous (every day of the month), the number of unites needed for treatment (NUNT) is then calculated as:

$$Required\ units\ per\ intake\ moment = 12.5\ mg/kg * 11\ kg = 138\ mg\ \approx 1\ unit$$

$$NUNT = 1\ unit * 5\ daily\ intake\ moments * 30\ days = 150\ units$$

Amoxicillin 50 mg/ml suspension
The recommended dosage for a child below five is 40 mg/kg twice daily. Assuming the duration of treatment is 5 days, the NUNT is then calculated as:

$$Required\ units\ per\ intake\ moment = {40\ mg/kg * 11\ kg}\Big/{50\ mg/ml} = 9\ ml$$

$$NUNT = 9\ ml * 2\ daily\ intake\ moments * 5\ days = 90\ units$$

Weighting for burden of disease

In the original framework, accessible medicines are weighted according to the regional burden of disease to address differences in demand between medicines (distinct from selecting medicines for the core set based on global burden of disease) [4]. This concept was applied to pediatric medicines as well, based on the GHEs [38]. Each medicine in the basket was assigned a GHE code for one or several disease(s) that are treated/cured/controlled by that medicine. Indications of the medicines were determined according to their uses as described in the WHO EMLc (see **Table 1**) [39]. Some antibacterial medicines were also assigned the additional code (370), as a proxy for the broad use of these medicines in a variety of bacterial diseases.

The weight that each medicine is given in the calculation was computed as the proportion of associated disability-adjusted life years (DALYs) for a medicine compared to the total sum of DALYs for all medicines surveyed. Of note, the GHEs include data for children 1-59 months and children 5-14 years. The weighting of children up to 12 years of age based on data for children up to 14 years old does not have a significant impact on the results as assigned weights are proportional weights.

Calculating SDG indicator 3.b.3

The age-specific SDG indicator 3.b.3 can be calculated with formula 1. Assessing availability and affordability of medicines, and subsequent weighting for regional disease burden, was done at the facility level, meaning that a separate score is calculated for each health facility surveyed. Facilities with at least 80% of medicines in the basket available and affordable were considered to have accessible medicines. This threshold was adopted by the WHO Global Action Plan on Non-Communicable Diseases and used as a reference [49]. **Table 2** presents a full summary of the adaptations to the original SDG 3.b.3 methodology to make it child-appropriate. A hypothetical working example is provided in Appendix 3.

Table 2 Comparison of the original and child-specific $SDG_{3.b.3}$ methodology.

Input	Original $SDG_{3.b.3}$ methodology [4]	Child-specific $SDG_{3.b.3}$ methodology
SDG indicator 3.b.3		
Calculation	- Based on individual facility scores. - Facilities considered as having accessible medicines when reaching an 80% threshold.	- Based on individual facility scores. - Facilities considered as having accessible medicines when reaching an 80% threshold.
Core set of globally relevant essential medicines		
Selection of medicines	- Defined on a global level. - Selected from 2017 WHO EML. - Selection process not described.	- Defined on a global level. - Selected from 2019 WHO EMLc. - Selection based on global burden of disease (top 10 conditions causing disability/mortality that can be treated with medicines), international treatment guidelines and expert consultation.

The basket	- One basket for all. - 32 tracer essential medicines for acute and chronic, communicable and non-communicable diseases.	- Baskets defined for two age groups (young children; school-aged children). - 22 tracer essential medicines for acute and chronic, communicable and non-communicable diseases for both young and school-aged children. - Age-appropriate formulations selected per age group.
Burden of disease	- Weighting according to regional burden of disease (in DALYs). - Based on WHO GHEs. - Pre-defined GHE codes, with overarching GHE code for 'infectious and parasitic diseases' for antibacterials. - Equal weights assigned to medicines that are used to treat the same disease.	- Weighting according to regional burden of disease (in DALYs). - Based on WHO GHEs, from period closest to year of survey. - Affiliated GHE codes determined according to the uses as described in EMLc. GHE codes for antibacterials determined according to uses as described in EMLc plus code for 'other infectious diseases'. - Equal weights assigned to medicines that are used to treat the same disease.
Availability of medicines		
Availability	- Captured as binary variable. - As surveyed.	- Captured as binary variable. - As surveyed.
Affordability of medicines		
Required inputs	- Captured as binary variable. - Calculated from the price of a medicine, the number of units needed for treatment, the NPL and the wage of the LPGW.	- Captured as binary variable. - Calculated from the price of a medicine, the NUNT, the NPL and the wage of the LPGW.
Number of units needed for treatment	- Total number of units needed per month or treatment course based on DDDs. - Process for defining duration of treatment not described.	- NUNT based on duration of treatment and recommended daily dosages per age or weight group. Weight-based dosing transformed to age-based dosing. - Recommended daily dosages and duration of treatment derived from international treatment guidelines.

DALY = Disability-adjusted life year; DDD = Defined daily dosage; EML = Essential Medicines List; EMLc = Essential Medicines List for Children; GHE = Global Health Estimates; LPGW = Lowest-paid unskilled Government Worker; NPL = National Poverty Line; NUNT = number of units needed for treatment; SDG = Sustainable Development Goal; WHO = World Health Organization.

Proof-of-concept

As proof-of-concept, the methodology described above was applied to three historical WHO/Health Action International (HAI) datasets for the young children age group (1 month-5 years) (see **Box 2** for an explanation of the WHO/HAI standardized methodology [50]).

Data on medicines' availability and price for Burundi (2013), China (2012) and Haiti (2011) was obtained from HAI. These datasets were selected because the highest absolute number of age-appropriate medicines that are listed in the proposed core set of medicines was included in

these surveys (11, 10 and 12 out of 22 medicines, respectively) [51]. Additionally, this selection represents countries with different income levels (e.g. Burundi and Haiti low-income countries, China an upper-middle income country) and from different geographical regions. To make the datasets appropriate for analysis, only the age-appropriate medicines as listed in **Table 1** were selected. A selection in participating health facilities was not made.

Data on NPLs were obtained from World Bank reports on poverty [52-54]. NPLs were adjusted for inflation and deflation between the year data was reported and the survey year using the Consumer Price Index (CPI) [55]. Monthly poverty lines were converted to daily time periods. LPGW wages were directly obtained from the datasets provided by HAI and thus required no corrections for the year of survey. Because regional data on burden of disease in DALYs is available for every five years only, the year closest in time to the year of survey was used (e.g. 2010 publication for China and Haiti and 2015 publication for Burundi) to weight for burden of disease [38].

In addition to estimating the overall SDG 3.b.3 indicator, mean individual facility scores were also calculated per country and sector. Results were disaggregated per medicine to investigate drivers of inaccessibility.

Box 2 Core elements of the WHO/HAI methodology.

The World Health Organization/Health Action International methodology

The World health Organization (WHO)/Health Action International (HAI) methodology is considered the gold standard for the collection of evidence on the availability and prices of medicines. This standardized methodology outlines the steps needed to plan and conduct a survey to generate reliable information on medicines' prices and availability.

Key elements of the methodology include:

- Data is collected in six geographical survey areas: a country's main urban center and five other areas.
- Health facilities – or medicine outlets – from the public, private and up to two other sectors are selected through a systematic approach. In each survey area, data are collected in at least five medicine outlets per sector.
- Up to 50 medicines are surveyed, including 14 core medicines that allow for global comparison.
- Data on the price and availability of medicines are gathered by data collectors during visits to the selected health facilities.
- For each medicine, data are collected on the originator brand and the lowest-priced generic equivalent found at each medicine outlet.

To ensure data quality of datasets, the collection of data is validated and all data is checked for any incomplete, erroneous or illegible data.

Note: adapted from World Health Organization (WHO) and Health Action International (HAI) [50]).

Results

Access to medicines for children aged 1 month to 5 years was calculated for each of the three case study countries for its different health sectors. Analysis of data from Burundi showed a stark contrast between lowest-price generic medicines (LPM) and the originator brand (OB), with a mean facility score of 40.3% for LPMs versus 0.0% for the OB. The public and mission sector provided more accessible medicines than the private sector. The difference between LPMs and the OB was not as pronounced in China with mean facilities scores of 22.3% and 16.5% respectively, with LPMs more accessible in the public sector and the OBs more in the private sector. In Haiti, access was calculated for the public sector, the private sector, the non-profit sector, and the mixed sector (health facilities managed by the government and non-profit organization together). Mean facility scores for LPMs were similar across the sectors, with an overall mean of 22.2%. For OB medicines, scores varied between 0.6% in the private sector and 15.1% in the public sector. Results on SDG indicator 3.b.3 and mean facility scores across health facilities from different sectors are summarized in **Table 3**.

Table 3 Facility scores for access to pediatric medicines for children aged 1-59 months of originator brand and lowest-price generic medicines in Burundi, China and Haiti.

	Sector	Number of facilities surveyed	Lowest-price generic		Originator brand	
			Mean facility score (%), range		Mean facility score (%), range	
Burundi (2013)	SDG indicator 3.b.3		0%			
	Public	23	49.1	[12.1-76.0]	0.0	[0.0-0.0]
	Private	27	29.1	[8.3-57.3]	0.0	[0.0-0.0]
	Mission	23	44.6	[11.5-76.0]	0.0	[0.0-0.0]
	Overall	**73**	**40.3**	**[8.3-76.0]**	**0.0**	**[0.0-0.0]**
China (2012)	SDG indicator 3.b.3		0%			
	Public	60	34.5	[0.0-54.7]	10.2	[0.0-32.4]
	Private	60	10.1	[0.0-58.6]	22.6	[0.0-32.4]
	Overall	**120**	**22.3**	**[0.0-58.6]**	**16.5**	**[0.0-32.4]**
Haiti (2011)	SDG indicator 3.b.3		0%			
	Public	54	20.4	[0.0-60.3]	15.1	[0.0-22.0]
	Private	35	25.9	[13.3-34.9]	0.6	[0.0-22.0]
	Non-profit	39	19.6	[0.0-41.6]	9.6	[0.0-22.0]
	Mixed	35	24.4	[0.0-44.0]	11.3	[0.0-22.0]
	Overall	**163**	**22.2**	**[0.0-60.3]**	**9.9**	**[0.0-22.0]**

None of the facilities in either of the three countries were categorized as providing sufficient access to medicines, as all facilities failed to reach the 80% threshold. This resulted in SDG indicator 3.b.3 outcomes of 0% in all three countries. The main driver for the low scores was the low availability of medicines, as illustrated in **Figure 1**. Notably, those medicines that were available on the day of survey were generally also affordable, with a few exceptions (four cefotaxime injections, six ceftriaxone injections, two ibuprofen tablets, one phenobarbital tablet). Age-appropriate dosage forms such as oral suspension or liquids were not associated with unaffordable prices in these case studies.

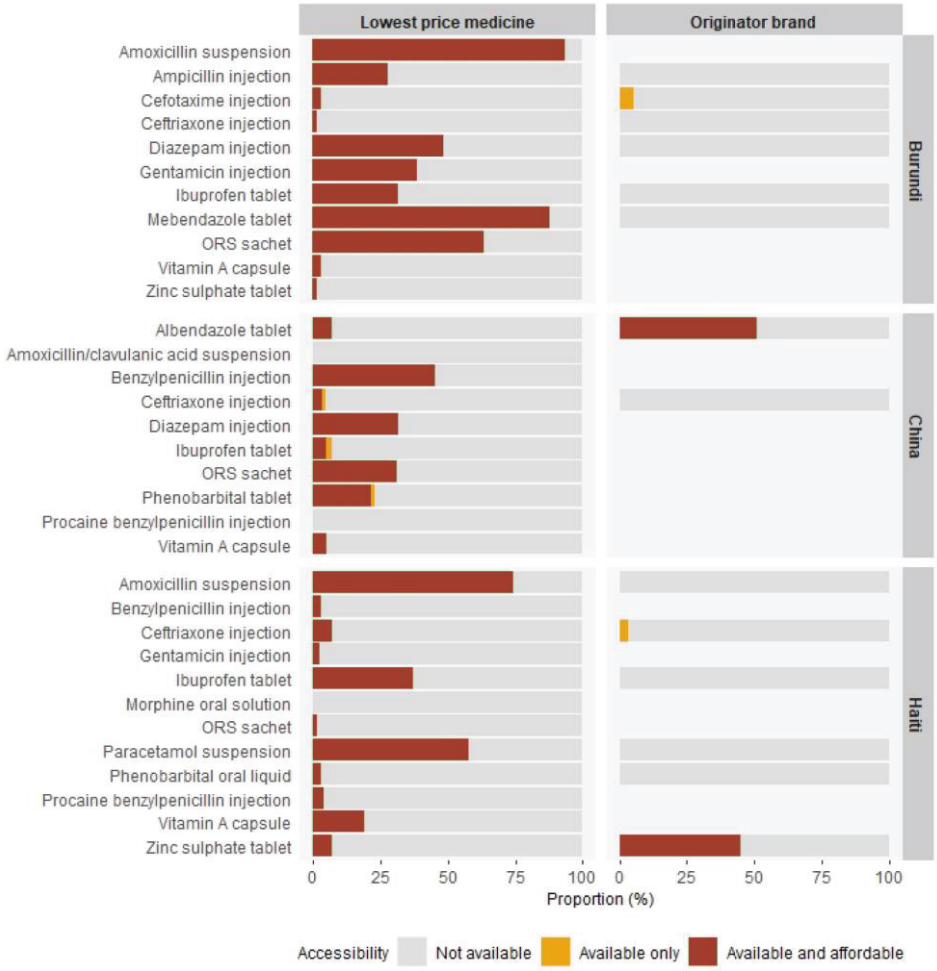

Figure 1 Proportion of medicines accessible in Burundi, China and Haiti.
ORS = oral rehydration salts.
Note: since the originator brand was not surveyed for all active ingredients, findings in the private sectors of all three countries are based on a very small number of medicines only.

Discussion

This paper proposes an adapted methodology that can be used to measure access to pediatric medicines, based on the principles embedded in SDG indicator 3.b.3. This novel methodology could be an important tool for policy-makers and program managers in identifying major barriers to access and developing appropriate policies to improve access to medicines for children. In adapting the methodology, two proposed core sets of pediatric medicines were established for children of different ages, taking into account their specific health needs and age-appropriate formulations. Careful approaches were taken to create the NUNT – a novel parameter – which enables affordability calculations across ages. The adapted methodology was successfully applied to data from three individual countries, providing proof-of-concept of this methodology.

With no reliable method for measuring access to pediatric medicines having been established yet, the child-specific methodology presented in this paper can provide guidance to others aiming to study access to medicines for children. The use of a single methodology and core set of medicines to express access to medicines will allow for inter-country comparability of the SDG indicator. Another important advantage of such a standardized tool is its ease of use. By predetermining which medicines and formulations should be surveyed, by providing the typical NUNT, and demonstrating how accessibility should be calculated, this method only requires countries to collect the facility data and some additional inputs. Yet, standardization can also be viewed as rigidity, which is inherent to any tool that uses a single core set for global reference. Local guidelines that recommend use of other active ingredients or formulations than those in the core set could lead to skewed outcomes. Therefore, this standardized method incorporates some flexibilities, allowing for several formulations or active ingredients from the same therapeutic class to be interchanged (i.e. antiepileptics, antimalarials, etc.). This allows countries to apply this method to their national situation. Additionally, we recognize that the proposed core set should be subject to regular updates, in accordance with updates to the WHO EMLc and international treatment guidelines.

Upon closer examination of the case studies of Burundi, China and Haiti, the widespread inaccessibility seen in the results seemed to stem from unavailable rather than unaffordable medicines, for both LPMs and OBs. A recent systematic review on children's medicines identified fourteen studies that reported on the availability of children's medicines and found a median availability of 38.1% and 24.2% for LPMs and OBs in the public sectors and of 35.9% and 21.1% in the private sectors, respectively [56]. With that, the unavailability of child medicines detected in the present case studies is in line with the results of the systematic review. The same systematic review identified eleven studies that reported on the affordability of medicines, based on the number of days' wages of the LPGW. In the public sector, affordability was 83.6% and 48.5% for LPMs and OBs, with 72.2% and 68.8% in the private sector. The results of this

systematic review emphasize the need for a method that combines the two dimensions into a single indicator, as separate evaluation of these elements overestimates actual access to medicines for the patient. Beyond that, some of the studies included in the systematic review included unrepresentative samples of medicines (e.g. studies focused on a single disease area or studies simply failing to consider child-appropriate formulations such as oral liquids or appropriate medicine strengths), again confirming the need for a standardized methodology to measure access to child medicines.

Before this methodology can, however, be applied on a widespread scale, several steps must be undertaken to further validate the methodology and examine the uncertainties introduced through our adaptations of the tool. Firstly, the proposed core sets of medicines for young children and school-aged children (not shown) should be validated through expert consultation. Additionally, the robustness of the adapted methodology with regard to the NUNT will need to be tested as it is an important variable when calculating affordability. The NUNT was determined based on recommended dosages and duration of treatment prescribed in international guidelines, which were often expressed as ranges. This generates some uncertainty when converting to a single NUNT. Also, determining a NUNT in many cases involved transformation of weight-based to age-based dosing through weight-to-age charts, introducing further uncertainties. The WHO provides international weight-for-age charts for boys and girls until the age of five [45] and ages 5-10 years [46], but no international charts are available for children above the age of 10. Therefore Dutch growth diagrams were used to approximate median weights of children 10-12 years [47]. Initial comparison of international and Dutch growth charts shows that differences, if any, are small and will likely have had no significant impact on the NUNT. Furthermore, the NUNT is a single number used to represent an entire age group. How big the uncertainties with regard to the NUNT are and whether a single NUNT is indeed sufficiently representative for an entire age group should become clear in sensitivity analyses. Additionally, the case studies now performed were on a subset of the complete core set for young children, limited by the small number of age-appropriate medicines that had been surveyed in the three case study countries. Sensitivity analyses should also be performed to determine the minimum number of medicines required for a reliable measure of accessibility. To perform meaningful sensitivity analyses, more data on child medicines is needed than was available for the present case studies.

An important strength of this child-specific methodology is the use of an existing, formally approved tool as starting point which was adapted to suit the needs of children. Core concepts used in the adapted methodology and its data requirements are therefore in line with conventional methods and data collection tools. However, through this approach our methodology also inherits some of the limitations of the original 3.b.3 indicator methodology. Particularly, weighting for regional burden of disease when calculating access at the facility level as done in the original methodology raises several concerns. For one, the methodology assigns

equal weights to medicines that are used to treat the same disease and thus counts the burden of this disease multiple times. To illustrate, the basket of medicines includes both oral rehydration salts and zinc sulphate for diarrheal diseases, whereas only retinol was selected for measles/vitamin A deficiency. This leads to disproportionate weighting for actual burden of disease when calculating access at the facility level. Disproportionality is also a concern for antibacterial medicines, which use may be overrepresented by using GHE code 20, a code that is linked to all infectious and parasitic diseases. Although a proxy for this GHE code was used in the present study (GHE code 370 for 'other infectious diseases'), additional analyses should demonstrate how different weighting approaches affect the results. Additionally, the quality of the underlying GHEs data is unclear, especially because these data may be more difficult to obtain for children than for adults. Lastly, arguments can be made that the current approach of weighting for burden of disease is undesirable because it implies that some medicines are more important than others, even though all medicines in the basket are essential medicines and should always be accessible.

On a similar note, expressing affordability as a function of a poverty line instead of the LPGW wage has been used previously [57], but a measure combining the NPL and LPGW wage as is used in the original 3.b.3 indicator has yet to prove itself. This is particularly relevant because it seems that somewhat less medicines were unaffordable in the present case studies than what was observed using the LPGW wage alone [56]. Further testing of the proposed child-specific methodology should include several scenarios for weighting for burden of disease and calculating affordability, which could lead to further adaptations of the methodology.

Since no facilities met the benchmark of 80% in our case study countries, the overall SDG indicator 3.b.3 was by definition 0% in all countries. Through this benchmarking approach relevant differences in access between countries and sectors were lost (e.g. access in Burundi was better with a mean facility score of 40.3% versus 22.3% and 22.2% in China and Haiti, respectively). Additionally, the detail required for identifying the major obstacles in accessibility is also missing when the SDG indicator is reported as a single outcome. This highlights that disaggregated data on a facility and medicine level is vital in understanding the drivers of inaccessibility to medicines, particularly when the indicator value reflects a sub-optimal level of access. We recommend that the indicator should therefore be reported in both a composite and disaggregated form.

To provide first evidence of the child-specific tool that we developed, we were limited to the use of historical datasets. In selecting suitable datasets for the case studies it was observed that only a small number of age-appropriate medicines are being surveyed in low- and middle-income countries [58]. The WHO/HAI datasets used for the present case studies were selected for their quality of data and relatively high inclusivity of age-appropriate medicines, yet they still included a modest sample of child-appropriate medicines. Further analyses on a dataset with a

higher number of age-appropriate medicines are thus required, which may need to be collected prospectively. Although the relevance of the findings to the current situation of Burundi, China and Haiti is limited because of the older data, the aim of providing proof-of-concept of the adapted methodology was achieved nonetheless. Finally, the individual facility data that support the findings of this study are not publicly available, but aggregated data per medicine and country can be obtained from the HAI website [51]. The aggregated data are sufficient to allow initial comparison of our methodology to previously existing tools.

Conclusion

This paper proposes a standardized methodology for measuring access to medicines for children that could complement the existing SDG indicator 3.b.3. This standardized method – once validated – can aid countries in assessing national accessibility to pediatric medicines in a validated manner and on a regular basis. The proposed validation steps of this method will help identify critical steps in the calculation and will determine its robustness, which could lead to further improvements of the method.

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Supplementary materials

Appendix 1: Validation of the proposed basket of medicines for children (1 month-5 years) through expert consultation

To ensure that the proposed basket of medicines for children aged 1 month to 5 years sufficiently addressed priority health needs in clinical practice, expert validation of the core set of essential medicines has taken place through an online survey.

Procedures

The survey was split in separate categories for each of the eleven priority diseases. Participants were asked whether they agreed with the initial selection, and whether any medicines were redundant or missing (yes/no). If respondents did not agree with the initial selection, or if they indicated that medicines were redundant or missing, they were asked to explain their position in a comment section.

Pilot

The developed survey was piloted with three participants, resulting in minor modifications in the framing of questions. Since no major changes were required, data from the pilot was used in the analysis.

Participants

A total of five experts per age group were initially asked to validate the primary selection of medicines. Practicing pediatricians and pharmacists specialized in pediatric medicines with at least three years' experience in the field were considered to be an expert. This relatively small number of experts was believed to be sufficient, since the initial selection of active ingredients was based on representative international treatment guidelines. Additionally, with the World Health organization (WHO) Essential Medicines List for Children (EMLc) serving as basis, the number of possible choices was limited. Little variation in responses was therefore expected.

Experts were identified through the researcher's network, and using snowball sampling techniques. All five respondents were (formerly) practicing pediatricians, with between 7 to 40 years of experience. Three WHO geographical regions were represented (e.g. African region, region of the Americas, European region), as well as all income levels according to the World Bank income classification 2021. Two participants were also part of the WHO 23rd Expert Committee on Selection and Use of Essential Medicines.

Data analysis

Agreement of experts on which active ingredients to in- or exclude was assessed. Experts were regarded as in agreement if ≥80% of the respondents indicated to agree with inclusion of the active ingredient. Similarly, if ≥80% of the respondents indicated that a specific active ingredient was redundant or missing, it was removed from or added to the selection, respectively. If no

consensus was reached (<80% agrees), active ingredients indicated as redundant or missing were compared across respondents. Comments provided by participants were analyzed in-depth and discussed by two authors to reach a decision.

Consolidation

The primary validation process resulted in the addition of four active ingredients to the basket, and the removal of two (see table 1 in main text). An additional consolidation round is needed to verify agreement of the experts with these changes.

Ethical approval

The validation of active ingredients through expert consultation was reviewed and approved by the Institutional Review Board of Utrecht University (reference number UPF2101).

Appendix 2: Number of units needed for treatment

Table S1 number of units needed for treatment of children 1-59 months.

Medicine name	Acceptable formulation	NUNT
Oral rehydration salts	Powder sachet 200 ml	2
	Powder sachet 500 ml	2
	Powder sachet 1L	1
Zinc sulphate	Cap/tab 20 mg	14
Carbamazapine	Cap/tab 100 mg	60
	Oral liquid 100 mg/5 ml	180
Phenobarbital	Cap/tab 30 mg	60
	Cap/tab 100 mg	30
	Injection 100 mg/ml	30
	Injection 200 mg/ml	15
	Oral liquid 15 mg/5 ml	600
Phenytoin	Cap/tab 25 mg	90
	Cap/tab 50 mg	60
	Cap/tab 100 mg	60
	Injection 50 mg/ml	60
	Oral liquid 25 mg/5 ml	480
	Oral liquid 30 mg/5 ml	420
Lamotrigine	Cap/tab 25 mg	60
	Cap/tab 50 mg	30
	Cap/tab 100 mg	30
Valproic acid	Cap/tab 100 mg	60
	Cap/tab 150 mg	60
	Cap/tab 200 mg	60
	Cap/tab 500 mg	30
	Oral liquid 200 mg/5 ml	240
Diazepam	Rectal solution 5 mg/ml	1
	Injection 5 mg/ml	1
Lorazepam	Parenteral solution 2 mg/ml	0.5
	Parenteral solution 4 mg/ml	0.5
Midazolam	Oromucosal solution 5 mg/ml	10
	Oromucosal solution 10 mg/ml	6
	Ampoule 10 mg/ml	6
Abacavir/lamivudine	Cap/tab 120/60 mg	60
Dolutegravir	Cap/tab 10 mg	60
Lopinavir/ritonavir	Cap/tab 40/10 mg	120
	Cap/tab 100/25 mg	60
Ferrous salt	Cap/tab 60 mg	28
	Cap/tab 200 mg	14
	Oral liquid 25 mg/ml	56
Albendazole	Cap/tab 200 mg	2
	Cap/tab 400 mg	1

Mebendazole	Cap/tab 100 mg	6
Artemether/lumefantrine	Cap/tab 20/120 mg	6
Artesunate/amodiaquine	Cap/tab 25/67.5 mg	6
	Cap/tab 50/135 mg	3
Artesunate/mefloquine	Cap/tab 25/55 mg	6
Dihydroartemisinin/piperaquine	Cap/tab 20/160 mg	6
	Cap/tab 20/320 mg	3
Artesunate/Sulfadoxine-pyrimethamine	Cap/tab 50/500/25 mg	1
	Cap/tab 500/25 mg (sulfadoxine-pyrimethamine)	1
Chloroquine	Cap/tab 100 mg	5
	Oral liquid 50 mg/5 ml	30
Artesunate	Cap/tab 50 mg	3
	Suppository 50 mg	3
Retinol	Cap/tab 25,000 IU	4
	Cap/tab 100,000 IU	2
	Cap/tab 200,000 IU	2
Paracetamol	Cap/tab 100 mg	150
	Suppository 100 mg	150
	Suspension 120 or 125 mg/5 ml	900
Morphine	Cap/tab (slow release) 10 mg	60
	Injection 10 mg/ampoule	30
	Oral liquid 10 mg/5 ml	300
Ibuprofen	Cap/tab 200 mg	90
	Oral liquid 200 mg/5 ml	180
Ethambutol + isoniazid + pyrazinamide + rifampicin	Cap/tab 100 mg (ethambutol)	60
	Cap/tab 400 mg (ethambutol)	30
	Oral liquid 25 mg/ml (ethambutol)	9
	Cap/tab 50/150/75 mg (isoniazid + pyrazinamide + rifampicin)	60
Amoxicillin	Cap/tab 250 mg	20
	Cap/tab 500 mg	10
	Powder for injection 250 mg/vial	20
	Powder for injection 500 mg/vial	10
	Powder for injection 1 g/vial	5
	Suspension 125 mg/5 ml	100
	Suspension 250 mg/5 ml	90
Amoxicillin + clavulanic acid	Cap/tab 100/125 mg	30
	Cap/tab 250/125 mg	15
	Cap/tab 500/125 mg	15
	Powder for injection 500/100 mg/vial	8
	Oral liquid 125/53.25 mg/5 ml	135
	Oral liquid 250/62.5 mg/5 ml	60
Ampicillin	Cap/tab 250 mg	40
	Cap/tab 500 mg	20
	Injection 500 mg/vial	20

	Injection 1 g/vial	10
Benzylpenicillin	Injection 1 MIU/vial	5
Gentamicin	Injection 10 mg/ml	40
	Injection 40 mg/ml	10
Ceftriaxone	Injection 250 mg/vial	28
	Injection 500 mg/vial	14
	Injection 1 g/vial	7
Cefotaxime	Injection 1 g/vial	18
Procaine benzylpenicillin	Injection 1 MIU/vial	10

NUNT = Number of Units Needed for Treatment.

Appendix 3: A hypothetical example of calculating SDG indicator 3.b.3 with the adapted indicator for children

Priority diseases were selected based on global burden of disease. Below, a hypothetical overview of global disease burden (in thousand Disability-Adjusted Life-Years) is shown for young children (infants, toddlers and pre-school children) and school-aged children. Values shown are already summed up for males and females within the same age group. For simplification, only three disease (in bold) are selected per age group.

Table S2 Hypothetical selection of priority diseases.

	Young children	School-aged children
Disease I	3,000	**10,500**
Disease II	**22,500**	**7,000**
Disease III	7,000	2,000
Disease IV	3,500	6,000
Disease V	**12,000**	**8,000**
Disease VI	**9,000**	5,500

Diseases selected are then linked to essential medicines. Associated medicines should be first-choice medicines used in primary health care, based on international treatment guidelines. For some diseases, multiple medicines or interchangeable medicines from the same therapeutic class may be included in the core set. Below a hypothetical core set of medicines for young children.

Table S3 Hypothetical selection of medicines and corresponding computational values.

	Associated medicines	Treatment duration	Number of units
Disease II	Medicine A	30	60
Disease V	Medicine B	14	14
	Medicine C	7	21
Disease VI	Medicine D	30	30
	Medicine E or Medicine F	3	6

For each medicine in the core set, the number of units needed for treatment is determined, based on the average maintenance dose in its main indication and the duration of treatment.

Availability of medicines in the core set for young children in country X is as follows:

Table S4 Hypothetical availability of selected medicines.

	Facility 1	Facility 2	Facility 3
Medicine A	1	1	0
Medicine B	0	0	0
Medicine C	1	1	1
Medicine D	1	0	1
Medicine E	1	0	1

1 = available and 0 = not available.

Note that Medicine F is not surveyed in country X, because it is considered interchangeable with Medicine E.

Only for medicines that were available on the day of data collection, price data is collected. The following (price) data is collected in country X. Prices are in local currency of country X.

Table S5 Hypothetical prices of selected medicines.

	Facility 1	Facility 2	Facility 3
Medicine A	320	460	-
Medicine B	-	-	-
Medicine C	1200	1600	1750
Medicine D	600	-	750
Medicine E	170	-	250

Medicine A was found in facility 1 for a price of 320 (in local currency). The number of units needed for a treatment course is 60 (2 units per day, continuous treatment).

The price of a daily dose is then calculated as:

$$price\ per\ treatment = \frac{unit\ price * units\ per\ treatment}{365/12} = \frac{320 * 60}{365/12} = 631$$

In country X, the national poverty line (NPL) is 1300 and the daily wage of the lowest-paid unskilled government worker (LPGW) is 2100 (both in local currency). Extra daily wages (EDW) of medicine A in facility 1 can then be calculated as:

$$EDW = \frac{NPL + price\ per\ treatment}{daily\ wage\ of\ LPGW} = \frac{1300 + 631}{2100} = 0.9$$

With EDW <1, medicine A in facility 1 is considered affordable.

Medicine C was found in facility 3 for a price of 1750. The number of units needed for a treatment course is 21 (3 units per day, 7 days of treatment).

$$price\ per\ treatment = \frac{1750 * 21}{365/12} = 1208 \quad \text{and} \quad EDW = \frac{1300 + 1208}{2100} = 1.2$$

With EDW >1, medicine C in facility 3 is considered unaffordable.

Repeated for all medicines with price data, affordability for young children is as follows:

Table S6 Hypothetical affordability of selected medicines.

	Facility 1	Facility 2	Facility 3
Medicine A	1	0	-
Medicine B	-	-	-
Medicine C	1	0	0
Medicine D	1	-	1
Medicine E	1	-	1

1 = affordable and 0 = not affordable.
Note: affordability cannot be computed for medicines without price data.

The weight to be applied to each medicine in the core set is calculated as the proportion of the medicine's specific regional DALYs compared to the total sum of DALYs in the basket. The regional burden may differ from the global burden of disease (see figure 1).

In this scenario, the total sum of DALYs in the basket is 36,000 DALYs (in thousands). The weight applied to medicine A can be calculated as:

$$Weight = \frac{Medicine\ A\ DALYs}{Total\ sum\ of\ DALYs} = \frac{9{,}000}{36{,}000} = 0.25$$

Repeated for all medicines, the following weights will be applied:

Table S7 Hypothetical disease burden of priority diseases.

	Disease	Disease burden	Weight
Medicine A	Disease I	9,000	0.25
Medicine B	Disease II	6,000	0.17
Medicine C	Disease II	6,000	0.17
Medicine D	Disease V	7,500	0.21
Medicine E	Disease V	7,500	0.21

Note that equal weights are assigned to medicines that are used to treat the same disease.

Combining two dimensions of access to medicines (see figure 2 and 3), only medicines that are both available and affordable are considered accessible. In country X, access for young children is as follows:

Table S8 Hypothetical accessibility of selected medicines.

	Facility 1			Facility 2			Facility 3		
	Av/aff		Access	Av/aff		Access	Av/aff		Access
Medicine A	1 / 1	→	1	1 / 0	→	0	0 / -	→	0
Medicine B	0 / -	→	0	0 / -	→	0	0 / -	→	0
Medicine C	1 / 1	→	1	1 / 0	→	0	1 / 0	→	0
Medicine D	1 / 1	→	1	0 / -	→	0	1 / 1	→	1
Medicine E	1 / 1	→	1	0 / -	→	0	1 / 1	→	1

1 = available/affordable/accessible, 0 = not available/affordable/accessible and - = no price data.
Av/aff = availability/affordability.

Applying the weights to the medicines (accessibility*weight) in facility 1 gives:

Table S9 Hypothetical weighted access scores for selected medicines.

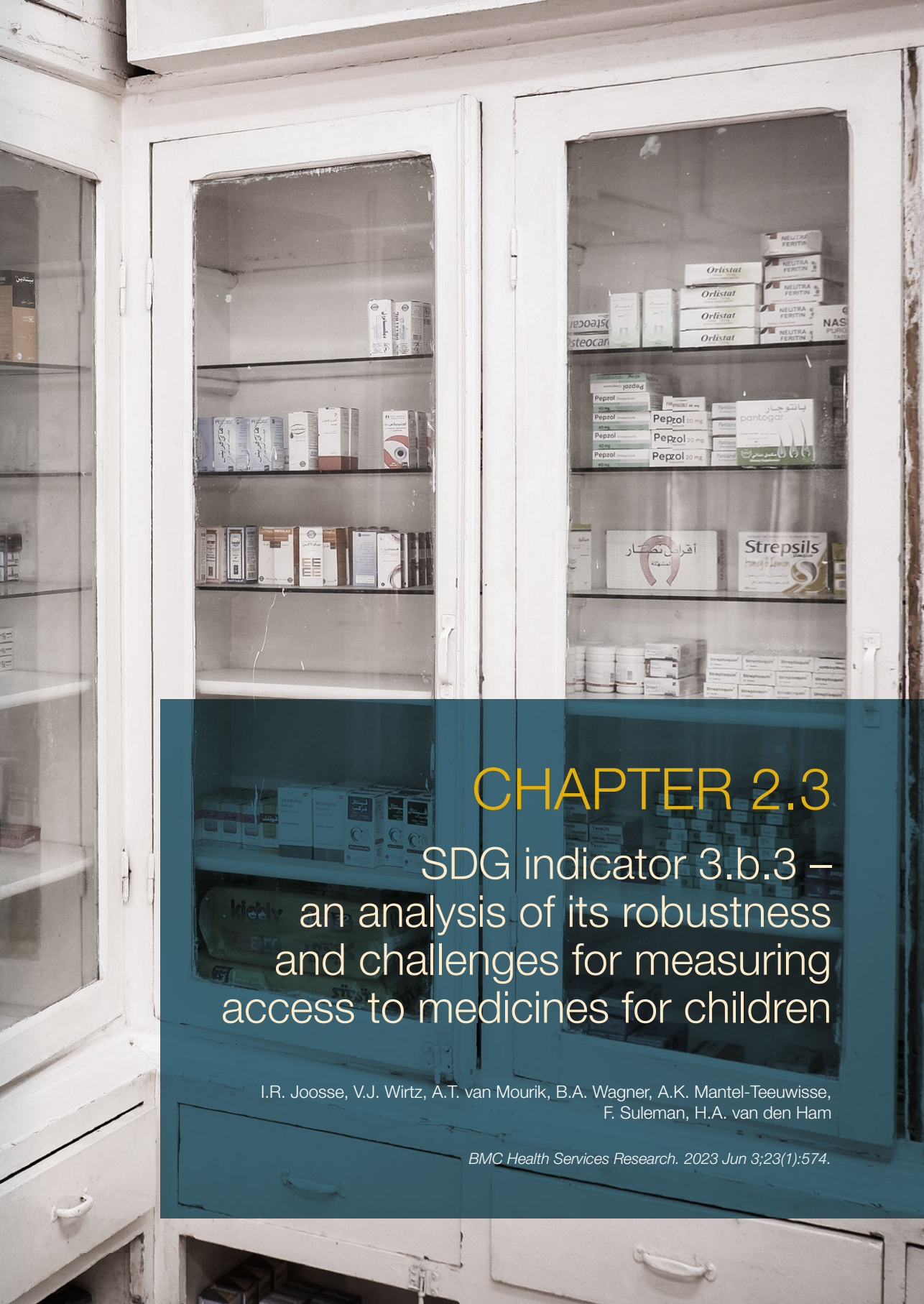
	Accessibility	Weight	Weighted accessibility
Medicine A	1	0.25	0.25
Medicine B	0	0.17	0
Medicine C	1	0.17	0.17
Medicine D	1	0.21	0.21
Medicine E	1	0.21	0.21
		Access (%) =	83%

Applying this to all facilities, facility 2 has a weighted access of 0% and facility 3 of 42%. These numbers are then transformed to a binary format, marking facilities that have a weighted access of ≥80% as facilities with accessible medicines. In this scenario, only facility 1 has a weighted access of ≥80% and is considered to have accessible medicines.

SDG indicator 3.b.3 for country X is then computed as:

$$SDG_{3.b.3.} = \frac{Facilities\ with\ accessible\ basket\ of\ medicines}{Surveyed\ Facilities} * 100\% = \frac{1}{3} * 100\% = 33\%$$


Bivatracin
BETADINE
Kaprofen
KETOLAC



CHAPTER 2.3

SDG indicator 3.b.3 – an analysis of its robustness and challenges for measuring access to medicines for children

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Abstract

Background

Sustainable Development Goal (SDG) indicator 3.b.3 monitors progress in medicines' accessibility for adults and has significant limitations when applying to medicines for children. An adapted indicator methodology was developed to fill this gap, but no proof of its robustness exists. We provide this evidence through sensitivity analyses.

Methods

Data on availability and prices of child medicines from ten historical datasets were combined to create datasets for analysis: Dataset 1 (medicines selected at random) and Dataset 2 (preference given to available medicines, to better capture affordability of medicines). A base case scenario and univariate sensitivity analyses were performed to test critical components of the methodology, including the new variable of number of units needed for treatment (NUNT), disease burden (DB) weighting, and the National Poverty Line (NPL) limits. Additional analyses were run on a continuously smaller basket of medicines to explore the minimum number of medicines required. Mean facility scores for access were calculated and compared.

Results

The mean facility score for Dataset 1 and Dataset 2 within the base case scenario was 35.5% (range 8.0-58.8%) and 76.3% (range 57.2-90.6%). Different NUNT scenarios led to limited variations in mean facility scores of +0.1% and -0.2%, or differences of +4.4% and -2.1% at the more critical NPL of $5.50 (Dataset 1). For Dataset 2, variations to the NUNT generated differences of +0.0% and -0.6%, at an NPL of $5.50 the differences were +5.0 and -2.0%. Different approaches for weighting for DB induced considerable fluctuations of 9.0% and 11.2% respectively. Stable outcomes with less than 5% change in mean facility score were observed for a medicine basket down to 12 medicines. For smaller baskets, scores increased more rapidly with a widening range.

Conclusion

This study has confirmed that the proposed adaptations to make SDG indicator 3.b.3 appropriate for children are robust, indicating that they could be an important addition to the official Global Indicator Framework. At least 12 child-appropriate medicines should be surveyed to obtain meaningful outcomes. General concerns that remain about the weighting of medicines for DB and the NPL should be considered at the 2025 planned review of this framework.

Introduction

Despite the considerable progress in child health that has been achieved in recent decades, high child morbidity and mortality rates remain an urgent challenge globally [1]. Recent data suggests that more than 50 countries worldwide will fail to meet the targets set under Sustainable Development Goal (SDG) 3.2 to end preventable deaths of children by 2030 [2]. Limited availability of affordable essential medicines for children contributes to child mortality. To improve this outcome, access to these medicines has been recognized as an important priority, outlined in SDG targets 3.8 and 3.b [3]. Measurement and monitoring of access to medicines is an integral part of this, and will aid national and international policy-makers in directing their efforts and formulating effective policies.

The United Nations (UN) under the leadership of the World Health Organization (WHO) has developed SDG indicator 3.b.3 to track progress on access to medicines (Figure 1) [4]. The novelty and significance of this indicator versus established methods for measuring access to medicines (e.g. the WHO/Health Action International (HAI) methodology) lies in the combined analysis of two crucial dimensions of access: availability and affordability. Indicator 3.b.3 has been part of the official Global Indicator Framework since 2017 and was re-classified in 2018 as a Tier II indicator, which means that the indicator is conceptually clear and has an established methodology, but data are not regularly produced by countries [5, 6].

Although access to medicines for children has recently been reported on in the context of the SDG 3 targets, the methodology as developed for indicator 3.b.3 was not employed [7]. This may be explained by the unfitness of this indicator for measuring access to child medicines, since it fails to address the unique requirements of children. Specifically, the indicator chiefly targets typical adult diseases such as type II diabetes and cardiovascular diseases, it fails to consider age-appropriate formulations, and the methodology depends on defined daily dosages (DDDs) to express affordability, which applies to adults only [8]. To address this gap and enable the measuring of access to child medicines, a conceptual methodology was developed based on the principles embedded in the existing SDG Indicator 3.b.3 [9]. Although proof-of concept for this adapted methodology was provided by applying the method to three historical datasets, the robustness of the adapted indicator could not be established in this pilot due to a lack of data on pediatric medicines in these datasets.

Before the child methodology can be applied on a larger scale, several validation steps must be undertaken to ensure the robustness of the methodology. This is of particular importance for the NUNT (i.e. Number of Units Needed for Treatment), a novel parameter that was introduced in the adapted methodology to substitute DDDs in the calculation of affordability of medicines and incorporates the dosages required by children of different ages. In addition to this,

sensitivity analyses should reveal how many child medicines need to be surveyed for a reliable measure of access.

Besides these validation steps, questions on the general framework of the indicator that were raised in previous research also call for further study [9]. These include concerns about the weighting for regional disease burden (DB) parameter (see **Figure 1**). This step was inserted when developing indicator 3.b.3 to increase the specificity of a global basket of medicines to a national context. However, there are concerns that the current weighting approach has introduced disproportionality due to 1) higher proportional contribution for indications for which there are multiple medicines in the basket and 2) antibacterial medicines that are weighted for indications for which they are not used. Other questions raised pertained to expressing affordability as a function of the National Poverty Line (NPL) in addition to the Lowest Paid unskilled Government Worker (LPGW) wage.

The aim of the present study is to determine the robustness of the adapted SDG indicator 3.b.3 methodology for children and to address remaining concerns through sensitivity analyses. This will not only help validate the adapted methodology for children but will also contribute to our understanding of the main SDG indicator 3.b.3.

Methods

To make indicator 3.b.3 appropriate for children, adaptations to the methodology presented in **Figure 1** encompassed 1) the selection of two new baskets of medicines for prevalent child diseases – including age-appropriate strengths and formulations for young children aged 1 month to 5 years and for school-aged children aged 5-12 years – and 2) the establishment of the NUNT [4]. A third adaptation tested in this proof-of-concept study pertained to the weighting for DB. Global Health Estimates (GHE) code 370 (for 'other infectious diseases') was used instead of code 20 (for 'infectious and parasitic diseases') for antibacterial medicines, because the latter code encompasses diseases such as hepatitis for which these medicines are not used. A detailed description of the adapted indicator methodology can be found in Appendix 1, including the core set of medicines for children 1-59 months that should be used in the calculation of indicator 3.b.3 (Table S1).

Data selection

The present study focused on children aged one month to five years. To secure sufficient availability and price data on eligible medicines for this age group for conducting meaningful sensitivity analyses, ten historical WHO/HAI datasets from eight countries (Bolivia (2008), Burundi (2013), China (2012), Haiti (2011), Kyrgyzstan (2010, 2015), Mongolia (2004), Sudan (2012, 2013), Tanzania (2012)) were combined into a single database [10]. Data on eligible medicines (e.g. those listed in Table S1) from the different datasets were pooled to constitute

Figure 1 Critical steps in calculating access to medicines with SDG indicator 3.b.3.
Note: adapted from United Nations, 2019 [4].

25 hypothetical facilities. In the pooling process, facilities from different datasets were matched to each other on sector and level of care as closely as possible. The resulting 25 hypothetical facilities each contained data on a range of eligible child formulations within the same therapeutic class, and often included duplicates of formulations due to the pooling of data from multiple countries. All data were corrected for inflation using the Consumer Price Index (CPI) and purchasing power parity (PPP) [11, 12].

From the resultant database, two distinct datasets were extracted. For Dataset 1, one medicine formulation per therapeutic class was extracted at random if medicines were interchangeable, irrespective of whether availability or price information was complete. In case of duplicates, data from one country was selected at random. In the extraction process for a second dataset (Dataset 2), a purposeful sampling strategy giving preference to medicines with data on price (e.g. medicines that had been available) was used. This second approach was chosen, because we hypothesized that it enabled more thorough analysis of the affordability dimension of the methodology. Each of the two datasets was composed of data on 19 medicines across 25 health facilities.

Additional data sources

Calculation of the SDG 3.b.3 indicator for children also requires data on the NUNT, NPLs, the LPGW wage and DB. The NUNT was predetermined for all medicine formulations in the basket and is based on the recommended dose and duration of treatment for an average child within the age group (Appendix 2). To investigate the robustness of this single parameter as a way to represent an entire age group, a minimum and maximum NUNT were also established.

NPL values for each of the eight countries that the datasets originated from proved difficult to obtain as these were not readily available in the public domain (and may not exist for some countries), so international reference poverty lines were used instead. As the data originated from countries with different income levels, three international reference values of $1.90/day (for low-income countries), $3.20/day (for lower-middle income countries) and $5.50/day (for upper-middle income countries) were used to avoid misrepresentation [13]. We calculated a single (average) value for the LPGW wage, based on local LPGW wages as reported in the ten original datasets. These were corrected for CPI and PPP and averaged to $5.94/day (range $1.72-9.60) [11, 12]. Data on DB were extracted from the GHEs according to the codes as indicated in the predetermined basket of medicines (see Table S1 in Appendix 1) [14].

Sensitivity analyses

To evaluate the robustness of the indicator methodology, we ran several scenarios with different input parameters to investigate the degree of variation in the outcomes. These sensitivity analyses targeted steps 1, 3 and 4 of the calculations as outlined in **Figure 2**. It is through these respective steps that methodological choices could affect the outcomes, whereas steps 2, 5 and

6 are solely determined by the pattern of the underlying data. An overview of the various scenarios that were run is provided in **Table 1**.

For the base case scenario (scenario A), standard NUNT values, an NPL of $1.90 and DB weights based on GHE code 370 (plus additional disease-specific codes, see Appendix 1) for antibacterial medicines were used. Across scenarios B to D, different approaches for calculating relative DB weights were tested (step 4 in **Figure 2**). Proportional weights assigned across scenarios A-E are provided in **Table 2**. The influence of variations to the NPL, the NUNT or both were explored In scenarios F-K (step 3 in **Figure 2**).

Scenarios A-K were repeated for Dataset 1 and Dataset 2. The mean and range of the facility scores and the SDG 3.b.3. indicator scores were calculated for all scenarios. To increase our understanding of how the affordability dimension responds to changes in the NPL and NUNT, accessibility of individual medicines was compared across scenarios A and G to K. Expected results of scenarios on affordability and facility scores are provided in **Table 1**.

To determine the smallest number of medicines that must be surveyed to obtain a stable outcome for the indicator (step 1 in **Figure 2**), scenario A was applied to a continuously smaller basket of medicines. For this analysis, a random medicine was removed from the basket at each repetition and the mean, SD and range of facility scores and the SDG 3.b.3 score were calculated. This analysis was performed for Dataset 1 only.

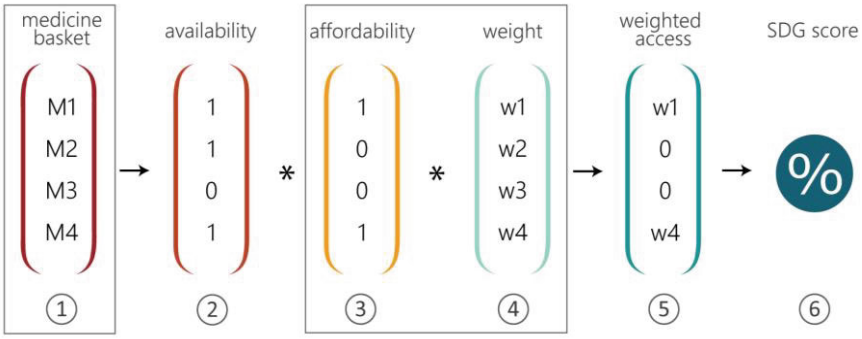

Figure 2 Matrix of weighted access to medicines in (adapted) SDG indicator 3.b.3.
The weighted access equals the facility score.
$M_{1\text{-}4}$ = medicine 1-4, $w_{1\text{-}4}$ = weight 1-4.

Results

General characteristics of Dataset 1 and Dataset 2 can be found in Appendix 3. For Dataset 1, the mean facility score of the base case scenario was 35.5%, with a SDG 3.b.3. score of 0%. For Dataset 2, both the mean facility score (76.3%) and SDG 3.b.3 score (40%) were considerably higher. The higher scores in Dataset 2 were the result of an increased number of medicines that were available in this dataset due to the purposeful sampling strategy as described earlier.

Figure 3a (Dataset 1) and **Figure 3b** (Dataset 2) show the mean and range of the facility scores across scenarios B-K relative to the base case scenarios (A) (see also Appendix 4). The ranges of facility scores in Dataset 1 were somewhat larger than those for Dataset 2, again the result of the sampling strategy.

Table 1 Overview of parameters and variations across scenarios.

Scenario	DB	NPL	NUNT	Expected effect compared to base case	
				on affordability	on facility scores
A base case	GHE code 370 for antibacterials; DB of medicines used for the same disease counted multiple times.	$1.90	Standard	NA	NA
B	GHE code 370 for antibacterials; DB of medicines used for the same disease divided by number of medicines.	$1.90	Standard	No effect	Variable[c]
C[a]	GHE code 20 for antibacterials; DB of medicines used for the same disease counted multiple times.	$1.90	Standard	No effect	Variable[c]
D	GHE code 20 for antibacterials; DB of medicines used for the same disease divided by number of medicines.	$1.90	Standard	No effect	Variable[c]
E[b]	No DB weighting applied	$1.90	Standard	No effect	Variable[c]
F	As scenario A	$3.20	Standard	Decrease	Decrease
G	As scenario A	$5.50	Standard	Decrease	Decrease
H	As scenario A	$1.90	Minimum	Increase	Increase
I	As scenario A	$1.90	Maximum	Decrease	Decrease
J	As scenario A	$5.50	Minimum	Decrease†	Decrease[d]
K	As scenario A	$5.50	Maximum	Decrease‡	Decrease[e]

DB = Disease Burden, NA = not available, NPL = National Poverty Line, NUNT = Number of Units Needed for Treatment, GHE = Global Health Estimates.

[a] Scenario C is equivalent to the weighing system used in the main SDG indicator 3.b.3 methodology.

[b] No DB weighting translates to equal weights for all medicines.

[c] Effect (increase/decrease) depends on patterns in underlying data, e.g. which medicines are accessible.

[d] Expected to increase compared to scenario G.

[e] Expected to decrease compared to scenario G.

Weighting for burden of disease

The different weighting approaches resulted in a 9% and 11% difference in mean facility scores between scenarios for Dataset 1 and Dataset 2, respectively. These variations also had considerable effects on the minimum and especially the maximum scores observed, with changes of more than 10% in facility scores for individual facilities (see scenarios B-E in **Figure 3**).

Table 2 Proportional weights (%) assigned to medicines in different burden of disease scenarios.

Medicine Scenario	A (base case)	B	C	D	E
	code 370; DB multiplied	code 370; DB divided	code 20; DB multiplied	code 20; DB divided	No weighting
Oral rehydration salts	8.5	12.1	3.9	5.6	5.3
Zinc sulphate	8.5	12.1	3.9	5.6	5.3
Phenytoin	0.3	0.3	0.1	0.1	5.3
Valproic acid	0.3	0.3	0.1	0.1	5.3
Diazepam	0.3	0.3	0.1	0.1	5.3
Ferrous salt	0.8	1.1	0.4	0.5	5.3
Mebendazole	0.8	1.1	0.4	0.5	5.3
Artemether+lumefantrine	6.2	8.8	2.9	4.1	5.3
Vitamin A	1.8	5.3	0.9	2.5	5.3
Paracetamol	4.5	4.0	4.5	3.3	5.3
Morphine	4.5	4.0	4.5	3.3	5.3
Ibuprofen	4.5	4.0	4.5	3.3	5.3
Amoxicillin	13.4	9.6	12.4	8.8	5.3
Ampicillin	13.4	9.6	12.4	8.8	5.3
Benzylpenicillin	13.4	9.6	12.4	8.8	5.3
Gentamicin	13.4	9.6	12.4	8.8	5.3
Ceftriaxone	2.7	3.9	12.0	17.7	5.3
Cefotaxime	2.7	3.9	12.0	17.7	5.3
Procaine benzylpenicillin	0.2	0.5	0.1	0.3	5.3
Total	100%	100%	100%	100%	100%

A = base case scenario, using GHE code 370 as a proxy for infectious diseases. **B** = GHE code 370, and the burden of a disease is divided over all medicines for treating that specific disease. **C** = GHE code 20 (original methodology). **D** = GHE code 20, and the burden of a disease is divided over all medicines for treating that specific disease. **E** = no DB weighting (e.g. equal weights for all medicines).

The national poverty line

Increasing the NPL from $1.90 to $3.20 led to almost equal results, but a further increase to $5.50 induced an expected decline of 6.5% and 8.6% in mean facility scores for Dataset 1 and Dataset 2, respectively. Despite the only $0.54 remaining difference between NPL and LPGW wage in the latter case, the majority of medicines that were available also remained affordable (see **Figure 4**).

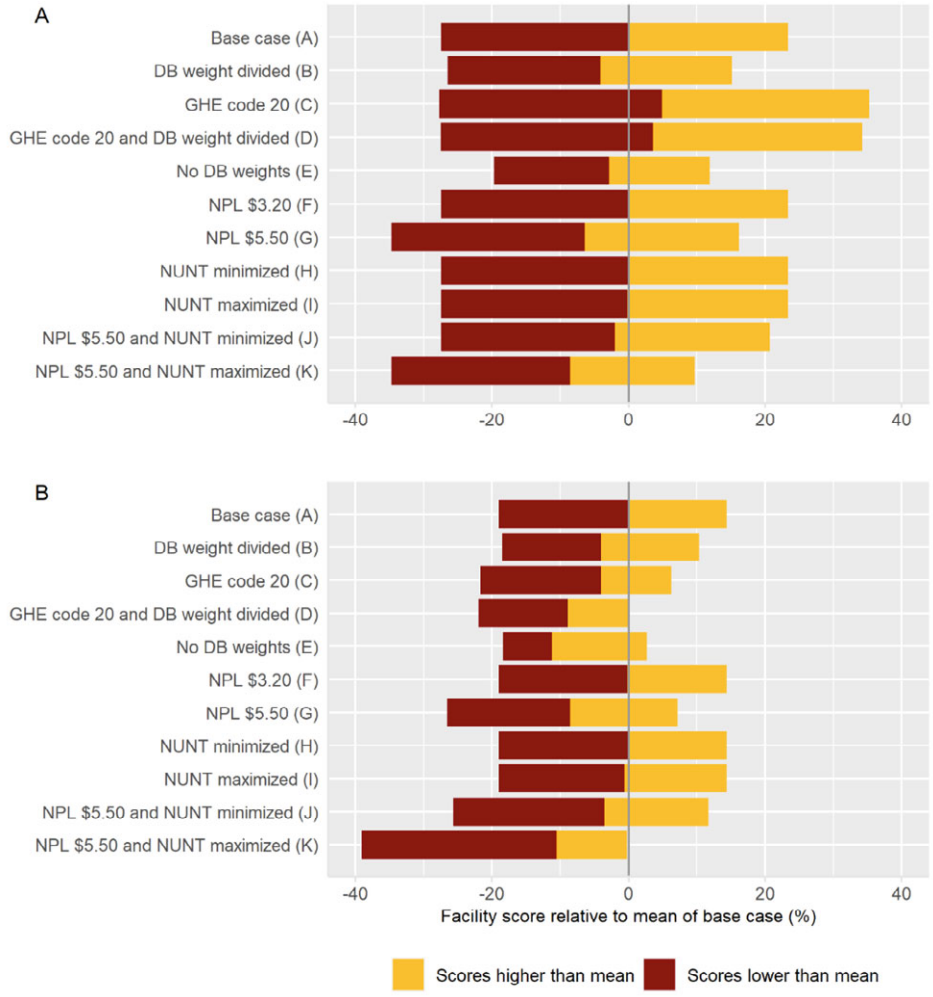

Figure 3 Mean, minimum and maximum facility scores of scenarios A-K.
A = Dataset 1, B = dataset 2.
DB = Disease Burden; GHE = Global Health Estimates; NPL = National Poverty Line; NUNT = Number of Units Needed for Treatment.

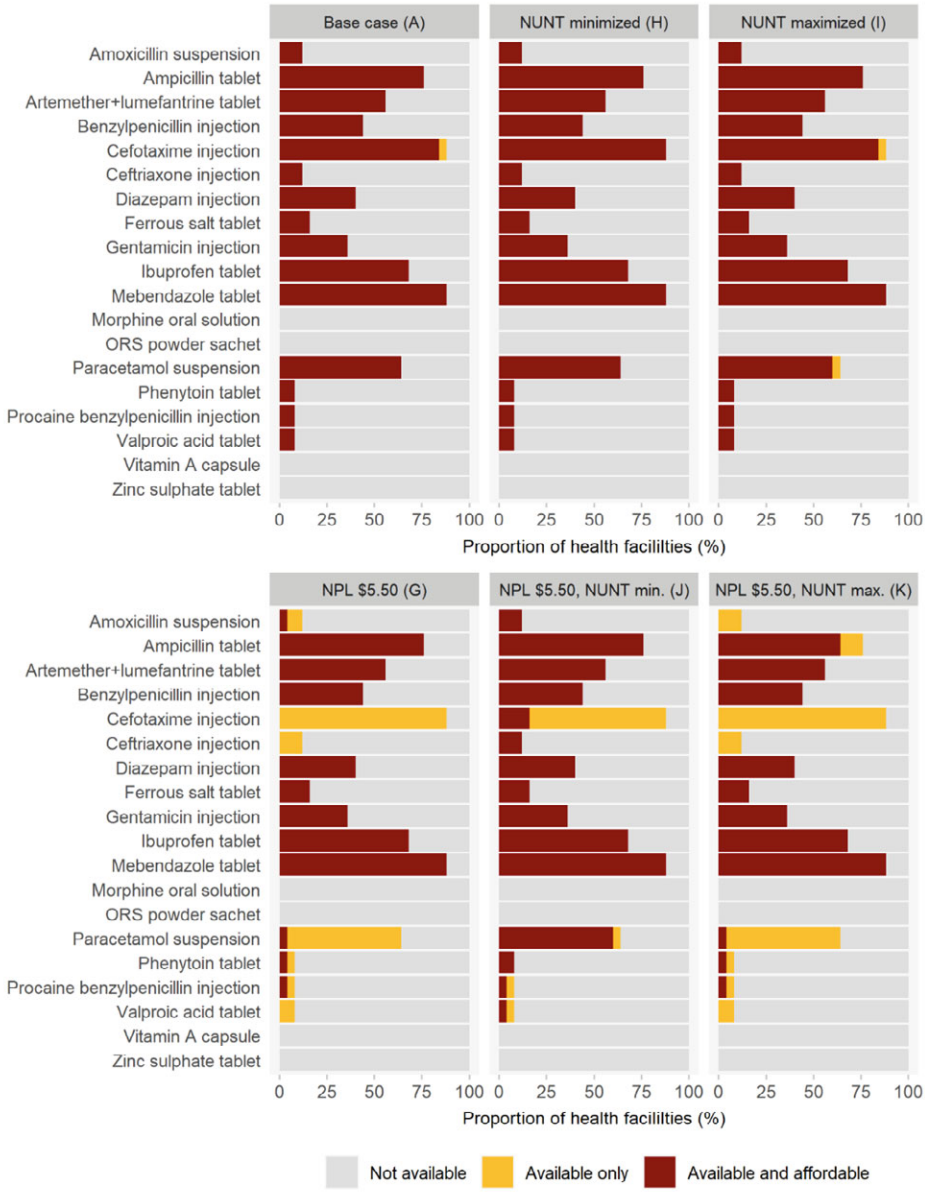

Figure 4 Availability and affordability of individual medicines for scenarios A and H-K for Dataset 1. NPL = National Poverty Line; NUNT = Number of Units Needed for Treatment; ORS = Oral Rehydration Salts.

The number of units needed for treatment

The mean facility scores remained stable within Dataset 1 while the NUNT was varied in scenarios H and I (+0.1% and -0.2%), whereas differences of +4.4% and -2.1% were observed between scenarios G and J or K at the more critical NPL of $5.50. Results were comparable for Dataset 2 (+0.0% (H vs. A), -0.6% (I vs. A), +5.0 (J vs. G), -2.0% (K vs. G)). When examining the effects at the individual medicine level, the effects of changes in the NUNT can be seen in more detail (**Figure 4**, Appendix 5). At the poverty line of $1.90, virtually all medicines that were available were also affordable, whichever NUNT used. At the poverty line of $5.50, as expected more medicines were unaffordable, but changes to the NUNT still had limited impact. The most considerable changes were in the (un)affordability of ceftriaxone injections and paracetamol suspensions, which were also associated with a wide range in NUNT values (Appendix 2).

Size of the medicine basket

Figure 5 shows the mean, SD and range of facility scores and the SDG 3.b.3 scores of a continuously reducing basket size (see also Appendix 6). With a decreasing number of medicines in the basket, scores became increasingly more unstable. Less than 5% change in mean facility score was observed for baskets with at least 12 medicines. For baskets smaller than 12 medicines, mean facility scores increased more rapidly before dropping greatly and the range of scores widened further. This generated mostly moderate changes in the SDG 3.b.3 scores.

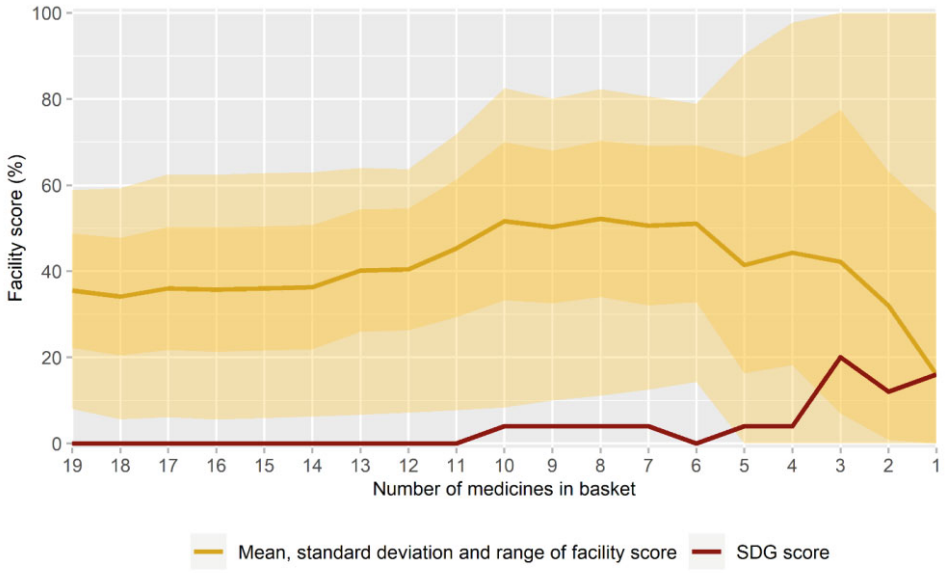

Figure 5 Facility scores and SDG 3.b.3 scores of an in size reducing basket.
SDG = Sustainable Development Goal.

Discussion

An adapted SDG indicator 3.b.3 methodology was developed to enable measuring of access to child medicines, but proof of its robustness had not yet been provided. With this study we aimed to provide this evidence through sensitivity analyses. These analyses have confirmed that the NUNT behaves as predicted, causing minimal to more modest variation in mean facility scores when a more critical value of the poverty line (i.e. NPL of $5.50) was used. Analyses have also demonstrated that stable results are obtained for medicine baskets of at least 12 child-appropriate medicines. Conversely, different proportional weights based on DB and higher NPL values were associated with considerable variation in facility scores.

Although there is no agreement on what degree of variation in facility scores should be considered relevant, we consider a difference in mean facility scores of less than 5% of limited influence. With that in mind, we consider the NUNT to be a reliable substitute for DDDs in this methodology. The comparable results in Dataset 1 versus Dataset 2 provide further evidence to the robustness of this parameter. Additionally, these results indicate that a single NUNT value can sufficiently represent use of a medicine in an entire age group of one month to five years. This is a crucial finding, because this indicator was designed to be inclusive of those not covered by the original indicator.

Repeated analyses on a continuously smaller number of medicines in the basket have demonstrated that there was limited variability in all outcomes when a basket of between 12 and 19 child medicines was used. Baskets smaller than 12 medicines led to increasingly diverging outcomes. Although the impact on the SDG 3.b.3 scores was still limited, larger fluctuations in SDG scores may be expected when the mean facility score (now 35.5%) is closer to the critical WHO threshold of 80% used as a reference in this methodology. The limited number of medicines in the basket could then result in more health facilities being falsely classified as (not) providing available and affordable medicines, since individual facility scores are more likely to end up just under or above the 80% threshold. We thus recommend that at least 12 medicines are used to determine access to medicines for children, although an even larger number of medicines will provide a more comprehensive picture.

In Scenario C – the weighting approach as used in the original methodology – the use of antibacterial medicines is exaggerated through the use of GHE code 20 in calculating their proportional weight. GHE code 20 is an overarching code used to represent all infectious and parasitic diseases, of which many are not treated with antibacterial medicines. With individual weights of 12.4% or 12.0%, this resulted in antibacterial medicines together accounting for 73.6% of the weighted access scores in this scenario. Medicines for pain and palliative care represented another 13.5%. If these nine medicines were available and affordable in a facility, it would be considered to provide accessible medicines, regardless of the status of the other ten

medicines. In contrast, one can almost certainly not score well on this indicator if one does not meet the standards for these nine medicines. These analyses thus reveal that the scoring system that is currently part of the original SDG 3.b.3 indicator methodology is highly disproportionate towards antibacterial medicines and overstates their importance.

This study included several alternative weighting approaches that were designed to minimize this disproportionality (scenarios A-D). The different approaches led to substantial differences in weights assigned between medicines and radical shifts between scenarios for individual medicines. Each tested alternative thus also seemed to lead to disproportionate weights (i.e. no longer reflecting the actual DB). Therefore, we propose that the weighting for DB is taken out of the methodology. Instead, all medicines should be given an equal weight in the calculations (i.e. scenario E).

Besides disproportionality, there are other arguments to support this recommendation. Primarily, all medicines that are part of the core sets are essential and should thus always be available and affordable. Additionally, the weighting procedure was designed to capture the demand for medicines, yet it fails to include the volume of medicines needed to meet this demand. In this methodology, availability is a binary variable and not a continuous measure. Without quantitative availability data, demand appears to be a rather empty element. A strong argument advocating in favor of weighting for DB is that the core set includes medicines for diseases such as malaria, tuberculosis and HIV/AIDS. The DB for these diseases may be negligible in some countries. However, the medicine basket is not fixed and already allows for some flexibility. If a disease is not prevalent in a country, a country may decide not to survey these medicines. Finally, the methodology was designed for countries to apply independently, and its ease of use is thus an important factor. Removing this step from the equation will simplify its use and interpretation of the results, which we have experienced to be much needed. Of note, although the indicator currently provides no opportunities for adding medicines to the basket that are of local importance when reporting to the UN – to maintain global comparability – additional medicines may be added when this methodology is used to inform policy-making at a national or regional level.

Our results confirm that a higher value of the NPL – or in other words a smaller difference between the NPL and daily LPGW wage – led to reduced facility scores. Although international reference poverty lines were used in the present study as a proxy for the NPL, it does indicate a potential problem with the expression of affordability as a function of these parameters. We experienced first-hand that it is difficult to obtain NPL values for all countries. Values that were successfully identified were often not from the same year as the survey data, requiring additional corrections. This may be acceptable when the NPL is only a few years older, use of increasingly outdated NPL values risks severely skewed results. These problems may, however, be irrelevant to governments that have access to country data not publicly available. Notably, we also

encountered an NPL that was higher than the LPGW wage (e.g. Kyrgyzstan), which would make all medicines unaffordable unless provided for free. Although this could be a testimony to reality, the use of the NPL in this indicator introduces additional uncertainties to those that already exist regarding the LPGW wage [15]. Another, more fundamental concern about the definition of affordability as used in this indicator is that it fails to consider that children do not have their own income and depend upon a caregiver for buying medicines. Methods that have been used previously to express affordability (e.g. number of days wages of the lowest-paid government worker that is needed to purchase a medicine) present the same challenge in children. The validity of the present and other methods of expressing affordability in reporting on access for children should be subject of future research [16].

Our findings show that the proposed child-specific indicator should be considered as a standard addition to the original 3.b.3 indicator in the Global Indicator Framework for tracking progress in the SDGs [5]. The issues encountered in calculating the adapted indicator are also strong predictors for similar problems in the original SDG 3.b.3 methodology as both rely on the same framework. With that, the proposed dropping of the weighting step should also be considered for the original indicator at the planned review round of the indicator framework in 2025 [17]. Until then, the same approach for weighting for DB should be used across countries and years to at least ensure comparability of results.

An important strength of this study is the pooling of data from historical datasets collected in different countries and years to obtain data on a range of medicines. This enabled us to perform a variety of sensitivity analyses on distinct aspects of the methodology, some of which would not have been possible otherwise. Although the datasets used were dated, this did not pose a limitation as it did not hinder us in our primary aim of determining the robustness of this methodology. A second dataset made it possible not only to confirm the results on different data, but also to gain additional insight into the effects of the affordability dimension. This is highly relevant, as the affordability of a medicine depends upon a large number of input variables. Although a valuable strength of the study, the pooling of data is also associated with several limitations. First, we were restricted to the use of estimates for some of the major input variables such as the LPGW wage and the NPL. Additionally, the pooling process of data from different years and countries required several correction and extraction steps that may have compromised the representability of the data. Nonetheless, the availability and affordability of medicines as observed in the present study are in line with the results of the proof-of-concept study and a recent systematic review [9, 18]. Finally, no strong conclusions about the type of medicines that are (un)affordable can be drawn as this exercise was strictly hypothetical.

Conclusions

Including a child appropriate SDG indicator 3.b.3 in the official Global Indicator Framework is instrumental in improving access to medicines for this often neglected group. This study has confirmed that using the NUNT to express affordability for children instead of DDDs provides reliable outcomes, corroborating that the elements that were changed to make the indicator appropriate for children are robust, whilst some of the underlying principles of indicator 3.b.3 are problematic. Given its disproportionate effects, the dropping of DB from the equation should strongly be considered at the 2025 planned review of the indicator framework. Furthermore, these analyses have reinforced the need for the development of methods to measure affordability that could substitute the current calculations based on an NPL and the LPGW wage given their limitations.

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Supplementary materials

Appendix 1: Detailed description of the adapted SDG indicator 3.b.3 for children

A core set of 22 essential, age-appropriate medicines was established (**Table S1**). This basket represents medicines for acute and chronic, communicable and non-communicable diseases in the primary health care setting.

Availability is determined for each medicine in the basket. Availability is a binary variable and is determined by the presence of the medicine on the day that the data collector visited the facility.

Affordability is determined based on the price of treatment per day and the ability to pay, which is determined by the National Poverty Line (NPL) and the Lowest-Paid unskilled Government Worker (LPGW) wage.

The price of treatment per day is determined by the unit price and the number of units needed for a course or month treatment (NUNT). Of note, the price of a medicine is only reported when the medicine was available.

$$Price\ per\ treatment\ (day) = \frac{unit\ price\ (day) * NUNT\ (month)}{365/12}$$

A medicine is considered affordable when no extra daily wages (EDW) are required for the LPGW to purchase a daily dose treatment of this medicine after fulfilling basic needs (represented by the NPL). The closer the NPL value and LPGW wage are to each other, the cheaper a medicine has to be to still be affordable.

$$Extra\ daily\ wages\ (EDW) = \frac{NPL + price\ per\ treatment\ (day)}{daily\ wage\ of\ LPGW}$$

The EDW is transformed into a binary variable.

$$\begin{cases} if\ EDW\ \leq\ 1, & affordability\ =\ 1, \\ otherwise, & affordability\ =\ 0 \end{cases}$$

Medicines are only considered accessible when they are both available and affordable in a facility.

Accessible medicines are given a relative weight (between 0-100%) according to the regional burden of disease to capture demand. Weights are determined through Disability Adjusted Life Years (DALYs) as can be found in the WHO Global Health Estimates (GHE).

Relative weights applied to each individual medicine can be calculated through the following steps:

1) Each medicine in the basket is assigned a GHE code for one or several disease(s) that are treated/cured/controlled by that medicine (table S1).
2) Each medicine is assigned the corresponding number of disability-adjusted life years (DALYs). If a medicine is used to treat multiple diseases, the DALYs for these diseases are summed.*
3) The total number of DALYs for the basket is calculated.
4) The proportional weight per medicine is calculated as the number of DALYs linked to each individual medicine divided by the total number of DALYs.
5) Medicines used in the treatment of pain and palliative care cannot be linked to a GHE code. Weights for these medicines are thus calculated by dividing 1 by the number of medicines in the basket.
6) The proportional total is calculated by summing the proportional weights from steps 4 and 5.
7) Final weights are calculated by dividing the proportional weights from step 4 and 5 by the proportional total.

*If a diseases is associated with multiple medicines, the burden for this specific is thus counted multiple times.

Facility scores are generated (0-100%), representing weighted access scores for individual health facilities. A facility provides access to medicines if 80% of the medicines are available and affordable, transforming it to a binary variable.

$$\begin{cases} if\ facility\ score\ \geq\ 80\%, & accessibility\ =\ 1, \\ otherwise, & accessibility\ =\ 0 \end{cases}$$

The adapted SDG indicator 3.b.3 score can be calculated as the number of health facilities with an available and affordable core set of child medicines divided by the total number of health facilities surveyed.

$$SDG_{3.b.3.} = \frac{Facilities\ with\ available\ and\ affordable\ basket\ of\ medicines\ (n)}{Surveyed\ Facilities\ (n)}$$

Table S1 Basket of essential medicines for children 1-59 months.

Affiliated disease (GHE code)	Medicine name	Acceptable formulations
Diarrhoeal diseases (110)	Oral rehydration salts	*Powder sachet 200 ml, 500 ml or 1L*
	Zinc sulphate	*Cap/tab 20 mg*
Epilepsy (970)	Carbamazapine	*Cap/tab 100 mg; oral liquid 100 mg/5 ml*
	OR Phenobarbital	*Cap/tab 30 mg or 100 mg; injection 100 mg/ml or 200 mg/ml; oral liquid 15 mg/5 ml*
	OR Phenytoin	*Cap/tab 25 mg, 50 mg or 100 mg; injection 50 mg/ml; oral liquid 25 or 30 mg/5 ml*
	OR Lamotrigine	*Cap/tab 25 mg, 50 mg or 100 mg*
	Valproic acid	*Cap/tab 100 mg, 150 mg, 200 mg or 500 mg; oral liquid 200 mg/5 ml*
	Diazepam	*Rectal solution 5 mg/ml; injection 5 mg/ml*
	OR Lorazepam	*Parenteral solution 2 mg/ml or 4 mg/ml*
	OR Midazolam	*Oromucosal solution 5 mg/ml or 10 mg/ml; ampoule 10 mg/ml*
HIV/AIDS (100)	Abacavir + lamivudine + dolutegravir	*Cap/tab 120/60 mg (abacavir/lamivudine)* ***AND*** *cap/tab 10 mg (dolutegravir)*
	OR Abacavir + lamivudine + lopinavir/ritonavir	*Cap/tab 120/60 mg (abacavir/lamivudine)* ***AND*** *cap/tab 40/10 mg or 100/25 mg (lopinavir/ritonavir)*
Iron-deficiency anemia (580)	Ferrous salt	*Cap/tab 60 mg or 200 mg; oral liquid 25 mg/ml*
	Albendazole	*Cap/tab 200 mg or 400 mg*
	OR Mebendazole	*Cap/tab 100 mg*
Malaria (220)	Artemether + lumefantrine	*Cap/tab 20/120 mg*
	OR Artesunate + amodiaquine	*Cap/tab 25/67.5 mg or 50/135 mg*
	OR Artesunate + mefloquine	*Cap/tab 25/55 mg*
	OR Dihydroartemisinin + piperaquine	*Cap/tab 20/160 mg or 20/320 mg*
	OR Artesunate + Sulfadoxine-pyrimethamine	*Cap/tab 50/500/25 mg or cap/tab 50 mg (artesunate)* ***AND*** *cap/tab 500/25 mg (sulfadoxine-pyrimethamine)*
	OR Chloroquine	*Cap/tab 100 mg; oral liquid 50 mg/5 ml*
	Artesunate	*Cap/tab 50 mg; suppository 50 mg*
Measles (150) Vitamin A deficiency (570)	Retinol	*Cap/tab 25,000 IU, 100,000 IU or 200,000 IU*
Pain and palliative care (weight = 1/T)	Paracetamol	*Cap/tab 100 mg; suppository 100 mg; suspension 120 or 125 mg/5 ml*
	Morphine	*Cap/tab (slow release) 10 mg; injection 10 mg/ampoule; oral liquid 10 mg/5 ml*
	Ibuprofen	*Cap/tab 200 mg; oral liquid 200 mg/5 ml*
Tuberculosis (30)	Ethambutol + isoniazid + pyrazinamide + rifampicin	*Cap/tab 100 mg or 400 mg or oral liquid 25 mg/ml (ethambutol)* ***AND*** *cap/tab 50/150/75 mg (isoniazid + pyrazinamide + rifampicin)*

Lower respiratory infections (390) Other infectious diseases (370)	Amoxicillin	*Cap/tab 250 mg or 500 mg; powder for injection 250 mg/vial, 500 mg/vial or 1 g/vial; suspension 125 mg/5 ml or 250 mg/5 ml*
	OR Amoxicillin + clavulanic acid	*Cap/tab 100/125 mg, 250/125 mg or 500/125 mg; powder for injection 500/100 mg/vial; oral liquid 125/53.25 mg/5 ml or 250/62.5 mg/5 ml*
	Ampicillin	*Cap/tab 250 mg or 500 mg; injection 500 mg/vial or 1 g/vial*
	Benzylpenicillin	*Injection 1 MIU/vial*
	Gentamicin	*Injection 10 mg/ml or 40 mg/ml*
Other infectious diseases (370) Meningitis (170)	Ceftriaxone	*Injection 250 mg/vial, 500 mg/vial or 1 g/vial*
	Cefotaxime	*Injection 1 g/vial*
Syphilis (50)	Procaine benzylpenicillin	*Injection 1 MIU/vial*

Cap/tab = capsule/tablet.

Appendix 2: Number of units needed for treatment

Table S2 Number of units needed for treatment (NUNT) for children 1-59 months.

Medicine name	Formulation	NUNT	Minimum	Maximum
Amoxicillin	Suspension 250 mg/5 ml	90	30	100
Ampicillin	Cap/tab 500 mg	20	10	40
Artemether/lumefantrine	Cap/tab 20/120 mg	6	3	12
Artesunate/Sulfadoxine-pyrimethamine	Cap/tab 50/500/25 mg	1	1	1
Benzylpenicillin	Injection 1 MIU/vial	5	5	5
Cefotaxime	Injection 1 g/vial	18	7	30
Ceftriaxone	Injection 250 mg/vial	28	7	40
Diazepam	Injection 5 mg/ml	1	1	1
Ferrous salt	Cap/tab 200 mg	14	7	14
Gentamicin	Injection 40 mg/ml	10	4	15
Ibuprofen	Cap/tab 200 mg	90	45	120
Mebendazole	Cap/tab 100 mg	6	6	6
Morphine	Oral liquid 10 mg/5 ml	300	60	720
Oral rehydration salts	Powder sachet 500 ml	2	1	6
Paracetamol	Suspension 120 mg/5 ml	900	240	1800
Phenytoin	Cap/tab 50 mg	60	30	120
Procaine benzylpenicillin	Injection 1 MIU/vial	10	10	10
Valproic acid	Cap/tab 150 mg	60	30	60
Vitamin A	Cap/tab 100,000 IU	2	1	6
	Cap/tab 200,000 IU	2	1	3
Zinc sulphate	Cap/tab 20 mg	14	5	14

Cap/tab = Capsule/tablet; IU = international units.

Note: the standard NUNT is based on a 30 months old child of 11 kg, the minimum and maximum NUNT values loosely correspond to a 1 month old child of 4 kg and a 5 year old of 18 kg respectively.

Appendix 3: General characteristics of datasets

Table S3 General characteristics of datasets 1 and 2.

Dataset 1			Dataset 2		
Medicine	Formulation	Original dataset	Medicine	Formulation	Original dataset
Amoxicillin	Suspension 50 mg/ml	Haiti (2011)	Amoxicillin	Suspension 50 mg/ml	Burundi (2013)
Ampicillin	Cap/tab 500 mg	Mongolia (2004)	Ampicillin	Cap/tab 500 mg	Mongolia (2004)
Artemether/ lumefantrine	Cap/tab 20/120 mg	Tanzania (2012)	Artesunate/sulfadoxine/ pyrimethamine	Cap/tab 50/500/25 mg	Sudan (2012)
Benzylpenicillin	Injection 1 MIU/vial	China (2012)	Benzylpenicillin	Injection 1 MIU/vial	China (2012)
Cefotaxime	Injection 1 g/vial	Bolivia (2008)	Cefotaxime	Injection 1 g/vial	Bolivia (2008)
Ceftriaxone	Injection 250 mg/vial	China (2012)	Ceftriaxone	Injection 250 mg/vial	Mongolia (2004)
Diazepam	Injection 5 mg/ml	Tanzania (2012)	Diazepam	Injection 5 mg/ml	Tanzania (2012)
Ferrous salt	Cap/tab 200 mg	Tanzania (2012)	Ferrous salt	Cap/tab 200 mg	Tanzania (2012)
Gentamicin	Injection 40 mg/ml	Burundi (2013)	Gentamicin	Injection 40 mg/ml	Kyrgyzstan (2015)
Ibuprofen	Cap/tab 200 mg	Kyrgyzstan (2010)	Ibuprofen	Cap/tab 200 mg	Haiti (2011)
Mebendazole	Cap/tab 100 mg	Bolivia (2008)	Mebendazole	Cap/tab 100 mg	Burundi (2013)
Morphine	Oral solution 2 mg/ml	Haiti (2011)	Morphine	Oral solution 2 mg/ml	Haiti (2011)
Oral rehydration salts	Powder sachet 500 ml	Haiti (2011)	Oral rehydration salts	Powder sachet 500 ml	China (2012)
Paracetamol	Suspension 24 mg/ml	Haiti (2011)	Paracetamol	Suspension 24 mg/ml	Sudan (2013)
Phenytoin	Cap/tab 50 mg	Haiti (2011)	Phenytoin	Cap/tab 50 mg	China (2012)
Procaine benzylpenicillin	Injection 1 MIU/vial	Haiti (2011)	Procaine benzylpenicillin	Injection 1 MIU/vial	Kyrgyzstan (2015)
Valproic acid	Cap/tab 150 mg	Kyrgyzstan (2010)	Valproic acid	Cap/tab 150 mg	Kyrgyzstan (2010)
Vitamin A	Cap/tab 200,000 IU	Burundi (2013)	Vitamin A	Cap/tab 100,000 IU	Haiti (2011)
Zinc sulphate	Cap/tab 20 mg	Burundi (2013)	Zinc sulphate	Cap/tab 20 mg	Haiti (2011)

Appendix 4: Results of scenarios A-K

Table S4 Results of scenarios A-K. All results are in percentages (%).

	Results dataset 1			Results dataset 2		
Scenario	Mean FS	Minimum FS	Maximum FS	Mean FS	Minimum FS	Maximum FS
A	35.5	8.0	58.8	76.3	57.2	90.6
B	31.4	9.0	50.6	72.2	57.7	86.6
C	40.4	7.8	70.7	72.2	54.9	82.5
D	39.1	7.9	69.6	67.3	54.3	76.4
E	32.6	15.8	47.4	65.1	57.9	78.9
F	35.5	8.0	58.8	76.0	57.2	90.6
G	29.0	0.8	51.6	67.7	49.7	83.4
H	35.6	8.0	58.8	76.3	57.2	90.6
I	35.3	8.0	58.8	75.7	57.4	90.6
J	33.4	8.0	56.1	72.7	50.6	87.9
K	26.9	0.8	45.2	65.7	37.2	76.0

FS = Facility score.

Appendix 5: Availability and affordability of individual medicines (dataset 2)

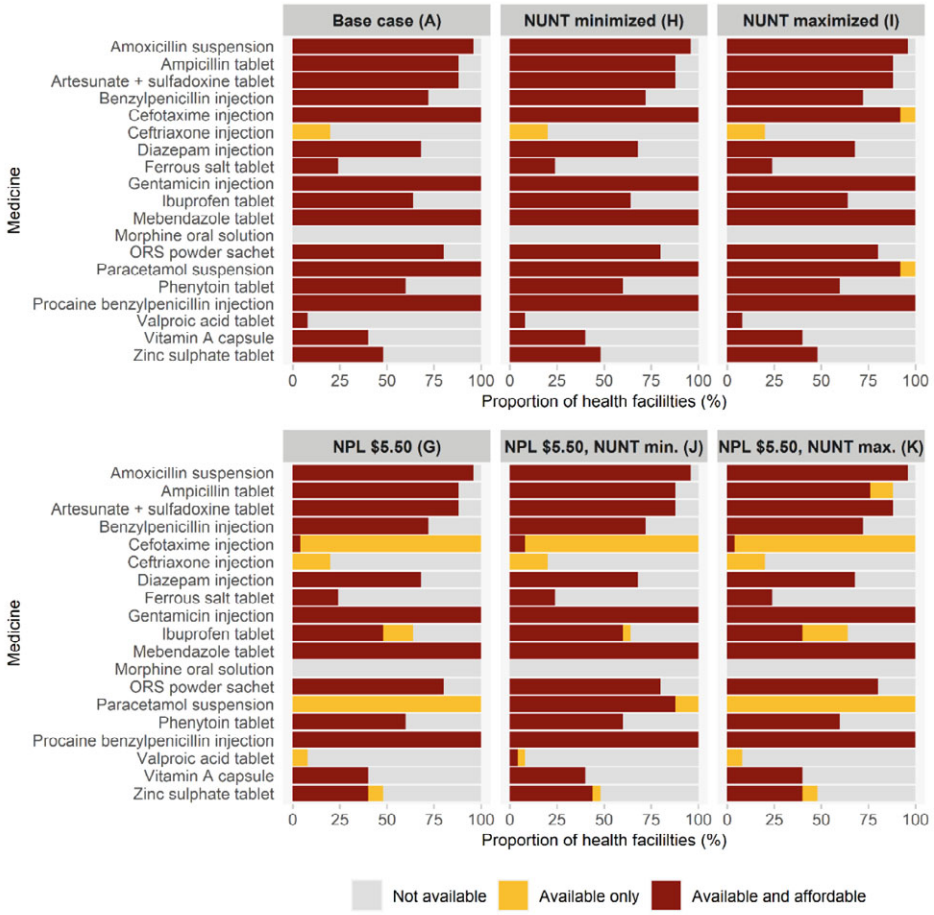


Figure S1 Availability and affordability of individual medicines for scenarios A and H to K for dataset 2.

NPL = National Poverty Line; NUNT = Number of Units Needed for Treatment; ORS = Oral Rehydration Salts.

Appendix 6: Results of analysis with reducing basket size

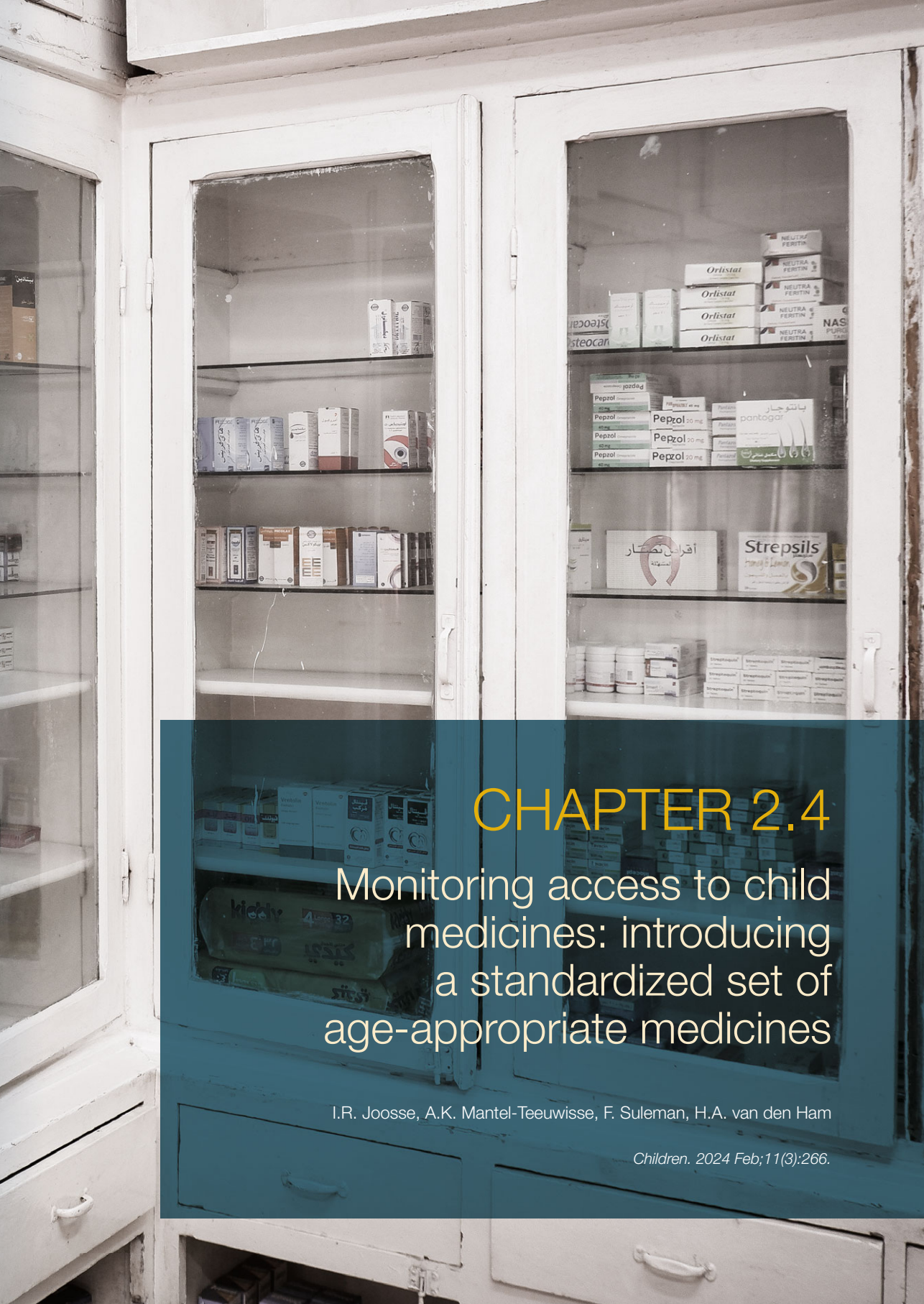
Table S5 Results of analysis with reducing basket size.

Number of medicines in basket	Mean	SD	Minimum	Maximum	SDG score
1	16.0	37.4	0.0	100.0	16.0
2	32.0	31.2	0.0	100.0	12.0
3	42.2	35.2	0.0	100.0	20.0
4	44.3	26.0	0.0	97.8	4.0
5	41.4	25.1	0.0	90.4	4.0
6	51.0	18.2	14.3	78.9	0.0
7	50.6	18.5	12.5	80.6	4.0
8	52.2	18.2	11.1	82.3	4.0
9	50.3	17.7	10.0	80.1	4.0
10	51.6	18.4	8.3	82.5	4.0
11	45.3	16.0	7.7	71.8	0.0
12	40.4	14.1	7.1	63.7	0.0
13	40.1	14.2	6.7	63.9	0.0
14	36.3	14.4	6.3	62.9	0.0
15	36.0	14.4	5.8	62.7	0.0
16	35.7	14.4	5.6	62.3	0.0
17	36.0	14.3	6.1	62.5	0.0
18	34.1	13.6	5.6	59.3	0.0
19	35.5	13.2	8.0	58.8	0.0

SD = standard deviation; SDG = sustainable development goal.

Note: all results are in percentages (%).


Bivatracin
BETADINE
Kaprofen
KETOLAC



CHAPTER 2.4

Monitoring access to child medicines: introducing a standardized set of age-appropriate medicines

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Abstract

Monitoring access to pediatric medicines as part of the Sustainable Development Goal (SDG) agenda for 2030 requires surveying age-appropriate medicines. This study aimed to develop tracer sets of essential age-appropriate medicines, for use in SDG indicator 3.b.3 or in conjunction with other methodologies for monitoring access to medicines. Two sets of medicines were developed: for young children (1 month to 5 years) and school-aged children (5-12 years). Priority diseases were selected based on global burden of disease and linked to active ingredients of first-choice according to treatment guidelines and the World Health Organization (WHO) model list of essential medicines for children (EMLc). To ensure clinical relevance, the Delphi technique was employed to identify areas of (dis)agreement among clinical pediatric experts. During two consultation rounds, experts were invited to indicate (dis)agreement. Five experts per each age group were largely in agreement with initial selections, but various therapeutic alternatives were suggested for addition. A second consultation round with five experts did not lead to major adjustments. The final sets included 26 treatment options for both groups. Specific age-appropriate formulations were selected from the WHO EMLc 2023. These two globally representative tracer sets of medicines consider the particular needs of children and could aid countries in the critical monitoring of accessibility to pediatric medicines.

Introduction

The substantial number of preventable child deaths persists as a challenge in resource-limited countries [1]. Essential medicines are a crucial component in achieving further reductions in child mortality [2]. However, these medicines can only save lives when they are available, affordable and acceptable to those who rely on them [3], which is frequently not the case [4]. As such, improving access to safe, effective and quality-assured medicines for all is an important target within the Sustainable Development Goals (SDGs), embodied within targets 3.8 and 3.b of the SDGs [5]. SDG indicator 3.b.3 – measuring the proportion of primary health facilities with a core set of relevant essential medicines available and affordable on a sustainable basis – was developed by the World Health Organization (WHO) to monitor countries' current performance and track progress [6].

Although monitoring of access to medicines is considered key in driving improvement and evaluating the impact of implemented solutions [7], SDG indicator 3.b.3 has significant limitations when applied to medicines for children [8]. These limitations stem from technical challenges in calculating affordability through the core metrics' reliance on adult dosing schemes (i.e. Defined Daily Dosages, DDDs), and the core set of essential medicines as defined by WHO being of limited relevance to children. This is evident from the small number of active ingredients that are a priority for children – given their propensity for different diseases compared to adults – and the lack of age-appropriate formulations in this core set. The latter is particularly relevant as children are a heterogeneous group requiring different dosages and with varying abilities to take medicines [9, 10]. Specifically, children under five typically lack the ability to swallow solid oral dosage forms (i.e. conventional tablets, capsules), whereas manipulation of medicines risks toxic or sub-therapeutic doses, dosing errors, and may affect stability of the product [11].

To allow monitoring of access to child-appropriate medicines through SDG indicator 3.b.3, we proposed and validated a methodology tailored to children, effectively addressing the technical challenges associated with calculating affordability [8, 12]. However, as part of these adaptations, the child indicator – similar to the original indicator – requires the survey of a standardized set of tracer essential medicines [6]. No standardized set of medicines specifically tailored to the needs of children was available, as any existing sets were either outdated, merely reflected the health needs of a subgroup of children, or failed to include major therapeutic areas such a tuberculosis and HIV/AIDS [13, 14]. As such, the aim of the present study was to develop a standardized tracer set of age-appropriate essential medicines – including medicines for both acute and chronic, as well as communicable and non-communicable diseases in the primary health care setting – representative for children of all ages.

Methods

Recognizing that children of different ages may require distinct dosage forms and strengths as well as other active ingredients, we created two core sets of medicines: children aged 1 month to 5 years (from now on referred to as *young children*) and children 5 to 12 years (from now on referred to as *school-aged children*).

Initial selection of core set

Similar to the original methodology [6], global burden of disease served as a foundation for identifying priority diseases in children. Ten diseases with the highest burden (and which can be managed with essential medicines as defined by WHO in 2021 [15]) were selected based on Global Health Estimates (GHEs) for each age group [16]. *Pain and palliative care* is not reflected in the GHEs, but was added separately as this is critical supportive care in many common conditions.

Priority diseases were then linked to essential medicines. As the core set is not meant to be a complete set of medicines but merely indicative of access, we limited ourselves to active ingredients of first choice in primary care which were also on the 7th WHO Model list of Essential Medicines for children (EMLc, 2019). For young children, the WHO pocket book of hospital care for children represented the core reference [17]. As a similar (global) comprehensive guideline for children aged above 5 years was not available, the South African Standard Treatment Guidelines (STGs) for primary care were used [18]. This low- and middle-income country (LMIC) has well-established procedures for developing and updating their Standard Treatment Guidelines, and its STGs are representative of the diseases encountered and resources available in other LMIC. For disease areas not sufficiently described in either reference, relevant disease-specific treatment guidelines developed by WHO were used [19-24]. These are global consensus guidelines targeted at LMIC, developed through a transparent, evidence-based decision-making process and subject to rigorous quality checking. If not available, other globally representative guidelines were selected [25, 26].

Expert consultation on active ingredients

To ensure that the primary selection sufficiently addressed the priority health needs in clinical practice, the Delphi technique was employed to identify areas of (dis)agreement among clinical experts. As an anonymous investigation method, the Delphi technique facilitates consensus-building among geographically diverse experts through iterated rounds of structured data collection and controlled feedback to participants [27]. Participant expertise is critical to the validity of this technique. In this study, pediatricians or pharmacists specialized in pediatrics with at least 2 years of experience (to ensure sufficient experiential knowledge) were considered eligible to participate. To represent the global nature of SDG indicator 3.b.3, we recruited experts from all over the world and from different income levels. Participants were initially recruited

from the 22nd WHO Expert committee on Selection and Use of Essential Medicines. This was complemented with experts recruited through a network approach. Recruitment took place between March 2021 and February 2023 and stopped when the survey was completed by 5 experts per age group.

In an online survey (Appendix 1), the background for the core set was described and an explanation was given for the selection of disease areas. For each disease area, the experts were presented with the selected active ingredients and requested to indicate (dis)agreement with this selection. Participant were invited to provide an explanation if they indicated disagreement and specify any redundant medicines. Additionally, alternatives from the 7th WHO EMLc for the disease were presented, and experts were asked to indicate if there were any active ingredients missing from the selection. In a second part of the survey, experts were invited to indicate which specific formulation (dosage form and strength) from the 7th WHO EMLc they believed was preferred for each active ingredient in the primary selection for the respective age group.

The survey was piloted among 3 experts. This led to only minor refinements to the survey's main part on active ingredient level, and results were hence used in final data analysis. Responses to the pilot questions on preferred formulations showed great variation in preferences between participants. From participants' comments it was deduced that their preference to a great extent depended on local availability of specific formulations. Due to these inconsistencies and in an effort to shorten the time needed to complete the survey, the questions on preferred formulations were eliminated from the final survey. Online surveys were conducted using validated and password-protected software (LimeSurvey®), and data were stored in line with legal requirements. Confidentiality of participants was maintained throughout the project.

In data analysis, (dis)agreement on active ingredient level was assessed. Areas of (dis)agreement were identified following an 80% consensus rule: ≥80% of respondents indicating agreement was considered consensus; ≥80% of respondents indicating an active ingredient to be redundant was considered reason to remove the respective active ingredient. If no consensus was reached (<80% agreement) or when alternatives were suggested, explanations provided were analyzed in-depth to reach a decision. This involved comparing provided justifications against treatment guidelines, the 8th WHO EMLc (2021) [28] and relevant literature. Since the initial core sets for the two age groups included many of the same active ingredients and disease areas, results were also cross-referenced between the two groups.

Upon completion of data analysis, adjustments were made to the initial selection based on the experts' input, and in alignment with the latest available treatment guidelines [29-31]. In a second consolidation round, experts that had previously participated and indicated to be willing to participate in a follow-up round were approached to take part in a second survey in April and May 2023. In the survey, experts were presented with the changes made to the initial selection and arguments for these changes. If alternatives previously suggested had not been added to

the selection, arguments were also provided. For each disease area, they were invited to indicate (dis)agreement. Due to the limited number of participants, all disagreements or comments were analyzed in-depth to reach a final selection of active ingredients.

Selecting child-appropriate formulations

Subsequently, specific formulations of active ingredients were selected because availability of age-appropriate formulations is required for safe and effective treatment. As there was little to no agreement in preferred dosage forms and strengths between participants, age-appropriate formulations were thus selected pragmatically. This selection was based on formulations as listed on the 9th WHO EMLc (2023) [32], the doses required per age group and practical assumptions (provided in Appendix 2). For instance, we deemed it unreasonable if a child had to take more than two solid oral dosage units during an intake moment. Recommended (maintenance) doses per day in children – used for its main indication in primary healthcare – were determined based on international treatment guidelines, or from the British National Formulary for Children (BNFC) if not specified in the respective guideline [33]. Weight-for-age charts were used to convert weight-based dosing to age-based dosing for the respective age groups [34-36]. Median weights of boys and girls within an age group were averaged to obtain a single measure per group. Medicines dosing based on body surface area were converted through an extra calculation step, using the Meeh type equation [37].

Formulations on the 9th WHO EMLc were then assessed for their appropriateness for the respective age group based on the required doses calculated and practical arguments (Appendix 2). Multiple formulations of an active ingredient could be appropriate for a single age group, to allow for variations in local market availability. Recommended doses were also used to estimate the number of units needed for treatment (NUNT), a child-specific parameter required to allow calculation of the indicator for children [8].

Results

A total of 11 priority disease areas were selected for each age group, with considerable overlap between age groups; diarrheal diseases, epilepsy, HIV/AIDS, iron-deficiency anemia, lower respiratory infections, malaria, meningitis, pain and palliative care, and tuberculosis were common across both groups. Measles and (congenital) syphilis were exclusively selected for young children, whereas asthma and migraine were unique for school-aged children. Upon examination of treatment guidelines, 25 (combinations of) active ingredients were selected (including therapeutic alternatives) for young children (**Table 1**), and 24 for school-aged children (**Table 2**). Some active ingredients were included under multiple disease areas.

Table 1 Initial and provisional selections of active ingredients for young children (aged 1 month to 5 years).

Initial selection	Provisional selection
Diarrheal diseases	
Oral rehydration salts	Oral rehydration salts
Zinc sulphate	Zinc sulphate
	Doxycycline AND/OR ciprofloxacin OR azithromycin[a]
Epilepsy	
Carbamazepine OR phenobarbital OR phenytoin	Carbamazepine OR phenobarbital OR phenytoin
Valproic acid	Valproic acid **OR lamotrigine**
Diazepam OR lorazepam OR midazolam	Diazepam OR lorazepam OR midazolam
HIV/AIDS	
Children <3 years: Abacavir + lamivudine + lopinavir/ritonavir OR zidovudine + lamivudine + lopinavir/ritonavir OR abacavir + lamivudine + nevirapine OR zidovudine + lamivudine + nevirapine	*Children 1 month-5 years*: **Abacavir + lamivudine + dolutegravir** OR abacavir + lamivudine + lopinavir/ritonavir
Children 3-5 years: Abacavir + lamivudine + efavirenz OR abacavir + lamivudine + nevirapine OR zidovudine + lamivudine + efavirenz OR zidovudine + lamivudine + nevirapine	
Anemia	
Ferrous salt	Ferrous salt
Mebendazole OR albendazole	Mebendazole OR albendazole
	Folic acid
	Hydroxocobalamin
Lower respiratory infections	
Amoxicillin	Amoxicillin **OR amoxicillin + clavulanic acid**
Ampicillin	Ampicillin
Benzylpenicillin	Benzylpenicillin **OR phenoxymethylpenicillin**
Gentamicin	Gentamicin
Ceftriaxone	Ceftriaxone **OR cefotaxime**
Malaria	
Artemether + lumefantrine OR artesunate + amodiaquine OR artesunate + mefloquine OR dihydroartemisinin + piperaquine OR artesunate + sulfadoxine-pyrimethamine	Artemether + lumefantrine OR artesunate + amodiaquine OR artesunate + mefloquine OR dihydroartemisinin + piperaquine OR artesunate + sulfadoxine-pyrimethamine **OR artesunate-pyronaridine**
Artesunate	Artesunate
Measles	
Retinol	Retinol
Meningitis	
Ceftriaxone	Ceftriaxone
Cefotaxime	Cefotaxime

Chloramphenicol + ampicillin	
Chloramphenicol + benzylpenicillin	
Pain and palliative care	
Paracetamol	Paracetamol
Ibuprofen	Ibuprofen
Morphine	Morphine
(congenital) syphilis	
Benzylpenicillin	Benzylpenicillin **OR** procaine benzylpenicillin
Procaine benzylpenicillin	**Benzathine penicillin**
Tuberculosis	
Ethambutol + isoniazid + pyrazinamide + rifampicin	Ethambutol + isoniazid + pyrazinamide + rifampicin

[a] Doxycycline or ciprofloxacin or azithromycin are appropriate choices for treatment of cholera. If doxycycline is selected for survey, either ciprofloxacin or azithromycin should also be added for treatment of dysentery.

(alternative) active ingredient added to selection active ingredient removed

Eight pediatricians and two pediatric pharmacists/pharmacologists participated in the first consultation round, amounting to five experts for each age group. Both of the pediatric pharmacists/pharmacologists were part of the school-aged group. The median years of experience was 17.5 (range 7-40 years). Experts had collectively gained experience across 13 countries from all income levels and across four WHO regions (African region, Region of the Americas, South-East Asian Region and European Region, see Appendix 3 for general characteristics of participants per age group).

Experts for both age groups were largely in agreement with the initial selection of active ingredients, with the exception of medicines for HIV/AIDS and lower respiratory infections (see **Table 3**). A considerable number of alternative active ingredients for addition to the core sets were suggested by the experts. Upon inspection of justifications provided for young children and review of relevant guidelines, chloramphenicol-based options were removed from the selection, four novel options were added (folic acid, hydroxocobalamin, benzathine penicillin and antibiotics for treatment of dysentery/cholera) and five therapeutic alternatives were added. Additionally, the separate treatment options for HIV/AIDS in children under or above three years of age were combined under a single option. Other than the addition of two novel treatment options for migraine, changes to the core set for school-aged children were largely similar to those for young children. Detailed argumentation for the changes in the selection, including justifications for not incorporating alternatives proposed by experts, can be found in Appendix 4.

Nine experts had previously indicated to be willing to participate in a follow-up round and were approached to take part again, of whom five completed the follow-up survey. These experts indicated overall agreement with the changes made to the core sets, with few areas of disagreement remaining (see Appendix 4). Specifically, participant 7 remarked that diarrheal

Table 2 Initial and provisional selections of active ingredients for school-aged children (aged 5 to 12 years).

Initial selection	Provisional selection
Asthma	
Salbutamol	Salbutamol
Budesonide	Budesonide
Diarrheal diseases	
Oral rehydration salts	Oral rehydration salts
Zinc sulphate	Zinc sulphate
	Doxycycline AND/OR ciprofloxacin OR azithromycin[a]
Epilepsy	
Carbamazepine OR phenobarbital OR phenytoin	Carbamazepine OR phenobarbital OR phenytoin
Valproic acid	Valproic acid **OR lamotrigine**
Diazepam OR lorazepam OR midazolam	Diazepam OR lorazepam OR midazolam
HIV/AIDS	
Abacavir + lamivudine + efavirenz OR abacavir + lamivudine + nevirapine OR zidovudine + lamivudine + efavirenz OR zidovudine + lamivudine + nevirapine	**Abacavir + lamivudine + dolutegravir** OR abacavir + lamivudine + lopinavir/ritonavir
Anemia	
Ferrous salt	Ferrous salt
Albendazole	**Mebendazole** OR albendazole
	Folic acid
	Hydroxocobalamin
Lower respiratory infections	
Amoxicillin	Amoxicillin **OR amoxicillin + clavulanic acid**
Ampicillin	Ampicillin
Benzylpenicillin	Benzylpenicillin OR **phenoxymethylpenicillin**
Gentamicin	Gentamicin
Ceftriaxone	Ceftriaxone OR **cefotaxime**
Malaria	
Artemether + lumefantrine OR artesunate + amodiaquine OR artesunate + mefloquine OR dihydroartemisinin + piperaquine OR artesunate + sulfadoxine-pyrimethamine	Artemether + lumefantrine OR artesunate + amodia-quine OR artesunate + mefloquine OR dihydroarte-misinin + piperaquine OR artesunate + sulfadoxine-pyrimethamine OR **artesunate-pyronaridine**
Artesunate	Artesunate
Meningitis	
Ceftriaxone	Ceftriaxone
Cefotaxime	Cefotaxime
Chloramphenicol + ampicillin	
Chloramphenicol + benzylpenicillin	
Migraine	
Ibuprofen	Ibuprofen
	Paracetamol

	Propranolol
Pain and palliative care	
Paracetamol	Paracetamol
Ibuprofen	Ibuprofen
Morphine	Morphine
Tuberculosis	
Ethambutol + isoniazid + pyrazinamide + rifampicin	Ethambutol + isoniazid + pyrazinamide + rifampicin

[a] Doxycycline or ciprofloxacin or azithromycin are appropriate choices for treatment of cholera. If doxycycline is selected for survey, either ciprofloxacin or azithromycin should also be added for treatment of dysentery.

(alternative) active ingredient added to selection active ingredient removed

diseases seldom have a bacterial origin and antibiotics would be irrational for this indication. Since four other participants indicated agreement with the addition of antibiotics, they were retained in the core set. Nonetheless, doxycycline was removed as an alternative for young children as it is to be used in children under 8 years in exceptional circumstances only [32]. A single participant – participant 10 – suggested that malaria treatment is situation specific, and with increasing resistance to artemisinin-based combination therapies (ACTs), the addition of quinine should be reconsidered. Because use of quinine is discouraged in the latest malaria treatment guidelines compared to ACTs [30], quinine was not added at this time. Two participants had reservations about the deletion of chloramphenicol combinations in the treatment of meningitis. Chloramphenicol had been removed out of an expert's concern for toxicity, but participants 4 and 7 expressed that this concern may extend to other active ingredients within the core set as well and may therefore not be sufficient justification for deletion. Since chloramphenicol is specified as second choice in bacterial meningitis on the WHO EMLc [32], and two other antibiotics are included in the core sets for this indication, we did not re-introduce it on the list at this time. Finally, participant number 7 also indicated disagreement with the addition of propranolol in the management of migraine but no arguments were provided. The final selections can be found in **Table 4** and **Table 5**.

For all active ingredients in the final selection, age-appropriate medicines were selected and the number of units needed for a course treatment was determined. These can be found in Appendix 5.

Table 3 Agreement of experts with initial selection of active ingredients and number of experts suggesting alternatives per disease area.

	Agreement with presented selection										Alternatives suggested by (n)	
	Young					School-aged					Young	School-aged
Participant no.	1	2	3	4	5	6	7	8	9	10		
Asthma											-	1
Diarrheal diseases											1	1
Epilepsy											2	2
HIV/AIDS (<3 years)											3	-
HIV/AIDS (>3 years)											3	2
Iron deficiency anemia											0	4
Lower respiratory infections											2	3
Malaria											2	2
Measles											0	-
Meningitis											1	1
Migraine											-	4
Pain and palliative care											0	0
Syphilis (congenital)											1	-
Tuberculosis											3	0

in agreement with selection
disagreement with selection
not completed by participant
not applicable to age group

LRI = lower respiratory infections.

Discussion

To enable the monitoring of access to medicines for children, this study proposes core sets of tracer medicines for two age groups with global implications and reflective of clinical practice. Although these tracer sets were primarily developed to enable monitoring of access to medicines for children as part of the SDG agenda, they hold broader relevance and can be used effectively in conjunction with other tools and methodologies such as the WHO/HAI methodology [38] and the forthcoming WHO Essential Medicines and Health Products Price and Availability Monitoring Mobile Application (MedMon) data collection tool [39]. The proposed core sets include medicines for the management of a range of childhood diseases which are together representative of access to child medicines in a country. With that, these tracer sets indirectly also contribute to other targets on the SDG agenda, such as the reduction of under-five mortality (target 3.2) and eradication of AIDS, tuberculosis and malaria (target 3.3) [5]. To accommodate different national contexts, the proposed tracer sets offer several flexibilities

through therapeutic alternatives and multiple acceptable formulations. The core sets for both age groups are largely similar in targeted disease areas and active ingredients, but critical differences arise from the selected age-appropriate formulations.

With the intention to encourage accountability at "the national, regional and global levels" and to "foster exchange of best practices and mutual learning", the United Nations (UN) have committed to systematic follow-up and review of agreed upon goals and targets through indicators [40]. To promote such global benchmarking of SDG indicator 3.b.3 there is a need for a universal methodology and by extension a standardized set of medicines for comparison. At the same time, it is acknowledged that for these indicators to be impactful for individual member states, the indicators must be country context-specific [41]. These inherent opposites cause friction, necessitating concessions to balance global comparability and national applicability. In the case of indicator 3.b.3, this is a delicate balance between creating a core set with global relevance, while also accommodating variations in local availability due to licensing and marketing differences, national best practices or guidelines, and local antimicrobial resistance patterns.

Table 4 Final selection of (combinations of) active ingredients for survey for young children (1 month-5 years).

No.	(Combinations of) active ingredients for survey	GHE code
	Anemia	**580 + 590**
1	Ferrous salt	
2	Mebendazole OR albendazole	
3	Folic acid	
4	Hydroxocobalamin	
	Diarrheal diseases	**110**
5	Oral rehydration salts	
6	Zinc sulphate	
7	Ciprofloxacin OR azithromycin	
	Epilepsy	**970**
8	Carbamazepine OR phenobarbital OR phenytoin	
9	Valproic acid OR lamotrigine	
10	Diazepam OR lorazepam OR midazolam	
	HIV/AIDS	**100**
11	Abacavir + lamivudine + dolutegravir OR abacavir + lamivudine + lopinavir/ritonavir	
	Lower respiratory infections	**370 + 390**
12	Amoxicillin OR amoxicillin + clavulanic acid	
13	Ampicillin	
14	Benzylpenicillin OR phenoxymethylpenicillin	
15	Gentamicin	
16a	Ceftriaxone OR cefotaxime	
	Malaria	**220**

17	Artemether + lumefantrine OR artesunate + amodiaquine OR artesunate + mefloquine OR dihydroartemisinin + piperaquine OR artesunate + sulfadoxine-pyrimethamine OR artesunate-pyronaridine	
18	Artesunate	
	Measles	**150 + 570**
19	Retinol	
	Meningitis	**170 + 370**
20[a]	Ceftriaxone	
21[a]	Cefotaxime	
	Pain and palliative care	**-**
22	Paracetamol	
23	Ibuprofen	
24	Morphine	
	(Congenital) syphilis	**50**
25	Benzylpenicillin OR procaine benzylpenicillin	
26	Benzathine penicillin	
	Tuberculosis	**30**
27	Ethambutol + isoniazid + pyrazinamide + rifampicin	

One active ingredient (or combination of active ingredients) must be selected per number (No.). A total of 26 active ingredients (or combination of active ingredients) are selected. Associated GHE codes are used when assigning weights according to burden of disease in calculating SDG indicator 3.b.3. Pain and palliative care is not associated with a GHE code.
GHE = Global Health Estimates.
[a] Ceftriaxone and cefotaxime are included for multiple indications.

Table 5 Final selection of (combinations of) active ingredients for survey for school-aged children (5-12 years).

No.	Final selection	GHE code
	Anemia	**580 + 590**
1	Ferrous salt	
2	Mebendazole OR albendazole	
3	Folic acid	
4	Hydroxocobalamin	
	Asthma	**1190**
5	Salbutamol	
6	Budesonide	
	Diarrheal diseases	**110**
7	Oral rehydration salts	
8	Zinc sulphate	
9[a]	Doxycycline AND/OR ciprofloxacin OR azithromycin	
	Epilepsy	**970**
10	Carbamazepine OR phenobarbital OR phenytoin	
11	Valproic acid OR lamotrigine	
12	Diazepam OR lorazepam OR midazolam	

	HIV/AIDS	**100**
13	Abacavir + lamivudine + dolutegravir OR abacavir + lamivudine + lopinavir/ritonavir	
	Lower respiratory infections	**390 + 370**
14	Amoxicillin OR amoxicillin + clavulanic acid	
15	Ampicillin	
16	Benzylpenicillin OR phenoxymethylpenicillin	
17	Gentamicin	
18[a]	Ceftriaxone OR cefotaxime	
	Malaria	**220**
19	Artemether + lumefantrine OR artesunate + amodiaquine OR artesunate + mefloquine OR dihydroartemisinin + piperaquine OR artesunate + sulfadoxine-pyrimethamine OR artesunate-pyronaridine	
20	Artesunate	
	Meningitis	**170 + 370**
21[b]	Ceftriaxone	
22[b]	Cefotaxime	
	Migraine	**990**
23[b]	Ibuprofen	
24[b]	Paracetamol	
25	Propranolol	
	Pain and palliative care	**-**
26[b]	Paracetamol	
27[b]	Ibuprofen	
28	Morphine	
	Tuberculosis	**30**
29	Ethambutol + isoniazid + pyrazinamide + rifampicin	

One active ingredient (or combination of active ingredients) must be selected per number (No.). A total of 26 (or 27 if doxycycline is selected) active ingredients (or combination of active ingredients) are selected. Associated GHE codes are used when assigning weights according to burden of disease in calculating SDG indicator 3.b.3. Pain and palliative care is not associated with a GHE code.
GHE = Global Health Estimates.
[a] Doxycycline or ciprofloxacin or azithromycin are appropriate choices for treatment of cholera. If doxycycline is selected for survey, either ciprofloxacin or azithromycin should also be added for treatment of dysentery.
[b] Included for multiple indications.

To foster global comparability of performance through international comparison, we utilized global tools as a foundation for the core sets. This involved global burden of disease estimates, complemented with treatment principles from widely accepted international treatment guidelines and selecting WHO EMLc listed medicines only. Although medicines of local importance may have been missed through this approach, the core sets are not meant to be exhaustive but rather to function as a tracer set that is indicative of overall access for children. However, it is worth noting that the selection of priority diseases was based on disease burden

(i.e. disability-adjusted life years) as opposed to disease prevalence. Childhood diseases with a high prevalence but low burden – such as eczema – may thus not be adequately captured. Similarly, global disease burden estimates for neonates are dominated by conditions such as preterm birth complications, birth asphyxia and birth trauma, neonatal sepsis and infections and congenital anomalies [16]. These are associated with high mortality, but are not representative of neonatal conditions managed at primary care level [42]. For example, vitamin K associated bleeding in neonates is not represented in the GHEs but considered standard of care for all newborns [43, 44]. As systematic data of neonatal conditions managed in primary care is lacking, neonates were excluded from the present study. We highlight this as an important field of future study.

We have attempted to increase national applicability of this indicator through several means. Firstly, insights from global pediatric experts were gathered to ensure that the tracer sets reflect their clinical practice. Moreover, possible acceptable alternatives were outlined in the core sets, granting countries the flexibility to select the most relevant active ingredients and formulations. Nonetheless, fundamental differences exist in disease burden across countries. This is particularly evident in the case of infectious diseases such as malaria, HIV/AIDS, and tuberculosis, of which the burden is relatively negligible in certain regions. SDG indicator 3.b.3 intends to correct for this by weighting for regional burden of diseases [6]. Whether this is the optimal approach to account for this remains to be determined [12]. Furthermore, the core sets comprise several medicines administered through injections. As the indicator targets primary healthcare facilities, it is important to note that in some countries these facilities may not be equipped or authorized to administer injections. Additionally, given the continuously evolving clinical insights, the availability of new age-appropriate formulations and revisions to guidelines, periodic review of the core sets is necessary. This will ensure that these core sets consistently reflecting these dynamics.

Although the present study provides the tools to start monitoring access to child medicines as part of the Sustainable Development Goal agenda, actual monitoring of access to child medicines – or medicines in general – requires the deficiencies in data to be addressed urgently [45]. Monitoring of access to medicines has previously failed as part of the Millennium Development Goals due to a lack of data [46], and this target was again omitted from the 2020 SDG progress report [47]. This data gap is not exclusive to indicator 3.b.3 [47], and calls for swift action from the international community to ensure that the important monitoring of SDGs can take place of all the indicators in the global indicator framework.

This study is subject to several limitations. Firstly, recruitment of pediatric care experts was complicated by the COVID-19 pandemic. Recruitment was therefore delayed and data was collected over a long period of time, primarily affecting the school-aged children group. This has had some impact on the initial consultation round – with treatment guidelines getting

updated in the meantime – but it is unlikely that this has affected the final results of this study, with a second consultation round having taken place in 2023. Secondly, a small number of experts per age group took part in this study, with limited attrition of experts in the second round. However, considering that the questions in our survey were not open-ended, but rather presented a predetermined selection of medicines to which the experts could indicate their agreement, the number of possible answers was restricted and less variability in responses was expected. Additionally, to ensure content validity, we cross-checked results across age groups for analogue disease areas and active ingredients. Thirdly, a pragmatic approach was used to select age-appropriate formulations for survey based on those listed on the WHO EMLc – whose 2023 update included a review of the age-appropriate formulations on the list [48] – and international treatment guidelines. This selection could not be validated by clinical experts as a pilot demonstrated that expert input was inconsistent. Finally, a few areas of disagreement remained after two consultation rounds with experts. These areas should be explored again in a periodic review of the core sets.

Conclusion

The monitoring of progress is a core element of the SDG agenda for 2023, and key in achieving progress in access to age-appropriate medicines. This study introduces two globally representative tracer sets of medicines that consider the particular needs of children, for the first time allowing systematic monitoring of access to pediatric medicines as part of the SDG agenda. Beyond this, the tracer sets can be used in conjunction with other existing tools and methodologies for measuring access to medicines. While these tracer sets are fundamental in the monitoring of access to child medicines, concerted efforts are needed to address the existing data deficiencies. Only through parallel endeavors can we draw nearer to achieving access to medicines for all.

Ethics statement

Ethical approval was obtained on 8 February 2021 from the Institutional Review Board (IRB) of the Department of Pharmaceutical Sciences of Utrecht University (reference number UPF2021).

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Supplementary materials

Appendix 1: Online survey questions

These surveys were conducted online with LimeSurvey®.

Young children

Title: A methodology for measuring access to medicines for children

Description: With this questionnaire, we will validate the selection of a core set of essential medicines for young children.

Welcome text

Dear participant, thank you for helping us by filling in this questionnaire.
This questionnaire is part of a project called 'A methodology for measuring access to essential medicines for children'. You are being asked to take part in this research project because you are an expert on the use of medicines in neonates or children. The questionnaire will take approximately 25 minutes of your time.
In case of questions, problems or remarks, you may contact Iris Joosse: [*email*].

Informed consent

I have been invited to participate in a research project, titled "Methodology for measuring access to essential medicines for children". I am being asked to take part in this project because I am an expert on the use of medicines in neonates or children.

I have read the information. I have had the opportunity to ask questions about it and any questions I have asked, have been answered to my satisfaction. I consent voluntarily to be a participant in this study. I am aware that I can withdraw at any point in time without negative consequences, and without providing any explanation.

I am aware that participation in this study is confidential. I consent to the use of my personal data in line with legal requirements such as the Data Protection Fundamental Directive in force in the EU for all EU personal data. I give permission for storing the research data for a period of ten years.

☐ I consent to participate in this study

Identifying Information

First name(s):
Last name:
Institution:
Position:
Expertise: *[Choose pediatrician OR neonatologist OR specialized pharmacist]*
Country:
Email contact:

Introduction

A key element in achieving universal health coverage (UHC) is the provision of access to medicines for all, as described in target 3.b. of the Sustainable Development Goals (SDGs)[1]. To monitor countries' performance and progress on improving access to medicines, SDG indicator 3.b.3. has been developed (formula 1)[2]:

$$SDG_{3.b.3.} = \frac{Facilities\ with\ available\ and\ affordable\ basket\ of\ medicines\ (n)}{Surveyed\ Facilities\ (n)} \quad (1)$$

The indicator includes three core concepts used for calculating indicator 3.b.3:

1) A core set of globally relevant essential medicines
2) Availability of medicines
3) Affordability of medicines

However, SDG indicator 3.b.3 has been developed and piloted for measuring access to medicines in general and is predominantly targeted at adults. The methodology as has been developed for adults does not necessarily apply to pediatric medicines. Having an indicator that can reflect the situation for children is essential, especially in the Sub-Saharan setting where a large part of the population consists of children under the age of fifteen.

Objectives

In the present study, we are adapting the original SDG indicator 3.b.3. computation methodology so that it can be used to calculate access to medicines for children. As part of creating a standardized methodology for measuring access to medicines for children, we have defined a core set of globally relevant essential (pediatric) medicines, that are indicative of the access to medicines in primary health care. The goal of this questionnaire is to validate our selection of medicines for young children with your expertise.

Validating the selection of active ingredients

The core set of essential medicines for children addresses the health needs of children for a variety of globally prevalent childhood diseases. Priority medicines for each disease are selected from the WHO model List of Essential Medicines for children (EMLc) 2019. Selection of active ingredients was based on three criteria:

[1] United Nations. Sustainable Development Goals Knowledge Platform. URL: sustainabledevelopment.un.org/?menu=1300.
[2] United Nations Statistics Division. SDG Indicators Metadata repository. 2019. URL: https://unstats.un.org/sdgs/metadata?Text=&Goal=3&Target=3.b.

1) Active ingredients are first-choice medicines, according to international treatment guidelines[3];
2) Active ingredients are not vaccines or non-pharmaceutical products (e.g. medicinal gas);
3) Cold chain management is not required for the active ingredient.

In this part of the questionnaire, we present our selection of active ingredients for young children. We ask you to indicate if you agree with our selection and if any active ingredients are redundant or missing.

Note: the core set of globally relevant essential medicines should be **indicative** of access to medicines for the majority of children/cases. It is **not** exhaustive or meant to cover all cases.

Start survey

In the tables below, the selection of active ingredients for eleven priority diseases in young children is shown. Column 1 shows the selection of active ingredients as made by the researchers. Column 2 shows alternative active ingredients included on the Essential Medicines List for Children (EMLc), that can be used to treat the condition.

Diarrhoeal diseases

Selected first-choice medicines	Alternative medicines on EMLc
Oral rehydration salts Zinc sulphate	Sulfamethoxazole + trimethoprim Azithromycin Cefotaxime Ceftriaxone Ciprofloxacin

1. Do you agree with the selection of active ingredients for diarrhoeal diseases?
   Yes
   No → If no, please indicate which medicine(s) is/are redundant and why.

2. In your opinion, are there any other medicines from the second column that should be considered essential first-choice? You may choose alternative active ingredients not shown above.
   Yes → If yes, please indicate which and why.
   No

Epilepsy

Selected first-choice medicines	Alternative medicines on EMLc
Carbamazapine or phenobarbital or phenytoin Valproic acid Diazepam or lorazepam or midazolam	Lamotrigine

3. Do you agree with the selection of active ingredients for epilepsy?

[3] WHO treatment guidelines were adhered to, if available.

Yes
No → If no, please indicate which medicine(s) is/are redundant and why.

4. In your opinion, are there any other medicines from the second column that should be considered essential first-choice? You may choose alternative active ingredients not shown above.
   Yes → If yes, please indicate which and why.
   No

HIV/AIDS

Selected first-choice regimens	Alternative medicines on EMLc
Children < 3 years	
Abacavir + lamivudine + lopinavir/ritonavir OR Zidovudine + lamivudine + lopinavir/ritonavir OR Abacavir + lamivudine + nevirapine OR Zidovudine + lamivudine + nevirapine	Ritonavir Raltegravir
Children >3 years	
Abacavir + lamivudine + efivarenz OR Abacavir + lamivudine + nevirapine OR Zidovudine + lamivudine + efivarenz OR Zidovudine + lamivudine + nevirapine	Atazanavir Darunavir Ritonavir Dolutegravir Raltegravir

5. Do you agree with the selection of active ingredients for HIV/AIDS for children <3 years?
   Yes
   No → If no, please indicate which medicine(s) is/are redundant and why.

6. In your opinion, are there any other medicines from the second column that should be considered essential first-choice in children <3 years? You may choose alternative active ingredients not shown above.
   Yes → If yes, please indicate which and why.
   No

7. Do you agree with the selection of active ingredients for HIV/AIDS for children >3 years?
   Yes
   No → If no, please indicate which medicine(s) is/are redundant and why.

8. In your opinion, are there any other medicines from the second column that should be considered essential first-choice in children >3 years? You may choose alternative active ingredients not shown above.
   Yes → If yes, please indicate which and why.
   No

Iron-deficiency anemia

Selected first-choice medicines	Alternative medicines on EMLc
Ferrous salt Mebendazole or albendazole	Folic acid Hydroxocobalamin

9. Do you agree with the selection of active ingredients for iron-deficiency anemia?
   Yes
   No → If no, please indicate which medicine(s) is/are redundant and why.

10. In your opinion, are there any other medicines from the second column that should be considered essential first-choice? You may choose alternative active ingredients not shown above.
    Yes → If yes, please indicate which and why.
    No

Lower respiratory infections

Selected first-choice regimens	Alternative medicines on EMLc
Amoxicillin Ampicillin Benzylpenicillin Gentamicin Ceftriaxone	Amoxicillin + clavulanic acid Phenoxymethylpenicillin Cefotaxime Piperacillin + tazobactam

11. Do you agree with the selection of active ingredients for lower respiratory infections?
    Yes
    No → If no, please indicate which medicine(s) is/are redundant and why.

12. In your opinion, are there any other medicines from the second column that should be considered essential first-choice? You may choose alternative active ingredients not shown above.
    Yes → If yes, please indicate which and why.
    No

Malaria

Selected first-choice medicines	Alternative medicines on EMLc
Artemether + lumefantrine Artesunate + amodiaquine Artesunate + mefloquine Dihydroartemisinin + piperaquine Artesunate + Sulfadoxine-pyrimethamine Artesunate	Artesunate + pyronaridine tetraphosphate Chloroquine Doxycycline Primaquine Quinine

13. Do you agree with the selection of active ingredients for malaria?
    Yes
    No → If no, please indicate which medicine(s) is/are redundant and why.

14. In your opinion, are there any other medicines from the second column that should be considered essential first-choice? You may choose alternative active ingredients not shown above.
    Yes → If yes, please indicate which and why.
    No

Measles

Selected first-choice medicines	Alternative medicines on EMLc
Retinol	X

15. Do you agree with the selection of active ingredients for measles?
    Yes
    No → If no, please indicate which medicine(s) is/are redundant and why.

16. In your opinion, are there any other medicines from the second column that should be considered essential first-choice? You may choose alternative active ingredients not shown above.
    Yes → If yes, please indicate which and why.
    No

Meningitis

Selected first-choice medicines	Alternative medicines on EMLc
Ceftriaxone Cefotaxime Chloramphenicol + ampicillin Chloramphenicol + benzylpenicillin	Amoxicillin Meropenem

17. Do you agree with the selection of active ingredients for meningitis?
    Yes
    No → If no, please indicate which medicine(s) is/are redundant and why.

18. In your opinion, are there any other medicines from the second column that should be considered essential first-choice? You may choose alternative active ingredients not shown above.
    Yes → If yes, please indicate which and why.
    No

Pain and palliative care

Selected first-choice medicines	Alternative medicines on EMLc
Paracetamol Ibuprofen Morphine	Methadone

19. Do you agree with the selection of active ingredients for pain and palliative care?
    Yes
    No → If no, please indicate which medicine(s) is/are redundant and why.

20. In your opinion, are there any other medicines from the second column that should be considered essential first-choice? You may choose alternative active ingredients not shown above.
    Yes → If yes, please indicate which and why.
    No

(Congenital) syphilis

Selected first-choice medicines	Alternative medicines on EMLc
Benzylpenicillin Procaine benzylpenicillin	Benzathine benzylpenicillin

21. Do you agree with the selection of active ingredients for syphilis?
    Yes
    No → If no, please indicate which medicine(s) is/are redundant and why.

22. In your opinion, are there any other medicines from the second column that should be considered essential first-choice? You may choose alternative active ingredients not shown above.
    Yes → If yes, please indicate which and why.
    No

Tuberculosis

Selected first-choice medicines	Alternative medicines on EMLc
Ethambutol + isoniazid + pyrazinamide + rifampicin	Rifapentine

23. Do you agree with the selection of active ingredients for tuberculosis?
    Yes
    No → If no, please indicate which medicine(s) is/are redundant and why.

24. In your opinion, are there any other medicines from the second column that should be considered essential first-choice? You may choose alternative active ingredients not shown above.
    Yes → If yes, please indicate which and why.
    No

Final questions

	Yes	No
25. I give permission to be acknowledged by name in the final publication of this study	☐	☐
26. I want to receive the final results of this study	☐	☐
27. If consensus is not reached after the first round of surveys, the study personnel may contact me for participation in an online focus group:	☐	☐

Thank you for your participation.

School-aged children

Title: A methodology for measuring access to medicines for children

Description: With this questionnaire, we will validate the selection of a core set of essential medicines for school-aged children.

Welcome text

Dear participant, thank you for helping us by filling in this questionnaire.

This questionnaire is part of a project called 'a methodology for measuring access to essential medicines for children'. You are being asked to take part in this research project because you are an expert on the use of medicines in neonates or children. The questionnaire will take approximately 25 minutes of your time.

In case of questions, problems or remarks, you may contact Iris Joosse: [*email*].

Informed consent

i have been invited to participate in a research project, titled "methodology for measuring access to essential medicines for children". I am being asked to take part in this project because i am an expert on the use of medicines in neonates or children.

I have read the information. I have had the opportunity to ask questions about it and any questions i have asked, have been answered to my satisfaction. I consent voluntarily to be a participant in this study. I am aware that i can withdraw at any point in time without negative consequences, and without providing any explanation.

I am aware that participation in this study is confidential. I consent to the use of my personal data in line with legal requirements such as the data protection fundamental directive in force in the EU for all EU personal data. I give permission for storing the research data for a period of ten years.

☐ I consent to participate in this study

Identifying information

First name(s):
Last name:
Institution:
Position:
Expertise: [Choose pediatrician OR neonatologist OR specialized pharmacist]
Country:
Email contact:

Introduction

A key element in achieving universal health coverage (UHC) is the provision of access to medicines for all, as described in target 3.b. of the Sustainable Development Goals (SDGs)[4]. To monitor countries' performance and progress on improving access to medicines, SDG indicator 3.b.3. has been developed (formula 1)[5]:

$$SDG_{3.b.3.} = \frac{Facilities\ with\ available\ and\ affordable\ basket\ of\ medicines\ (n)}{Surveyed\ Facilities\ (n)}$$

The indicator includes three core concepts used for calculating indicator 3.b.3:

1) A core set of globally relevant essential medicines
2) Availability of medicines
3) Affordability of medicines

However, SDG indicator 3.b.3 has been developed and piloted for measuring access to medicines in general and is predominantly targeted at adults. The methodology as has been developed for adults does not necessarily apply to pediatric medicines. Having an indicator that can reflect the situation for children is essential, especially in the Sub-Saharan setting where a large part of the population consists of children under the age of fifteen.

Objectives

In the present study, we are adapting the original SDG indicator 3.b.3. computation methodology so that it can be used to calculate access to medicines for children. As part of creating a standardized methodology for measuring access to medicines for children, we have defined a core set of globally relevant essential (pediatric) medicines, that are indicative of the access to medicines in primary health care. The goal of this questionnaire is to validate our selection of medicines for school-aged children with your expertise.

Validating the selection of active ingredients

The core set of essential medicines for children addresses the health needs of children for a variety of globally prevalent childhood diseases. Priority medicines for each disease are selected from the WHO model List of Essential Medicines for children (EMLc) 2019. Selection of active ingredients was based on three criteria:

[4] United Nations. Sustainable Development Goals Knowledge Platform. URL: sustainabledevelopment.un.org/?menu=1300.
[5] United Nations Statistics Division. SDG Indicators Metadata repository. 2019. URL: https://unstats.un.org/sdgs/metadata?Text=&Goal=3&Target=3.b.

1) Active ingredients are first-choice medicines, according to international treatment guidelines[6];
2) Active ingredients are not vaccines or non-pharmaceutical products (e.g. medicinal gas);
3) Cold chain management is not required for the active ingredient.

In this part of the questionnaire, we present our selection of active ingredients for school-aged children. We ask you to indicate if you agree with our selection and if any active ingredients are redundant or missing.

Note: the core set of globally relevant essential medicines should be **indicative** of access to medicines for the majority of children/cases. It is **not** exhaustive or meant to cover all cases.

Start of questions

In the tables below, the selection of active ingredients for eleven priority diseases in school-aged children is shown. Column 1 shows the selection of active ingredients as made by the researchers. Column 2 shows alternative active ingredients included on the Essential Medicines List for Children (EMLc), that can be used to treat the condition.

Asthma

Selected first-choice medicines	Alternative medicines on EMLc
Salbutamol or other short-acting beta-agonist inhaler Budesonide or other corticosteroid inhaler	Epinephrine (adrenaline)

1. Do you agree with the selection of active ingredients for asthma?
   Yes
   No, because…

2. In your opinion, are any alternative medicines that are on the EMLc missing from the selection?
   Yes, because…
   No

Diarrhoeal diseases

Selected first-choice medicines	Alternative medicines on EMLc
Oral rehydration salts Zinc sulphate	Sulfamethoxazole + trimethoprim Azithromycin Cefotaxime Ceftriaxone Ciprofloxacin

3. Do you agree with the selection of active ingredients for diarrhoeal diseases?
   Yes

[6] WHO treatment guidelines were adhered to, if available.

No, because…

4. In your opinion, are any alternative medicines that are on the EMLc missing from the selection?
   Yes, because…
   No

Epilepsy

Selected first-choice medicines	Alternative medicines on EMLc
Carbamazapine or phenobarbital or phenytoin Valproic acid Diazepam or lorazepam or midazolam	Lamotrigine

5. Do you agree with the selection of active ingredients for epilepsy?
   Yes
   No, because…

6. In your opinion, are any alternative medicines that are on the EMLc missing from the selection?
   Yes, because…
   No

HIV/AIDS

Selected first-choice regimens	Alternative medicines on EMLc
Abacavir + lamivudine + efivarenz Abacavir + lamivudine + nevirapine Zidovudine + lamivudine + efivarenz Zidovudine + lamivudine + nevirapine	Atazanavir Darunavir Ritonavir Dolutegravir Raltegravir

7. Do you agree with the selection of active ingredients for HIV/AIDS?
   Yes
   No, because…

8. In your opinion, are any alternative medicines that are on the EMLc missing from the selection?
   Yes, because…
   No

Iron-deficiency anemia

Selected first-choice medicines	Alternative medicines on EMLc
Ferrous salt Albendazole	Folic acid Hydroxocobalamin

9. Do you agree with the selection of active ingredients for iron-deficiency anemia?
   Yes
   No, because…

10. In your opinion, are any alternative medicines that are on the EMLc missing from the selection?
    Yes, because…
    No

Lower respiratory infections

Selected first-choice regimens	Alternative medicines on EMLc
Amoxicillin	Amoxicillin + clavulanic acid
Ampicillin	Doxycycline
Benzylpenicillin	Phenoxymethylpenicillin
Gentamicin	Cefotaxime
Ceftriaxone	Piperacillin + tazobactam

11. Do you agree with the selection of active ingredients for lower respiratory infections?
    Yes
    No, because…

12. In your opinion, are any alternative medicines that are on the EMLc missing from the selection?
    Yes, because…
    No

Malaria

Selected first-choice medicines	Alternative medicines on EMLc
Artemether + lumefantrine	Artesunate + pyronaridine tetraphosphate
Artesunate + amodiaquine	Chloroquine
Artesunate + mefloquine	Doxycycline
Dihydroartemisinin + piperaquine	Primaquine
Artesunate + Sulfadoxine-pyrimethamine	Quinine
Artesunate	

13. Do you agree with the selection of active ingredients for malaria?
    Yes
    No, because…

14. In your opinion, are any alternative medicines that are on the EMLc missing from the selection?
    Yes, because…
    No

Meningitis

Selected first-choice medicines	Alternative medicines on EMLc
Ceftriaxone Cefotaxime Chloramphenicol + ampicillin Chloramphenicol + benzylpenicillin	Amoxicillin Meropenem

15. Do you agree with the selection of active ingredients for meningitis?
    Yes
    No, because…

16. In your opinion, are any alternative medicines missing from the selection?
    Yes, because…
    No

Migraine

Selected first-choice medicines	Alternative medicines on EMLc
Ibuprofen	Paracetamol Propranolol

17. Do you agree with the selection of active ingredients for migraine?
    Yes
    No, because…

18. In your opinion, are any alternative medicines that are on the EMLc missing from the selection?
    Yes, because…
    No

Pain and palliative care

Selected first-choice medicines	Alternative medicines on EMLc
Paracetamol Ibuprofen Morphine	Methadone

19. Do you agree with the selection of active ingredients for pain and palliative care?
    Yes
    No, because…

20. In your opinion, are any alternative medicines that are on the EMLc missing from the selection?
    Yes, because…
    No

Tuberculosis

Selected first-choice medicines	Alternative medicines on EMLc
Ethambutol + isoniazid + pyrazinamide + rifampicin	Rifapentine

21. Do you agree with the selection of active ingredients for tuberculosis?
    Yes
    No, because…

22. In your opinion, are any alternative medicines that are on the EMLc missing from the selection?
    Yes, because…
    No

Final questions

	Yes	No
23. I give permission to be acknowledged by name in the final publication of this study	☐	☐
24. I want to receive the final results of this study	☐	☐
25. If consensus is not reached after the first round of surveys, the study personnel may contact me for participation in an online focus group:	☐	☐

Thank you for your participation.

Appendix 2: Pragmatic assumptions in selecting age-appropriate formulations

As the group represents a range of ages and weights, required doses were also calculated for the smallest and biggest child in the respective age group. These lower and upper acceptable limits were used to make an approximation of appropriate dosing and the number of required units for a course treatment (number of units needed for treatment, NUNT). If there are no alternative dosage forms on the WHO EMLc, the respective dosage form is automatically considered appropriate.

Table S1 Pragmatic assumptions in selecting age-appropriate formulations.

Dosage form	Assumptions
Solid oral dosage forms	Solid oral dosage forms cannot be split[a].
	A minimum of 1 and a maximum of 2 units are administered per recommended intake moment.
Oral liquids	A minimum of 0.5 and a maximum of 10 ml are administered per recommended intake moment.
	Required millilitres (between 1-10 ml) are rounded to whole numbers.
Rectal dosage forms	Administration of a single unit only.
	Rectal dosage forms cannot be split.
Parenteral dosage forms	If oral or rectal dosage forms are available on the WHO EMLc, they are given preference over parenteral dosage forms.
	At least 1 vial/ampoule is used per day. A vial/ampoule can be used for multiple intake moments on the same day.

[a] Although splitting may be an appropriate alternative in individual cases or when no other dosage form is available, it is not the preferred option as manipulation risks administrating toxic or sub-therapeutic doses through inaccurate dosing, as well as dosing errors.

Appendix 3: General characteristics of participants

Table S2 General characteristics of participants.

	Young children (n)	School-aged children (n)
Expertise		
Paediatrician	5	3
Paediatric pharmacist/ pharmacologist	0	2
WHO region where experience was gained		
African region	3	3
Region of the Americas	1	0
South-East Asian region	0	2
European region	2	1
World Bank income classification[a]		
Low-income country	3	1
Lower-middle income country	1	4
Upper-middle income country	2	0
High-income country	3	1

[a] Income classification 2022-2023.

Note: experts could have gained experience across multiple countries.

Appendix 4: Justifications in (un)alterations in initial core sets of medicines and results of consolidation round with experts

The tables below provide justification for changes and non-changes made to the initial selections of active ingredients, as also provided to experts in the consolidation round.

Table S3 Justifications for (un)alterations in initial selection for young children.

Disease area	Arguments for (un)alternations in initial selection for young children
Diarrheal diseases	To address prevalent diarrheal diseases with a bacterial origin (e.g. cholera, dysentery), several **antibacterial** options were added to the selection.
Epilepsy	**Lamotrigine** was added as an alternative to valproic acid, particularly for refractory epilepsy and in case of drug interactions. Although **levetiracetam** may be essential in specific populations, this medicine is currently not included in the WHO Model List of Essential Medicines for Children (one of our selection criteria). It is therefore also not included in the present selection.
HIV/AIDS	The initial selection was changed to reflect the first-choice medicines as described in the 2021 updated WHO HIV/AIDS guidelines. A separate basket for children under and over 3 years of age is no longer required.
Anaemia	To address anaemias other than iron-deficiency anaemia only, **folic acid** and **hydroxocobalamin** were added to the selection.
Lower respiratory infections	**Amoxicillin-clavulanic acid** was added as alternative to amoxicillin alone, as it may provide wider coverage. **Phenoxymethylpenicillin** was added as an oral alternative to **benzylpenicillin**. **Cefotaxime** was added as alternative to **ceftriaxone** for several reasons, because it only requires once-daily dosing and it may be a more affordable option. Additionally, there is registered microbial resistance to ceftriaxone.
Malaria	A sixth **ACT** alternative was added to reflect the 2022 updates to the WHO Malaria guidelines. **Quinine** was not added as its use is discouraged compared to ACTs in recent treatment guidelines. **Primaquine** is appropriate for use in specific cases only, and is therefore not considered one of the core medicines in malaria.
Meningitis	**Chloramphenicol** combinations were removed due to toxicity reports.
Congenital syphilis	**Benzylpenicillin** and **procaine benzylpenicillin** are now considered alternatives. **Benzathine penicillin** was added for treating asymptomatic syphilis.

ACT = Artemisinin-based combination therapy.

Table S4 Justifications for (non) changes in initial selection for school-aged children.

Disease area	Arguments for (un)alterations in initial selection for school-aged children
Diarrheal diseases	To address prevalent diarrheal diseases with a bacterial origin (e.g. cholera, dysentery), several **antibacterial** options were added to the selection.
Epilepsy	**Lamotrigine** was added as an alternative to valproic acid, particularly for refractory epilepsy and in case of drug interactions. Although **levetiracetam** may be essential in specific populations, this medicine is currently not included in the WHO Model List of Essential Medicines for Children (one of our selection criteria). It is therefore also not included in the present selection.
HIV/AIDS	The initial selection was changed to reflect the first-choice medicines as described in the 2021 updated WHO HIV/AIDS guidelines, and those available on the WHO EMLc 2021
Anaemia	To address anaemias other than iron-deficiency anaemia only, **folic acid** and **hydroxocobalamin** were added to the selection. **Mebendazole** was added as an alternative to albendazole.
Lower respiratory infections	**Amoxicillin-clavulanic acid** was added as alternative to amoxicillin alone, as it may provide wider coverage. **Phenoxymethylpenicillin** was added as an oral alternative to **benzylpenicillin**. **Cefotaxime** was added as alternative to **ceftriaxone** for several reasons, because it only requires once-daily dosing and it may be a more affordable option. Additionally, there is registered microbial resistance to ceftriaxone.
Malaria	A sixth **ACT** alternative was added to reflect the 2022 updates to the WHO Malaria guidelines. **Quinine** was not added as its use is discouraged compared to ACTs in recent treatment guidelines. **Primaquine** is appropriate for use in specific cases only, and is therefore not considered one of the core medicines in malaria.
Meningitis	**Chloramphenicol** combinations were removed due to toxicity reports.
Migraine	**Paracetamol** was added to the selection for acute migraine attacks, **propranolol** for potential prophylaxis.

ACT = Artemisinin-based combination therapy.

Table S5 Agreement of experts with changes made to the selection of active ingredients.

Disease area	Active ingredient	Type of change	Young		School-aged		
		Participant no.	2	4	6	7	10
Diarrheal diseases	Doxycycline, ciprofloxacin and azithromycin	Added to the selection (as alternatives)					
Epilepsy	Lamotrigine	Added to the selection as alternative					
	Levetiracetam	Expert suggestion not adopted					
HIV/AIDS	Abacavir + lamivudine + dolutegravir and abacavir + lamivudine + lopinavir/ritonavir	Replacing previous selection					
Anaemia	Folic acid	Added to the selection					
	Hydroxocobalamin	Added to the selection					
	Mebendazole	Added to the selection as alternative					
LRI	Amoxicillin-clavulanic acid	Added to the selection					
	Phenoxymethylpenicillin	Added to the selection					
	Cefotaxime	Added to the selection					
Malaria	Artesunate-pyronaridine	Added to the selection					
	Quinine	Expert suggestion not adopted					
	Primaquine	Expert suggestion not adopted					
Meningitis	Chloramphenicol	Removed from selection					
Migraine	Paracetamol	Added to the selection					
	Propranolol	Added to the selection					
Congenital syphilis	Benzylpenicillin and procaine benzylpenicillin	Combined as alternatives					
	Benzathine penicillin	Added to the selection					

in agreement with change(s)
disagreement with change(s)
not completed by participant
not applicable to age group

LRI = lower respiratory infections.

Appendix 5: Age-appropriate formulations and associated number of units needed for treatment

Table S6 Appropriate formulations and associated number of units needed for treatment for young children (1 month-5 years).

Active ingredient	Appropriate formulations	NUNT
Abacavir/lamivudine	Tablet (dispersible, scored) 120/60 mg	60 units
Albendazole	Tablet (chewable, scored) 400 mg	1 unit
Amoxicillin	Powder for oral liquid 125 mg/5 ml	100 ml
	Powder for oral liquid 250 mg/5 ml	90 ml
	Solid oral dosage form 250 mg	20 units
	Solid oral dosage form 500 mg	10 units
	Tablet (dispersible, scored) 250 mg	20 units
	Tablet (dispersible, scored) 500 mg	10 units
Amoxicillin/clavulanic acid	Powder for oral liquid 125/31.25 mg/5 ml	100 ml
	Powder for oral liquid 250/62.5 mg/5 ml	90 ml
	Tablet 500/125 mg	10 units
	Tablet (dispersible) 200/28.5 mg	20 units
	Tablet (dispersible) 250/62.5 mg	20 units
Ampicillin	Powder for injection 500 mg in vial	20 vials
Artemether/lumefantrine	Tablet 20/120 mg	6 units
	Tablet (dispersible) 20/120 mg	6 units
Artesunate	Injection, ampoule containing 60 mg	1 ampoule
	Rectal dosage form 50 mg	1 unit
	Tablet 50 mg†	3 units
Artesunate/amodiaquine	Tablet 25/67.5 mg	6 units
	Tablet 50/135 mg	3 units
Artesunate/mefloquine	Tablet 25/55	6 units
Artesunate/pyronaridine	Granules 20/60 mg	6 sachets
Azithromycin	Solid oral dosage form 250 mg	1 unit
	Powder for oral liquid 200 mg/5 ml	6 ml
Benzathine penicillin	Powder for injection 1.2 million IU (900 mg) in vial	1 vial
Benzylpenicillin	Powder for injection 600 mg (1 million IU) in vial	20 vials
	Powder for injection 3 g (5 million IU) in vials	10 vials
Carbamazepine	Oral liquid 100 mg/5 ml	240 ml
	Tablet (chewable) 100 mg	60 units
	Tablet (chewable) 200 mg	30 units
	Tablet (scored) 100 mg	60 units
	Tablet (scored) 200 mg	30 units
Cefotaxime	Powder for injection 500 mg in vial	28 vials
	Powder for injection 1 g in vial	14 vials

Ceftriaxone	Powder for injection 500 mg in vial	14 vials
	Powder for injection 1 g in vial	7 vials
Ciprofloxacin	Oral liquid 250 mg/5 ml	18 ml
	Solid oral dosage form 100 mg	12 units
	Solid oral dosage form 250 mg	6 units
Diazepam	Rectal gel 5 mg/ml in 0.5 ml rectal delivery system	1 tube
	Rectal solution 2 mg/ml in 1.25 ml rectal tube	1 tube
	Rectal solution 2 mg/ml in 2.5 ml rectal tube	1 tube
Dihydroartemisinin/piperaquine	Tablet 20/160 mg	6 units
	Tablet 40/320 mg	3 units
Dolutegravir	Tablet (dispersible, scored) 10 mg	60 units
Ethambutol	Tablet 100 mg	60 units
	Tablet (dispersible) 100 mg	60 units
Ferrous salt	Oral liquid equivalent to 25 mg iron/ml	90 ml
Folic acid	Tablet 1 mg	30 units
	Tablet 5 mg	30 units
Gentamicin	Injection 40 mg/ml in 2 ml vial	5 vials
Hydroxocobalamin	Injection 1 mg in 1 ml ampoule	4 ampoules
Ibuprofen	Oral liquid 100 mg/5 ml	480 ml
	Oral liquid 200 mg/5 ml	240 ml
Isoniazid	Tablet 100 mg	30 units
	Tablet (dispersible) 100 mg	30 units
Isoniazid/pyrazinamide/rifampicin[c]	Tablet (dispersible) 50/150/75 mg	60 units
Isoniazid/rifampicin[c]	Tablet (dispersible) 50/75 mg	60 units
Lamotrigine	Tablet 25 mg	60 units
	Tablet 50 mg	30 units
	Tablet 100 mg	30 units
	Tablet (chewable, dispersible) 25 mg	60 units
	Tablet (chewable, dispersible) 50 mg	30 units
	Tablet (chewable, dispersible) 100 mg	30 units
Lopinavir/ritonavir	Tablet (heat stable) 100/25 mg	60 units
Lorazepam	Injection 2 mg/ml in 1 ml ampoule	1 ampoule
Mebendazole	Tablet (chewable) 100 mg	6 units
	Tablet (chewable) 500 mg	1 unit
Midazolam	Solution for oromucosal administration 5 mg/ml in 1 ml pre-filled syringe	1 syringe
	Solution for oromucosal administration 5 mg/ml in 1.5 ml pre-filled syringe	1 syringe
	Solution for oromucosal administration 10 mg/ml in 0.5 ml pre-filled syringe	1 syringe

	Solution for oromucosal administration 10 mg/ml in 0.75 ml pre-filled syringe	1 syringe
	Injection 1 mg/ml in 5 ml vial[a]	1 vial
	Injection 5 mg/ml in 1 ml vial[a]	1 vial
Morphine	Granules (slow release) 20 mg	30 sachets
	Oral liquid 10 mg/5 ml	180 ml
	Tablet (slow release) 10 mg	30 units
	Tablet (slow release) 20 mg	30 units
Oral rehydration salts (ORS)	Powder for dilution in 200 ml	5 sachets
	Powder for dilution in 500 ml	2 sachets
	Powder for dilution in 1 L	1 sachet
Phenobarbital	Oral liquid 15 mg/5 ml	300 ml
Paracetamol	Oral liquid 120 mg/5 ml or 125 mg/5 ml	840 ml
	250 mg/5 ml	360 ml
	Suppository 100 mg	120 units
	Tablet (dispersible) 10 mg	240 units
	Tablet 15 mg	120 units
	Tablet 30 mg	60 units
	Tablet 60 mg	30 units
	Tablet 100 mg	30 units
Phenoxymethylpenicillin	Powder for oral liquid 250 mg/5 ml	60 ml
	Solid oral dosage form 250 mg	20 units
Phenytoin	Oral liquid 30 mg/5 ml	420 ml
	Solid oral dosage form 25 mg	90 units
	Solid oral dosage form 50 mg	60 units
	Tablet (chewable) 50 mg	60 units
Procaine benzylpenicillin	Powder for injection 1 g (1 million IU) in vial	10 vials
Pyrazinamide	Tablet 400 mg	30 units
	Tablet 500 mg	30 units
Retinol	Capsule 100 000 IU	4 units
	Capsule 200 000 IU	2 units
	Oral oily solution in multidose dispenser	2 ml
Rifampicin	Oral liquid 20 mg/ml	240 ml
	Solid oral dosage form 150 mg	30 units
Sulfadoxine-pyrimethamine[b]	Tablet 500/25 mg	1 unit
Valproic acid	Oral liquid 200 mg/5 ml	300 ml
	Tablet (crushable) 100 mg	120 units
	Tablet (enteric-coated) 200 mg	60 units
Zinc sulphate	Solid oral dosage form 20 mg	14 units

For each active ingredient (or combination of active ingredients) selected in main text table 4 an appropriate formulation must be selected for survey. Flexible oral dosage forms (chewable,

dispersible or scored tablets) should be given priority, if registered in the country.
NUNT = number of units needed for treatment.
[a] For buccal administration when solutions are not available.
[b] Only in combination with artesunate 50 mg tablet.
[c] Only in combination with ethambutol (and pyrazinamide). If fixed-dose combinations are not selected, all four active ingredients must be surveyed separately.

Table S7 Appropriate formulations and associated number of units needed for treatment for school-aged children (5-12 years).

Active ingredient	Appropriate formulations	NUNT
Abacavir/lamivudine	Tablet (scored, dispersible) 120/60 mg	90 units
Albendazole	Tablet (chewable, scored) 400 mg	1 unit
Amoxicillin	Solid oral dosage form 500 mg	20 units
	Tablet (dispersible, scored) 500 mg	20 units
Amoxicillin/clavulanic acid	Tablet 500/125 mg	20 units
Ampicillin	Powder for injection 1 g in vial	20 vials
Artemether/lumefantrine	Tablet 20/120 mg	12 units
	Tablet (dispersible) 20/120 mg	12 units
Artesunate	Injection, ampoule containing 60 mg	1 ampoule
	Rectal dosage form 100 mg	1 unit
	Tablet 50 mg[+]	6 units
Artesunate/amodiaquine	Tablet 50/135 mg	6 units
	Tablet 100/270 mg	3 units
Artesunate/mefloquine	Tablet 100/220	3 units
Artesunate/pyronaridine	Tablet 60/180	6 units
Azithromycin	Solid oral dosage form 250 mg	2 units
	Solid oral dosage form 500 mg	1 unit
Benzylpenicillin	Powder for injection 600 mg (1 million IU) in vial	40 vials
	Powder for injection 3 g (5 million IU) in vial	10 vials
Budesonide	Inhalation (aerosol) 100 mcg per dose	60 doses
	Inhalation (aerosol) 200 mcg per dose	30 doses
Carbamazepine	Tablet (chewable) 200 mg	60 units
	Tablet (scored) 200 mg	30 units
	Tablet (scored) 400 mg	30 units
Cefotaxime	Powder for injection 1 g in vial	14 vials
	Powder for injection 2 g in vial	14 vials
Ceftriaxone	Powder for injection 1 g in vial	14 vials
Ciprofloxacin	Oral liquid 250 mg/5 ml	48 ml
Diazepam	Rectal gel 5 ml/ml in 2 ml rectal delivery system	1 tube
	Rectal solution 4 mg/ml in 2.5 ml rectal tube	1 tube

Dihydroartemisinin/piperaquine	Tablet 40/320 mg	6 units
Dolutegravir	Tablet 50 mg	30 units
Doxycycline	Oral liquid 50 mg/5 ml	8 ml
	Solid oral dosage form 50 mg	2 units
	Solid oral dosage form 100 mg	1 unit
	Tablet (dispersible) 100 mg	1 unit
Ethambutol	Tablet 400 mg	30 units
Ferrous salt	Oral liquid equivalent to 25 mg iron/ml	150 ml
	Tablet equivalent to 60 mg iron	60 units
Folic acid	Tablet 5 mg	30 units
Gentamicin	Injection 40 mg/ml in 2 ml vial	10
Hydroxocobalamin	Injection 1 mg in 1 ml ampoule	4 ampoules
Ibuprofen	Oral liquid 100 mg/5 ml	1080 ml
	Oral liquid 200 mg/5 ml	600 ml
	Tablet 200 mg	120 units
Isoniazid	Tablet 100 mg	60 units
	Tablet 300 mg	30 units
	Tablet (dispersible) 100 mg	60 units
Lamotrigine	Tablet 50 mg	60 units
	Tablet 100 mg	30 units
	Tablet 200 mg	30 units
	Tablet (chewable, dispersible) 50 mg	60 units
	Tablet (chewable, dispersible) 100 mg	30 units
	Tablet (chewable, dispersible) 200 mg	30 units
Lopinavir/ritonavir	Tablet (heat stable) 100/25 mg	120 units
Lorazepam	Injection 2 mg/ml in 1 ml ampoule	1 ampoule
Mebendazole	Tablet (chewable) 500 mg	1 unit
Midazolam	Solution for oromucosal administration 5 mg/ml in 2 ml pre-filled syringe	1 syringe
	Solution for oromucosal administration 10 mg/ml in 1 ml pre-filled syringe	1 syringe
	Injection 5 mg/ml in 3 ml vial[a]	1 vial
Morphine	Granules (slow release) 20 mg	30 sachets
	Granules (slow release) 30 mg	30 sachets
	Oral liquid 10 mg/5 ml	540 ml
	Tablet (slow release)	90 units
	Tablet (slow release)	60 units
	Tablet (slow release)	30 units
Oral rehydration salts	Powder for dilution 200 ml	10 sachets
	Powder for dilution 500 ml	4 sachets
	Powder for dilution 1 L	2 sachets
Paracetamol	Oral liquid 250 mg/5 ml	960 ml

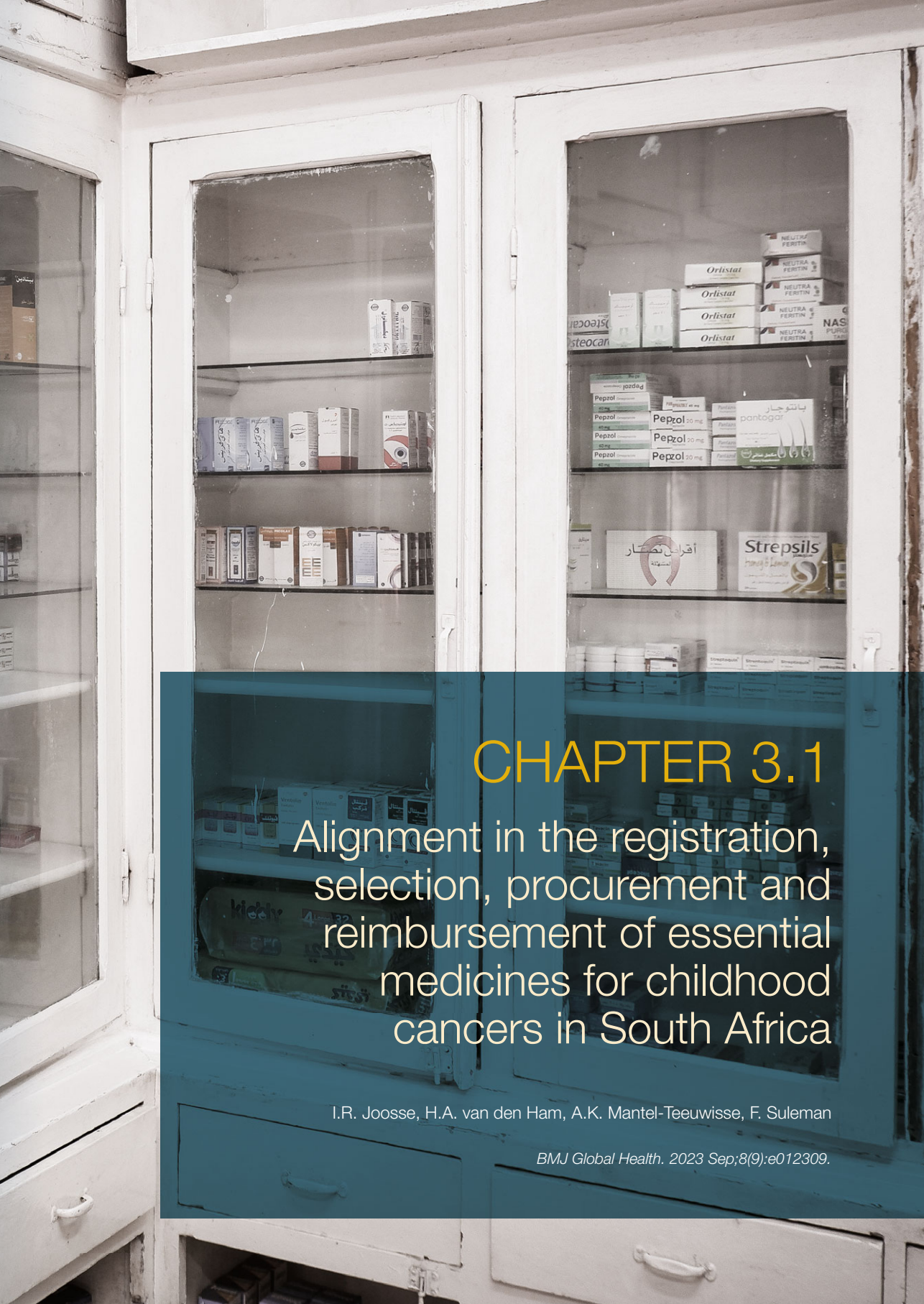
	Tablet 250 mg	120 units
	Tablet 325 mg	120 units
	Tablet (dispersible) 250 mg	120 units
Phenobarbital	Tablet 30 mg	120 units
	Tablet 60 mg	60 units
	Tablet 100 mg	30 units
Phenoxymethylpenicillin	Powder for oral liquid 250 mg/5 ml	60 ml
	Solid oral dosage form 250 mg	20 units
Phenytoin	Oral liquid 30 mg/5 ml	600 ml
	Solid oral dosage form 50 mg	120 units
	Solid oral dosage form 100 mg	60 units
	Tablet (chewable) 50 mg	120 units
Propranolol	Tablet 20 mg	60 units
Pyrazinamide	Tablet 400 mg	60 units
	Tablet 500 mg	60 units
Rifampicin	Solid oral dosage form 150 mg	60 units
	Solid oral dosage form 300 mg	30 units
Salbutamol	Metered dose inhaler (aerosol) 100 mcg	180 doses
Sulfadoxine-pyrimethamine[b]	Tablet 500/25 mg	1 unit
Valproic acid	Oral liquid 200 mg/5 ml	600 ml
	Tablet (enteric-coated) 200 mg	120 units
	Tablet (enteric-coated) 500 mg	60 units
Zinc sulphate	Solid oral dosage form 20 mg	14 units

For each active ingredient (or combination of active ingredients) selected in main text table 5 an appropriate formulation must be selected for survey. Flexible oral dosage forms (chewable, dispersible or scored tablets) should be given priority, if registered in the country.
NUNT = number of units needed for treatment.
[a] For buccal administration when solutions are not available.
[b] Only in combination with artesunate 50 mg tablet.

CHAPTER 3

A health system analysis of access to pediatric oncology medicines – the South African case study


Bivatracin
BETADINE
Kaprofen
KETOLAC



CHAPTER 3.1

Alignment in the registration, selection, procurement and reimbursement of essential medicines for childhood cancers in South Africa

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Abstract

Introduction

The effectiveness of a health system in providing access to medicines is in part determined by the alignment of several core pharmaceutical processes. For South Africa's public health sector these include the registration of medicines, selection and subsequent procurement through national tenders. Registration, selection and reimbursement are key processes in the private sector. This study assessed the alignment of forementioned processes for essential pediatric oncology medicines in South Africa.

Methods

A selection of priority chemotherapeutics, anti-emetics and analgesics in the treatment of five prevalent childhood cancers in South Africa was compared to those listed in 1) the World Health Organization Essential Medicines List for Children (WHO EMLc) 2021, 2) the registered health products database of South Africa, 3) the relevant South African National Essential Medicines Lists (NEML), 4) bid packs and awarded tenders for oncology medicines for 2020 and 2022, and 5) oncology formularies from the leading Independent Clinical Oncology Network (ICON) and two private sector medical aid schemes. Consistency between these sources was assessed descriptively.

Results

There was full alignment for 25 priority chemotherapeutics for children between the NEML, the products registered in South Africa and those included on tender. Due to unsuccessful procurement, access to seven chemotherapeutics was potentially constrained. For antiemetics and analgesics, eight of nine active ingredients included on the WHO EMLc were also registered in South Africa and on its NEML. An exploratory assessment of private sector formularies showed many gaps in ICON's formulary and two medical scheme formularies (listing 33% and 24% of the chemotherapeutics, respectively).

Conclusion

Despite good alignment in public sector pharmaceutical processes, access constraints to essential chemotherapeutics for children may stem from unsuccessful tenders. Private sector formularies show major gaps, however it is unclear how this translates to access in clinical practice.

Introduction

Childhood cancer is an emerging challenge in low- and middle-income countries (LMIC) including South Africa (SA) [1]. With reported survival rates of about 52%, SA is lagging behind other better-resourced countries [2]. An important reason for this is the late detection of the cancer and children subsequently presenting late with advanced disease [2]. The aggressive and fast-spreading nature of many pediatric cancers further contributes to this [3].

Chemotherapy is one of the basic modalities of childhood cancer management and a major determinant of outcomes [4]. Although chemotherapy was reported to be "available for most cancers the majority of the time" in SA [4], other sources suggest the opposite and care may be compromised due to unaffordable or unavailable medicines [5,6]. Unavailability is reported to arise from inconsistent drug supplies, stock-outs and unregistered medicines [6,7]. Furthermore, treatment is inaccessible for some patients due to long travel distances to specialized treatment facilities, poor knowledge and understanding of cancer and inadequate referral pathways [8]. Besides chemotherapy and other antineoplastics, supportive medicines for the management of pain and nausea are essential for improving adherence and quality of life and humanizing care [9, 10].

Access to cancer medicines – as any medicine – is underpinned by several processes in the pharmaceutical value chain that occur at a national level. The first step towards accessible medicines is the *registration*, or market authorization, of a drug by a national drug regulatory agency [11]. Subsequent *selection* includes the identification of prevalent health problems and corresponding priority medicines, usually in the form of a formulary or national essential medicines list (NEML) and corresponding standard treatment guidelines (STGs) [12]. The World Health Organization (WHO) model Essential Medicines Lists (EML) may be used as a guide for national selection processes. Insurance r*eimbursement* is often linked to selection processes. *Procurement* involves the managing of tenders or other procurement strategies, and establishing contract terms and ensuring adherence to these [12]. Those medicines that have been designated as essential should ideally be given priority in procurement as well. *Distribution* and *use* complete the circle. Alignment of these pharmaceutical processes is essential for access, as a disruption in any of these processes leads to failure of the entire system [12].

In the South African context, *registration* is regulated by the South African Health Products Regulatory Authority (SAHPRA) for both the public and private sector [13]. *Selection* in the public sector entails the South African NEML, which is established according to different levels of care and guided by the principles of the WHO EML [14, 15]. Primary and secondary level NEMLs are extracted from STGs, but the tertiary and quaternary levels only have an approved NEML. All medicines on the NEML should subsequently be *procured* through a national tender; alternatively they may be bought out by individual provinces or hospitals if a contract was not

awarded following a tender process [15]. Ideal access pathways for medicines, including access pathways in the South African context, are illustrated in **Figure 1**.

For SA's private medical insurance schemes, the *selection* of medicines consists of protocols, guidelines and formularies that are established by each individual scheme and per benefit option (e.g. tier) [16]. With respect to (pediatric) cancer, guidance is provided by managed care organizations such as Independent Clinical Oncology Network (ICON) and South African Oncology Consortium (SAOC), yet schemes are permitted to adapt if required [16]. ICON guidelines are reportedly used by the majority of medical schemes. *Reimbursement* of cancer medicines and other medical costs directly depends on a member's benefit limit and those services outlined in the respective scheme's protocols and formularies [15] (**Figure 1**). Beyond the benefit limit only Prescribed Minimum Benefits (PMBs, e.g. a defined set of benefits that all members of all medical schemes have access to regardless of their benefit option) must be covered. Despite this compulsory cover, medical schemes are reported to use treatment protocols and medicine formularies to control costs, forcing some patients to pay out-of-pocket for PMB conditions if medicines are not on the respective protocol or formulary [16]. Another major structure that determines access to medicines in SA's private sector is the Single-Exit-Price (SEP) legislation that mandates that a single maximum price can be charged for a medicine (excluding dispensing fees). These prices are recorded in the Medicine Price Registry (MPR) [15].

The effectiveness of SA's health system in providing the medicines required for effective management of childhood cancers to a large extent depends on the alignment of the pharmaceutical processes described above [14]. Although the operational policies are in place and theoretical relations defined [17], the operationalization of these processes is unclear. Therefore, the present study aimed to evaluate the alignment of these pharmaceutical processes for pediatric cancers in SA, through a comparison of medicines databases, lists and formularies. This study can contribute to a better understanding of barriers and facilitators that determine access to pediatric oncology medicines, and can help identify critical areas for policy development while SA is moving towards National Health Insurance [18].

Methods

Selection of medicines

To allow comparison of pharmaceutical processes, a selection of priority active ingredients in the treatment of prevalent cancers in children under the age of 15 years was made. Basis for this selection were the five most prevalent childhood cancers, identified through reports in scientific literature and the South African National Cancer Registry [2, 19]. The five childhood cancers selected were acute leukemias, brain tumors, lymphomas, nephroblastoma and retinoblastoma. Priority active ingredients were subsequently identified for these cancers through a guideline for the management of pediatric cancers in a low-resource context

(*Pediatric cancer in Africa*, 2017 [9]). An Africa-wide guideline was used since SA's public sector standard treatment guidelines (STGs) do not include chapters on childhood cancers. Clinical guidelines from managed care organization SAOC and ICON are not available in the public domain. Other international treatment guidelines fail to reflect SA's resource-limited setting and hence were not deemed compatible. Antineoplastics (including cytotoxic medicines, targeted therapies and hormones) as well as supportive medicines (antiemetics and analgesics) were eligible. The guideline did not specify which formulations should be used.

Data sources and characteristics

The basket of active ingredients was compared to those medicines listed in or on:

A) **The World Health Organization's (WHO) Essential Medicines List for Children (EMLc) 2021**

SA's national essential medicines list (NEML) process is reported to align well with the WHO process [14], yet it remains unclear how the active ingredients on the NEMLs align to the WHO EMLc [20]. We therefore included this category to assess the NEML's alignment to WHO's model list for international reference.

Besides active ingredients, information on child-appropriate dosage forms and strengths was also extracted from the WHO EMLc.

B) **The database of the South African Health Products Regulatory Authority**

Medicinal products approved for use in SA are recorded in this database [13].

We sought for active ingredients in the database on non-proprietary name and brand name(s) if necessary on 16 June 2022. Registered dosage forms and strengths were extracted.

C) **National Essential Medicines Lists**

As cancer management predominantly takes place in specialized tertiary and quaternary hospitals, antineoplastic medicines are listed on SA's *Tertiary and Quaternary Level Essential Medicines List* updated in 2022 [21]. This NEML is intended for both adults and children and lists active ingredients and approved indications. Supportive medicines were sought for in the 2017 *(Pediatrics) Hospital Level Standard Treatment Guidelines and Essential Medicines List for South Africa* [22].

As the NEMLs (and STGs) do not specify formulations, only data on active ingredients was extracted.

D) **Antineoplastic medicines tendered for and awarded in SA's national tenders**

Oncology and immunological agents are tendered for in a separate tender. Tender round HP04-2020ONC for the period 1 July 2020 to 30 June 2022 and the additional tender round HP04-2020ONC/01 for products not awarded in the first round were included, as well as tender round HP04-2022ONC for 1 July 2022 to 30 June 2024 [23]. The additional tender round for 2022-2024 (HP04-2022ONC/01) was excluded, as this tender was send out for bidding but results had not been published by January 2023.

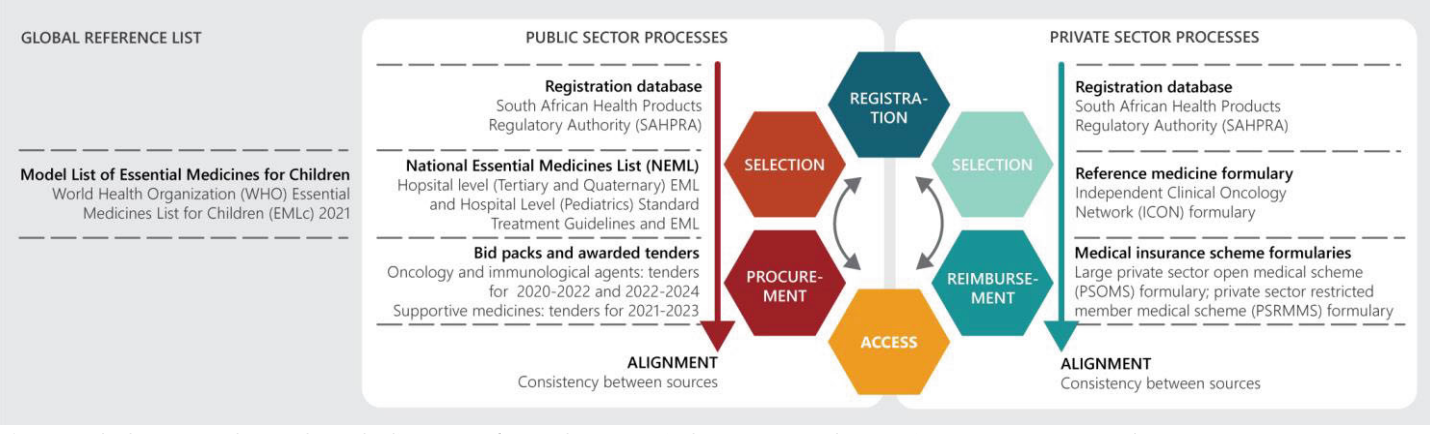

Figure 1 Ideal access pathways through alignment of core pharmaceutical processes, and respective resources compared.
Note: this figure does not capture loophole arrangement for unregistered access. Core domains *distribution* and *use* not shown.

Supportive medicines were procured through other tenders, mostly the tender for oral solid dosage forms (HP09-2021SD and HP09-2021SD/01) [23].
Data on active ingredients and dosage forms and strengths included on bid packs and whether or not products were subsequently awarded were extracted. If products were not awarded in the main tender for 2020 but the additional round was successful, the procurement was still deemed successful in our analyses.

Besides an assessment of the public sector lists and databases described above, an exploratory comparison of processes in SA's private sector was conducted. Therefore, the basket of active ingredients was also compared to those medicines listed on:

E) **The Independent Clinical Oncology Network (ICON) formulary**
Managed care organization ICON provides protocols and guidelines, including an oncology formulary that is used as a reference in SA's private sector [24]. As the clinical guidelines and protocols created by ICON and SAOC are not publicly available, ICON's oncology formulary is used as a reference for SA's private sector. This formulary does not include supportive medicines.
Formularies from October 2020, April 2021 and July 2022 were compared. Data on active ingredients and dosage forms were extracted.

F) **Private sector medical aid scheme formularies**
The formularies from a large private sector open medical scheme (PSOMS) and the Medicines Price List (MPL) of a private sector restricted member medical scheme (PSRMMS) for oncology were obtained and compared [25, 26]. The PSOMS's formularies, which included supportive medicines, for quarters 1 and 2 of 2020, 2021 and 2022 were included. PSRMMS's oncology MPLs from October 2020, December 2021 and September 2022 were compared.
Data on active ingredients and dosage forms were extracted.

Consistency between sources and consequent accessibility of childhood cancer medicines was assessed descriptively on active ingredient level. Public (data sources A-D) and private sector (data sources A, E and F), as well as antineoplastic versus supportive medicines were examined separately (see **Figure 1**). Medicines were considered accessible if no barriers were found in the national pharmaceutical processes/sources.

An additional examination into the marketing status of solid oral dosage forms was performed (both antineoplastic and supportive medicines) since these formulations are generally more difficult to manipulate (e.g. dose adjustments through breaking, crushing, etc.) than injectable medicines. Additionally, solid oral dosage forms increase the possibility for treatment closer to the patient's home, whereas injectable medicines must be administered in a hospital setting. This makes the accessibility of specific age-appropriate formulations essential for improving access. Data sources A, B and D were compared, as well as source G:

G) **Medicine Price Registry (MPR)**

The SEP of all medicinal products to be sold in SA's private sector must be recorded in the MPR [27]. Inclusion of a product in the MPR indicates that the medicine is for sale on the private market, where inclusion in the SAHPRA database only indicates regulatory approval. We sought for active ingredients in the registry on non-proprietary name and brand name(s) if necessary as at 17 November 2022. Registered dosage forms and strengths were extracted.

Results

A total of 25 priority antineoplastics were identified from the guideline for the five selected cancers (**Table 1**), as well as 19 active ingredients (including within-class alternatives) for general supportive care (**Table 2**). This basket of 44 active ingredients was used as a reference for comparing SA's pharmaceutical processes. WHO's model EMLc listed 21 (84%) of the antineoplastic medicines in the basket, and 9 (47%) of the supportive drugs.

Antineoplastics in South Africa's public healthcare sector

Of the 25 antineoplastics in the basket, 19 (76%) were found in the SAHPRA database (**Table 1**). Although chlorambucil and mercaptopurine could not be identified in the database despite the use of several different search terms, these active ingredients were found in the private sector's MPR. This implies that these products are in fact registered in SA and that the SAHPRA database is incomplete.

All 21 medicines registered in the country were also found on the NEML, showing perfect alignment between the registration and selection step. Agreement between the two essential medicine lists was 90%, with only 2 out of 21 active ingredients that were included on the WHO EMLc missing from the NEML (i.e. dactinomycin and procarbazine).

At the procurement level, we found almost full agreement between medicines on the NEML and those active ingredients included in the bid pack for the national tenders (results not shown). Of note, the two glucocorticoids (i.e. dexamethasone and predniso(lo)ne) were not included in the oncology tender (but may have been included in other tenders) and the procurement step could therefore not be assessed for these drugs. Of the remaining 19 drugs on the NEML, 12 (63%) were successfully procured in both 2020 and 2022. Ultimately, we found no barriers in access for 56% of the basket (14/25), intermittent access for 2 antineoplastic agents (8%) and constrained access for 9 (36%) products, 5 of which due to procurement restraints only (**Table 1**).

When looking in more detail at the procurement step of antineoplastic medicines (**Table 3**), we noticed that a very low proportion of medicines was successfully tendered for in the main tender round of 2020, with 7 (33%) of the 21 that was tendered for getting awarded. In the additional

tender that was finalized over 5 months later, 7 active ingredients were additionally awarded (including a second formulation of folinic acid) but the tender remained unsuccessful for another 7 products. The 2022 tender round was considerably more successful, with only 6 of 21 (29%) products not getting awarded. No new tender contracts were awarded yet following an additional tender round by SA's Department of Health (DoH).

Table 1 Comparison of antineoplastics in South Africa's public sector core pharmaceutical processes.

Active ingredient	WHO EMLc	SAHPRA	NEML	Procurement	Accessibility
H02Ab Glucocorticoids					
Dexamethasone	✓	✓	✓!	-	✓!
Prednisolone	✓	✓	✓!	-	✓!
L01A Alkylating agents					
Chlorambucil	✗	!	✓	✓	✓
Chlormethine	✗	✗	✗	✗	✗
Cyclophosphamide	✓	✓	✓	✓	✓
Ifosfamide	✓	✓	✓	✓	✓
Lomustine	✗	✗	✗	✗	✗
L01B Antimetabolites					
Cytarabine	✓	✓	✓	✗	✗
Mercaptopurine	✓	!	✓	✓	✓
Methotrexate	✓	✓	✓	✓	✓
L01C Plant alkaloids and other natural products					
Etoposide	✓	✓	✓	✗	✗
Vinblastine	✓	✓	✓	✗	✗
Vincristine	✓	✓	✓	✓	✓
L01D Cytotoxic antibiotics and related substances					
Bleomycin	✓	✓	✓	✗	✗
Dactinomycin	✓	✗	✗	✗	✗
Daunorubicin	✓	✓	✓	✗	✗
Doxorubicin	✓	✓	✓	✓	✓
Idarubicin	✗	✓	✓	✗	✗
L01X Other antineoplastic agents					
(L-)Asparaginase	✓	✓	✓	✗	✗
Carboplatin	✓	✓	✓	✓	✓
Cisplatin	✓	✓	✓	✓	✓
Procarbazine	✓	✗	✗	✗	✗
Tretinoin	✓	✓	✓	✓	✓

V03AF Detoxifying agents for antineoplastic treatment					
Calcium folinate	✓	✓	✓	✓	✓
Mesna	✓	✓	✓	✓	✓

✓ = yes/always; ✓ = sometimes; ✗ = no/never; ✓ = corticosteroids are not included in the tertiary and quaternary level essential medicines list but rather included on the 2017 (Pediatrics) Hospital Level Standard Treatment Guidelines and Essential Medicines List for South Africa. Corticosteroids were not part of the tender for oncology and immunological agents. ! = Not found in SAHPRA database, but can be found in Medicines Price Registry. Inclusion of childhood oncology medicines on essential medicines lists and the South African registration database; whether successfully procured in 2020 and 2022 national tenders for oncology and immunological agents; and consequences for perceived access.
NEML = National Essential Medicines List; SAHPRA = South African Health Products Regulatory Authority; WHO EMLc = World Health Organization model Essential Medicines List for children.

Supportive medicines in South Africa's public healthcare sector

Table 2 shows a variety of medicines that may be used in the management of (anticipatory) nausea and vomiting and nociceptive pain. A large majority of 17 of 19 (89%) of these supportive care medicines is registered for use in SA. Potential barriers in access due to medicines not being listed on the NEML were found for 10 (53%) supportive medicines. Compared to the WHO EMLc, we identified no barriers in access for 8 of 9 (89%) active ingredients, the one exception being the antiemetic aprepitant.

Antineoplastics in South Africa's private healthcare sector

In an exploratory assessment of private sector alignment, **Table 4** shows that there may be many gaps in access. The ICON formulary that can be used as guidance by the private sector medical schemes in establishing their own formulary shows many gaps as compared to the WHO EMLc and NEML, including for medicines such as the glucocorticoids, cytarabine and mercaptopurine. From 2020 to 2021, several products seem to be removed from the formulary, for which the reasons are unknown. No new products were added to the formulary during this time. In contrast, the PSOMS seems to have added more products to their formulary in 2021. Despite that, the scheme still shows major gaps as compared to ICON and the EMLs. Of the 21 active ingredients on the NEML, only 7 (33%) were on the formulary in 2022. For members of a restricted medical scheme, a meager 5 (24%) active ingredients were listed between 2020 and 2022.

Table 2 Comparison of supportive care medicines in South Africa's public sector core pharmaceutical processes.

Active ingredient	WHO EMLc	SAHPRA	NEML	Accessibility
Paracetamol	✓	✓	✓	✓
NSAIDs				
Ibuprofen[a]	✓	✓	✓	✓
Niflumic acid[a]	✗	✗	✗	✗
Diclofenac[a]	✗	✓	✗	✗
Weak opioids				
Codeine[a]	✗	✓	✗	✗
Tramadol[a]	✗	✓	✗	✗
Nalbufine[a]	✗	✗	✗	✗
Buprenorphine[a]	✗	✓	✗	✗
Strong opioids				
Morphine[a]	✓	✓	✓	✓
Fentanyl[a]	✗	✓	✗	✗
5-HT3 antagonists				
Granisetron[a]	✓	✓	✓!	✓
Ondansetron[a]	✓	✓	✓	✓
Benzodiazepines				
Lorazepam[a]	✓	✓	✓	✓
Alprazolam[a]	✗	✓	✓!	✓
Dopaminergic antagonists				
Metoclopramide	✓	✓	✓	✓
Prochlorperazine	✗	✓	✗	✗
Other antiemetic agents				
Aprepitant[a]	✓	✓	✗	✗
Dexamethasone	✓	✓	✓	✓
Fosaprepitant[a]	✗	✓	✗	✗

✓ = yes; ✗ = no; ✓! = not included on pediatric hospital level standard treatment guidelines and essential medicines list, but inclusion of childhood oncology medicines on essential medicines lists and the South African registration database and consequences for perceived access.
NEML = National Essential Medicines List; SAHPRA = South African Health Products Regulatory Authority; WHO EMLc = World Health Organization model Essential Medicines List for children. rather on the 2022 Tertiary and Quaternary Level Essential Medicines List.
[a] within-class alternatives [9].

Solid oral dosage forms in South Africa's public and private healthcare sector

An exploratory assessment of pharmaceutical policy processes specifically for solid oral dosage forms was performed (Appendix 1), containing all (child-appropriate) solid oral dosage forms as listed in the WHO EMLc for the registered active ingredients in our basket. Where the WHO EMLc generally listed several dosage strengths for oral solids, not all of these strengths were registered in SA. Additionally, although some products are registered in the country, not all of them seem to be accessible in both the public and private sector (e.g. (successfully) tendered for or found in MPR). For example, dexamethasone 4 mg tablets and morphine 10 mg immediate release tablets do not seem to be accessible in either sector.

Discussion

The key pharmaceutical processes of registration, selection and procurement of medicines for five major childhood cancers seem to be aligned in SA's public healthcare system, indicating good operationalization of SA's policies and processes. The bottleneck seems to lie in the procurement of essential medicines through national tenders. Private sector formularies listed a limited selection of priority chemotherapeutics, indicating potential restrictions in what may be reimbursed to their beneficiaries.

While our findings also indicate alignment with international processes, the few gaps in comparison to the WHO EMLc may have a big impact. In fact, in a 2022 cross-sectional survey to determine priority essential childhood cancer medicines, dactinomycin was in the top 10 of most frequently selected drugs by pediatric oncologists when asked what medicines would achieve greatest benefit in children [28]. Thus, the lack of market authorization for dactinomycin in SA indicates that deficiencies in therapeutic care exist. Although certain legislative loophole arrangements – in SA's case in the form of Section 21 access – can still allow the use of unregistered drugs after named-patient approval, this access pathways is associated with a range of challenges [29]. These include the obtaining of hospital and/or provincial approval and the associated administrative burden on clinicians, the universally limited budgets to buy products outside of the NEML, and considerable delays in supply when products need to be imported. In SA's private sector, medical schemes are under no obligation to reimburse section 21 medicines [16].

Procurement issues potentially constraint access to some of the key chemotherapeutics in the management of childhood cancers such as cytarabine and etoposide [25]. From the evidence obtained in this study it cannot be deduced whether submitted bids were not awarded by the DoH or whether companies are not submitting any bids, but anecdotal evidence suggests that the DoH's price expectations are too low to make bidding profitable [29]. Additionally, even if

some products were eventually successfully awarded in an additional tender for 2020-2022, this supplementary round brings a considerable delay of about 4 months based on the tender documents. These delays also affected core chemotherapeutics such as doxorubicin and vincristine [28]. Noteworthy, DoH's price expectations were unchanged for the additional tender round. In the meantime products must be bought out by provincial governments or individual hospitals to meet the demand, putting considerable strain on hospital pharmacists and continuous supply cannot be guaranteed during this time [30].

Table 3 Details of public sector procurement of oncology medicines in 2020 and 2022.

	2020		2022
Active ingredient	Main tender	Additional tender	Main tender
Chlorambucil	✓	-	✓
Cyclophosphamide	✗	✓	✓
Ifosfamide	✗	✓	✓
Cytarabine	✗	✗	✗
Mercaptopurine	✓	-	✓
Methotrexate	✓✗	✗	✓
Etoposide	✗	✗	✓
Vinblastine	✓	-	✗
Vincristine	✗	✓	✓
Bleomycin	✗	✗	✗
Daunorubicin	✗	✗	✗
Doxorubicin	✗	✓	✓
Idarubicin	✗	✗	✗
(L-)Asparaginase	✗	✗	✗
Carboplatin	✗	✓	✓
Cisplatin	✗	✓	✓
Tretinoin	✓	-	✓
Folinic acid	✓✗	✓	✓
Mesna	✗	✓	✓
Granisetron	✓	-	✓
Ondansetron	✓	-	✓

✓ = yes; ✓✗ = at least one of multiple dosage forms; ✗ = number of contracts awarded for oncology agents in national tender rounds HP04-2020ONC, HP04-2020ONC/01 and HP04-2022ONC. All products were included on the bid pack, unless indicated with '-'. Additional tender round for 2022 (HP04-2022ONC/01) has not been finalized at the time of writing and is therefore not include above.

Note: products not registered in South Africa are not shown in table.

Table 4 Comparison of antineoplastics in South Africa's private sector formularies.

Active ingredient	WHO EMLc	NEML	ICON medicine formulary			PSOMS formulary			PSRMMS MPL Oncology		
			2020	2021	2022	2020	2021	2022	2020	2021	2022
H02Ab Glucocorticoids											
Dexamethasone	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
Predniso(lo)ne	✓	✓	✗	✗	✗	✓	✓	✓	✗	✗	✗
L01A Alkylating agents											
Chlorambucil	✗	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗
Chlormethine	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Cyclophosphamide	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✗
Ifosfamide	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✗
Lomustine	✗	✗	!	!	!	✗	✗	✗	✗	✗	✗
L01B Antimetabolites											
Cytarabine	✓	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗
Mercaptopurine	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
Methotrexate	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	✗
L01C Plant alkaloids and other natural products											
Etoposide	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓
Vinblastine	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✗
Vincristine	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓
L01D Cytotoxic antibiotics and related substances											
Bleomycin	✓	✓	!	!	!	✗	✗	✗	✗	✗	✗
Dactinomycin	✓	✗	!	!	!	✗	✗	✗	✗	✗	✗
Daunorubicin	✓	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗

Doxorubicin	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓
Idarubicin	✗	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗
L01X Other antineoplastic agents											
(L-)Asparaginase	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
Carboplatin	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓
Cisplatin	✓	✓	✓	✓	✓	✗	✗	✓	✓	✓	✓
Procarbazine	✓	✗	!	!	✗	✗	✗	✗	✗	✗	✗
Tretinoin	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
V03AF Detoxifying agents for antineoplastic treatment											
Calcium folinate	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
Mesna	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗

✓ = Yes; ✗ = No; ! = indicated as essential and accessible through section 21 legislation.

Inclusion of childhood oncology medicines on the World Health Organization and South Africa's national essential medicines list; compared to the ICON medicine formularies, a large PSOMS' formularies and a PSRMMS Oncology MPLs for 2020, 2021 and 2022.

ICON = Independent Clinical Oncology Network; MPL = Medicines Price List; NEML = National Essential Medicines List; PSOMS = private sector open medical scheme; PSRMMS = private sector restricted member medical scheme; WHO EMLc = World Health Organization model Essential Medicines List for children.

Although our findings indicate potential difficulties in procurement, actual accessibility remains hard to predict based on these tender documents alone: medicines can be procured through buy-outs if contracts were not awarded, or medicines may be in short supply despite a contract. With regimens generally consisting of four or five active ingredients, even intermittent supply issues for one drug can negatively impact care for these aggressive cancers; omitting or switching of drugs is undesirable and could have detrimental effects [2, 7]. Surveys on the ground are required to get a more complete picture of supply and availability issues and how these impact patient outcomes.

Notwithstanding the considerable number of red crosses for *access* to supportive medicines, we have identified no major issues in accessibility of these active ingredients based on the *registration* and *selection* step alone. Not only are the gaps in registration status and NEML selection largely in line with international guidelines [20], but also not all within-class alternatives are required to be accessible if another from the same therapeutic class is (also stipulated in guideline [9]). It is, however, relevant that at least one alternative can be accessed if the medicine of first choice is not well tolerated. In this South African case study, we find that at least one active ingredient per class should be accessible – except for weak opioids. This gap does not seem problematic, since there is no international consensus on their use due to a lack of evidence [31]. In the *other antiemetics* group, the inclusion of aprepitant on the NEML could be an important future addition, since aprepitant or analogues may be used as a further escalation in care if other antiemetics are insufficient [7, 10].

Although minimum coverage in the private sector (e.g. PMB level) is supposed to be similar to the care as provided in the state sector and across all medical schemes [15], major gaps are visible as compared to the WHO EMLc and the public sector's NEML. This misalignment already starts in the ICON formulary and is further exacerbated for the two medical scheme formularies. Although the large PSOMS is reported to take guidance from ICON [16], the inconsistencies between both formularies rather imply that other resources and factors also play a role in the establishment of their formularies. With that, the role of ICON in the private healthcare system is unclear [16].

The rather large number of red crosses for the ICON formulary and two private sector medical schemes must, however, be interpreted with caution. Reimbursement of cancer therapy for many medical aid plans depends on monetary benefit limits: a predetermined amount from which consultation fees, various investigative scans and treatments including medicines are initially funded [16]. It is only after this limit has been reached that patients may be restricted to formularies to avoid co-payments, especially if their diagnosis is not one of the 270 PMB covered indications (including some pediatric cancers). With that, the gaps identified may be of particular relevance to those without additional oncology benefits and PMB-level insured members. In addition, schemes may opt to use specific oncology protocols to define processes in care and

access to medicines, but these are not publicly available. Nonetheless, it is difficult to predict what these results mean for individual medical schemes and insured members. This lack of transparency in what will be – or will not be – covered and when these formularies apply, creates challenges for members when having to navigate the system [16].

In the interpretation of all of our findings we acknowledge that even when no major barriers seem to exist on the active ingredients level, access may be more constrained for specific finished pharmaceutical products (FPPs). This is of particular importance for oral dosage forms in pediatrics, since different dosage strengths are required for children of different ages and manipulation of products could introduce quality issues and errors [32]. An exploratory assessment of solid oral dosage forms was conducted with this in mind, but the lack of data in the NEML and ICON's formulary on specific (required) FPPs prevented more comprehensive comparisons. The absence of accurate guidance on required FPPs in these sources constitutes a significant gap in itself, particularly as these documents guide subsequent procurement. A more detailed NEML, potentially complemented by STGs, could address this deficiency. Alternatively, making SAOC's and ICON's treatment guidelines publicly available could play an important role in addressing this gap.

Nevertheless, the fact that some products were not found in either the tender bid packs nor the MPR in the exploratory assessment implies that these common products may no longer be marketed in SA. With that, this exploratory assessment confirmed anecdotal reports that products are disappearing from the market [29]. Similarly, ICON referred to bleomycin access through a section 21 exemption, despite a bleomycin product having market authorization in SA. This again implies that the registered product is not widely available in SA, and alternative, equivalent products may be accessed via this loophole arrangement.

A limitation of this study is that an Africa-wide treatment guideline from 2017 was used to inform our basket, due to a lack of a South African equivalent. This may have resulted in active ingredients of local importance being missed, particularly some of the innovative medicines that may not be available in most of the other countries on the African continent. Additionally, treatment protocols, clinical insights and available therapies may have changed since then. For example, chlormethine, tramadol and niflumic acid do not seem to be medicines of first choice anymore, also explaining their absence from the WHO EMLc and national sources. Nonetheless, most of the priority medicines were also identified as such in a recent international survey among pediatric oncologists and pediatricians in LMICs [28], showing general representativeness of our sample. Additionally, details on FPPs were not provided in this resource – nor in some of the other data sources – limiting our analyses to active ingredient level and hence limiting the accuracy of our findings. Despite its limitations, the present basket allowed us to study the alignment of pharmaceutical processes, as was the primary aim of this study. Furthermore, we were limited to the use of publicly available data for this study. This also

restricted us to the use of data on tenders as a proxy for *procurement* as a whole. The SAHPRA database was used to assess *registration* status, but it is unclear as to how often this database is updated. To mitigate the risk of incomplete data, the MPR was used to verify whether medicines were on the private market meaning they must have been registered. Finally, in the interpretation of these findings we must stress that even though we have not identified any barriers in access to the majority of these active ingredients via database evaluation, this does not guarantee that a medicine is indeed available on the shelf. The conduct of longitudinal availability surveys would be of particular complementary value to our findings.

The novelty and significance of this study lie in the scope of pharmaceutical processes studied. Where previous studies in other countries have compared national EMLs with the WHO model list [33-35] or with national drug registries [11], this study is the first to include data on *procurement* and potential *reimbursement* in addition to (international) *selection* and *registration*. By studying these steps together, a more comprehensive picture of potential gaps was obtained and specific bottlenecks could be identified. With that, the present study also emphasizes the need for making information publicly available, including treatment guidelines, procurement documents and outcomes. Finally, the exploratory assessments performed highlight the importance of checking multiple sources to validate findings and enable the placing of results in the often complex context of a health system.

Conclusion

Fundamental pharmaceutical processes in SA's public health system showed extensive alignment for medicines used in the treatment of five major childhood cancers, but access to priority antineoplastic and supportive medicines in the management of these cancers is threatened due to unsuccessful procurement of drugs in national tenders, or an absence of active ingredients or specific formulations on the South African market. Private sector formularies showed major gaps, but it is unclear how oncology benefits/formularies align to international guidelines as these are not transparent. Additionally qualitative research or quantitative surveys are needed to get a better understanding of the challenges in accessing childhood oncology medicines.

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Supplementary materials

Appendix 1: Registration and marketing status of solid oral dosage forms

Table S1 Registration and marketing status of WHO EMLc recommended solid oral dosage forms.

	Not registered	Registered	Registered and found in MPR	Registered, found in MPR and nationally procured[a]
Antineoplastics				
Dexamethasone[b]	tablet 2 mg	tablet 4 mg		
Predniso(lo)ne[b]	tablet 25 mg			tablet 5 mg
Cyclophosphamide[b]	tablet 25 mg			tablet 50 mg
Mercaptopurine				tablet 50 mg
Methotrexate[b]				tablet 2.5 mg
Etoposide[b]			tablet 50 mg tablet 100 mg	
Tretinoin				capsule 10 mg
Calcium folinate[b]	tablet 5 mg tablet 25 mg			tablet 15 mg
Mesna[b]	tablet 400 mg tablet 600 mg			
Supportive medicines				
Paracetamol[b]				tablet 500 mg
Ibuprofen[b]			tablet 600 mg	tablet 200 mg tablet 400 mg
Morphine[b]		tablet immediate release 10 mg		tablet modified release 10-200 mg
Ondansetron[b]				tablet 4 mg tablet 8 mg
Metoclopramide[b]				tablet 10 mg
Aprepitant	capsule 165 mg		capsule 80 mg capsule 125 mg	
Dexamethasone[b]	tablet 0.75 mg tablet 1.5 mg	tablet 0.5 mg tablet 4 mg		

Status of WHO EMLc recommended solid oral dosage forms of active ingredients registered in South Africa.

MPR = Medicines Price Registry; WHO EMLc = World Health Organization model Essential Medicines List for children.

[a] Based on national tender rounds – including bid packs and awarded contracts – for oncology and immunological agents (2020 and 2022) and solid dosage forms (2021).

[b] Other injectable, oral liquid or rectal dosage forms are registered for use in South Africa.


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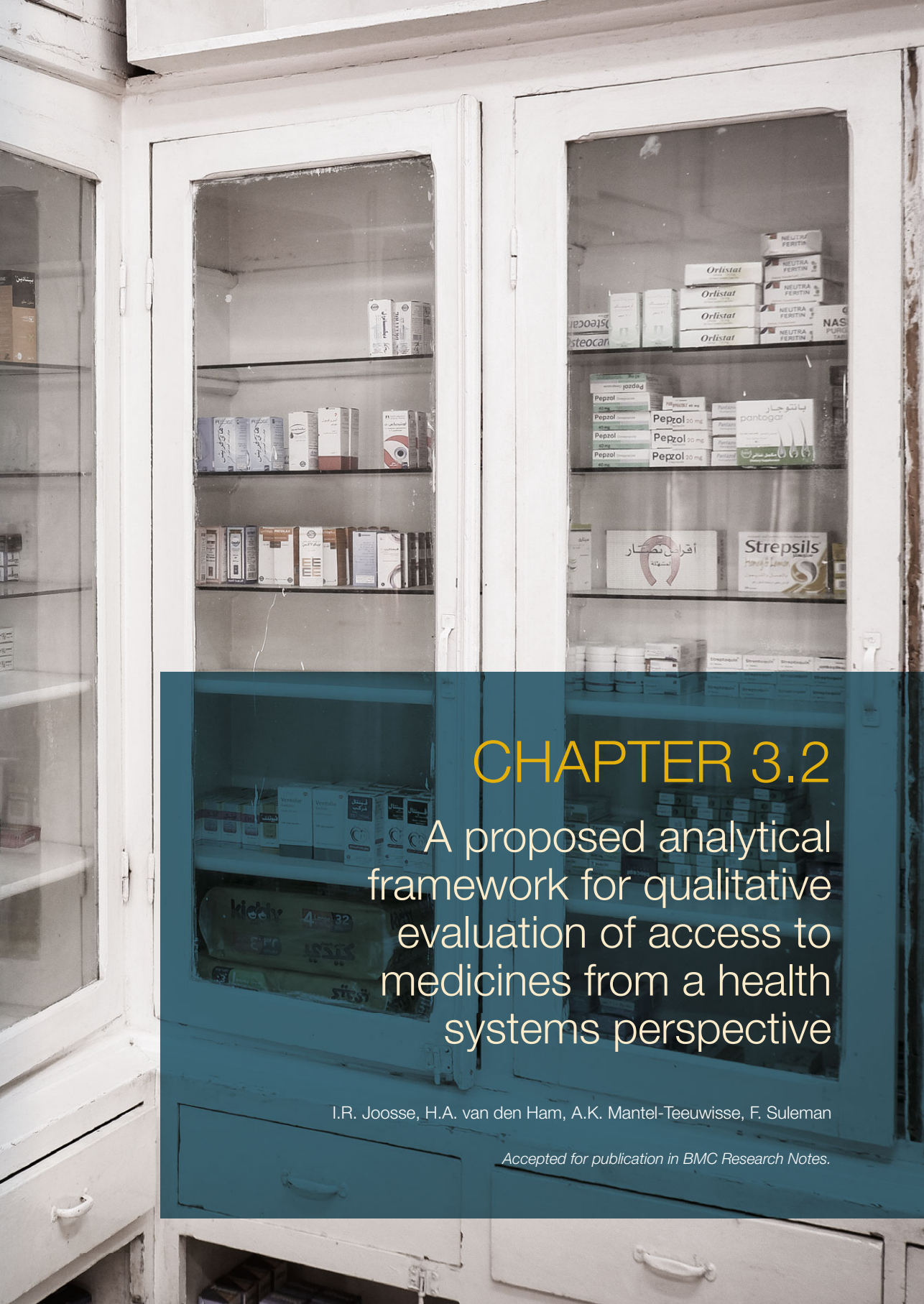
BETADINE
Kaprofen
KETOLAC



CHAPTER 3.2

A proposed analytical framework for qualitative evaluation of access to medicines from a health systems perspective

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Abstract

Objective

Despite global recognition that access to medicines is shaped by various interacting processes within a health system, a suitable analytical framework for identifying barriers and facilitators from a system's perspective was needed. We propose a framework specifically designed to find drivers to access to medicines from a country's health system perspective. This framework could enable the systematic evaluation of access across countries, disease areas and populations and facilitate targeted policy development. This framework is the byproduct of a larger study on the barriers and facilitators to childhood oncology medicines in South Africa.

Results

Eight core (pharmaceutical) functional processes were identified from existing frameworks: I) *medicine regulation*, II) *public financing and pricing*, III) *selection*, IV) *reimbursement*, V) *procurement and supply*, VI) *healthcare delivery*, VII) *dispensing* and VIII) *use*. National contextual components included *policy and legislation* and *health information systems*. To emphasize the interlinkage of processes, the proposed framework was structured as a pharmaceutical value chain. This framework focusses on national processes that are within a country's control as opposed to global factors, and functional mechanisms versus a country's performance or policy objectives. Further refinement and validation of the framework following application in other contexts is encouraged.

Introduction

Medicines are considered a key component of health systems and a major contributor to health outcomes [1]. Access to medicines is determined by the interaction between a multitude of factors and processes, not just in the pharmaceutical value chain but also within the broader context of the health system [2]. Research on accessibility of medicines is often focused on a particular process in isolation from related elements [3-5], or on the downstream effects for the patient – e.g. availability and affordability [6-10]. However, the entirety of the pharmaceutical system must be taken into consideration to get a comprehensive understanding of the drivers of accessibility.

To that end, we set out to get a better understanding of the drivers and barriers that determine access to pediatric oncology medicines in South Africa. To enable a comprehensive analysis of the issues influencing health system efficiencies and its ability to provide equitable access to childhood cancer medicines, we looked to available analytical tools to inform our qualitative analyses and development of an interview guide. The Paediatric Oncology System Integration Tool (POSIT) was reviewed and deemed suitable for constructing an interview guide [11]. POSIT was developed to facilitate analyses of the performance of childhood cancer programs in low- and middle-income countries (LMIC) within the context of their health system. Although medicines are only one element of a health system, many of the system functions and performance goals for health systems outlined in POSIT align with those for medicines.

However, thematic analysis of in-depth interviews with stakeholders soon revealed the limitations of POSIT in applying it specifically in the context of access to medicines, with several functional domains that are unique for pharmaceuticals missing from the framework. Missing elements included the regulation and registration of medicines, the selection of essential medicines, and preparing, dispensing and safe administration of pharmaceuticals. Other existing frameworks on access to medicines were either limited in scope or lacked specificity on pharmaceutical processes and were therefore not considered appropriate alternatives [2, 12-16].

With no single existing framework fit for the qualitative analysis of barriers and enablers in access to medicines, we aimed to develop a new analytical framework specifically designed to evaluate access to medicines from a health systems perspective within a country. Such a framework could yield a comprehensive health systems overview of drivers of access and concrete recommendations for improvement and policy development from stakeholders' perspectives.

Core components of an access to medicines framework

To inform core pharmaceutical functional processes, elements from two existing frameworks were used to construct a new framework: 1) the childhood cancer system functional domains in POSIT [11], and 2) the pharmaceutical management framework published in 'MDS-3: Managing Access to Medicines and other Health Technologies' [12]. *Managing Drug Supply-3* (MDS-3) is a reference guide detailing sustainable management of essential medicines in LMIC.

The analytical framework proposed by Bigdeli and colleagues was not used to construct our framework [2]. Although their framework is tailored to medicines and provides a complete overview of the complex components, levels and interconnections that determine access to medicines, it was developed for use in policy design whereas we sought to analyze drivers of access by understanding how effective collective action across the value chain through numerous stakeholders supports access to medicines. Additionally, we wanted to focus on national processes that are within a country's sphere of influence as compared to global mechanisms. The framework proposed by the World Health Organization (WHO) in 2004 targets performance dimensions (e.g. *sustainability*, *affordability*, etc.) rather than functional processes (e.g. *regulation*, *reimbursement*, *dispensing*, etc.) and focusses on key outcomes for coordinated global action, and was therefore not used [13]. The WHO guidelines on developing National Medicines Policies [14] and derivatives [15, 16] are policy oriented and may not adequately capture the practical effects and lived experiences of such policies or the performance of functional pharmaceutical processes, and position medicines vertically rather than integrated in the health system.

The five functional domains of POSIT (e.g. *governance*, *financing*, *demand generation*, *health information systems* and *service delivery*) were combined with the four basic functions of pharmaceutical management (e.g. *selection*, *procurement*, *distribution* and *use* (including *prescribing* and *dispensing*)) and contextual elements *management support* and *policy, law and regulation*. **Figure 1** provides a schematic representation of the generation of the framework.

From that, we identified eight core functional process: I) *medicine regulation*, II) *public financing and pricing*, III) *selection*, IV) *reimbursement*, V) *procurement and supply*, VI) *healthcare delivery*, VII) *dispensing* and VIII) *use* (including social and societal aspects). Other core components that influence the context under which the functional processes are taking place are *policy and legislation* and *health information systems*. Recognizing that each element builds on a previous component, we chose to map the framework as a pharmaceutical value chain (panel A, **Figure 2**) [17]. This figure also illustrates how the framework was applied to the qualitative study of barriers and facilitators in access to pediatric cancer medicines in South Africa (panel B), while

highlighting additional aspects that did not emerge in this specific case study but were recognized as potentially relevant elements in analogous frameworks (panel C) [11-16].

Policy and legislation

Policy and legislation captures how the pharmaceutical system and broader healthcare structures within a country are organized, managed, and regulated through policies, laws or mandates [11]. The political environment is also covered within this theme.

Medicine regulation

Regulation involves the marketing registration of medicines, pharmacovigilance activities, the licensing for manufacturing, distributing, storage and sale of pharmaceuticals, as well as importation and exportation [12]. Substandard and falsified medicines may also be considered here.

Public financing and pricing

Public financing involves the generation, pooling, and allocation of public funds to cover medicines and services [11]. This may also include donations. Private funding is considered under *reimbursement*. *Pricing* considers the prices and affordability of medicines and mechanisms used to regulate prices. Frequently used pricing mechanisms include internal reference pricing, external reference pricing and value-based pricing [18].

Selection

Selection encompasses the identification of prevalent health problems and selecting evidence based treatments of choice, choosing individual medicines and preferred dosage forms, and deciding which medicines will be available at each level of a health care system [12], usually in the form of a national Essential Medicines List (NEML) or formulary, and Standard Treatment Guidelines (STGs). This element also considers processes for making non- NEML or non-formulary listed medicines available to patients.

Reimbursement

We consider *reimbursement* to include the coverage of pharmaceuticals in national or social medical insurance plans, subsequent reimbursement prices by third party payers, mechanisms to determine reimbursement prices, co-payments and the regulation of private sector medical insurance schemes [11, 19]. This element also considers processes for reimbursement/payment of medicines that are not covered by insurance schemes.

Procurement and supply

Procurement and supply entails the selection and management of procurement methods – including tenders. In addition, distribution processes are also covered within this theme, encompassing aspects related to customs, stock control, and delivery to drug depots and health facilities [12]. Availability of medicines in health facilities is also considered here.

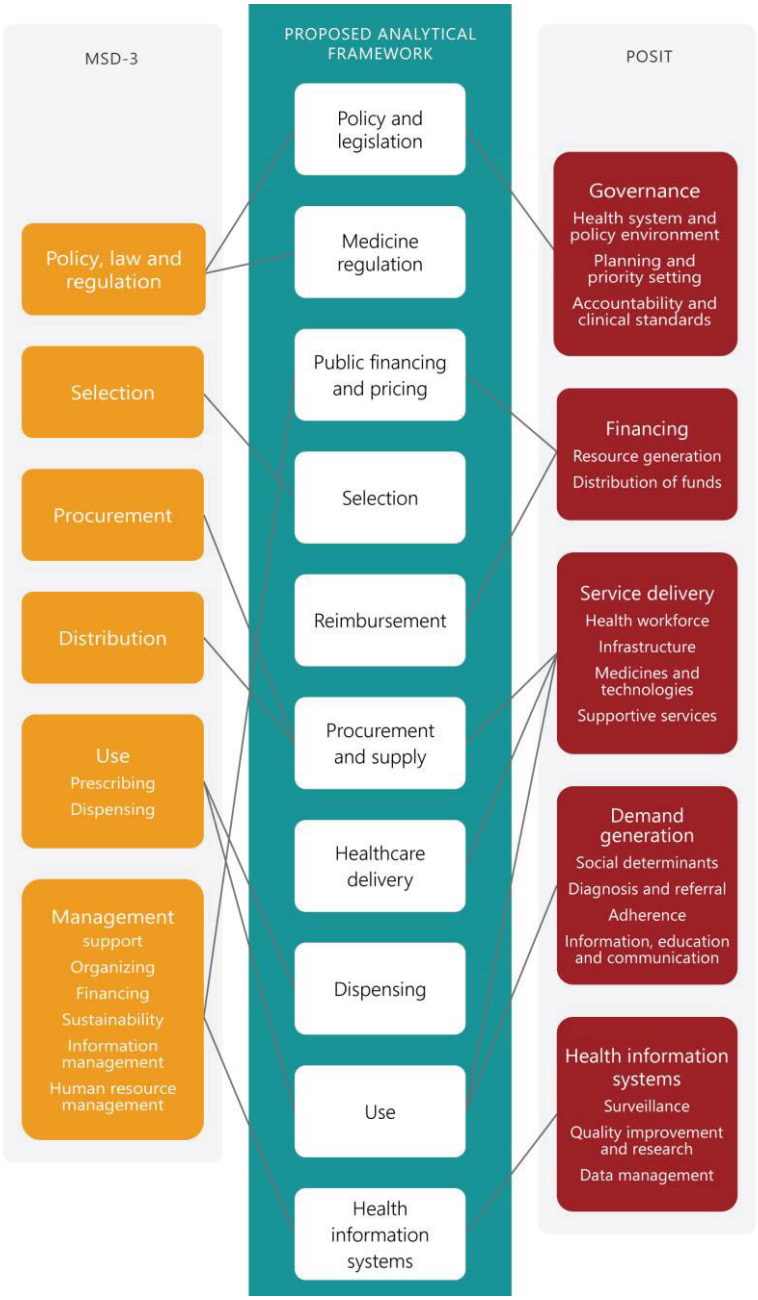

Figure 1 Mapping of POSIT [11] and MDS-3 [12] to construct a new analytical framework to identify barriers and facilitators to medicines' access.
POSIT = Paediatric Oncology System Integration Tool; MSD-3 = Managing Drug Supply-3.
Note: performance goals and dimensions as well as functional subdomains of POSIT not shown.

Healthcare delivery

Healthcare delivery encompasses a range of structures, resources, services, healthcare professionals and other individuals required for the diagnosis and provision of care [11]. We consider prescribing of medicines to be part of this component.

Dispensing

Dispensing comprises the process of preparing and giving or administering a medicine by a pharmacist or other healthcare professional to a named patient, frequently on the basis of a prescription [12]. However, over-the-counter (OTC) use and self-medication may also be considered here.

Use

We consider *use* as the proper medicine consumption by the patient, as well as the ability of people to command appropriate healthcare resources. This includes patients' knowledge on available health services and treatments, physical accessibility of services, and acceptability of services and medicines within associated social and societal structures [20].

Health information systems

This component captures by which means data about disease burden and clinical patterns, health outcomes, and the achievement of objectives in the health system is collected, analyzed and reviewed [11, 12]. Monitoring and surveillance are a critical element herein.

Discussion

In current literature, an increasing number of studies describe and analyze access to medicines from a country's health system perspective [21-25], but a complete and suitable framework to facilitate a qualitative analysis was missing. In previous studies, elements from different frameworks needed to be combined to arrive at a suitable structure for analysis [22-25], similar to our own experience. This illustrates the necessity for an amended framework for qualitative research on access to medicines that encompasses the full scope of national functional domains in the pharmaceutical value chain. Similar to Bigdeli et al. and POSIT, we have adopted a health systems perspective on access to medicines, to highlight the interconnectedness of medicines and pharmaceutical processes with other key variables within the health system [2, 11].

Unlike most other existing framework, functional domains ('*what we need to do*') rather than performance dimensions ('*what we aim to achieve*') were taken as basis for this framework [2, 11, 13]. Although we consider these performance dimensions to be critical in policy design and development, the level of detail required to identify barriers is missing when performance is suboptimal. The proposed framework was specifically designed to address this gap in understanding how effective collective action across the value chain by numerous stakeholders

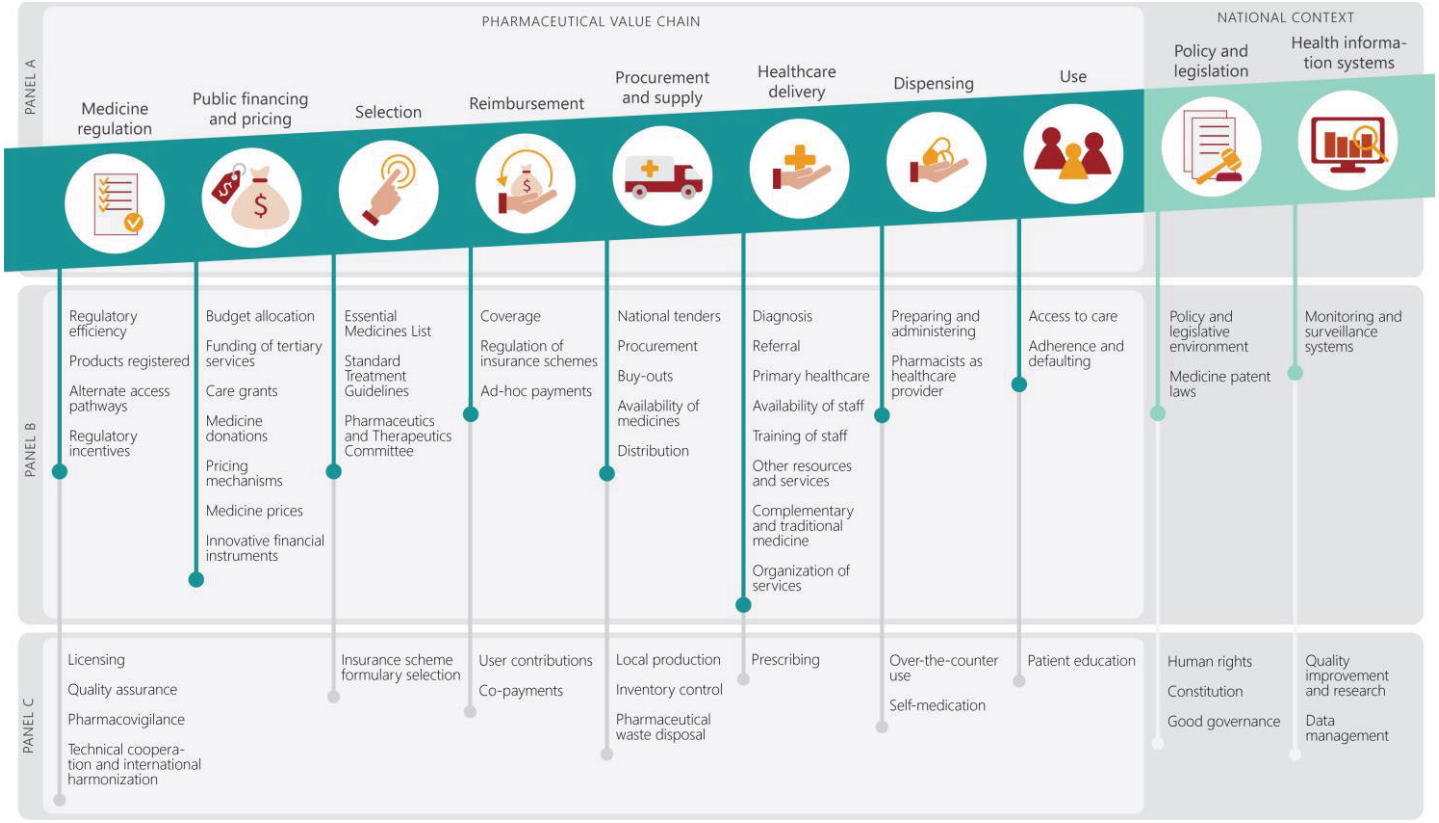

Figure 2 Proposed analytical framework for barriers and facilitators in access to medicines.
Panel A = general proposed analytical framework for access to medicines. Panel B = analytical framework applied to the study of barriers and facilitators in accessing childhood oncology medicines in South Africa (emerging cross-cutting themes not shown). Panel C = additional aspects to be considered in alternative contexts.

supports access to medicines. Additionally, when applying our framework to a case study of childhood oncology medicines in South Africa, we have experienced that important performance dimensions of access spontaneously emerge (e.g. *availability*, *equity*, *affordability*, etc.), further enriching the findings.

Rather than providing a checklist through which one could perform a gap-analysis of whether specific policies or processes are in place, we provide an open structure for a qualitative assessment of how functional processes operate and how they impact access. For even when a given policy or process is theoretically in place, its practical effects and lived experiences may differ from what was intended. For example, a national tender process might be in place, but tenders can fail due to too strict participation requirements. Our open structure distinguishes our framework from prior works, and allows for more in-depth discussion and probing. Recognizing that existing frameworks and key documents were designed for different purposes, the proposed framework is meant to complement earlier work rather than replace them. An important strength of this novel framework is its intuitiveness. Critical processes that take place between the moment a medicine is registered for use in the country and actual use by the patient are compartmentalized to facilitate each component's in-depth analysis, while also emphasizing the interaction between pharmaceutical processes, other healthcare services and actors and social factors. Correspondingly, all six WHO health system building blocks are captured within our framework [1]. The proposed framework was designed to be used in conjunction with different qualitative pharmaceutical policy analysis methods to derive a complete picture of the situation, including analyses of policy documents (such as a national medicines policy) and public information sources, key informant or patient interviews, and health facility surveys. Finally, in order to adequately capture all practical effects and lived experiences of existing policies and processes, analyses should encompass stakeholders across the value chain and not be restricted to policy-makers.

Limitations

Inevitably, the compartmentalization of functional components in the pharmaceutical value chain oversimplifies the complexities of the health system and may underplay the importance of upstream factors that determine access to care. It also divides processes which are highly interlinked. At the same time, separating these components helps to put boundaries around complex processes, which minimizes the risk of key functional processes being overlooked, and thus facilitates identification of a range of barriers and enablers. Furthermore, this framework is not all-encompassing. We provide a general structure for systematic analysis of drivers of inaccessibility, but the analysis of access in different countries, therapeutic areas or populations may require the evaluation of other subdomains within these core components. We emphasize that this tool should not be considered a universal checklist, and adaptions to national health

systems may be necessary. Additional cross-cutting themes that cannot be captured in a single core component may also be identified during analysis. Besides these emerging themes, global processes such as *market forces*, *innovation* and *manufacturing* – that undeniably have an impact on access to medicines as well – are not included in this framework as these are often beyond a country's influence [2].

This framework is one outcome of a larger study looking into the barriers and facilitators to childhood oncology medicines in South Africa. With that, there was no protocolized, systematic approach to develop this framework. However, we have nonetheless taken careful approaches to ascertain that it reflects key processes and factors, having taken existing frameworks into consideration in the design of our framework [2, 11-13] and undertaken further verification through iterative discussions among authors.

Conclusion

We propose a widely applicable analytical framework for studying qualitative access to medicines from a country's health system perspective, outlining critical functional processes in the pharmaceutical value chain. We believe this framework could facilitate future analyses of barriers and enablers in accessing medicines, leading to a systematic understanding of determinants of access and potentially guiding targeted policy development. Although we expect the framework to be appropriate for studying other countries, diseases and populations in a structured manner, it is the derivative of a single case study in South Africa. It has yet to prove its usefulness across different contexts, and refinements may be needed to ensure its broad applicability and comprehensiveness. Testing and implementing the proposed framework in various contexts will contribute to its refinement and practical utility.

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Bivatracin
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Kaprofen
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CHAPTER 3.3

Access to childhood cancer medicines in South Africa: a health systems analysis of barriers and enablers

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Submitted

Abstract

Background

Understanding challenges in access to childhood cancer medicines is key in improving outcomes for children in South Africa and reducing health inequities. We sought to identify what barriers and facilitators determine current perceived access to childhood cancer care in South Africa through in-depth interviews with stakeholders in South Africa's public and private sectors.

Methods

Qualitative semi-structured interviews were conducted with 29 key health system stakeholders (September – November 2022), including policy makers and regulators, medical insurance scheme informants, medicine suppliers, healthcare providers and civil society stakeholders. Interviews were audiotaped and transcribed verbatim. Transcripts were theme coded through an inductive-deductive approach by the first author and verified by a second author, structuring determinants of access to medicines according to the pharmaceutical value chain.

Results

Barriers and facilitators were identified across all components of the pharmaceutical value chain, and categorized in functional and contextual themes. Key barriers in access to childhood cancer medicines and treatment included 1) a lack of political commitment to childhood cancers, 2) the lack of registration of new medicines and discontinuation of essential chemotherapeutics, 3) incomplete insurance coverage for childhood cancers, 4) stock-outs of essential medicines, 5) the inability to access care including travel to healthcare facilities, and 6) low awareness on childhood cancers among primary healthcare workers. Proposed priority interventions to address some of these issues include the enabling of flexibilities in pricing, ensuring transparency and consistency in decision-making and healthcare spending, and improved training of primary healthcare staff, nurses and pharmacists on childhood cancers.

Conclusion

This first comprehensive study of determinants of access to childhood cancer medicines in South Africa from the perspective of different stakeholders within the broader context of the healthcare sector provides context-specific evidence to enable appropriate policy development for improved access to childhood cancer care and reduced inequities.

Introduction

Medicines are a core modality of childhood cancer treatment and vital for survival. Improving and sustaining access to essential oncology medicines is crucial for countries aiming to reduce cancer mortality and associated disease burden among their children [1]. South Africa is among those low- and middle-income countries (LMIC) wanting to reach the World Health Organization's (WHO) Global Initiative for Childhood Cancer (GICC) target of at least 60% overall survival for children [1], with current national survival rates of about 50% [2,3]. Barriers in access to cancer medicines for the general population – including unaffordable medicines, stock-outs and inconsistent drug supplies and discontinued manufacturing of medicines by industry [4-6] – may also affect children. Besides a lack of access, other factors that are reported to contribute to poorer survival rates in this group are delays in diagnosis resulting in advanced disease and a worse prognosis, lack of treatment capacity, physical barriers to access care services and treatment abandonment [7].

South Africa currently has a two-tiered healthcare system [8,9]. The proposed National health Insurance (NHI) – with a centralized health financing scheme – is intended to significantly reduce the pervasive health inequities experienced by the socio-economically disadvantaged [10]. Until NHI has been achieved, healthcare is offered to all South Africans for a small fee relative to their income in the public – government funded – sector. Some groups, such as children under 6 years of age and the poorest, are exempted from these fees. Approximately 84% of the South Africans depend on the public sector for their healthcare [11], which is further characterized by a complex pharmaceutical system, in which core processes such as medicine registration and the selection of essential medicines are managed by national bodies, whereas subsequent medicine procurement and care provision are organized provincially. Patients at private sector hospitals and clinics pay for healthcare via medical aid schemes (i.e. insurance) or are faced with out-of-pocket (OOP) payments [4]. In 2020, only about 15% of the population belonged to a medical scheme [12].

To reduce South Africa's childhood cancer mortality and health inequities, a better understanding of how the various pharmaceutical processes may contribute to inaccessibility of cancer medicines is needed. The present study aimed to conduct a health systems analysis of barriers and enablers in accessing pediatric oncology medicine in South Africa. This study can aid in strengthening the health system and identifying crucial policy development areas as South Africa moves towards implementing NHI.

Methods

Participants

Invitations to participate in this study were sent via email to 57 stakeholders in South Africa's pharmaceutical value chain. Five key stakeholder groups 1) policy-makers and regulators, 2) medical insurance scheme representatives, 3) medicine suppliers, 4) healthcare providers, and 5) civil society stakeholders) were chosen to represent all steps in the pharmaceutical value chain (i.e. policy and legislation, medicine regulation, financing and pricing, selection, reimbursement, supply and procurement, healthcare delivery, dispensing, use, monitoring and surveillance). Participants were purposefully selected for their involvement with pediatric oncology medicines, but their activities did not need to be confined to childhood cancers only. Those exclusively involved in adult oncology were excluded from the study. The recruitment process was further informed by referrals from participants during the interview process.

Interview guide

We developed a semi-structured qualitative interview guide drawing from the Paediatric Oncology Systematic Integration Tool (POSIT) to understand key aspects that influence access to childhood cancer medicines [13]. Four main categories used in the interview guide mirrored those of POSIT: *governance*, *financing*, *social aspects* and *medicine delivery* (adapted from *service delivery*). Within these broad categories, open-ended interview questions were constructed to explore barriers and facilitators that stakeholders experienced or perceived in accessing childhood cancer medicines in both the public and the private healthcare sectors (see Appendix 1). A draft of the interview guide was tested in a mock interview and piloted with one participant, which led to minor refinements of the guide.

Data collection and analysis

All interviews were conducted in English from September to November 2022 by IRJ, an academic researcher with prior experience in conducting interviews and who had no previous connection with the participants. Interviews were conducted online or on a convenient location close to the participants' place of residence or work and lasted approximately 45 minutes. All interviews were audiotaped after written and verbal consent from the participant and notes were made during the interviews. Following verbatim transcription, two transcripts were coded together by IRJ and FS to develop a robust coding approach and ensure consistent interpretation. The remaining transcripts were coded by the first author alone. As validation, coding of five interviews (one per stakeholder group) was verified by researcher HAvdH to ensure that no themes were missed and themes were coded consistently. Discussions were held to clarify any disagreements in coding and to reach consensus. Subsequent thematic analysis took place through a mixed approach. The deductive analysis was based on components of the health system in which the pharmaceutical chain resides, which includes two national contextual components (policy and

legislation; monitoring and surveillance) and eight functional components of the pharmaceutical value chain (medicine regulation; financing and pricing; selection; reimbursement; supply and procurement; healthcare delivery; dispensing; use) [14]. The inductive analysis following a modified grounded theory approach [15] where data was coded iteratively to capture emergent themes. Confidentiality of participants was maintained, and data were stored in line with legal requirements such as the Protection of Personal Information Act (POPIA).

Results

A total of 29 stakeholders responded positively to our invitation, and participated in qualitative in-depth interviews (7 policymakers and regulators, 5 medical insurance scheme representatives, 7 medicine suppliers, 6 healthcare providers, 4 civil society stakeholders). Reasons for not wanting to participate included not considering themselves an expert in (childhood) oncology, or having left the field. An overview of participant characteristics is provided in Appendix 2. An overview of identified barriers and facilitators, structured according to the pharmaceutical value chain, is provided in **Figure 1**. In addition to these, four cross-cutting themes emerged during data analysis which intersect multiple components (advocacy; awareness; equity; non-governmental organizations). Additional stakeholder quotes are presented in Appendix 3.

Policy and legislation

Participants repeatedly indicated that pediatric cancers are not a priority due to the small number of children affected compared to adult cancers (and other disease areas). Having no official definition for what constitutes a rare disease complicates this political prioritization. In formulating pharmaceutical policies, both policy-makers and medicine suppliers indicated a lack of constructive dialogue between government and affected stakeholders. It was also indicated that – although a ministerial advisory committee and national cancer strategic framework (NCSF) for cancers exists – it does not include a clear policy for pediatric oncology specifically. Additionally, clarity on its operationalization and subsequent implementation are wanting, likely undermined by a lack of capacity at government level. To ensure implementation of drafted policies, the alignment of policy development and funding through treasury needs to be re-examined.

Prices of medicines in the private sector are currently regulated through the Single Exit Price (SEP) policy, which dictates a universal price at which medicines are sold by the manufacturer to all distributors/dispensers in the country, also removing previously allowed discounts. The manufacturer is free to set the SEP, which must be disclosed publicly. Participants widely agreed that although the SEP policy increased accountability when first implemented in 2004, it now induces higher pricing because suppliers fear other countries use the disclosed prices for international reference pricing. The policy was not considered transparent by most participants,

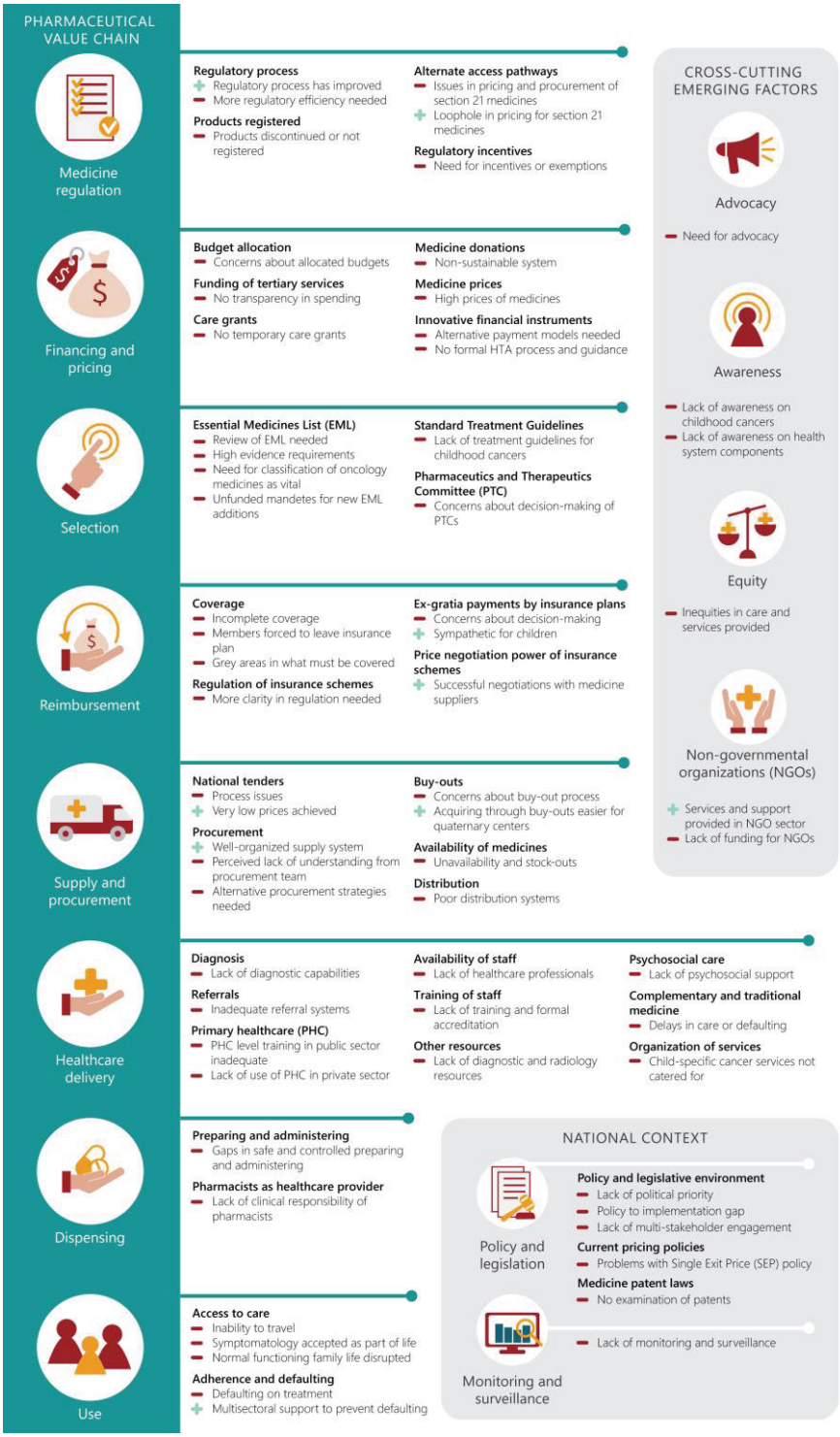

Figure 1 Summary of barriers and facilitators in access to childhood oncology care.

as manufacturers are still free to determine their prices. The lack of flexibility in pricing complicates reasonable pricing or discounting for rare diseases such as pediatric cancers. Finally, South African patent laws need to be revisited, as medicine patent are not sufficiently examined before granting them, thereby also contributing to higher pricing.

> *"In the single exit pricing system, there is, as far as I'm concerned, no transparency, even though government sees it as a transparent system. What is transparent is the price. Yes, we advertise the price. But it's still the pharmaceutical company that is actually deciding and determining the price."*
>
> *Participant 21, civil society*

Medicine regulation

Patient access to novel medicines has become faster in recent years in South Africa, for the regulatory process has become more streamlined and has started to line up with best practices globally. Despite these improvements, participants expressed the hope to further expedite the process and reduce duplication of efforts through harmonization with neighboring countries or a reliance model with other international regulators.

Nonetheless, many participants indicated that key childhood cancer medicines are not registered in South Africa, which means they cannot be listed on the Essential Medicines List (EML) and affecting pricing and reimbursement as well. In pediatric oncology, this is a multipronged problem: 1) there are significant problems with older but essential products being discontinued, 2) there is a lack of age-appropriate formulations, and 3) newer products are never filed for registration due to the small market. To incentivize registration of orphan drugs, there is a need for regulatory incentives such as expedited approvals, exemptions from importation requirement or tax reductions.

Section 21 of the Medicines and Related Substances Act 1965 (Act 101 of 1965) allows pre-registration access to medicines and thus provides an alternative access pathway. This access pathway was associated with many issues, including 1) a lack of transparency in their pricing, 2) exponential pricing for small patient groups due to post-importation testing and local packaging requirements, 3) limited compensation by insurers for these medicines, and 4) considerable delays in acquiring products, which can be detrimental for childhood cancers. As section 21 medicines are not subject to the SEP policy requirements, there are opportunities for discounting and price negotiations with manufacturers. One medicine supplier indicated that, hence, this access pathway is sometimes preferred for small patient populations.

> *"If you've got a pediatric oncology patient or a patient that needs something tomorrow morning, if it's unlicensed, that's not happening. That process can be anywhere from two to four weeks, to get a product from the US or from Europe, into South Africa."*
>
> *Participant 19, policy-maker/regulator*

Financing and pricing

With regard to budget allocation for health services, including medicine procurement, participants expressed concerns about allocated budgets based on what was historically assigned, as well as concentration of funds in one province (Western Cape). Healthcare providers also expressed frustration at the lack of transparency in the spending of the National Tertiary Services Grant (NTSG) – a grant that can be used by public sector hospitals to procure medicines outside of the EML – desiring clarity on the available budgets and where it is spent, if not on pediatric oncology. Furthermore, participants indicated a need for renewal of a temporary grant system to assist families with increased expenses due to cancer treatment. Participants had mixed feelings about medicine donations, being grateful for the support yet cautious about continuity of services when donations are discontinued.

High cancer medicine prices were broadly identified as a barrier. Some participants expressed incomprehension at the high prices, since marketing of medicines on the South African market generally occurs much later than in Europe or the United States. The need for alternative reimbursement/payment models in the pricing of novel and orphan medicines was thus repeatedly voiced by stakeholders across the value chain. However, the lack of Health Technology Assessment (HTA) and a responsible agency in South Africa was identified as an obstacle in achieving this. In the private sector, participants indicated a need for clarity around the definition of value and the role of HTA in reimbursement decisions, with consistency across medical schemes.

> *"We know that we're actually not the first country that's prioritized for the introduction of a new molecule. […] But we are subjected to the same requirements by companies who say: "I need to recoup the money that I put into making this drug". […] Firstly, but secondly, the purchasing power parity of the rand, what a rand buys to what a pound buys in the UK, those are two different things. But we find ourselves paying exactly the same prices, especially when it comes to oncology drugs. And we feel that is very much unfair."*
>
> *Participant 5, policy-maker/regulator*

Selection

The Standard Treatment Guidelines (STGs) and associated National Essential Medicines List (NEML) are key in guiding the rational use of resources and medicines in the South African public sector. Childhood cancer medicines are used exclusively in tertiary or quaternary settings and therefore included in the tertiary/quaternary NEML. This list is – unlike the primary and secondary NEML – not accompanied by STGs. This was viewed as logical by health care providers, given that these medicines are solely prescribed by experts, whereas policy-makers voiced worries about the lack of accountability of services. Additionally, policy-makers and regulators indicated that the current tertiary/quaternary NEML is still adult-dominated, due to the limited attention that has been paid to (less prevalent) pediatric indications since inception

of the list. A thorough review of the completeness of the NEML was thus advised. Pediatric oncologists should be actively involved in this, whose engagement in and advocacy on this matter was previously felt to be missing by policy-makers and regulators. On the other hand, healthcare professionals expressed having difficulties in getting childhood cancers medicines on the NEML, as evidence for children is often more anecdotal and based on expert opinion. Current NEML evidence requirements do not cater for this and should be reviewed. However, even when medicines do make it on the NEML, expensive medicines in particular risk being designated as an unfunded mandate by individual provinces that lack the funds to cover their procurement. This threatens the sustainability of the NEML system. Finally, one participant advocated for oncology medicines to be classified as *vital* instead of *essential* because of its progressive nature, which could trigger faster responses from the procurement team in case of stock-outs.

> *"So at the moment, a lot of policy is driven from a very strong evidence-based medicine perspective. […] Problem when you're sitting around the table and trying to make decisions about pediatric oncology, is that that evidence base is largely derived from adults medicine, and quite often very weak compared to on the ground clinical outcomes."*
>
> *Participant 14, medicine supplier*

At local level, concerns were raised about decision-making of Pharmaceutics and Therapeutics Committees (PTCs). These committees govern medicines use at provincial, district, sub-district and health facility level, and must approve use of medicines outside of the NEML. Voiced concerns included 1) their lack of transparency and consistency in decision-making and spending, 2) the lack of expertise of committee members in pediatric oncology, which was felt to be necessary to understand why patients require medicines outside of the NEML, 3) duplication of efforts across provinces and hospitals, 4) high evidence requirements, which preclude approval, and 5) the time and effort clinicians need to invest to prepare a motivation for a given medicine.

> *"The representatives on the PTC is not very often oncologists. So if you're not an oncologist, you're not going to know how important the drug is that we are motivating for."*
>
> *Participant 24, healthcare professional*

Reimbursement

Over 70 medical aid schemes are available in South Africa to assist with managing medical expenses within the private sector. However, civil society stakeholders indicated that many families with medical insurance do not have cancer benefits, having purchased only basic insurance plans (at so called prescribed minimum benefit (PMB) level) or not having purchasing specific cancer coverage options. Treatment components which are almost always excluded

from coverage include blood works, prosthetic limbs and palliative care. High co-payments may be imposed on families without cancer coverage, or once insurance benefits are exceeded. These may force members to leave their insurance plan and seek treatment in public sector facilities. Other families are forced to abandon their insurance because income was lost due to one parent needing to accompany the child during treatment.

> *"In the private sector, it's dependent on the medical scheme. And if they don't have cancer benefits, then you're stuck. And I mean, that's the reality because the majority of people do not buy medical insurance with the perspective that my child is going to be diagnosed with cancer, so most people have hospital plans. So they have a basic and a hospital plan. And therefore they don't have any of the plans that would cover cancer treatments, and cancer treatments in the private sector is horrifically expensive."*
>
> *Participant 21, civil society*

However, insurance schemes may opt to reimburse medicines and services not part of an individuals benefit package. These are called ex-gratia (or ad-hoc) payments. Participants had several concerns about the decision-making process for these payments, which include 1) the lack of clinical evidence that complicates decision-making, 2) that the extent to which clinicians and parents advocate for a medicine affects the outcome of the decision, and 3) the lack of transparency and consistency in decision-making of insurance schemes. Medical scheme representatives indicated that they are sympathetic towards children and often offer (partial) coverage.

Several deficiencies in the regulation of insurance schemes, provided by the Council for Medical Schemes, were also revealed by participants. These included controversies over what must be covered by insurers, due to 1) unclarity when treatment is for cancer eradication versus palliative care, and 2) private sector facilities pointing to standards of care in public sector facilities where treatment options may be more limited. In addition to this, reform was requested on 1) how PMBs are defined, potentially based on which services are essential versus which diagnoses are covered, and 2) guidance of the Council for Medical Schemes to funders which medicines to reimburse, to increase consistency in the process and decisions towards reimbursement.

> *"So the big issue is like, where is the treatment for cancer eradication versus palliative care, etc? Those are not necessarily fully defined exactly what should be covered, not covered. But because most medical schemes create financial limit, inevitably, it blurs the line."*
>
> *Participant 8, medical aid scheme representative*

Supply and procurement

For the public sector, those medicines that are on the NEML are procured through national tenders. Participants indicated that although very low medicine prices are achieved through this system, not all products are successfully tendered for due to a lack of bids. Medicine suppliers suggested that the State's low price expectations can make bidding unprofitable. It was

suggested that the possibilities for pooled procurement should be investigated to increase suppliers' interest in the South African market, and by extensions that of other countries in the region. Other reasons for unsuccessful tenders include low volumes needed by the state and too comprehensive requirements keeping suppliers from bidding. Instead, suppliers were criticized for pursuing more advantageous pricing through buy-outs. Other concerns about the tender process include the lack of accountability when suppliers are unable to supply what has been agreed upon, as well as misalignment between tender cycles – which run for two or three years – and entry of new (generic) products on the market.

> *"First of all, they don't tender for it. If they do tender, then they actually at times give you delays in acquiring. […] I would say 80% of them are good. But the problem with chemotherapies is it comes in a package. And you can't suddenly say I'll use half of your package and the other half [not]."*
>
> *Participant 3, policy-maker/regulator*

Medicines not successfully procured through the tender process and products that are not listed on the NEML must be acquired through a buy-out process. This process is organized provincially or locally. Buy-outs – needed regularly in pediatric oncology – are associated with several drawbacks according to participants. These include that 1) procurement can be delayed given that buy-outs take time, with insufficient stocks to bridge the interim, 2) provinces have limited budget to spend on medicine procurement, further complicating this process and 3) supply cannot be guaranteed for products not on contract. Given that childhood oncology treatment is often concentrated in major quaternary centers, the buy-out process is easier to navigate because these centers have bigger budgets and well-established contacts with suppliers.

On a local level, some healthcare providers indicated having reliable and timely procurement processes in place in their respective hospital, whereas others expressed frustration at the lack of compassion and urgency from other members in the procurement chain when confronted with stock-outs. Participants speculated that not all members are aware that medicines on the NEML should always be available. Additionally, communication with the provincial medicine depot can be arduous, causing delays in procurement. Some healthcare providers also suggested that distribution systems are inadequate, with products not reaching treatment facilities or no ability to maintain cold chain.

> *"Nowadays you just send it with the ambulance driver and you can't even maintain like cold chains and things. There are no pharmacy courier services available anymore. So there's no way of getting therapies in any reasonable time actually from one hospital pharmacy to another."*
>
> *Participant 26, healthcare professional*

As a result of these barriers, some healthcare providers reported recurrent stock-outs in their facilities, while others indicating having almost no shortages. If stock-outs occurred, it resulted

in disrupted treatments or medicines omitted from treatment regimens. Although shortages can sometimes be solved by buying items from private sector facilities, 1) there is usually a delay of 4-5 days disrupting treatment and 2) private sector stocks are insufficient to supply the entire public sector. Besides shortages of chemotherapeutics, availability of antiemetics and palliative care medicines at pharmacies for use at home is often problematic.

Healthcare delivery

Late detection of childhood cancers was stressed as a major contributor to poor outcomes in the public sector by all stakeholder groups. Several factors contribute to late diagnoses, including delayed health seeking behavior, poor recognition of symptoms by primary healthcare (PHC) workers and the general public, consequent misdiagnoses, and a lack of diagnostic tests performed at PHC level. To achieve earlier detection, participants proposed that the general level of training at PHC level requires improvement, including training on recognizing cancer symptoms and doing bloodwork. Participants also suggested that overburdening of the clinics contributes to low motivation of personnel and missed diagnoses.

Further delays in diagnosis and treatment often occur due to the limited number of pediatric facilities and specialists in the country. Additionally, participants indicated interprovincial referrals – necessary because not all provinces have pediatric oncology units – can be uncertain in both the public and private sector. In the private sector, late detection of cancers may be due to parents passing over PHC level, and immediately seeking healthcare from specialists instead. Waiting times at hospitals may thus contribute to delayed diagnoses.

Participants highlighted a lack of healthcare professionals at all levels of care and from all disciplines, including pediatric oncologists, hematologists, specialized nurses and pharmacists, palliative care specialists and PHC workers. The shortages lead to overburdening, staff leaving, long waiting times, and untrained staff performing duties for which they received no training. The insufficient number of healthcare professionals is compounded by a lack of (formal) training opportunities for oncology pharmacists, pediatric oncology nurses and palliative care specialists, according to healthcare professionals themselves. Participants called for formal training platforms, formal accreditation for pediatric oncologists and hematologists, and continued monitoring and development of skills on the work floor.

> *"First of all, pediatrics have got no nurse trained [in] pediatric oncology [...]. And there's no training platforms for them either."*
>
> *Participant 3, policy-maker/regulator*

> *"As a pharmacist, I don't like the fact that I'm teaching myself everything, there isn't support in terms of equipping the people who are in the field. It's tragic that I did not learn about pediatric oncology yet I'm expected to practice in it."*
>
> *Participant 25, healthcare professional*

Besides chemotherapy, other resources and disciplines are involved in diagnosis, treatment and follow-up care. Multiple barriers were identified in these. Firstly, healthcare professionals indicated that there is an increasing need for diagnostic and radiologic resources such as PET (positron emission tomography) and/or CT (computed tomography) scanners. Secondly, participants considered mental health of children with cancer not to be a priority in the public sector, again compounded by overburdened staff. There are almost no government-provided social workers. Thirdly, a participant pointed out that there is historically little attention for palliative care, with 1) palliative care currently not being a recognized specialty, 2) little to no dedicated pediatric palliative care services available in hospitals and 3) insufficient coverage within medical aid plans. In fact, limited knowledge of healthcare professionals on palliative care even contributes to discontinuation of palliative care and insufficient stocks of morphine in pharmacies. Despite this, recognition for palliative care in oncology seems to be increasing.

On an organizational level, healthcare professionals pointed out that cancer services are centered around adults, with little recognition for the needs of children. Examples mentioned include the lack of oncology services over the weekend (although pediatric regimens can run 5-7 days), or children aged 12 and older being treated in adult wards.

Dispensing

Several participants expressed concerns about the quality of pharmaceutical oncology care. In particular, the preparing and mixing of therapies performed without equipment or training is concerning. This is compounded by deficient Good Pharmaceutical Practice (GPP) guidelines. In addition to this, chemotherapeutics are regularly administered by individuals without appropriate training due to a lack of pediatric oncology nurses. Pharmaceutical care may also be compromised due to a lack of clinical responsibility of pharmacists, despite their involvement being considered crucial in pediatric oncology by healthcare professionals.

> *"If you read the GPP [Good Pharmaceutical Practice] documents, you will see that it is non-committal. It allows a wide scope of practice. So what is happening at the moment in South Africa is the most of the mixing of chemotherapy is happening in doctor-driven practices in facilities that are not registered with the Pharmacy Council."*
>
> ***Participant 14, medicine supplier***

Use

A range of stakeholders highlighted the social barriers around childhood cancer treatment. Families' inability to travel was considered an important one, given that distances to specialized treatment facilities can be far and travel costly. Establishing pediatric cancer care facilities closer to home was recommended by all stakeholder groups. Another social barrier identified was the generally delayed health-seeking behavior, because symptomatology may be accepted as part of life. This was indicated as a complicating factor to late diagnoses. Other parents may be late to bring their child to a health facility because they seek help from traditional healers first.

Finally, cancer treatment may considerable disrupt the life of the child and its family on multiple levels, due to missing school, fragmented families for an extended period of time, and lost earnings by the caregiver accompanying the child.

Potential defaulting on treatment was also identified as a user barrier. Healthcare professionals and civil society stakeholders attested that defaulting happens occasionally, due to 1) resistance to surgeries, particularly inoculations and amputations, 2) caregivers' believe that the child has been cured when it shows signs of improvement, and 3) financial constraints. Some abandon chemotherapy treatment temporarily to consult a traditional healer, significantly contributing to poorer outcomes. Multisectoral support by non-profit-provided social workers and invested physicians – as well as financial aid – can help to prevent defaulting.

> *"Patients do not even have money for food. So they would rather concentrate on what is essential than getting the child to the hospital and spending money on transport to the hospital."*
>
> *Participant 24, healthcare professional*

Monitoring and surveillance

Participants indicated little resources being allocated to monitoring and surveillance, also demonstrated by an inaccurate cancer registry. Electronic instead of paper-based healthcare records were proposed as a means to facilitate surveillance and identify missed diagnoses. More accurate prevalence rates could contribute towards easier price negotiations and increased access.

> *"So in the Western Cape, they're building an electronic health record. You can see somebody was seen at a clinic. Somebody could look at this from the outside and go, hang on that doesn't look right. In a rural area, that paper record is inaccessible. And we don't know who's being missed, nobody is checking."*
>
> *Participant 2, policy-maker/regulator*

Emerging cross-cutting themes

Several themes emerged as intersecting barriers across multiple components of the pharmaceutical value chain. These included:

Advocacy

A range of stakeholders – including policymakers – indicated the need for advocacy by clinicians, and advocacy and non-governmental organizations (NGOs) on numerous issues. These included 1) the manufacturing or marketing of (discontinued) medicines, 2) inclusion of essential childhood oncology medicines in the NEML, 3) lack of clinical standards for pediatric oncology, 4) coverage of childhood oncology medicines within the PMBs, and 5) policy development for childhood cancers and rare diseases in general. However, despite its emphasized importance, there were opposing views on whether adult and child oncology advocacy should be unified or

separated. Additionally, civil society stakeholders considered their advocacy efforts effective, whereas policymakers and regulators expressed that they had not picked up on any advocacy for pediatric oncology.

Awareness

All stakeholder groups emphasized the need for increased awareness on childhood cancers, among PHC workers, traditional healers, early childhood development systems (schools and baby clinics) and the general public. In like manner, there was felt to be insufficient awareness on 1) referral pathways among patients, 2) Section 21 access among prescribers and patients, 3) medical aid rules among members, and 4) bone marrow transplants among possible donors.

Equity

All stakeholder groups pointed out persistent inequities in (access to) childhood cancer services, between 1) urban and rural areas, 2) between the public and private sector, 3) between facilities – within both the private and public sector, 4) between medical aid schemes, and 5) between provinces.

Non-governmental organizations

Healthcare providers and civil society stakeholders highlighted the importance of NGOs in the pediatric oncology field, by providing numerous essential services and support, including 1) awareness programs among PHC workers, traditional healers and general public, 2) travel aid, accommodation, food packages and toiletries for public sector parents, 3) wheelchairs and pressure mattresses for at home, 4) financial assistance to pay medical aid member fees and co-payments, 5) monetary support for prosthetics, and 6) psychosocial support services. However, civil society stakeholders experienced financial challenges as they are not supported through government funding, despite providing several essential services.

Discussion

Health systems research is vital to inform policy development and advocacy efforts for childhood cancer in LMICs, enabling the identification of barriers to childhood cancer care and facilitating targeted health system improvements to address them effectively [19]. We performed such a comprehensive health systems analysis of determinants of access to childhood cancer medicines in South-Africa, providing context-specific data on how various national pharmaceutical processes contribute to access. Key issues in accessing medicines – noted by multiple stakeholders or indicated as major barrier by stakeholders – include 1) a lack of political priority given to childhood cancer (medicines), 2) no registration of novel drugs as well as discontinuation of traditional chemotherapeutics from the market, 3) incomplete insurance coverage for childhood cancers and 4) (intermittent) stock-outs of essential medicines. However, broader health system determinants relevant to childhood cancer care

were also identified, including low awareness on childhood cancers among PHC staff and the general public, and patients' inability to access care facilities. The need for flexibilities in the SEP policy, regulatory incentives for orphan medicines, transparency in decision-making processes and healthcare spending, and improved training of PHC staff, nurses and pharmacists in pediatric oncology emerged as priority interventions to improve childhood cancer medicine access and equity in South Africa.

In an LMIC still battling high rates of HIV and TB [20], the lack of consideration given to childhood cancers – also compared to more common adult cancers – is not unexpected, yet remains highly problematic due to the aggressive nature and unique treatment requirements of pediatric cancers. Limited policy commitment for pediatric oncology was also observed in other countries on the African continent [21, 22], and LMICs elsewhere [23]. Interviews with stakeholders revealed that the limited attention for childhood cancers is encountered in all stages of the South African pharmaceutical value chain, from the policy arena to the organization of healthcare services and among cancer advocacy organizations. The rarity of these diseases further complicates the lack of priority given to them. In a country without an official definition of what a rare disease entails, a new way of dealing with these type of diseases is urgently required: from targeted policy development, to creating regulatory incentives for small patient populations, tailored pricing solutions and HTA, adapting evidence requirements by decision-making bodies (the NEML committee, PTCs, and for ad-hoc payment decisions) as well as reflecting childhood cancer treatment modalities in PMBs.

However, in a country with limited legislative capacity, the present focus on achieving NHI leaves little room for addressing the deficiencies in existing healthcare policies, despite the evident need and desire for it [24]. Still, other possible interventions that do not require major legislative changes exist and include the need for (improved) training platforms for PHC staff, nurses and pharmacists in pediatric oncology, more clarity on regulations in the private funding environment by the Council for Medical Schemes, increased transparency in decision-making processes, revising GPP guidelines and expansion of existing awareness efforts [25]. Internally, provinces and hospitals should address known inefficiencies in procurement [5, 26] and educate their personnel where necessary.

Interviews with stakeholders from different provinces and hospitals again highlighted the differences between some of the centers of excellence in the provinces of Western Cape and Gauteng compared to the other treatment facilities in the country [27]. Where some participants reported having well-organized supply systems and no problems acquiring products outside of the NEML, others faced significant obstacles in getting access to products that are not on the NEML. This disparity highlights the importance of the NEML in providing access to medicines. The apparent lack of engagement from some of the specialized treatment centers in the NEML is thus particularly detrimental for some of the smaller units, that would benefit from the large

quaternary hospitals taking the lead in improving these core structures and advocating for more essential childhood cancer medicines on the NEML. This could also reduce the number of medicines that need to be bought out [5], increasing the affordability and sustainability of the system as a whole. Additionally, since the expansion of services – especially by establishing new pediatric cancer units in provinces where there are currently none – was reiterated as an important intervention to increase access, a more inclusive NEML would benefit novel treatment units as well.

An important strength of this study is the number of stakeholders interviewed (n=29), together representative of the wide range of stakeholders. This complete analysis of the South African pharmaceutical value chain has identified known [4-7, 25-28] and unknown weaknesses in the system, providing a comprehensive overview of the barriers and facilitators to access. Although our aim was to obtain a better understanding of how various pharmaceutical processes contribute to inaccessibility of childhood cancer medicines, the interviews brought forth broader health system barriers. Given the tight link between access to medicines and broader care delivery – particularly in cancer care – these factors have been incorporated in the overview. To which extent the identified barriers may impact adults was not specifically studied, but we infer that several factors likely affect the general population as well. Additionally, we did not study international drivers of access (such as international market forces, global shortages, and R&D and innovation) which undeniably affect access on a country level. Furthermore, despite the significant number of participants, our sample did not include participants from all nine South African provinces. With that, this study is not an exhaustive comparison of regional barriers but rather an analysis of the entire system, indicative of the systemic issues at play. Finally, despite efforts to limit participant and researcher biases (i.e. introducing the study, establishing rapport with participants, asking probing questions, using a standardized interview guide), these biases are inherent to this type of research and cannot be completely eliminated.

Conclusion

This is the first comprehensive study of determinants of access to childhood cancer medicines in South Africa, adding to a growing evidence base on access to childhood cancer medicines in LMICs. The substantial number of – larger or smaller – barriers identified across the pharmaceutical value chain suggests that a step-wise approach is needed to address the issues. The context-specific evidence generated can enable appropriate policy development and advocacy efforts for improved access to childhood cancer medicines and reduced health inequities.

Ethics statement

Institutional approval was obtained from the Science-Geosciences Ethics Review Board (SG ERB) of Utrecht University (Bèta S-22784) and the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal (BREC/00004635/2022).

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Supplementary materials

Appendix 1: Interview guide

[Introduction]

Policy environment or governance.

[This theme captures the means by which childhood cancer services are organized, managed, and regulated. It includes topics such as the policy environment, priority setting and clinical standards.]

What can you tell me about the policy environment for childhood cancers?

Do you know of any policies being developed to improve access?

Is childhood cancer a priority in your view? What do you think about that?

What is your view on clinical standards for childhood cancers?

What do you think are barriers or facilitators to access here in your experience?

How do you think the policy environment is different for childhood cancer medicines versus medicines for children and adults in general?

Financing

[Financing encompasses the generation, pooling, and allocation of collective funds to cover childhood cancer medicines, as well as the methods of payment for individuals and organizations involved in childhood cancer care.]

Can you tell me about how the funds for childhood cancer medicines are generated?

Can you tell me about how the funds for medicines are distributed and how this impacts access to these medicines?

Probes:
- Innovative financial instruments
- coverage for childhood cancer; special access programs
- compensation for childhood cancer
- payment methods

What do you think are barriers or facilitators to access here in your experience?

How do you think financing is different for childhood cancer medicines versus medicines for children and adults in general?

Social aspects of care

[This theme includes population characteristics and health behavior.]

What is your view on social determinants and access and adherence to cancer medicines? Probes: income level, distance to health facility, patient characteristics.

What do you think are barriers or facilitators to access here in your experience?

How do you think social aspects are different for childhood cancer medicines versus medicines for children and adults in general?

Medicine delivery

[This theme covers the structures, resources, and medicines required for the direct provision of care.]

Can you tell me about the procurement, storage and distribution of childhood oncology medicines and how this impacts access to these medicines?

Can you tell me about the availability, prescription and use of these medicines and how this impacts access to these medicines?

What do you think are barriers or facilitators to access here in your experience?

How do you think medicine delivery is different for childhood cancer medicines versus medicines for children and adults in general?

[Closure]

Appendix 2: Participant characteristics

Table S1 Baseline characteristics of participants.

Group	Participants (n)	M/F (n)	Age (median; range)	Years of experience (median; range)
Policy makers and regulators	7	3/4	57 (38-62)	25 (7-41)
Medical schemes	5	2/3	50 (36-61)	25 (11-28)
Medicine suppliers	7	5/2	42 (33-58)	11 (5-30)
Civil society	4	1/3	48 (43-62)	16 (6-25)
Healthcare providers	6	2/4	48 (34-66)	17 (2-37)
All	29	13/16	49 (33-66)	19 (2-41)

M = male; F = female.

Appendix 3: Selected stakeholder quotes for identified barriers and facilitators

Table S1 Selected stakeholder quotes.

POLICY AND LEGISLATION	
Policy and legislative environment	
Lack of political priority	
Policy maker/ regulator	"It's [pediatric oncology] such a small area that often I do think it gets neglected as being thought of as something on its own. We always try to consider pediatric oncology when we're looking at the general oncology space, but it doesn't always fit nicely into that kind of basket."
Policy to implementation gap	
Medicine supplier	"My concern with South Africa is that we are very good at writing policy documents, we are very good at saying what we want. However, when it comes to implementation, it's quite slow."
Civil society	"There are a lot of things that can be done in terms of law, policy, setting up institutions or units within government. But all of that is hamstrung by lack of state capacity."
Lack of multi-stakeholder engagement	
Medicine supplier	"There's a huge need for government and the private sector – and here the private sector we talk about funders, physicians and the pharma industry – to have actual dialogues. And I think this is something which is missing. And I don't like to say it, but it generally is because government is extremely difficult to nail down, to get to a meeting, or to understand who the right level of stakeholder is."
Policy maker/ regulator	"I think in engaging government [...], at least from my experience what we find is that from the stakeholders like your pharma industry stakeholders, they engage government from a combative point of view. Which does not help anybody, because everybody then ends up being defensive."
Current pricing policies	
Problems with Single Exit Price (SEP) policy	
Civil society	"In the single exit pricing system, there is, as far as I'm concerned, no transparency, even though government sees it as a transparent system. What is transparent is the price. Yes, we advertise the price. But it's still the pharmaceutical company that is actually deciding and determining the price."
Medicine supplier	"So the two biggest barriers for us is reference pricing [by other countries], international benchmark pricing, and the SEP. Because our SEP is visible, and it's published on a public website, and everybody [other countries] can access that."
Medicine patent laws	
No examination of patents	
Civil society	"So there are issues in patent law in South Africa that... [...] South Africa grants many more patents than comparable countries like India and Argentina. And there's been comparisons done, that show this, we grant an inordinate amount of patents, often poor quality, secondary patents. And that's due to various shortcomings in our law. [...] But we don't examine patents, we grant them and then they get appealed. [...] So that's one thing once a patent is granted, it's very hard in our legal framework to overturn the patent."

REGULATION	
Regulatory process	
Regulatory process has improved	
Healthcare professional	"The regulatory process here used to be quite long and laborious, but it's become fairly streamlined, so the average time to registration of a generic item is about 250 days and for a new chemical entity about 500 days. So, it's fairly expedited compared to the past."
More regulatory efficiency needed	
Medicine supplier	"The hope – obviously – is that with our regulator we can also move to sort of a reliance model, where the South African regulator can start looking at how the first launch country regulators – like the FDA or the European Union – are dealing with these things, and hopefully piggyback off of a lot of that.
Civil society	"And I guess one of the solutions that people keep talking about is kind of regulatory harmonization? Which I think is critically important."
Registered products	
Products discontinued or not registered	
Healthcare professional	"I think biggest barriers for us are, obviously, the fact that some of your medication are just not registered for whatever reason that may be."
Policy maker/ regulator	"I mean we constantly get companies who are discontinuing medications because they're just not a... it's just not economical for them."
Healthcare professional	"There's no child friendly formulations [available], right? That is like, we are always trying to find our way around. Even etoposide capsules, it's a 50 milligram capsule, children sometimes need less than that. Even getting the capsule is like finding a piece of gold."
Alternate access pathways	
Issues in pricing and procurement of section 21 medicines	
Medicine supplier	"If you've got a pediatric oncology patient or a patient that needs something tomorrow morning, if it's unlicensed, that's not happening. That process can be anywhere from two to four weeks, to get a product from the US or from Europe, into South Africa."
Medical scheme	"When you do that [section 21 access], then you have to go and procure outside of the country, and you have to find who's going to deliver the best price. [...] Was that the cheapest price or not?"
Loophole in pricing for section 21 medicines	
Medicine supplier	"Section 21, which allows you pre-registration access, is probably the best way to deal with this [high molecule costs] long term. Because unlike once you get it registered when we have to have a single exit price which becomes visible to the rest of the world, your section 21 is not visible. So for small patient numbers, you can actually come up with a pricing solution which is more relevant to maintaining access for those patients."
Regulatory incentives	
Need for incentives or exemptions	
Policy maker/ regulator	"I think we probably have to think out the box in terms of orphan diseases, that kind of priority, how do you prioritize rare pediatric cancers? You know, is there a tax break, is there a VAT, do you have a regulatory environment that is quick through the process to do that, how do we make it viable for that? I think that's not been well discussed."

Medicine supplier	"To have products available in local packs is a barrier, because it's quite costly and increases the cost price of medicine and then eventually the SEP. So if we can have exemption from those requirements, I think there will be a definite increase in access."

FINANCING AND PRICING	
Budget allocation	
Concerns about allocated budgets	
Policy maker/ regulator	"And our budget, it's not at the moment much… it's more historically assessed. Oh you spend so much, so I give you 10% more. They don't look at what is needed and what the gap is, you see."
Funding of tertiary services	
No transparency in spending	
Healthcare professional	"There's this national tertiary grant that we can access. But I don't know what's happening with this national tertiary grant. […] Can we access this NTS [National Tertiary Services]? Is this NTS budget available? Because we should be able to access this national tertiary grant, if the budgets elsewhere is being exhausted."
Care grants	
No temporary care grants	
Healthcare professional	"In the past, we could apply for grants for our patients. So while they are on treatment, we apply for the grant, for them to at least have transport money to get to the hospital, we could actually motivate for the grant to be renewed every two years or every three years. And once a treatment is completed, we can say stop the grant. That system has completely fallen away."
Medicine donations	
Non-sustainable system	
Policy maker/ regulator	"It's often a difficult avenue though, to kind of manage I think, and I mean I think – I know it's bad to say – but often we look at donations with a little bit of skepticism, because they are great for a period of time and then they come to an end and then the service that you were providing, now all of a sudden you need to either find funds to cover it or all patients then go without the service, so that's just one of the concerns in that space."
Medicine prices	
High prices of medicines	
Policy maker/ regulator	"We know that we're actually not the first country that's prioritized for the introduction of a new molecule. […] But we are subjected to the same requirements by companies who say: "I need to recoup the money that I put into making this drug". […] Firstly, but secondly, the purchasing power parity of the rand, what a rand buys to what a pound buys in the UK, those are two different things. But we find ourselves paying exactly the same prices, especially when it comes to oncology drugs. And we feel that is very much unfair."
Innovative financial instruments	
Alternative reimbursement/payment models needed	
Policy maker/ regulator	"If you want to look to attract, then you need to have innovative modeling in terms of how you would consider payment, what your reimbursement models are, we need

	innovative reimbursement models in less prioritized diseases, various diseases, we need to find how to do that. And so that's a leap. That's, that's a new language."
No formal HTA process and guidance	
Medicine supplier	"If we had some sort of independent organization who could look at these and give guidance to both the government and the private sector, that makes sense. What I don't like at the moment is because the government don't really ask for it, we just use the HTA as almost a value add when you're trying to go into a tender process or buy-out process. In the private sector, every funder wants you to submit an HTA to them, and each of them charge you a fee for reviewing it. But yet, they don't have a outcome in terms of what that means for reimbursement."

SELECTION	
Essential Medicines List (EML)	
Review of EML needed	
Policy maker/ regulator	"The kick starter has been adult medicine for whatever it was, adult oncology, adult cardiology, it was always going to be adult because that were the big users. And so it's only now this realization that pediatric psychiatry is important, or pediatric neurology and that… So I think there's a lot of catching up to do to inform decision-making on the EML. And so I think we're very behind on that."
High evidence requirements	
Medicine supplier	"So at the moment, a lot of policy is driven from a very strong evidence-based medicine perspective. […] Problem when you're sitting around the table and trying to make decisions about pediatric oncology, is that that evidence base is largely derived from adults medicine, and quite often very weak compared to on the ground clinical outcomes."
Need for classification of oncology medicines as vital	
Policy maker/ regulator	"We've been fighting a long time asking for these drugs to become vital on the VEN [vital – essential – necessary] analysis for WHO. We think it's so important, it shouldn't be essential, it should be vital, like adrenaline or like any of those drugs. Because, one, the cancer is growing when you don't treat. Number two is, if you treat ineffectively, you don't get the responses you're supposed to get. And so these are challenging endpoints that are contributing significantly to the poor outcomes that we have within the developing world."
Unfunded mandates for new EML additions	
Civil society	"And then all the province will just come back and say it's an unfunded mandate, meaning you've put it on the essential medicines list. So yes, it may be on the EML but sorry, either me or the province don't have the money to actually buy it."
Standard Treatment Guidelines (STGs)	
Lack of treatment guidelines for childhood cancers	
Policy maker/ regulator	"It [lack of STGs for childhood cancers] makes it difficult to hold health systems to account to a standard. If something is on the essential medicines list and there's a clear standard treatment guideline, it's very easy to point to a lack of service and say that's what is guaranteed, and you're not doing it. When you've just got a [tertiary essential medicines] list without details, it's open to interpretation."
Policy maker/ regulator	"The reason why we don't create STGs for tertiary drugs, is the fact that these drugs are being utilized by specialists. And because they're being utilized by those people,

	you need to know your work to get to that level. And so it doesn't make sense to us to create, and to include them into any document."
Pharmaceutics and Therapeutics Committee (PTC)	
Concerns about decision-making of PTCs	
Policy maker/ regulator	"So each PTC meeting, it's confidential and there isn't clear reporting. What was paid for, what wasn't paid for, why it wasn't paid for and how much was even paid. So we aren't very good at transparency of expenditure in the public sector."
Healthcare professional	"Because the provincial PTC, half the time they are not meeting often, especially during COVID they didn't have any meetings. Or the process stops there just because they would say 'not enough evidence' or 'too expensive'. It's not vital."
Healthcare professional	"The representatives on the PTC is not very often oncologists. So if you're not an oncologist, you're not going to know how important the drug is that we are motivating for."
Healthcare professional	"There's so much duplication of what we [all provincial PTCs] are doing."

REIMBURSEMENT	
Coverage	
Incomplete coverage	
Civil society	"In the private sector, it's dependent on the medical scheme. And if they don't have cancer benefits, then you're stuck. And I mean, that's the reality because the majority of people do not buy medical insurance with the perspective that my child is going to be diagnosed with cancer, so most people have hospital plans. So they have a basic and a hospital plan. And therefore they don't have any of the plans that would cover cancer treatments, and cancer treatments in the private sector is horrifically expensive."
Members forced to leave insurance plan	
Civil society	"Most cases, I find it's because the one parent has to leave their jobs. So the income has either been cut in half or has like busy financial needs."
Grey areas in what must be covered	
Medical scheme	"So the big issue is like, where is the treatment for cancer eradication versus palliative care, etc. Those are not necessarily fully defined exactly what should be covered, not covered. But because most medical schemes create financial limit, inevitably, it blurs the line."
Medicine supplier	"Now, the prescribed minimum benefit, fine as a concept, that really points to the standard of care which is available in the public sector. And what we've all seen, I mean, the standard of care in the public sector, unfortunately, is going nowhere. [...] So that has a direct and maybe a convenient consequence for the private funders in saying when we start bringing in innovation around, for example, rare diseases or new innovations in oncology, they don't have to pay for it."
Regulation of insurance schemes	
More clarity in regulation needed	
Medical scheme	"The way that the regulations are structured, medical scheme benefits are determined based on the size of the wallet that they come with. And I think that's unfortunate. [...] So yes, you need a prescribed minimum benefits that's probably more clearly defined, and we're talking about it must not be defined on the basis of diagnosis, but on the basis of essential services."

Medicine supplier	"And our frustration, I guess, is we have to negotiate with around 80 independent funders, all of them with different scheme designs, trying to figure out how you can actually bring a molecule to patients. And I think what would be really useful is the Council for medical schemes, who regulates the private funders, if they could make bring clarity around that process towards reimbursement."
Ex gratia payments by insurance schemes	
Concerns about decision-making	
Medical scheme	"And a lot of times it's a lack of clinical evidence, a lack of trials with regards to the drug that they're asking for. You know, especially in the younger lot of children, like under a year or two years of age, we find that even where we do want to help and pay, there's nothing to base a particular decision on."
Medical scheme	"If you look at cancer, it is an emotive condition. So, the extent to which medical aid are flexible in doing that [ad-hoc payments], it depends on the amount of pressure that is being put on. In this case, it would be the pressure by the member as well as the treating physician"
Policy maker/ regulator	"They [PTC meetings] are behind closed doors. Then each one is an individual case, they don't set precedent and they are not open about the reasons for their decisions. It's non transparent, but it could also be variable."
Sympathetic for children	
Medical scheme	"We tend to be sympathetic where there is absolutely no other treatment alternative."
Price negotiation power of insurance schemes	
Successful price negotiations with medicine suppliers	
Medical scheme	"If you [pharmaceutical company] want access, you need to bring it down to this [price] level. If you get more patients than this number, you need to gradually reduce the price. So that strategy sometimes works, especially on the PMB medicines."

SUPPLY AND PROCUREMENT	
National tenders	
Process issues	
Policy maker/ regulator	"First of all, they don't tender for it. If they do tender, then they actually at times give you delays in acquiring. [...] I would say 80% of them are good. But the problem with chemotherapies is it comes in a package. And you can't suddenly say I'll use half of your package and the other half..."
Medicine supplier	"Maybe they didn't meet certain requirements, because there's many requirements for the tender in terms of credit ratings, or good standing with the Department of Health, or maybe they don't have a BEE [Black Economic Empowerment] certificate. [...] There's many other requirements within a tender that could render your submission invalid."
Healthcare professional	"Companies who have the state tender, have to supply the medicine based on the contract they have. But when they can't, they're meant to provide within 14 days, but a lot of them don't. And no one ever holds them accountable."
Very low prices achieved	
Medicine supplier	"With the tenders in the public sector, I think that's pricing that nobody can compete with. I think the companies go in so low on those pricing, that actually greatly affects how many people they [public sector] can actually assist with."

Procurement	
Well-organized supply system	
Healthcare professional	"We don't have those barriers as a major problem in terms of procurement, things are in place where all of that gets done by the pharmaceutical side of the hospital."
Perceived lack of understanding from procurement team	
Healthcare professional	"The buyout has to be done in what they call PPSD [Provincial Pharmaceutical Supply Depot]. […] So and very often that is where the problems occur because very often, we [physicians] don't have access to them [PPSD]. They don't communicate with us. They don't really know what is happening on the ground here. They don't know what the physicians face."
Alternative procurement strategies needed	
Civil society	"Because they say the [South] African market is too small. That's why I'm coming back to pooled procurement across regions. […] If you are able to actually pool for sub-Saharan Africa, there's a bigger market, there's a bigger possibility."
Buy-outs	
Concerns about buy-out process	
Policy maker/ regulator	"As soon as there's no tenders then you have to buy these drugs on an open market system. And nobody can guarantee supply because it's not contracted."
Policy maker/ regulator	"These are the things, the barriers that do then impact the care of the child because if you're waiting two to three months or something, you're not sure how the child is going to be."
Acquiring through buy-outs easier for quaternary centers	
Healthcare professional	"Most of the hospitals where we treat these patients are quaternary. And I think all of them are affiliated to a university. So it has its advantages in the sense that we've got the budget for acquiring and buying most of the medications that we need without any major problems."
Availability of medicines	
Unavailability and stock-outs	
Policy maker/ regulator	"I think the other thing is that you put all your money in one basket. If that company goes, you've got nowhere to order from. Or if there are companies that do make it, but they don't make the quantities we want, because we [State sector] service about 75-80% of the population. So you will get these company, the other companies, they make quantities for the other 20%. So when you run out, they cannot supply, they cannot supply you."
Distribution	
Poor distribution systems	
Healthcare professional	"Nowadays you just send it with the ambulance driver and you can't even maintain like cold chains and things. There are no pharmacy courier services available anymore. So there's no way of getting therapies in any reasonable time actually from one hospital pharmacy to another."

HEALTHCARE DELIVERY	
Diagnosis	
Lack of diagnostic capabilities	
Policy maker/ regulator	"A lot of our children are coming at a late stage of disease, rather than at an early stage. And that's compounded by many factors. One is poor recognition of the clinical presentation [at primary healthcare center level], two is lack of standards to do the test."
Referrals	
Inadequate referral systems	
Policy maker/ regulator	"Another barrier is just the uncertainty of how our tertiary services are organized. So at the moment some province is not going to have [public sector] tertiary hospitals at all. How do they get their patients to another province is a little uncertain. There's meant to be interprovincial transfers and accounting for that, it's not working."
Policy maker/ regulator	"And the referrals aren't that easy because of the limited amount of clinics and specialists available, so the delays will be there. And the costs I think incurred by parents for this are quite large."
Primary healthcare (PHC)	
PHC level training in public sector inadequate	
Medicine supplier	"There's lack of education at the primary clinics about cancers that needs to be… so the primary health care workers need to be upskilled on identification of cancers, on doing bloodwork."
Lack of use of primary care in private sector	
Medical scheme	"Unfortunately, in the private funding environment, the emphasis has been put on referred care hospice, it's more referred and hospi[tal] centric. And the emphasis is not significantly on the primary care. So when you're talking about childhood [cancer], where there's limited screening, that first point of care becomes absolutely critical […], so your providers are well trained to be able to pick up early signs of potential problems."
Availability of staff	
Lack of healthcare professionals	
Policy maker/ regulator	"There's only so many specialists within the country, so patients have to travel or are limited to go into these particular clinics where they have long waiting times, dates that are really far in the future."
Healthcare professional	"Our young oncologists, or even very experienced staff, is leaving the country and there's a brain drain."
Training of staff	
Lack of training and formal accreditation	
Policy maker/ regulator	"First of all, pediatrics have got no nurse trained [in] pediatric oncology […]. And there's no training platforms for them either."
Healthcare professional	"Because there's no formalized training, it's up to individuals [palliative care specialists] to upskill themselves."
Medicine supplier	"And there is no formal program in South Africa for pharmacists to obtain oncology pharmaceutical care."
Healthcare professional	"As a pharmacist, I don't like the fact that I'm teaching myself everything, there isn't support in terms of equipping the people who are in the field. It's tragic that I did not learn about pediatric oncology yet I'm expected to practice in it."

Other resources	
Lack of diagnostic and radiology resources	
Policy maker/ regulator	"Suppose radiotherapy units in the public sector, it's an increasing problem, and so oncology patients – adult and pediatric – are battling to get access either to diagnostics or to radiological intervention."
Medicine supplier	"There's also barriers with diagnostic testing. So there's often, we don't have that the tests available or we don't have PET scans available in the public sector or they're out of commission."
Psychosocial care	
Lack of psychosocial support	
Civil society	"They are so overwhelmed, the staff, with the amount of children that they have in [public sector] hospital I don't think the mental health is such a priority."
Palliative care	
Lack of priority	
Healthcare professional	"And palliative care was just a massive gap that we just haven't paid enough attention to. And it's suddenly starting to get the recognition that it needs."
Limited knowledge	
Healthcare professional	"So morphine is technically available at every hospital, [but] it's not ordered by a pharmacy, because it's not always prescribed by the doctors, because there's still such a gap in knowledge around morphine. You know, if a child presents and they're on morphine, one of the first things they do is stop the morphine because it must be the morphine that's causing whatever."
Complementary and traditional medicine	
Delays in care or defaulting	
Healthcare professional	"There's a strong cultural belief still in tradition. They first seek the help of a traditional healer [...], and it takes sometimes – often – very long for them ultimately to get to us and by the time they get to us, it's too late. The cancer is at a stage four."
Healthcare professional	"But it can also mean that they default treatment to go and seek an alternative. Because a lot of the patients we work with don't actually believe that cancer is really cancer, they think that it's a manifestation of an ancestor being unhappy."
Organization of services	
Child-specific cancer services not catered for	
Healthcare professional	"The second thing is: pediatric regimens run on average five to seven days. In a state facility we operate, we function Monday to Friday, there is no oncology service provided over the weekend. [...] So there is no on-call service for oncology, because the adults don't get chemo over the weekend."

DISPENSING	
Preparing and administering	
Gaps in safe and controlled preparing and administration	
Medicine supplier	"If you read the GPP [Good Pharmaceutical Practice] documents, you will see that it is non-committal. It allows a wide scope of practice. So what is happening at the moment in South Africa is the most of the mixing of chemotherapy is happening in doctor-driven practices in facilities that are not registered with the pharmacy Council."

Pharmacist as healthcare provider	
Lack of clinical responsibility of pharmacists	
Healthcare professional	"Here a pharmacist has got no clinical responsibility for a patient, they are making decisions around availability and not mixing therapies and whatever. But in theory, they are never around the table [with other healthcare professionals], having that clinical input. And just responsibility. And again, in pediatric oncology, isn't that essential?"

USE	
Access to care	
Inability to travel	
Policy maker/ regulator	"Time, lost earnings. You know. Who's going to accompany the child. Can they afford that? Massive social issues around that."
Healthcare professional	"Patients do not even have money for food. So they would rather concentrate on what is essential than getting the child to the hospital and spending money on transport to the hospital."
Civil society	"It [childhood cancer care] is quite centralized as well, which was quite a big challenge for people and you know, you have to travel 100 kilometers or 300 or whatever kilometers to go to the place where you get your cancer treatment."
Symptomatology accepted as part of life	
Policy maker/ regulator	"The population generally, coming from the legacy of a party and of the past, are not people that go to doctors on a drop of a hat. They often go much later, they accept lots of medical symptomatology as being a normal part of life."
Normal functioning family life disrupted	
Civil society	"In South Africa, the makeup of the family is so different, particularly in our townships and in our communities. We have from child headed households to households managed by the granny or the gogo [grandmother], single mom households. […] So we've had many times where families, the mommy's here, […] and the young adult son or daughter must take care of the younger siblings."
Civil society	"[…] the requirements of treatment and having a family back at home where they have their husband or their spouse or partner at home and more children at home and not being able to provide financially to the home."
Healthcare professional	"It's a cost emotionally on the patient, they're kids, they have to come with the parents. Now where's the parents staying, what's the parent eating? Then they miss out on school, because again, they have to be admitted."
Adherence and defaulting	
Defaulting on treatment	
Healthcare professional	"And then it's an education problem, often. You know, the parents agree to something but the family are completely against it. And then patients are lost to follow-up, they don't come back, especially when we're talking about big surgeries, like amputations and inoculations and just the general resistance to surgery."
Healthcare professional	"If you do start the treatment, they do see a response to the treatment, they think that the child is cured, and they default follow-up. And that's one of the reasons why they default follow-up."
Civil society	"Because that has happened often, where parents default on treatment because accessibility and finances is a challenge."

Multisectoral support to prevent defaulting	
Civil society	"But CHOC [Childhood Cancer Foundation] has made a very, very big impact in terms of helping parents to access the pediatric oncology wards. So the defaulting statistics have definitely decreased. And because also not only the transport fund, but the role of the social worker in the ward."

MONITORING AND SURVEILLANCE	
Lack of monitoring and surveillance	
Policy maker/ regulator	"So in the Western Cape, they're building an electronic health record. You can see somebody was seen at a clinic. Somebody could look at this from the outside and go, hang on that doesn't look right. In a rural area, that paper record is inaccessible. And we don't know who's being missed, nobody is checking."
Policy maker/ regulator	"And we've got a problem with our cancer registry, our cancer reporting system, that is underfunded, not terribly accurate, and hampers our ability to use those data to advocate."

CROSS-CUTTING EMERGING THEMES	
Advocacy	
Need for advocacy	
Policy maker/ regulator	"But I think it also needs a lot of advocacy from various role players to try encourage people to… or companies to produce these medications."
Medicine supplier	"I would say the health activists to get involved, is to make sure that the important childhood cancers are picked up and reflected under the prescribed minimum benefits."
Policy maker/ regulator	"So what I like to say is that I don't hear anything around patient access for pediatric oncology. And one would expect somebody in my position and my traverse in the environment that I would hear that, that somebody would be shouting at me, somebody would be criticizing us, somebody would be saying something, and I'm hearing nothing of that."
Awareness	
Lack of awareness on childhood cancers	
Healthcare professional	"I think awareness and education is probably the most important and when we talk about it, we're talking about awareness and education among healthcare workers, primary health care workers, firstly, and then go a step further and say, even traditional healers, and then going even further and saying in the general population."
Lack of awareness on health system components	
Medicine supplier	"And then that referral pathway is not clearly defined. People don't know how to go through the system, or how to navigate the system."
Policy maker/ regulator	"But also in the private sector, […] what medical aid schemes do is they will publish their medical aid scheme rules for example, then you would get members that don't read. What they are eligible for, what they can access and what not. So I see that is a major problem as well."
Equity	
Inequities in care and services provided	

Policy maker/ regulator	"[…] the differences in per capita allocation between private and public dramatically differ. So just the resources available for a child in the private sector are very different from resources available in the public sector."
Policy maker/ regulator	"Because if you are in a rural area, you can't have access to a specialist. They might miss the diagnosis. But if you are in a city where there's access to tertiary hospitals, whether it's the private or public sector, you've got a bigger chance of your condition being diagnosed early."
Healthcare professional	"Why should there be a difference between what I get in the Northern Cape versus what I get in the Free State versus what I get in the Western Cape? It all comes from the same taxpayer"
Non-governmental organizations (NGOs)	
Services and support provided in NGO sector	
Civil society	"At this stage, because of the lack of services being provided by government, or in the private sector, it is the nonprofits that are providing the services. And that would be from early detection, or creating awareness, right through to psychosocial support, right through to end of life care. So if it hadn't been for the nonprofits, we would have certainly a disaster in this country."
Healthcare professional	"But we do depend quite heavily on NGOs, for assistance with a lot of things, for housing, for outpatients, for transport money, even to hand out food packets when they come just as an incentive for them to come to the hospital."
Lack of funding for NGOs	
Civil society	"I think one of the things that is a challenge is the fact that CHOC [Childhood Cancer Foundation] does not receive any government funding. And yet we provide such a crucial support role to the to the state's patients, you know, and I think that more assistance, financial assistance is needed from the state to charities in the cancer sector."


Bivatracin
BETADINE
Kaprofen
KETOLAC

CHAPTER 3.4

The caregiver's experience of childhood cancer treatment in South Africa

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Abstract

Background

This study explored the treatment-related, financial and psychological experiences of caregivers during cancer treatment of their children in South Africa's (SA) public and private sectors.

Methods

In this exploratory study, three focus groups were conducted with caregivers of children undergoing cancer treatment in SA's public healthcare sector. A fourth small focus group with two parents in the private sector was conducted online. A mixed-methods approach was employed using a combination of thematic analysis and grounded theory.

Results

Of the 20 public sector caregivers, many expressed frustration at the number of visits to primary healthcare clinics before being referred. Caregivers had difficulties coping with and accepting the diagnosis, alongside managing continued care for the child and other children at home. Support received by family and community members was varied. Financial strain was an important concern. The two private sector parents indicated greater levels of support and no financial hardship, but expressed similar levels of emotional stress.

Conclusion

These caregiver experiences indicate that improvements are urgently needed in the recognition of childhood cancer symptoms at primary healthcare level in SA. They also highlight a need for increased financial support from government through social grants, travel allowances and nutritional support.

Introduction

With current survival rates of approximately 50% [1, 2], South Africa is committed to achieving the World Health Organization's (WHO) Global Initiative for Childhood Cancer (GICC) target of at least 60% overall survival for children [3] and improving the lives of those living with or surviving cancer [4]. To achieve this, the need for health systems strengthening and addressing the persistent health disparities [5, 6] were recognized as priorities within the National Cancer Strategic Framework (NCSF) [4].

To effectively inform policy development, an understanding of the barriers and facilitators in access to childhood cancer treatment is required. Therefore, a comprehensive health system analysis, with a particular focus on medicines, was undertaken [7, 8]. Key barriers identified – through a study of policy documents and interviews with stakeholders in both the public and the private healthcare setting – included a lack of political priority given to childhood cancer (medicines), novel therapeutics not seeing market registration as well as the discontinuation of traditional chemotherapeutics, incomplete insurance coverage for childhood cancers, bottlenecks in medicine procurement leading to (intermittent) stock-outs of essential medicines, low awareness on childhood cancers among primary healthcare staff as well as the general public and patients' inability to access care facilities.

To complement the views and opinions of stakeholders, an understanding of the user perspective – or in this case the caregiver perspective – is pivotal [9,10]. In prior research conducted globally, caregivers reported considerable financial and emotional difficulties in the diagnostic stages due to long delays and erratic referral pathways [11]. Physical and emotional difficulties were also experienced during treatment, due to the chemotherapy, hospitalization, and the drastic change in their lives [12], as well as financial hardships [13-15]. In studies conducted in Sub-Saharan Africa, the need for financial assistance, clear information on the disease, emotional, spiritual and psychological support as well as material support was identified [16-19]. A single, small-scale study exploring the informational needs of South African parents identified a similar need for information about the diagnosis and treatment [20].

In South Africa almost 85% of the population relies on the government-funded public health sector; where health services and medications are provided at a nominal fee based on one's income, with exceptions for specific groups such as children under six and the economically disadvantaged [21]. The non-governmental organization (NGO) Children's Hematology Oncology Clinics (CHOC) Childhood Cancer Foundation provides additional support to caregivers reliant on public sector healthcare through the provision of free housing during a child's course of treatment , as well as meals, toiletries, transport to healthcare facilities and small travel allowances [22]. Global evidence detailing the consequences of childhood cancer on caregivers [11-20] may not directly translate to the South African context, such as support

mechanisms provided by NGOs to caregivers in the public sector. Those who seek medical services at private sector clinics and hospitals typically cover their expenses through medical aid schemes (commonly known as health insurance) or face out-of-pocket (OOP) payments [21]. This sector is typically excluded from research into caregiver experiences [15-17].

Therefore, we sought to examine the experiences of caregivers in the South African context; with the aim of confirming the barriers and facilitators as perceived by professionals [8], whilst identifying other potential determinants influencing caregiver experiences that previous stakeholder interviews have not uncovered. This context-specific evidence can contribute to the development of targeted policy interventions to facilitate improved access to childhood cancer care and reduce inequities in South Africa.

Methods

Three semi-structured focus group interviews were conducted with groups of 4-10 caregivers of children with cancer in the South African public health care system. The scope of the present study was expanded to include the private sector in line with prior research activities [7,8]. A single small focus group was conducted with caregivers from this sector.

Participants

Caregivers were defined as any adult that accompanied and provided care for the child while receiving cancer treatment. Caregivers of children at any phase were eligible (diagnosis and staging, undergoing treatment, or treatment completed). Caregivers could include parents, grandparents, aunts and uncles, older brothers or sisters, or other persons living with and providing for the child. No particular exclusion criteria were applied, allowing any willing participant to join provided that they met the aforementioned definition of caregiver and had completed the informed consent document.

Public sector participants were recruited from the CHOC accommodation facilities in Durban (KwaZulu-Natal) and Cape Town (Western Cape) through convenience sampling. Prior to the sessions, caregivers were informed about the study by CHOC staff. On the day of the interview, caregivers present at the facility were informed about the aims and procedures of the study by the researchers and then invited to participate. All those invited agreed to participate.

Private sector participants were recruited through another non-profit organization, which raises funds and awareness for families affected by childhood cancer. A foundation representative assisted in contacting caregivers involved with the foundation, approaching caregivers and informing them of the study. Six caregivers who had expressed interest in participating were forwarded to the researcher (IRJ), who contacted the caregivers to provide details about the

aims and procedures of the study and invite them to participate. Attempts to schedule a focus group session were unsuccessful with four of the six caregivers.

Procedures

The public sector focus groups were held in a common room at the respective CHOC accommodation facility in October 2022, whilst the private sector session took place online in November 2022. At the start of the interview, all participants gave their written consent to participate and completed a short questionnaire consisting of basic demographic data (such as age, sex, relation to the child, etc.). CHOC staff members or other participants assisted those of whom could not read or write in English sufficiently enough to complete the informed consent form and demographic survey for themselves. To avoid interference, researchers refrained from providing any assistance beyond the necessary clarifying information. Each participant was assigned a number to ensure their anonymity and to facilitate transcription of audio-recordings. Participants were asked about 1) the cancer journey, 2) the impact of the diagnosis and treatment on their lives and their family, 3) support, 4) experiences accessing care services, 5) financial experiences and costs made, and 6) unmet needs during the cancer journey (see Appendix 1). The interview guide was informed by prior research [16-20] and was tested during the first session with caregivers, which led to minor modifications of the guide. All public sector sessions were moderated by IRJ (and FS), female academic researchers experienced in conducting interviews and with no prior connection to the participants. Sessions were conducted in the presence of a CHOC social worker or other staff members who could translate when the participant responded in Zulu (session 1) or Afrikaans (session 2). The third session was conducted in English/Xhosa whereby one of the participants also acted as translator. The private sector interviews were conducted online in English by IRJ. All interviews lasted for approximately 40 minutes.

Data analysis

Audiotapes were transcribed verbatim and, when necessary, translated to English by a local translator. Transcripts were coded by IRJ and verified by FS to ensure that no themes were missed. Subsequent thematic analysis of the public sector sessions took place through a mixed approach, utilizing a deductive component based on themes previously identified in literature [14-16] alongside an inductive analysis following a grounded theory approach whereby data was coded iteratively to capture emerging themes. Data saturation was reached by the third session. An exploratory comparison was made between the themes identified in the public sector sessions and those that emerged within the private sector session.

Results

A total of 20 caregivers from the public sector participated in the focus groups, of whom 15 participated actively in discussions via verbal contribution. One caregiver withdrew from their session due to overwhelming emotions. The caregivers that did not participate verbally during their session indicated their agreement by nodding and other non-verbal cues, but chose not to contribute verbally despite encouragement from the moderator to do so. The majority of caregivers identified themselves as either black (70%) or colored (25%), with 65% being the mother of the child (see **Table 1**). There were two participants – both mothers – for the private sector session.

Public sector findings

Four major topics emerged from the data: 1) experiences with the health system, 2) emotional and psychological impact, 3) financial experiences and 4) external support structures. The issues and experiences associated with each of the main topics occurred at different societal levels, with 'emotional and psychological impact' and 'financial experiences' mainly occurring at the caregiver's individual level, 'external support structures' exclusively taking place at a community level, and 'experiences with the health system' appearing at all levels (individual, community and (health) system's level). An overview of all extracted themes and subthemes is provided in **Figure 1**.

Experiences with the health system

Many caregivers shared experiences of testing and diagnoses being severely delayed, despite having made several visits to a primary healthcare clinic over multiple months before the child was finally referred for further testing to a hospital. Caregivers expressed their consequent frustration with the healthcare system and the primary point of care.

> *I started noticing that she was not okay in January this year I think. She started getting sick, fever, nausea. [I] took her to the clinic for like two months, until I went to the GP – a doctor – who told me to go immediately to the hospital.*
>
> *P7, mother*

> *The sister then goes to another sister and says: 'the child's iron is low, why didn't she come to the hospital?' Then I said: 'I came here for a long time, many years that I have been coming, the child has something wrong, and no one listened to me'.*
>
> *P12, aunt*

Another participant shared that the diagnosis was initially delayed due to them seeking help from a traditional healer first:

Table 1 General characteristics of participants.

	n	%	n	%
	Public sector participants		Private sector participants	
Number of participants	20	100	2	100
Age group				
15-24 years	3	15	0	0
25-34 years	9	45	0	0
35-44 years	4	20	0	0
45-54 years	2	10	2	100
>55 years	2	10	0	0
Gender				
Male	1	5	0	0
Female	19	95	2	100
Race				
Black	14	70	0	0
Colored	5	25	0	0
White	0	0	2	100
Unknown	1	5	0	0
Relation to child				
Parent	13	65	2	100
Grandparent	2	10	0	0
Other	5	25	0	0
Age of child				
0-2 years	4	20	0	0
3-5 years	4	20	0	0
6-8 years	6	30	0	0
9-12 years	4	20	0	0
12-15 years	2	10	2	100
Highest level of education completed				
Primary school	9	45	0	0
Secondary school	10	50	0	0
Diploma	0	0	1	50
University	1	5	1	50

> *It started with the child having pain in her eyes. We thought that it is our tradition, that maybe there is something we didn't do, we did what we thought we should do.*
>
> ***P17, unspecified caregiver***

Caregivers described that the diagnosis and treatment required repeated referrals and transfers to different hospitals, often far away or even in a different province. The repeated travel, usually far away, imposed considerable financial strain on the family (see 'financial strain'). The caregiver

was compelled to be away from home for extended periods of time so as not to leave their child alone during treatment.

> *They admitted her for 2 months at Mandela, she was discharged on the 6th of September, then we went for check up on the 13th of September, then they said the cancer has spread inside the eye. And then we were transferred to Frere [Eastern Cape]. When we got to Frere, they checked her, they said her cancer is close to the brain, they said they don't have treatment for her, she will be attended by doctors from here [Cape Town, Western Cape].*
>
> *P17, other caregiver*

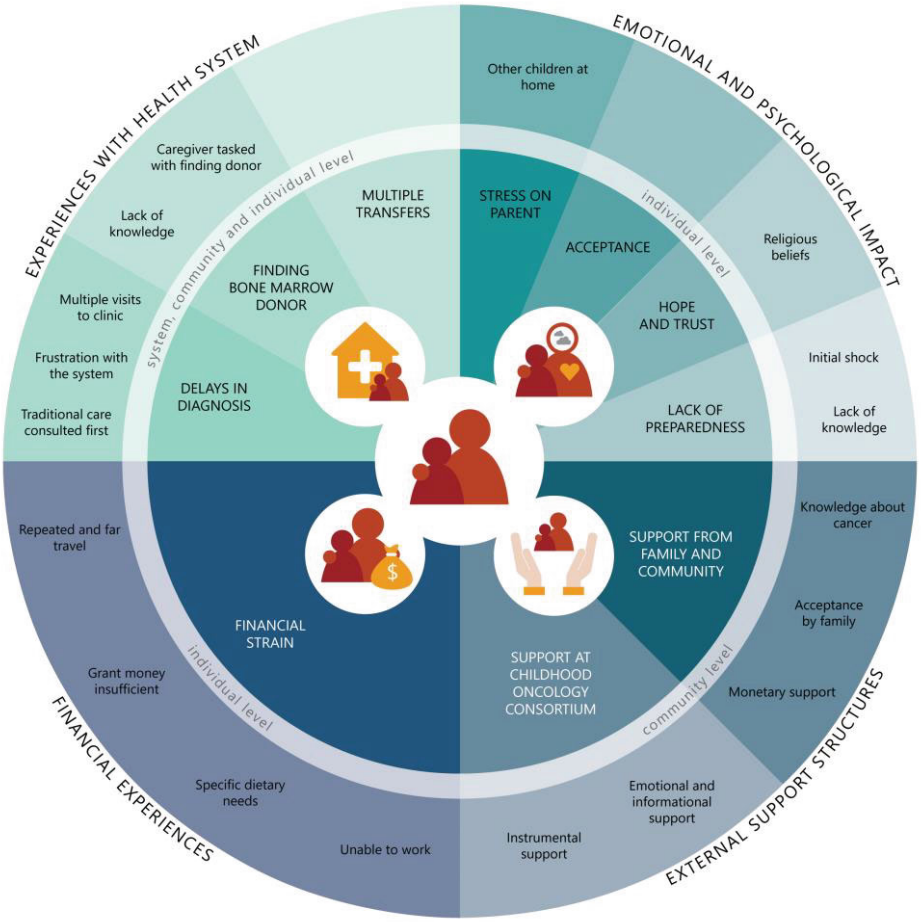

Figure 1 Caregiver experiences in accessing pediatric cancer treatment in the public sector. Each quadrant displays one of four main topics, including associated themes and subthemes, and at which level they occur.

Several caregivers shared their experiences with finding a bone marrow donor and undergoing subsequent transplants, indicating an (initial) lack of knowledge and understanding regarding donorship, coupled with the expectation to locate a suitable donor among family members. This imposed a further burden on the caregiver.

> *Her doctor told me [that] she must get a donor, [but] I know nothing about donors, because this is the first time to get cancer, to get a sick child like her. Her doctor told me I must look for a donor [...].*
>
> ***P19, mother***

Emotional and psychological impact

Caregivers described feeling great shock and pain at the child's diagnosis, compounded by a lack of knowledge on what the diagnosis entails and fearing for their child's life. During their accounts of their experiences, several caregivers displayed strong emotions and expressed grief. One parent with intense emotions withdrew from the session at this stage.

> *When they told me at the hospital that the child has cancer, I cried. I cried because I didn't know what cancer is like, because I would hear that cancer kills.*
>
> P8, unspecified caregiver

> *[...] In the beginning it was too much for me to think of how I feel, it was hard, I didn't know what it meant.*
>
> ***P13, mother***

Following the initial shock – having received more information on the disease and its prognosis – most caregivers expressed they had accepted the diagnosis.

> *I've accepted that my grandchild has cancer. But we were surprised because it's for the first time we have someone who has cancer at home.*
>
> ***P1, grandmother***

In most caregivers, particularly in those whose children were further along in the treatment phase, acceptance was accompanied by hope and gratefulness. Many referred to their religious beliefs as an important source of hope.

> *Thank you that my child can see, thank you that my child has hope. Thank you for everything. You must just have that gratefulness. I don't have to worry, there are angels, the angels will look after my children there.*
>
> ***P16, mother***

> *I don't know how I will handle the aplastic anemia, but I do know one thing: God is with us.*
>
> ***P12, aunt***

Another great source of hope were the stories of other children at the ward and at the accommodation facility. One parent described that due to hearing other caregivers' experiences she realized her own child's situation was not as somber:

> *If you get some information about some other children, it was very hard for them to grow and be better, than mine was not that bad. So that gives you kind of hope that maybe she's gonna survive this. I have to be strong and just try and continue.*
>
> *P7, mother*

Despite having accepted the diagnosis and having faith in a good outcome, nearly every caregiver expressed feeling burdened by the journey. Their stress was not only related to the child diagnosis and their suffering, but also due to having other duties besides taking care of the sick child. Having other children at home that they could not take care of was a significant stressor.

> *So, the journey is so traumatizing. […] Today she's feeling well, sometimes she's not feeling well. It's been ups and downs. […] As for myself, I think I need someone to talk to. Like a professional someone, to help me balancing things. I'm struggling to juggle between taking care of the kids and taking care of my schoolwork. So I even… I don't know how to cope. I don't know what to do anymore. I don't know where to start. So I'm struggling.*
>
> *P3, mother*

Financial experiences

Besides emotional stress, many caregivers experienced having difficulties coping financially as well. Despite the Childhood Cancer Foundation providing some monetary support to cover travel expenses to those living far away, the repeated travel to treatment facilities imposed great financial hardship on caregivers.

> *There are days that I struggle to get to the hospital. There were days that I did not have taxi fare, I made my way, I walked, the taxi dropped me, I had to walk very far to get to the hospital. […] Now in this month, […] this is my third week at the hospital. The blood [count] stays low. So for me, every week […] I must go see where I can get money […]. And next week I must be there again.*
>
> *P13, mother*

Multiple caregivers reported that the Child Support Grant, which for some was the only source of income, remained insufficient to cover the additional expenses associated with cancer treatment. South African Social Security Agency (SASSA) Child Support Grant is a government grant intended to support lower-income households in South Africa in taking care of a child. At the time of interview, the grant amount was 450 ZAR (South African Rand; ±25 USD) per child per month.

> *We come from far and the child support grant doesn't help with anything, it gets used up on transport. The children can't even have clothes because the money is used on transport to the hospital.*
>
> ***P4, mother***

Besides travel expenses amounting to significant additional costs, increased appetite and the need for special foods impose further financial pressure on the household.

> *If there's food parcels, we would also like to receive them because we can't afford. Since our children are sick, they need special diets to keep them healthy. So, we can't afford that with the child support grant.*
>
> ***P8, unspecified caregiver***

> *Because what must your child eat? [What] your child is on, it makes them eat a lot. I did experience before the medications, she wasn't so fat. She's gaining weight now, like a lot. And because she's eating a lot, my cupboards, it's empty. […] Last night, it's like 'mummy I'm hungry'. I couldn't offer her anything because I mean, there's nothing. And I did leave my job to look after her. And now who is there to provide?*
>
> ***P13, mother***

Lastly, economic hardship was exacerbated for some caregivers, who were forced to leave their jobs to accompany their child during treatment, resulting in a significant reduction in income. One parent reported being granted unpaid leave during the treatment period.

> *At work, they said […] family responsibility is only 5 days, no more than 5 days. They said they are going to give me unpaid leave yesterday. And then that is not easy for me because I used to have money.*
>
> ***P20, mother***

External support structures

Social support from families and communities encountered in this study can broadly be categorized according to three types of assistance, 1) emotional, 2) instrumental (or tangible) and 3) informational support [23]. Caregivers had widely varying experiences in terms of receiving these support types from family and the community. While some received extensive support, others reported receiving no support at all.

> *My whole community supports me, my work supports me, my boss… […] They pray for my child, the church, every Wednesday evening they pray for her. I just have such a lot of support.*
>
> ***P16, mother***

> *Yes, there is support, from my parents, and my aunts, there aren't other people who can support me besides them.*
>
> *P17, unspecified caregiver*

> *Maybe for me, it is like people don't like to help, they don't like to be there, so I had to get used to that.*
>
> *P13, mother*

Instrumental support from family and the community in some cases entailed monetary support:

> *For me, yes I did get support, my cousin's sister did send for me something, money and also last year, they did give me some money and then this year also they did give me some money.*
>
> *P20, mother*

> *From church, I do get something.*
>
> *P18, grandmother*

That lack of support that some caregivers perceived was attributed to a lack of knowledge about cancer in the family and community. This perceptions seemed to stem from the misconception that the absence of severe symptoms implies the disease is non-serious.

> *I'm not getting support from family. They were surprised that the child has cancer. No one believes that the child has cancer because the child can walk, is not bed ridden. The child can walk. When I sleep in the hospital no one sees that this is serious.*
>
> *P6, aunt*

Besides support from family and the community, there is considerable assistance provided through the Childhood Cancer Foundation. When discussing the foundation, the room's ambiance lifted noticeably, prompting some caregivers to laugh and smile. According to caregivers, emotional and informational support was not only provided through the foundation itself and its social worker in the ward, but also through other caregivers at the accommodation. Lastly, informational support was also provided by healthcare professionals.

> *But seeing that I'm not the only one going through this, sitting with these women here, honestly, it really does give me hope and keeps me strong because now I know I'm not alone. There are many of us.*
>
> *P9, mother*

In addition to emotional and informational support, the Childhood Cancer Foundation provides critical instrumental support to caregivers.

> *Your CHOC house help us a lot for those who are far, you see, because they gave us toiletries and everything, food, a place to sleep, playing room for the kids. […] it is nice because they have transport for us, they have food for us. Sometimes here at hospital we don't have food when we are there, we don't have food, at least here there is enough food for us.*
>
> *P20, mother*

Private sector findings

Experiences from caregivers in the private sector showed significant differences compared to caregivers seeking treatment in the public sector. This section describes the experiences of two private sector caregivers for each of the four main themes identified in the public sector.

Experiences with the health system

Caregivers expressed great appreciation at the care received at their respective treatment centers. In contrast to public sector experiences, caregivers attested that symptoms were recognized immediately, resulting in swift intervention.

> *[Name of child] moaned about leg pain last November, we thought it was growing pains. But in January, it seemed to get worse. So we booked [an appointment] on the Friday I found a doctor, we had an appointment on the Monday, the Monday night the specialist phoned and the Tuesday we were admitted to hospital.*
>
> *P22, mother*

Different to the public sector, caregivers described that they had the opportunity to utilize facilities and amenities provided by the hospital, including a bed or sleeper couch and food and drinks.

> *And the hospital was very, very accommodating. They had a parents menu as well. So I got three meals a day that was included as well. […] And then they also had mini fridges, where you could store some of your own things as well. So in terms of catering, it's made it a lot easier, especially for the kids because they can get quite picky.*
>
> *P22, mother*

Emotional and psychological impact

Psychological and emotional experiences were fairly similar to those in the public sector, with caregivers expressing distress at the diagnosis and the impact in their daily lives and that of their families. Hope, trust and acceptance were not prominently discussed, as both children had nearly completed their treatment and achieved positive outcomes.

Financial experiences

Both families were members of a medical aid scheme and had invested in fairly comprehensive coverage prior to the diagnosis. As a result, insurance covered the majority of the medical

expenses, except for blood transfusions. Neither caregiver reported substantial financial hardship due to the disease, in sharp contrast to the public sector caregivers.

> *So what my son's oncologist did is she worked out what the cost of the program would be more or less. So in the beginning, when [name of child] was first diagnosed, she motivated with [medical insurance scheme] and they made available 200,000 Rand for last year, and that pulled us through.*
>
> *P21, mother*

External support structures

Caregivers reported receiving considerable emotional support from their families and broader community, particularly from the schools. Neither caregiver required instrumental support from a non-profit organization.

> *It was very uplifting to me to see the support that I got from the community.*
>
> *P22, mother*

Discussion

This study provides evidence of the emotional and financial challenges faced by caregivers in South Africa's public healthcare setting when dealing with childhood cancer. The primary reasons for these hardships were the extensive travel expenses and associated prolonged periods of absence from home. While caregivers generally conveyed satisfaction with the care and support received at treatment facilities, they also expressed frustration towards the primary point of care in the public healthcare sector whereby delays in both testing and diagnosis were often remarked upon. The experiences of caregivers seeking care in the private sector confirmed the persistent inequities in the health system, with greater overall satisfaction with health services, financial protection from medical expenses and the resources to cover indirect costs such as travel expenses and dietary needs.

Our findings strongly align with prior research conducted among caregivers in the public sector in other African countries, reaffirming the previously reported lack of knowledge on childhood cancer, impact of repeated travel, financial difficulties, emotional and psychological burdens, along with the need for instrumental support [16-19]. However, in contrast to other recent studies, the support already provided by the Childhood Cancer Foundation in South Africa emerged as a critical contextual factor in the interpretation of caregivers' financial experiences. Because despite offering some financial assistance and instrumental support (via the provision of food and accommodation) to caregivers, significant financial strain was still experienced. Furthermore, the foundation also extends emotional and psychological assistance through a dedicated social worker in the ward and their staff at the accommodation facility. While we

emphasize the importance of continued emotional and psychological support from the foundation – as well as support from the caregiver's own community – we identified no apparent need for additional support in this aspect. Similarly, the need for additional informational support was not directly raised [20]. Healthcare professionals and the foundation together seem to be adept at foreseeing caregivers' needs in this area. The significance of other parents within the ward was echoed in this regard [16]. Notably, our study did not find evidence of unavailable medicines or supplies, nor a need for improved care at hospital level [17].

During focus group sessions with caregivers, no new major barriers to access emerged in comparison to interviews conducted with a range of stakeholders in South Africa's pharmaceutical value chain; however, we were able to confirm firsthand the barriers that had previously been identified [8]. This indicates that healthcare providers and civil society in particular have a good understanding of user barriers. Nonetheless, this study sheds light on the emotional and psychological impact of childhood cancer on caregivers and provides a more nuanced insight into the extent of financial strain experienced by caregivers. The financial strain in this context is attributed to increased costs for travel and catering to the specific dietary requirements of the children; alongside this, there may be a (partial) loss of income, all the while balancing their responsibilities of supporting their families at home. Children exhibiting (hospital) food aversions or preferences was reiterated by caregivers in the private sector, underscoring the need for accustomed foods as an area of attention. The potentially far-reaching financial consequences of incomplete insurance coverage for those in the private sector [8] could not be confirmed in this study, as both participants had taken out sufficient coverage.

To address the concerns and needs of caregivers of children with cancer in South Africa's public sector, and reduce the inequities between both sectors, it is vital that families are financially protected from economic hardship through more adequate travel allowances and nutritional support. Healthcare professionals have previously indicated the need for a renewal of a temporary care grant system [8], which can compensate families for increased costs and loss of income whilst undergoing cancer treatment. At present, only children with a permanent disability due to cancer, those who have undergone limb amputation or inoculation, are eligible for a care dependency grant. Additionally, the provision of cancer care closer to home and limiting transfers as much as possible could reduce the financial burden on families significantly, but potentially also lessen the impact of cancer treatment on their daily lives and increase access to care [8]. The need for expansions of services in regions with insufficient care provision was also recognized in the NCSF [4]; as was the need for improved training of primary care personnel on recognizing childhood cancers. Finally, increased awareness on childhood cancers in the community may limit some of the emotional distress on caregivers and increase support.

Our findings recount the experiences of caregivers of children undergoing cancer staging or treatment. Our sample did not include caregivers of children who had completed their treatment. Despite this, the barriers we identified bears some significance for these survivors. Specifically, existing literature suggests that psychological distress in caregivers of childhood cancer survivors may persist long-term [24]. Additionally, families of childhood cancer survivors reportedly often struggle with continued financial challenges due to ongoing follow-up care and poorer health [25, 26]. The needs and barriers experienced by childhood cancer survivors in South Africa and their families warrant further study.

An important strength of this study is that it allowed us to triangulate the experiences of caregivers with a broader health system analysis, confirming the user barriers as perceived by other stakeholders involved. Additionally, although the number of private sector participants was limited, this is to our knowledge the first study to include private sector caregivers, affirming and emphasizing the differences between the public and private sectors. However, this small sample is likely not representative of all families seeking care in South Africa's private sector, some of whom may not have adequate insurance coverage and could face catastrophic expenditures. We highlight this as an important area for further study.

This study is also subject to several limitations. Firstly, the recruitment of participants from the foundation's accommodation facility has led to selective recruitment, potentially missing caregivers with fewer needs for external support as well as families with no access to treatment or those defaulting. As a result, specific reasons for treatment abandonment are not fully captured in this study. However, the findings further contribute to building a foundational understanding of the factors involved [18]. Additionally, participating accommodation facilities were located in Cape Town and Durban and were linked to large tertiary and quaternary treatment centers. Experiences in other regions and smaller tertiary centers may be different, especially in regard to the availability of medicines and supplies. Finally, some participants had a greater contribution to the discussions while others were silent, with limited interactions between participants. This implies that some participants were uncomfortable sharing in this setting or on this (emotional) topic. This may have been particularly relevant for the male participant in an otherwise female-dominated session. This could have led to some experiences not being reported to the same extent as others. To mitigate potential participant barriers, the focus group interview setting was deliberately chosen to foster a sense of comfort among like-minded individuals, the sessions were conducted at the accommodation facility that was familiar to caregivers, and participants could respond to questions in their native language.

Conclusion

This exploratory study provides evidence of user barriers in childhood cancer treatment, confirming and complementing findings from previous research. The experiences of caregivers in South Africa highlight that improvements are needed in the recognition of early signs of cancer at public sector primary care level. Despite indispensable emotional, informational and instrumental support provided by not-for-profit organizations, there is an increased need for financial support from the government through temporary social grants, travel allowances and nutritional support.

Ethics statement

Institutional approval was obtained from the Science-Geosciences Ethics Review Board (SG ERB) of Utrecht University (Bèta S-22784) and the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal (BREC/00004635/2022).

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Supplementary materials

Appendix 1: Semi-structured guide for focus group sessions

[Introduction]

General questions

Can you tell us a little about your family and your experience with the disease and care of your child?

Can you tell us what the disease has meant for you and your family?

Support

Is anyone supporting you or your family?

Accessing care and medicines

Do you know of any experience or story where a caregiver had issues accessing cancer services or medicines for their child? Please tell us more about that.

Financial aspects

We would now like to ask you a few more questions about the costs of cancer care for children.
What can you tell us about the costs caregivers have to make for their child's cancer care?

- Probes: consultation costs, investigation/imaging costs, medicines cost, transportation/travel costs, food and other related costs.
- Is there anything that the hospital has provided for you and your child? If yes, what? (Meals, fruit, travel costs, place to stay, other)
- Do you have medical insurance? If so, what did it (not) cover? (*private sector only*)

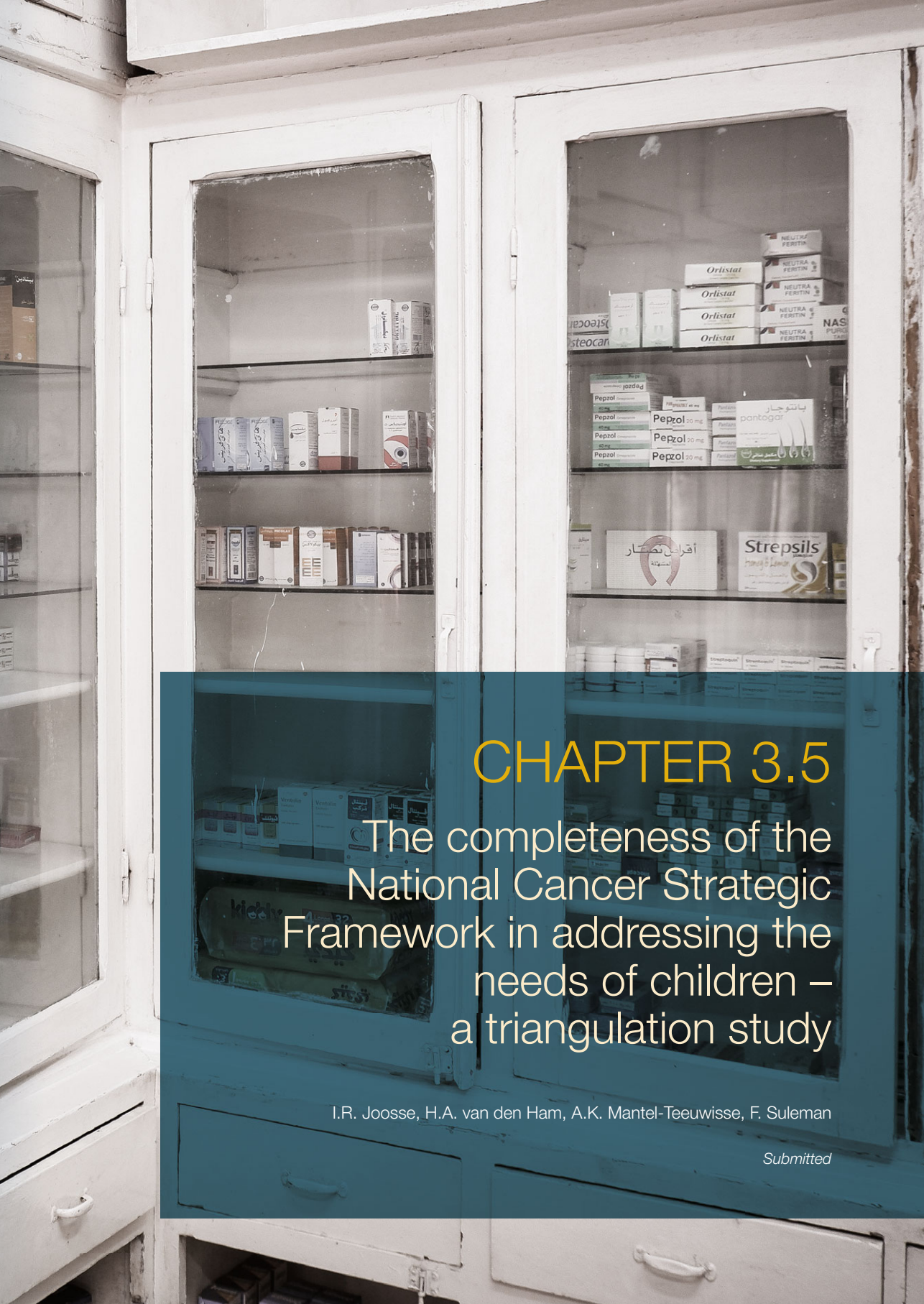
Closing

What do you need or what did you need at any point in your journey to make it better to make it easier?

Is there anything that you would like to say that I haven't already asked?

[Closing]


Bivatracin
BETADINE
Kaprofen
KETOLAC



CHAPTER 3.5

The completeness of the National Cancer Strategic Framework in addressing the needs of children – a triangulation study

I.R. Joosse, H.A. van den Ham, A.K. Mantel-Teeuwisse, F. Suleman

Submitted

Abstract

Aim

A better understanding of the scope of the National Cancer Strategic Framework (NCSF) could lead to improvements aiding the framework's ultimate objective of reducing the burden of cancer. Accordingly, we aimed to evaluate the completeness of the NCSF in addressing issues related to childhood cancer treatment, in particular pediatric oncology medicines.

Methods

To identify what barriers and facilitators determine current access to childhood oncology medicines in South Africa, in-depth interviews were conducted with 29 stakeholders in South Africa's public and private healthcare sectors. Key health system stakeholders included policy makers and regulators, medical insurance scheme informants, medicine suppliers, healthcare providers and civil society stakeholders. Identified barriers were categorized according to the components of the pharmaceutical value chain, and combined with a health system's approach to acknowledge the linkages of medicines with other building blocks of the health system. Identified barriers were then compared to the limitations and interventions as discussed in the 2017-2022 NCSF to identify areas for improvement in the framework.

Findings

We identified three recurrent gaps in the NCSF in relation to childhood cancers, representing a range of issues throughout the pharmaceutical value chain: 1) childhood cancers are neglected compared to adult cancers, in both the policy arena and the organization of healthcare services, 2) there are particular challenges for childhood cancers due to their rarity, thus requiring targeted interventions (e.g. regulatory incentives, tailored pricing solutions and customized evidence requirements by decision-making bodies), and 3) children must be accompanied by a caregiver during treatment, causing several social and financial issues for their families.

Conclusions

The areas in which childhood cancers are different from adult cancers should be acknowledged and given particular consideration in an update of the NCSF, as not to neglect this vulnerable group in the framework and further health systems strengthening.

Introduction

Childhood cancer comprises a diverse range of heterogenous cancers that manifest in children and adolescents [1]. These cancers differ from cancers affecting adults in two key aspects. Firstly, they have a distinct etiology, different tumor biology and microscopic appearance, and primarily arise in developing tissues and organs. Secondly, childhood cancers are often aggressive and marked by rapid growth over a short time [2]. Paradoxically, their rapid growth also renders them more susceptible to chemotherapy compared to many adult cancers. Timely initiation of treatment, which may also include surgery and radiotherapy, often holds the potential for a cure [1].

In South Africa, approximately 1000 children under the age of 19 receive a cancer diagnosis every year [3]. However, this figure is believed to account for less than half of those who develop cancer [4]. Despite the relatively small number of children affected by childhood cancers, the disease is an emerging challenge in South Africa and other low and middle-income countries (LMIC) [4, 5]. Survival rates of approximately 50% for childhood cancers in South Africa as compared to those in some high-income countries (reported to be as high as 80-90% [6]) are of great concern [7, 8]. Known reasons for these poorer survival rates are diverse, and include late diagnosis of the disease, a lack of treatment capacity at healthcare facilities, physical obstacles to using healthcare services, and barriers in accessing cancer medicines through unaffordable prices, stock-outs and discontinued manufacturing of essential medicines [9-11].

The 2017-2022 National Cancer Strategic Framework (NCSF) is intended to guide health legislation and policy-making for cancers on all levels of the health system, outlining key interventions and establishing a single platform to coordinate the different activities and stakeholders [4]. As the core framework and development plan it is imperative that the NCSF includes all those affected by the disease, including children. Although the NCSF identifies childhood cancer as a national priority, policy analyses conducted in the context of other LMIC have shown that policy directives for childhood cancers are often vague, hindering progress and resource allocation [12-14]. Hence, we aimed to evaluate the completeness of the NCSF in addressing issues related to childhood cancer and identify specific concerns for this population. Considering that childhood cancers are more reliant on chemotherapy than adults [1], we had a particular focus on pediatric oncology medicines.

Methods

We employed data source and method triangulation [15] to contextualize quantitative and qualitative data generated in prior research to the NCSF, using the following data sources:

A. Quantitative data derived from an analysis of policy documents.

Alignment of key pharmaceutical processes in the context of essential childhood cancer medicines was studied, through a comparison of the World Health Organization (WHO) Model list of Essential Medicines for Children (EMLc); the registered health products database of the South African Health Products Regulatory Authority (SAHPRA), the National Essential Medicines List (NEML) and relevant tender documents for antineoplastics and supportive medicines [16].

B. Qualitative data generated through individual in-depth interviews with stakeholders in the pharmaceutical value chain.

A health system analysis was conducted to identify barriers and facilitators in access to childhood cancer treatment and medicines in South Africa. Twenty-nine semi-structed, in-depth interviews were conducted with professional stakeholders in the pharmaceutical value chain, including policy makers and regulators (n = 7), medical insurance scheme informants (n = 5), medicine companies and suppliers (n = 7), healthcare providers (n = 6) and civil society stakeholders (n = 4). Interviews were conducted between September and November 2022 and questions covered aspects related to governance, financing, social aspects and service and medicine delivery. The barriers and facilitators identified were categorized according to the pharmaceutical value chain, i.e. policy and legislation, medicine regulation, financing and pricing, selection, reimbursement, supply and procurement, healthcare delivery, dispensing and use(r).

C. Qualitative data derived from focus group discussions with caregivers of children with cancer.

Four semi-structured focus group interviews (three in the public sector context and one in the private sector) were conducted with caregivers of children with cancer to explore their experiences in accessing and using cancer services. A total of 22 caregivers (20 caregivers of children receiving care in the public health care system and two in the private sector) participated in the sessions, organized in October and November 2022. Participants were asked about the cancer journey, the impact of the diagnosis and treatment on their lives and that of their family, whether they received support, their experiences in accessing care services, financial experiences and costs made, and any unmet needs during the cancer journey.

These data sources were triangulated to create a complete overview of barriers in access to childhood cancers treatment and then compared to the limitations and interventions as proposed in the 2017-2022 NCSF [4]. Identified barriers were perceived as addressed if any

reference was made to the barrier in the NCSF – whether literally or implied – in either the limitations, the description of different service delivery platforms or in the proposed strategies and goals. A reference did not need to be specific to childhood cancers, but could be more general.

Subsequently, the authors engaged in a consensus process – leveraging the data and explanations provided in the individual studies – to assess which barriers predominantly affect treatment of childhood cancers and hence require particular intervention and which issues have broader implications yet warrant special consideration regarding their impact on children.

Results

A total of 59 barriers – differing in size and impact on access to childhood cancer treatment and medicines – were identified through the triangulation of policy documents, stakeholder interviews and focus group sessions. The barriers include some unique to childhood cancer, alongside obstacles applicable to other cancers or populations, as well as general health system challenges that also have an impact on childhood cancers.

The NCSF acknowledged 25 of the barriers arising from our research. Nonetheless, five barriers require additional intervention to reduce the impact on children. Of the 34 barriers not addressed in the NCSF, we assessed that 6 predominantly affect children and require specific intervention and 11 have broader implications but warrant special consideration in the context of childhood cancer. Although general action may still needed to address the remaining 17 barriers, no additional activities for children would be required. An overview of all barriers assessed is provided in **Table 1**, as well as whether they were acknowledged and require specific intervention or consideration for children.

The next sections outline those barriers that require particular intervention or consideration in the context of childhood cancer.

Policy and legislation

Several professional stakeholders indicated that no concrete political priority is given to childhood cancers, resulting in a lack of targeted strategies for childhood cancers. This is likely due to the small number of children affected compared to adult cancers. Some of the barriers are inherent to rare diseases (described in more detail below), and specific interventions for cancers affecting smaller patient numbers – incorporated within the larger strategic framework – are thus appropriate.

Within national legislation, stakeholders also highlighted significant issues with the Single Exit Price (SEP) policy. Specifically, they expressed dissatisfaction with the lack of transparency in the policy as manufacturers are still free to set launch prices, and indicated that the policy induces

higher pricing due to external reference pricing schemes by other countries. Additionally, although pharmaceutical suppliers indicated willingness to provide medicines at lower prices to small patient populations based on compassionate grounds, the current pricing policies offer no flexibilities for discounting. A permanent price reduction is not desired by manufacturers because the SEP policy requires prices to be transparent, and manufacturers are not willing to have a lower price made visible to other countries. Exemptions for rare diseases may provide particular opportunities to amend the SEP policy.

Medicine regulation

To incentivize registration of orphan medicines, stakeholders indicated that there is a need for regulatory incentives such as expedited approvals, exemptions from importation requirement or tax reductions, which could increase access to some of the innovative medicines used in treating childhood cancer.

Section 21 provides an alternative access pathway for medicines that are not (yet) registered in the country (or medicines that were deregistered) on a named patient basis. Some essential childhood cancer medicines are only accessible through this pathway. Because the SEP policy does not apply to section 21 medicines, discounted prices are hence possible and stakeholders indicated that this access pathway may even be preferred for small patient populations. However, this pathway was also associated with exponential pricing for small patient groups due to freight costs, post-importation testing and local packaging requirements. Considerable delays in acquiring the products may occur due to administrative processes, the time it takes to ship it from Europe or the Americas to South Africa, and subsequent clearance by customs. Exponential pricing and further delays could be avoided if exceptions were in place for rare diseases such as childhood cancers.

In addition, although deregistration of older products was highlighted as a problem in the NCSF, this issue has a particular impact on children because treatment of childhood cancers is so reliant on these traditional chemotherapeutics.

Financing and pricing

Childhood cancer medicines are primarily listed on the NEML for tertiary and quaternary level of care, and therefore financed through the National Tertiary Services Grant (NTSG). No specific part of the budget is allocated to (childhood) cancers, and budget may also be used to acquire medicines that are not on the NEML. In practice, healthcare professionals have indicated that they have been unable to access this budget when attempting to acquire medicines for childhood cancer treatment, because the budget was exhausted elsewhere. Considering that childhood cancer medicines are confined to the NTSG, children are particularly affected by the lack of transparency of NTSG spending and potentially inequitable allocation.

Additionally, the previously existing system of temporary care grants has been abolished. This care grant could be awarded to families while undergoing cancer treatment, to cover the additional costs associated with treatment. Some children may qualify for the (permanent) disability grant that is still available, when they had a limb or eye removed due to the cancer. However, this excludes most children with cancer. Particular advocacy is needed for children around this issue.

Selection

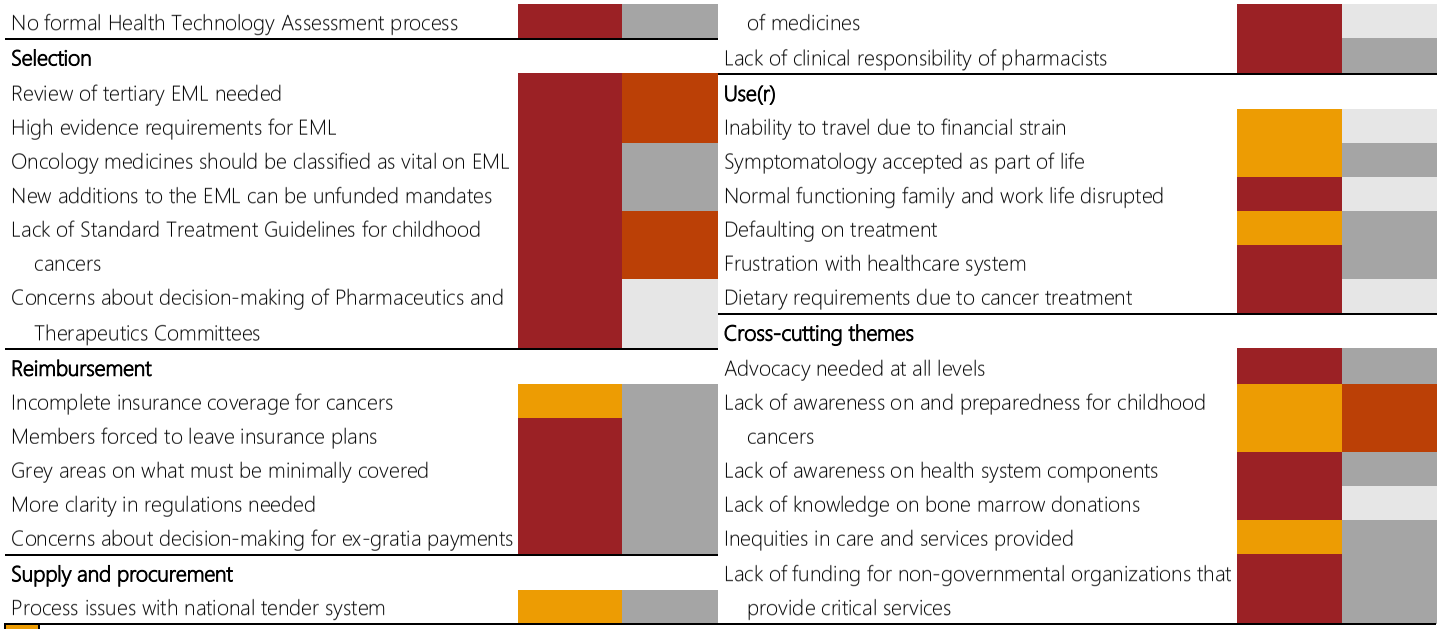
With the inception of the NEML and Standard Treatment Guidelines (STGs), public healthcare in South Africa has been rationalized and limited resources have been used effectively. With that, the NEML and STGs are key in providing access to medicines and essential childhood cancer medicines missing from this list leads to a cascade of complications. Yet, policy-makers and regulators indicated that the current tertiary/quaternary NEML is still adult-dominated, and limited attention that has been paid to pediatric indications since inception of the list. A thorough review of the completeness of the NEML was advised, with active involvement from pediatric oncologists, along with developments of STGs for some of the more prevalent childhood cancer types to increase accountability and access.

Paradoxically, stakeholders have indicated that it is difficult to have pediatric oncology medicines added to the NEML, due to the strict criteria and evidence requirements applied by the selection committee. It is widely known that clinical evidence in children is often missing or weak, which is even more pronounced for rare diseases [2]. In many cases expert opinion constitutes the core type of evidence, which is not accepted by the committee. Therefore, the high evidence requirements preclude orphan medicines from being added to the NEML.

If medicines are not included on the NEML, access to them can only be attained after approval from a local or regional Pharmaceutics and Therapeutics Committees (PTCs), usually paid for from the NTSG. The PTC appraises a request based on the justifications provided by the healthcare provider and the evidence presented. This process is associated with numerous obstacles, in addition to the issues associated with accessing the NTSG budget. Specifically, stakeholders expressed concerns because the committee members often have no expertise in childhood cancers. It was felt that medicines for childhood cancers were not getting approved because the committee members did not understand the urgent need for these medicines at that point of treatment. Additionally, similar high evidence requirements as for the NEML preclude these medicines from approval. Finally, there is no transparency and consistency in the decision-making of these PTCs, and the process can be delayed for up to four weeks. As such, revised and transparent procedures are necessary to facilitate better access to cancer medicines not listed on the NEML, including pediatric oncology medicines.

Table 1 Barriers in access to childhood cancer treatment acknowledged in or missing from the NCSF, and those requiring specific intervention or consideration for children.

Barriers identified through triangulation	Addressed in NCSF?	Attention required?
Monitoring and surveillance		
Lack of monitoring taking place for cancers		
Policy and legislation		
Lack of political priority given to childhood cancers		
Policy-making to implementation gap		
Lack of multi-stakeholder engagement in policy-making		
Transparency and pricing problems in Single Exit Price policy		
Medicine patent laws have various shortcomings		
Medicine regulation		
More regulatory efficiency needed to avoid duplication		
Need for regulatory incentives or exemptions		
Medicines not registered or older products deregistered		
Issues in pricing and reimbursement of section 21 medicines		
Financing and pricing		
Concerns about allocation of provincial budgets		
No transparency in spending of Tertiary Services Grant		
No temporary care grants for families		
Medicine or equipment donations are not sustainable		
Medicines are high priced		
Alternative payment models needed for innovative products		
Alternative procurement strategies needed		
Lack of urgency from procurement team		
Concerns about buy-out of medicines		
Unavailability and stock-outs of medicines		
Poor distribution systems		
Healthcare delivery		
Lack of diagnostic capabilities leading to late diagnosis		
Inadequate referral systems including repeated transfers		
Primary healthcare level training inadequate in public sector		
Primary healthcare level insufficiently utilized in private sector		
Lack of healthcare professionals across healthcare levels		
Lack of formal training and accreditations for childhood cancers		
Lack of diagnostic and radiology resources		
Lack of psychosocial support		
Lack of priority given to palliative care services		
Delays in care or defaulting due to complementary and traditional care		
Child-specific services not catered for		
Dispensing		
Gaps in safe and controlled preparing and administering		



EML = Essential Medicines List.

Supply and procurement

To increase manufacturers' interest in the South African market – and that of other countries in the region – the possibilities for multi-country pooled procurement should be investigated. This is particularly relevant for diseases with small patient numbers, such as childhood cancers.

In addition to this, healthcare professionals experienced a lack of understanding and urgency from other professionals involved in the procurement of medicines. It was felt that (impending) stock-outs were not communicated timely by members of the procurement team and little effort was made to resolve any issues urgently. The usually aggressive childhood cancers are specifically impacted by this perceived lack of understanding and efficiency. Additional training of professionals working in the procurement and distribution chain is needed, as well as more efficient set-up of the procedures involved.

Healthcare delivery

Many barriers in the delivery of cancer services are already addressed in the NCSF, but three barriers require special intervention or consideration for children. First, inadequate referral pathways may have a more pronounced impact on children, because childhood cancers are treated in public sector facilities concentrated in Western Cape and Gauteng. Hence, some children and their caregivers need to travel long distances – often crossing provincial borders – for treatment. This further disrupts family life and hampers frequent commuting between the treatment facility and the place of residence. Additionally, caregivers indicated that multiple referrals from facility to facility was needed during the diagnosing, staging and treatment of the cancer. These put considerable strain on families, particularly since travel is associated with high costs. The NCSF recognizes that more efficient referral pathways are needed and that the secondary level of care may be skipped for cancers. To avoid delays and reduce strain on the caregiver, this special population could be considered as a test group if alternative referral pathways are tested.

The lack of skilled healthcare professionals was highlighted in the NCSF, which includes a significant lack of nurses specialized in childhood oncology and pediatric oncology pharmacists. Contributing to this shortfall, there is a particular deficit of training programs and opportunities in this field, significantly impacting the quality of care. Establishing continuous development tracks including periodic retraining and retesting is imperative to maintain consistent skills in this critical field.

Healthcare providers noted a third substantial gap: some hospitals, although offering childhood oncology services, do not specifically cater to the needs of children with cancer. A striking example is the closing of hospital pharmacies over the weekend, even though some pediatric chemotherapy regimens continue over the weekend. This constitutes an urgent organizational gap that needs to be addressed locally.

Dispensing

Healthcare professionals expressed that there are gaps in the preparing and administering of oncology medicines including those for children. Safe administration may threatened because staff is not adequately trained to administer chemotherapy to children. In addition to this, the quality of oncology medicines may be compromised, because the controlled environment to prepare these medicines (such as a laminar airflow cabinet) is not available in all treatment facilities. This particularly affects small-scale private sector cancer facilities as well. Additionally, healthcare providers indicated that when pharmacy services are not continuously available, medicines are being prepared by untrained individuals in an uncontrolled environment. Children are at greater risk for compromised quality of care because they typically depend on liquid or intravenous dosages forms.

Use(r)

Financial strain was emphasized as an important concern by caregivers, due to travel requirements and the specific dietary requirements of children undergoing chemotherapy. Because children are typically accompanied by a caregiver, an added burden stems from double travel expenses and the necessity for caregivers to arrange their own accommodation and cover their own food expenses. Although non-governmental organizations provide significant assistance to caregivers through accommodation facilities and meals, caregivers continue to experience considerable strain. Moreover, their professional life and their family dynamics may be disrupted due to continued absence. This, in turn, exerts emotional and psychological pressure on the caregiver and the child. The need for financial and nutritional support was thus highlighted.

Awareness

Awareness raising and education campaigns are highlighted as key interventions in the NCSF, yet we identified a significant gap in their scope because campaigns aimed at lifestyle interventions and screening are of minimal relevance for childhood cancers. Through the discussions with caregivers, it became evident that many South Africans were not aware that cancer can also affect children. This lack of awareness – among both the general public and healthcare professionals working in primary healthcare – makes timely diagnosis less likely. There are important opportunities to increase awareness on childhood cancer by actively engaging schools, and other early childhood development systems.

Finally, bone marrow transplantations are lifesaving therapies for some childhood cancers, but a general lack of awareness and knowledge on this topic – among (caregivers of) recipients and especially potential donors – was identified as an important barrier. To broaden access to this life-saving therapy and enable more children to benefit from bone marrow transplantations, an expanded pool of donors, especially from non-white backgrounds, is essential.

Discussion

Our analysis revealed various gaps in the NCSF, indicating that although the framework provides a general understanding of overarching issues along the pharmaceutical value chain, specific barriers for childhood cancers remain unaddressed. Essentially, the gaps can be distilled into three aspects: 1) a tendency to neglect childhood cancers compared to adult cancers, 2) there are distinct challenges arising from the rarity of childhood cancers, requiring targeted interventions, and 3) children are typically accompanied by a caregiver during treatment, putting additional emotional and financial strain on these families. Our findings underscore the need to increase attention for the impact of these barriers on children, thereby enabling more appropriate policy-making tailored to the needs of this special population.

The neglect of childhood cancer was evident along the value chain, spanning the policy arena, regulatory and selection processes and extending to the organization of healthcare services. However, the omission of childhood cancer from the broader cancer agenda is paradoxical. Despite being consistently emphasized as a priority, the NCSF is adult-dominated and fails to propose any interventions or strategies specifically tailored to address the unique needs of children. This irony becomes more apparent when considering the NCSF's own emphasis on prioritizing curable cancers to optimally allocate limited resources – a category that includes childhood cancers [1].

The deficient policy commitments to childhood cancer are in line with findings in other LMIC, where vague directives have previously been described and highlighted [12-14]. However, there are also reports of LMIC that have succeeded in creating political priority for childhood cancers and establishing sustainable financing [17]. Civil society engagement was instrumental therein. Additionally, childhood cancer – with its relatively high cure rates in a manageable patient pool – could function as a test cohort for cancer policy interventions, for it has been hypothesized that successful childhood cancer programs may have a positive spill over effect to benefit adult cancers [18]. This could ensure improved access for both populations.

To enhance prioritization, there needs to be recognition that childhood cancers are distinct from adult cancers and may have other requirements. While there are notable similarities and interventions that could benefit other cancers, it's crucial not to overlook issues exclusive to children or those affecting them differently. In the present study, we have highlighted key items that are of specific concern for children and warrant attention.

The rarity of childhood cancers poses challenges in access but at the same time provides opportunities through numerous policy instruments such as regulatory incentives, tailored pricing solutions and customized evidence requirements by decision-making bodies [19]. However, fundamental to such prioritization is an operational definition of what constitutes a

rare disease in the South African context. Notably, any interventions aimed at childhood cancers could thereby extend benefits to other rare diseases, mitigating some of the challenges associated with these diseases and promoting more equitable access [20, 21].

The emotional and financial toll of childhood cancer on families has been described in the context of other LMIC and was confirmed in the present study [22-24]. Although the NCSF acknowledges the financial, geographical and logistical barriers associated with cancer treatment, our hypothesis suggests that these barriers have a more significant impact on families faced with childhood cancers. This impact can be attributed to the highly concentrated provision of childhood cancer care and the fact these patients are typically accompanied by a caregiver who requires food and accommodation.

A notable strength of our approach lies in the triangulation of quantitative and qualitative data derived from three distinct methodologies. This resulted in a comprehensive overview of barriers in access to childhood cancer treatment, allowing for a meaningful comparison with the NCSF. In line with the NCSF, we adopted a health system perspective. However, our specific emphasis on medicines in the health system allowed us to uncover barriers that might have otherwise been overlooked. We focused on barriers specifically relevant for children. However, our analysis of the scope of the NCSF is equally applicable to adult cancers, revealing opportunities for further expansions of the framework for the general population.

This study inherits limitations from the data sources utilized. Furthermore, during stakeholder interviews, clarity was not always achieved regarding whether identified barriers were specific to children or had broader implications. In such instances, a consensus approach was employed by the authors to deduce the barrier's impact, introducing a potential for different interpretations of the data.

Recommendations

In order to improve survival and reduce the burden of childhood cancer on South African families, representation of issues that affect children in the NCSF is key. This begins with acknowledging that childhood cancers are a distinct group of cancers requiring targeted intervention. Fundamental therein is a clear operational definition for rare diseases, facilitating prioritization and integration into the pharmaceutical value chain. Given its crucial role in determining access to medicines, a thorough review of the NEML concerning childhood cancer medicines is urgently needed. Finally, the implementation of (continuous) training programs in childhood cancer is pivotal for delivering high-quality care and should be promptly initiated.

Conclusion

Our findings expose a tendency within the 2017-2022 NCSF to overlook the distinct challenges associated with childhood cancers. The aspects in which childhood cancers are different from adult cancers should be acknowledged and warrant special consideration and intervention in any future update of the NCSF, as not to neglect this vulnerable group in the framework and further health systems strengthening efforts.

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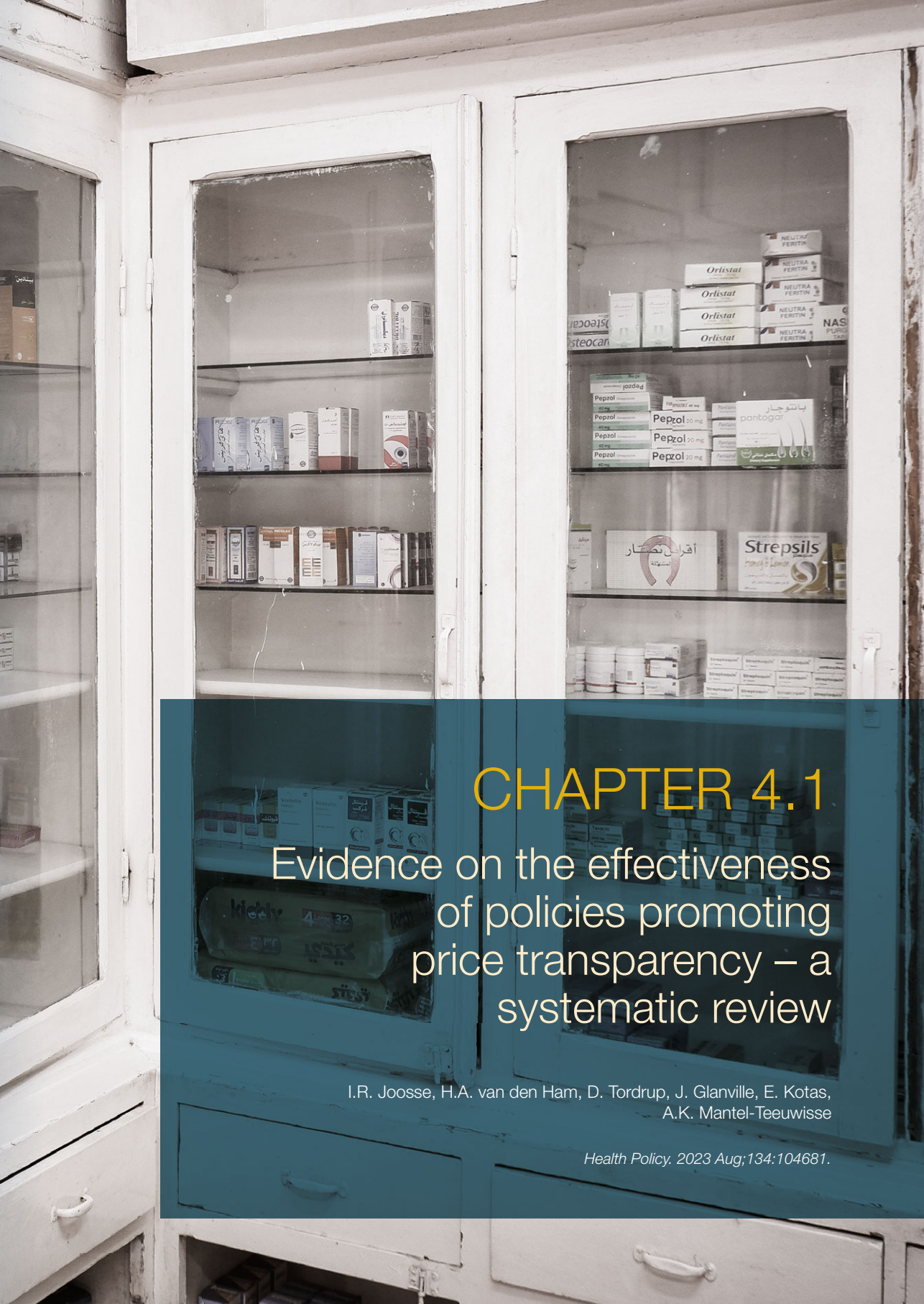
CHAPTER 4

The evidence landscape for pharmaceutical pricing policies


Bivatracin
BETADINE
Kaprofen
KETOLAC



CHAPTER 4.1

Evidence on the effectiveness of policies promoting price transparency – a systematic review

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Abstract

Policies promoting price transparency may be an important approach to control medicine prices and achieve better access to medicines. As part of a wider review, we aimed to systematically determine whether policies promoting price transparency are effective in managing the prices of pharmaceutical products. We searched for studies published between January 1, 2004 and October 10, 2019, comparing policies promoting price transparency against other interventions or a counterfactual. Eligible study designs included randomized trials, and non-randomized or quasi-experimental studies such as interrupted time-series (ITS), repeated measures (RM), and controlled before-after studies. Studies were eligible if they included at least one of the following outcomes: price (or expenditure as a proxy for price and volume), volume, availability or affordability of pharmaceutical products. The quality of the evidence was assessed using the GRADE methodology. A total of 32011 records were retrieved, two of which were eligible for inclusion. Although based on evidence from a single study, public disclosure of medicine prices may be effective in reducing prices of medicines short-term, with benefits possibly sustained long-term. Evidence on the impact of a cost-feedback approach to prescribers was inconclusive. No evidence was found for impact on the outcomes volume, availability or affordability. The overall lack of evidence on policies promoting price transparency is a clear call for further research.

Introduction

In recent years, improved price transparency of pharmaceuticals has emerged as an important yet highly debated approach to manage medicine prices. This approach is believed to contribute to expanded access to medicines through the reduction of medicine prices [1]. In both the 2019 Fair Pricing Forum and the 72nd World Health Assembly (WHA) the need for reliable information on medicine prices was emphasized, leading to the WHA's adoption of a resolution on advancing the transparency of markets for pharmaceuticals (WHA 72.8) [2, 3].

The importance of promoting price transparency has also been reflected in various initiatives and regulations aiming to enhance transparent pricing. One such example is the Medicines Transparency Alliance (MeTA) initiative by the World Health Organization (WHO), which sought to develop national-level multistakeholder platforms to share data on the selection, procurement, quality, availability, pricing, promotion and use of medicines [4-6]. Another example is the European Union (EU) Transparency directive which requires the publication of the list prices of all reimbursable medicines in Europe [7].

The underlying rationale for promoting price transparency is that it may improve economic efficiency, as conventional economic theory indicates; assist policymakers and researchers through reliable price information; empower buyers to negotiate more strategically; increase accountability of manufacturers and governments for prices; and promote cost-effective decision-making by prescribers and patients [8, 9]. Conversely, a lack of price transparency may give rise to corruption as confidential agreements may compromise accountability, especially in healthcare systems with weak governance [8, 10]. These theories cut across four levels where transparency may occur: 1) the reporting of R&D and production costs, 2) the disclosure of net transaction prices to stakeholders as an input to price benchmarking, 3) the disclosure and control of prices along the supply chain, and 4) the communication of prices to prescribers or patients [8].

At the same time, there are concerns that improving transparency may lead to an increase in prices for lower-income countries, as manufacturers might abandon differential pricing schemes and apply uniform pricing for all countries to refrain from the appearance of unfair pricing [11]. Other harmful effects suggested are discouraged entry in poorer markets, reduced competition and lessened incentives for investments [11, 12]. Despite the different claims that have been made, the impact of transparency measures on medicine accessibility remains largely theoretical thus far. It is, however, essential that governments and policy-makers implement measures that have proven to be effective. The 2015 WHO Guideline on Country Pharmaceutical Pricing Policies, which aimed to assist countries in evidence-based policy-making, did not include guidance on policies promoting price transparency [13]. The update of the 2020 Guideline therefore called for identification and assessment of the available evidence on price

transparency measures, among nine other pricing policies [14]. Hence, the purpose of this systematic review is to determine whether policies promoting price transparency are effective in managing the prices of pharmaceutical products, with consideration to their impact on the volume, availability and affordability of these products. This review also aims to elucidate what contextual factors and implementation strategies may influence the effects of such policies.

Methods

This systematic review was undertaken according to the principles of systematic reviewing embodied in the Cochrane Handbook and guidance document published by the Centre for Reviews and Dissemination (CRD) [15, 16]. The methodology and detailed search strategies have been described in detail previously [17, 18].

As part of a wider review on ten pharmaceutical pricing policies, this paper only addresses policies promoting price transparency as a pricing approach.

Search strategy and selection criteria

An extensive literature search was performed between September 5 and October 10, 2019, for relevant articles published from 2004 to the search date in a large number of databases including but not limited to Ovid MEDLINE (Ovid), Embase (Ovid), Social Science Citation Index, EconLit, and the NHS Economic Evaluations Database (NHS EED). A variety of grey literature sources were also searched. The main structure of the search strategy comprised concepts pertaining to 1) non-specific pharmaceutical pricing policies (e.g. terminology related to pricing/prices combined with terms for medicines) or to 2) pharmaceuticals and one of ten specific pricing policies, among which were policies promoting price transparency (e.g. terminology related to pricing/prices combined with terms for transparency, including related terms such as disclosure, rebates, sharing, and accountability). Supplementary search approaches included reference-list checking and contacting experts.

Box 1 Definition of the policy intervention.

Promoting price transparency

The sharing, disclosure and dissemination of information related to medicine prices to the public and relevant parties to ensure accountability. Full price transparency includes the publication of medicine prices at all price types (e.g. ex-factory prices, pharmacy retail prices), the disclosure of the net transaction prices of medicines between the suppliers (e.g. manufacturers, service providers) and the payers/purchasers (governments, consumers), the sharing and publication of the contents of pricing arrangements, such as risk-sharing schemes and other managed-entry agreements, including the actual pricing and input factors that determine a medicines prices (e.g. production costs, R&D costs, added therapeutic value).

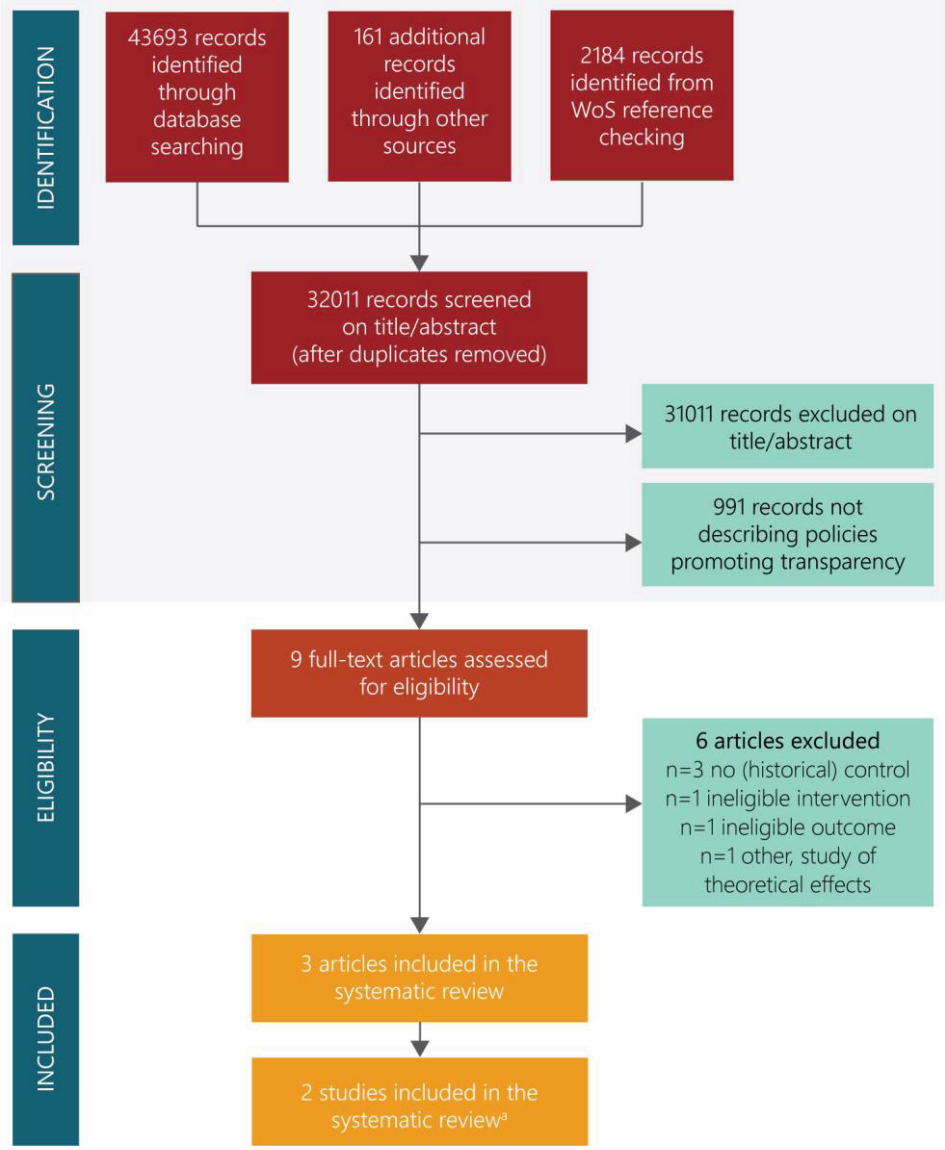

Figure 1 Flow chart of study selection.
The number of articles identified through database searching and screening by title and abstract shown in grey apply to the overall search; as per protocol the database search included search terms for all ten specific pricing policies among which policies promoting price transparency was one. The lower part of the flow chart shown in white is specific to the selection of studies on policies promoting price transparency.
WoS=Web of Science.
[a] Two articles are part of the same study, but were published separately. These references are considered one study.

Selection criteria

This systematic review only included studies that used robust experimental or observational study designs comparing policies promoting price transparency (see **Box 1**) to at least one comparator or counterfactual [15]. Study designs including randomized trials and non-randomized or quasi-experimental studies (including interrupted time-series (ITS), repeated measures (RM), panel data analyses, and controlled before-after studies) were considered strong designs. Single policies, or combinations of policies, were considered eligible. Studies reporting at least one of the primary outcomes of interest, i.e. price (or expenditure as a proxy), volume, availability or affordability, were eligible for inclusion. Medicine prices reported at all levels of the supply chain (e.g. ex-factory price, wholesale price, retail price, or patient price) were considered eligible. Outcomes in both public, private and mixed public-private settings were of interest.

Study selection

A single researcher assessed all titles and abstracts identified from the database searches and removed the obviously irrelevant records based on titles and abstracts. Two reviewers independently screened the titles and abstracts of potentially eligible records, with disagreements adjudicated by a third reviewer. The full texts of studies identified as potentially relevant were then subject to an eligibility check by two members of the review team independently (TB and CL or IRJ and HAvdH) before data extraction. Disagreements about study selection were resolved by discussion, and if consensus could not be reached, a third reviewer (DT or AKM-T) was consulted.

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Data extraction and quality assessment

Data from included studies was extracted by one member of the review team (IRJ or LT) using a standardized data extraction form, including information on study design, setting and subjects, interventions including implementation strategies, outcomes, and results including contextual factors. Extracted data was verified by a second reviewer (HAvdH or DT) for accuracy.

The risk of bias in each included study was assessed by the extracting reviewer and checked by a second reviewer. Any disagreements were resolved by discussion until a consensus was

reached. The assessment was done according to the EPOC guidelines, in which bias assessment criteria were adapted to study design [19]. Randomized and non-randomized trials and controlled before-after studies were assessed on nine criteria; ITS and RM studies were assessed on 8 criteria; and a set of four assessment criteria applied to all other study types. An explanation of the bias criteria is presented in Appendix 1.

The quality of the evidence was assessed by use of the GRADE methodology [20]. GRADE evidence levels were determined by considering the body of evidence available for each (sub-)intervention. Domains of scoring were the risk of bias, inconsistency of results, indirectness of evidence, imprecision of results, and 'other' (Appendix 2). Studies were upgraded in the 'other' domain if strong observational study designs were used (ITS, RM, panel data/regression analysis), according to precedent in literature [21]. The resultant certainty of the evidence was expressed as high, moderate, low or very low.

Data analysis

Substantial expected differences in the characteristics and contexts of included studies meant we did not aim to undertake a meta-analysis. Instead, we provided a narrative summary describing the quality of the studies, the relationship between interventions and patterns discerned in the data.

Results

Electronic database and grey literature searches identified 43,693 records for all ten pricing policies combined. The review of relevant reference lists and other sources yielded a further 2,345 records. After removal of duplicates, 32,011 articles were screened by title and abstract, resulting in 1,000 potential articles to be included in the wider review. Nine of these articles were specific to policies promoting price transparency at first sight. After full-text screening, three scientific articles covering two policy measures were included in this section of the systematic review (**Figure 1**). Specifically, two articles (Moodley 2019a, Moodley 2019b) are part of the same study, one addressing originator pharmaceuticals while the other addresses both originator and generic pharmaceuticals [22,23]. These references are considered to be one study in this review, according to Cochrane guidelines. Six studies were excluded, because of a lack of a historical control [24–26], primary outcomes of interest were not reported [27], theoretical effects were studied [28] and one study was considered off-topic after reading the full text [29].

Both studies identified had an interrupted time series design, one examining data from the United Kingdom [30] and one being set in the private sector in South Africa [22, 23] (**Table 1**). Langley et al. included antibiotics and inhaled corticosteroids and examined the effects of a cost-feedback approach to prescribing physicians on drug expenditure. Moodley et al. considered the top 50 medicines in the private sector and examined the effects of mandatory

public disclosure of medicine prices along the supply chain. The results were categorized according to their level of intervention. The results of the risk of bias assessment are presented in **Table 2**. The study by Langley et al. was associated with a low risk of bias across all domains, and overall certainty of evidence was assessed to be moderate. The study by Moodley et al. was associated with an unclear risk of bias across three of eight domains. None of these potential biases were considered to be of major influence on the results, and the overall risk of bias was thus considered to be low in this study. The certainty of evidence was assessed to be low for measures promoting public price disclosure due to serious indirectness. Detailed results of the overall quality assessment (GRADE) are provided in Appendix 3.

Table 1 Summary of included studies.

	Study type	Setting	Subjects of study	Intervention	Outcomes
Langley 2018 et al. [30]	ITS	United Kingdom	Antibiotics and inhaled corticosteroids	A cost-feedback approach to prescribers: the provision of information on the cost of drugs in electronic prescribing to clinicians in a hospital setting	Price outcomes (weekly expenditure; weekly cost per patient)
Moodley 2019 et al. [22, 23]	ITS	South Africa	Top-50 originator medicines dispensed in private sector by volume and corresponding generics	The Single-Exit-Price (SEP): mandatory disclosure of fixed medicine prices, that are composed of the weighted average of the sales price, the logistics fee and value-added taxes. All discounts and off-invoice rebates are removed. Applies to the private sector. The disclosed prices are made publicly available on the South African Medicine Price Registry website	Price outcome (relative change in medicine price)

ITS = Interrupted time series.

Communicating prices to prescribers or patients

Langley et al. examined the impact of cost-feedback to prescribers in a hospital setting [30]. Clinicians were provided with extra information on the costs of drugs during prescribing, with the simple aim of informing them of the costs of their decision without intending to direct their prescription behavior. The intervention was implemented in November 2014 in the hospital's electronic prescribing system, which permitted the costs of the medicine of choice to be added to the display that the prescribing clinician sees immediately prior to selecting the drug.

The study reported expenditure outcomes for antibiotics and inhaled corticosteroids (**Table 3**). For antibiotics, a decrease of GBP -3.75 (p=0008) in weekly costs paid by the patient was observed immediately after implementation of the intervention, whereas the trend slightly

increased with GBP 0.10 (p=0.015) over a twelve-month period. For inhaled corticosteroids, a small change in trend was seen in weekly costs per patient of GBP -0.03 (p=0.11), but no other changes were observed. The authors were not able to explain the contradictory results in both drug classes. There was no evidence on the impact of this intervention subtype for the outcomes volume, availability or affordability, because these outcomes were not included in the study.

Disclosure and control of prices along the supply chain

Moodley et al. examined the impact of a national measure that introduced a transparent pricing system in the private market, in the context of the South African Single Exit Price (SEP) policy [22, 23]. In an attempt to reduce medicine costs, the 2004 SEP ensures that there is a fixed price for all private sector prescription medicines sold by the manufacturers to distributors and dispensers in the country. The SEP must be publicly disclosed and is composed of the weighted average of the sales price, the logistics fee and value-added taxes, and determined by the manufacturers themselves. Simultaneously, all bonuses, discounts and sampling of medicines were removed. This was complemented with a regulated maximum percentage annual increase and regulation of dispensing fees at retail level. The disclosed prices are made available on the South African Medicine Price Registry website.

Table 2 Risk of bias assessment of included studies.

Bias type	Langley 2018	Moodley 2019[a]
Interrupted time series and repeated measures studies		
Intervention independent	⊕	⊕
Appropriate analysis	⊕	⊕
Pre-specified shape of effect	⊕	⊕
Intervention to affect data collection	⊕	?
All study types		
Incomplete outcome data	⊕	?
Knowledge of allocated intervention	⊕	⊕
Selective outcome reporting	⊕	⊕
Other bias	⊕	?

[a] Moodley et al. [22] was assessed to have an unclear risk of bias across three domains due to the source of data not being described in detail (*intervention to affect data collection*), possible bias due to missing data (*incomplete outcome data*) and the outcome measure not being described in detail (*other bias*). The second reference [23] was similar to the first, except that the analysis method was not reported. However the two references are by the same authors, using the same dataset and methodology. As the analysis is appropriately reported in one of the studies (low risk of bias) but with less detail in the other (unclear risk of bias), it is reasonable to assume both studies are of equal quality. Overall the risk of bias is considered to be low for the two publications collectively.

Table 3 Summary of findings of Communicating prices to prescribers or patients.

Communicating prices to prescribers or patients compared to no price communication				
Medicines: Antibiotics and inhaled corticosteroids **Settings:** United Kingdom **Intervention:** Cost-feedback to prescribers **Comparison:** No policy				
Outcomes	**Impacts**	**No. of studies**	**Certainty of the evidence (GRADE)**	**Comments**
Price				
Weekly cost per patient	It is uncertain if a cost-feedback approach leads to a difference in costs, because the evidence is inconclusive.	1	Moderate ⊕⊕⊕◯	A cost-feedback approach was associated with an immediate significant reduction in costs for antibiotics. No difference was observed for inhaled corticosteroids. Antibiotics showed an increasing trend in costs after the intervention, whereas the approach was associated with a slightly decreasing trend for inhaled corticosteroids.
Volume				
-	No studies meeting the inclusion criteria were found	0	-	-
Availability				
-	No studies meeting the inclusion criteria were found	0	-	-
Affordability				
-	No studies meeting the inclusion criteria were found	0	-	-

[a]GRADE Working Group grades of evidence
High = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different[b] is low.
Moderate = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different[b] is moderate.
Low = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different[b] is high.
Very low = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different[b] is very high.
[b] Substantially different = a large enough difference that it might affect a decision.

The study included 50 medicines within three samples (a 'global core' for international comparison, a 'regional core' for items important in the region, and a 'supplementary list' for products of local importance) as per the WHO/HAI (i.e. Health Action International) methodology. It reports on the prices of medicines paid for by the patient, obtained from dispensing files and claims data. Medicine prices in retail pharmacies across all three samples were reduced immediately following the SEP policy, for both originator and generic medicines (**Table 4**). Mean reduction was greater for generics. Global core percentage price reduction ranged from 2.45% to 9.12% for originator medicines and 18.50% to 91.52% for generics; regional core reduction was 1.77% to 42.17% for originators and -0.70% to 78.03% for generics; supplementary list price reduction was 11.68% to 55.86% for originators and 9.78% to 78.49% for generics. A (significant) negative change in trend implying continued benefit on patient prices was observed in 26 out of 50 originator medicines and 23 out of 73 generic medicines. The impact of this intervention subtype on the outcomes volume, availability or affordability was not studied.

Discussion

Following extensive searches, we found only two studies assessing an intervention promoting price transparency in a manner sufficiently robust for inclusion in this review. It is worth noting that the SEP, while introducing transparency in the private market, also included aspects of price control other than price transparency. With that, evidence on measures that exclusively promote price transparency is even more limited. Nevertheless, the results show that the majority of patient prices of both originator and generic medicines were reduced following a national measure that introduced transparency on the level of the manufacturer. Not only did this policy achieve the intended price reduction, it has also improved accountability of manufacturers through mandatory price disclosure. Findings on the impact of cost-feedback approaches to prescribers are considered inconclusive, due to inconsistent results for different therapeutics. Information about the effects on volume, availability or affordability is currently missing for all transparency initiatives. The 2020 WHO Guideline on Country Pharmaceutical Pricing Policies suggests that countries improve the transparency of pricing and prices, informed by the limited research evidence and additional qualitative information that was considered [14]. These considerations include the notion that transparent pricing or prices could serve multiple purposes, including increased citizen engagement and facilitating other pricing policies such as external reference pricing.

The 2015 WHO Guideline on Country Pharmaceutical Pricing Policies did not yet include policies promoting price transparency in its scope [13]. Despite considerable attention for price transparency measures on the international stage since then, this was not reflected in the amount of robust evidence currently available. Similarly, a recent scoping review [9] on

countries' price transparency initiatives, with a somewhat broader setup that included other study designs as well, confirms that there is limited robust evidence on price transparency policies. This scoping review identified 12 studies, none of which would have been considered eligible for our systematic review. A WHO Technical Report on the pricing of cancer medicines [8] again confirmed that the amount of strong evidence is limited. The small number of studies reporting on the effectiveness of price transparency measures may be due to the complexity inherent to performing this research [31]. At the same time, price transparency measures are currently not common practice, which further contributes to the lack of studies of their real-world effectiveness.

Table 4 Summary of findings of policies promoting disclosure and control of prices along the supply chain.

Disclosure and control of prices along the supply chain compared to no disclosure and control				
Medicines: 50 medicines originator medicines and corresponding generic medicines divided over a Global and Regional Core, and supplementary lists based on WHO/HAI survey methodology **Settings:** South African private sector **Intervention:** Price disclosure at the national level (Single Exit Price) **Comparison:** No policy				
Outcomes	**Impacts**	**No. of studies**	**Certainty of the evidence (GRADE)**	**Comments**
Price				
Medicine price	The Single Exit Price policy may be effective in reducing prices of originator and generic medicines immediately after implementation. Benefits may be sustained in originator medicines, whereas long term effects of the Single Exit Price policy on generic medicines may be variable.	1	Low ⊕⊕◯◯	Medicine prices in all samples (global core, regional core, supplementary list) were reduced immediately following the SEP policy for both generic and originator medicines. Mean reduction was greater for generics. Continued benefit on medicine prices through a negative change in trend was observed in approximately half of the originator medicines and a third of the generic medicines.
Volume				
-	No studies meeting the inclusion criteria were found	0	-	-
Availability				
-	No studies meeting the inclusion criteria were found	0	-	-

Affordability				
-	No studies meeting the inclusion criteria were found	0	-	-

[a]GRADE Working Group grades of evidence
High = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different[b] is low.
Moderate = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different[b] is moderate.
Low = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different[b] is high.
Very low = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different[b] is very high.
[b] Substantially different = a large enough difference that it might affect a decision.

The WHA's resolution to advance the transparency of markets for pharmaceuticals was considered controversial [3, 32]. Although the large majority of WHO Member States considered price transparency measures to be key in achieving better access to price data and universal health coverage (UHC), the resolution was strongly contested by several countries. These countries argued that the assessment of potential negative implications of price transparency measures had been insufficient. Specifically, concerns were expressed about the impact of the resolution on developing countries, as improved transparency may threaten differential pricing arrangements [32]. The controversy that the resolution triggered reflects the paradoxical situation of price transparency measures. Without compelling evidence on the impacts of price transparency measures, countries may be cautious to conform to the resolution and implement transparency initiatives. However, without the implementation of novel transparency measures to inform new research, the opportunities for high quality research on the effectiveness of transparency interventions are limited. This 'Catch-22' appears to be borne out in the volume of literature identified in this systematic review. Despite this paradox, the resolution may inspire novel policies promoting price transparency to be implemented, which may present new opportunities for research.

The strengths of our systematic review include the use of a rigorous methodological approach, following a pre-defined protocol [17]. We used a sensitive search strategy containing a wide range of terms, designed to retrieve both records that referred to non-specific pharmaceutical pricing policies as well as to price transparency measures specifically. Furthermore, we performed an extensive database search and searched the grey literature, as well as used supplementary search approaches such as checking relevant reference lists and contacting experts. This search strategy reduced the risk of missing potentially relevant studies. Risk of bias and strength of the evidence base were assessed using a validated guideline [19, 20] and were determined in duplicate to minimize bias and error.

Our study has several limitations. As noted before, the search resources included grey literature sources. Although important to include such resources, many of the databases have very limited search and exporting functionalities. For those resources, we had to use a more limited range of search terms. This pragmatic search approach is a limitation of the search methods, but should be seen within the wide range of search approaches described above. Another limitation might arise from the heterogeneity of price transparency measures, which may often be interwoven with other pricing policies or which may not be described as a transparency measure by the authors of the study. To minimize this limitation, a standard systematic review approach of using a highly sensitive search approach was used with a broad definition of price transparency policies and search terms, which would identify all types of transparency measures were used. Nevertheless, there is always the chance of missing relevant studies. However, we note that experts in the field were consulted to mitigate this risk. Additionally, the scoping review on transparency measures mentioned earlier, did not identify any studies that we had missed [9]. Finally, due to the nature of policy research, no randomized controlled trials were available to inform on the effectiveness of price transparency measures. Therefore, the certainty of the evidence is lessened due to the use of strong yet quasi-experimental study designs.

The evidence identified on price transparency measures may be limited in applicability, despite its broad relevance in both high- and low-income economies [33-35]. The study by Langley et al. [30] focused on two groups of therapeutics only, one of which being antibiotics. The prescription of antibiotics in a high-income setting is expected to be highly regulated and guided by antibiotic susceptibility, so results may not be applicable to other therapeutics. As price transparency initiatives are believed to be promising in a broad range of medicine groups including innovative, anticancer, and other high-priced medicines [35, 36], future research should examine the effects of transparency measures in other medicine classes before extrapolating these results. Furthermore, this study was set in a high-income economy that generally requires no co-payment by patients. While these results may be applicable to similar settings, generalizability to healthcare systems in which patients' ability to pay could influence physician's prescribing behavior is challenging. Similarly, the SEP introduced uniformity in the private market through a transparent pricing system with fixed prices, with the final goal of reducing pharmaceutical expenditures. These results may inform design of policies with similar objectives, but do not immediately apply to other price transparency challenges such as the disclosure of R&D costs. Finally, the overall evidence was limited to only measures could include. The generalizability of our results to other healthcare systems should therefore be viewed with consideration to context, until such a time when more evidence has been produced. Despite these limitations, this first systematic review is a first step in informing national and regional governments and other policy-makers such as hospital boards or insurance providers on effective policies for managing the prices of pharmaceuticals using transparency measures.

Although opportunities for research on transparency measures seem to be limited due to a 'Catch-22' dilemma, it is crucial that when such opportunities do present, efforts of policy-makers and researchers are coordinated. This will help to ensure the collection of data for adequate monitoring of these policies. The conduct of small pilots may help to increase opportunities for evidence generation on the one hand and overcome the reluctance of policy-makers on the other. These future studies should focus on all levels that transparency measures may occur in, and not only on medicine prices or expenditures, but likewise on outcomes such as the volume, availability and affordability of medicines. There should also be a particular focus on unintended and potentially harmful effects of these policies, both in high- as well as in low-income settings. Additionally, the limited amount of evidence currently available is insufficient to elucidate what contextual factors and implementation strategies may influence the effects of such policies, and should be the object of further study.

Conclusion

In conclusion, the lack of quantitative and comparative evidence assessing the impact of policies promoting price transparency is a clear call for further research. Collaborative pilots involving both national governments and researchers could help to align their interests and overcome the current inertia in evidence development. Additional evidence is needed to confirm the impact of a wide range of transparency measures on the management of medicine prices in countries all over the world. The evidence that is currently available, although from a single study, indicates that a national measure introducing price transparency along the supply chain may be effective in managing medicine prices.

Acknowledgements

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Supplementary materials

Appendix 1: Description and interpretation of risk of bias domains

Table S1 Description and interpretation of risk of bias domains as applied in the systematic review [1].

Bias domain	Explanation
Bias domains specific to interrupted time series and repeated measures studies only	
Intervention independent	Low risk" if there are compelling arguments that the intervention occurred independently of other changes over time and the outcome was not influenced by other confounding variables/historic events during study period. If Events/variables identified, note what they are. "High risk" if reported that intervention was not independent of other changes in time.
Appropriate analysis	"Low risk" if data were analyzed appropriately e.g. if autoregressive integrated moving average (ARIMA) models were used OR time series regression models were used to analyze the data and serial correlation was adjusted/tested for OR reanalysis performed. "High risk" if the outcomes were not analyzed appropriately. "Unclear risk" if not specified in the paper.
Pre-specified shape of effect	"Low risk" if point of analysis is the point of intervention OR a rational explanation for the shape of intervention effect was given by the author(s). Where appropriate, this should include an explanation if the point of analysis is NOT the point of intervention. "High risk" if it is clear that the condition above is not met.
Intervention to affect data collection	"Low risk" if reported that intervention itself was unlikely to affect data collection (for example, sources and methods of data collection were the same before and after the intervention). "High risk" if the intervention itself was likely to affect data collection (for example, any change in source or method of data collection reported).
Bias domains applicable to all study types	
Incomplete outcome data	"Low risk" if missing outcome measures were unlikely to bias the results (e.g. the proportion of missing data was similar in the intervention and control groups/pre- and post-intervention periods or the proportion of missing data was less than the effect size i.e. unlikely to overturn the study result). "High risk" if missing outcome data was likely to bias the results. "Unclear risk" if not specified in the paper (not assuming 100% complete data unless stated explicitly).
Knowledge of allocated intervention	"Low risk" if the authors state explicitly that the primary outcome variables were assessed blindly, or the outcomes are objective. Primary outcomes are those variables that correspond to the primary hypothesis or question as defined by

	the authors. "High risk" if the outcomes were not assessed blindly. Score "Unclear risk" if not specified in the paper.
Selective outcome reporting	"Low risk" if there is no evidence that outcomes were selectively reported (e.g. all relevant outcomes in the methods section are reported in the results section). "High risk" if some important outcomes are subsequently omitted from the results. "Unclear risk" if not specified in the paper.
Other bias	"Low risk" if there is no evidence of other risk of biases.

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Appendix 2: Description and interpretation of GRADE assessment criteria

The Cochrane Effective Practice and Organisation of Care (EPOC) guidance for the development of GRADE and Summary of Findings tables outlines the process of GRADE assessment of observational evidence. The GRADE assessment is based on five domains: risk of bias, inconsistency, indirectness, imprecision, and "other". In this appendix, we clarify the interpretation of these assessment domains.

Table S2 Description and interpretation of GRADE assessment criteria.

Domain	Definition by EPOC [1]	Interpretation and adaptation
Risk of bias	As outlined in appendix 1	
Inconsistency [2]	Inconsistency refers to an unexplained heterogeneity of results. GRADE suggests rating down the quality of evidence if large inconsistency in study results remains after exploration of a priori hypotheses that might explain heterogeneity. Judgment of the extent of heterogeneity is based on similarity of point estimates, extent of overlap of confidence intervals, and statistical criteria including tests of heterogeneity and I^2.	As the study types, outcomes and analyses methods tend to vary, we considered inconsistency to indicate the directionality of evidence. In cases where a point estimate of effect was not statistically significant, the directionality is considered regardless of the precision of the estimate.
Indirectness [3]	Includes consideration of - Indirect (between study) comparisons - Indirect (surrogate) outcomes - Applicability (study populations, interventions or comparisons that are different than those of interest)	The original meaning was consistent with the purposes of the present review.
Imprecision [4]	Includes consideration of whether the recommendation would differ, if the true effect would lie at either extreme of the confidence interval.	Analogously, we considered the precision around the estimate of the effect.
Other	N/A	Other sources of bias may be related to any features of the study not captured by the points above, or by the risk of bias assessment.

	In particular, we considered external validity (generalisability of the evidence) to be of relevance.

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Appendix 3: Certainty assessments of evidence

Table S3 Certainty assessment (GRADE) of evidence for communicating prices to prescribers or patients.

No of studies	Design (number)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Certainty (overall score)
Outcome: Price							
1 [1]	ITS (I)	Low risk (0)	No serious inconsistency (0)	No serious indirectness (0)	No serious imprecision (0)	Study design (+1)	Moderate ⊕⊕⊕◯
Outcome: Volume							
Outcome: Availability							
Outcome: Affordability							

Table S4 Certainty assessment (GRADE) of evidence for Disclosure and control of prices along the supply chain

No of studies	Design (number)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Certainty (overall score)
Outcome: Price							
1 [2,3]	ITS (I)	Low risk (0)	No serious inconsistency (0)	Serious indirectness (-1)[a]	No serious imprecision (0)	Study design (+1)	Low ⊕⊕◯◯
Outcome: Volume							
Outcome: Availability							
Outcome: Affordability							

[a] The SEP was associated with serious indirectness, because there appear to be multiple aspects of price control other than transparency.

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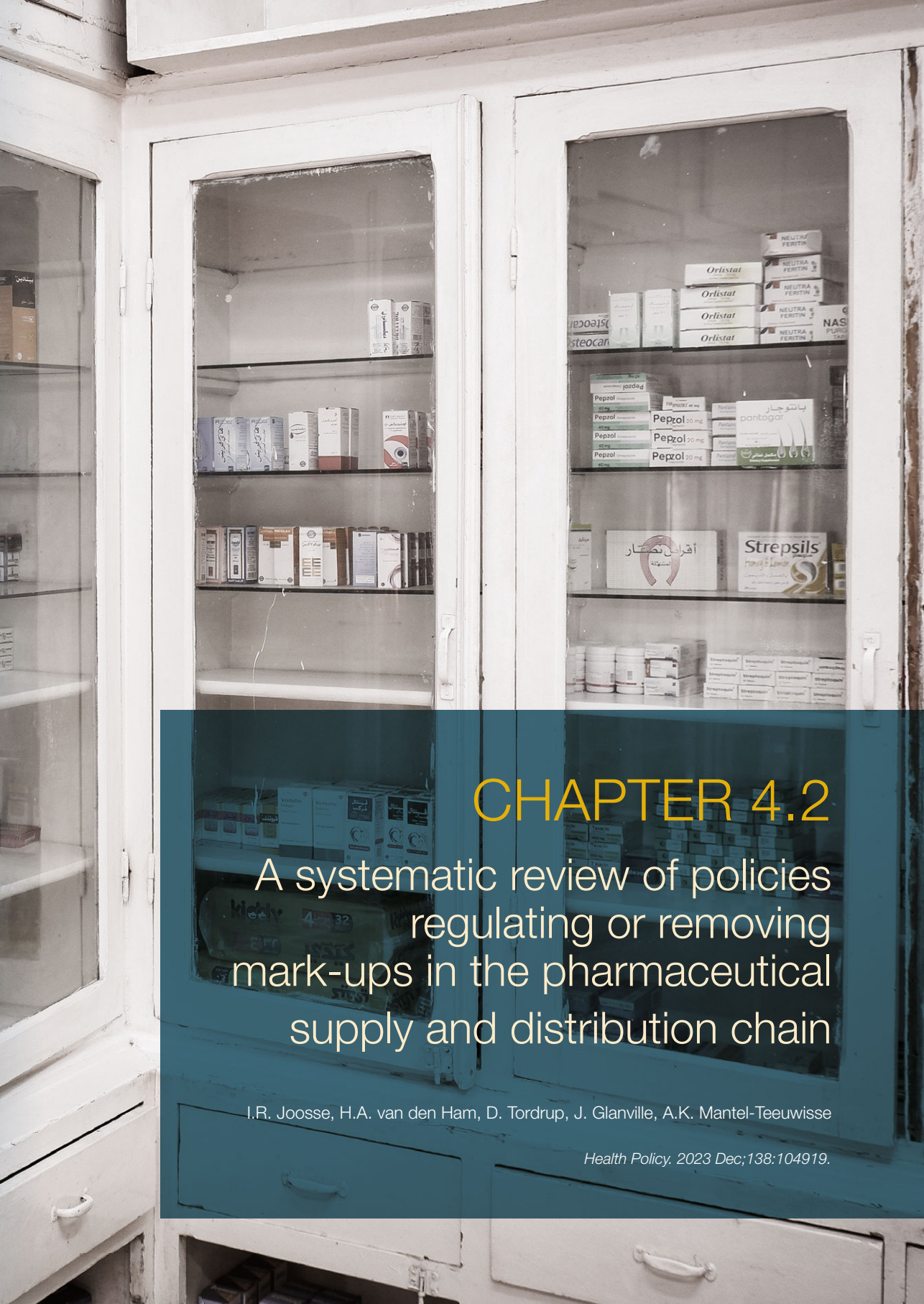
Bivatracin
BETADINE
Kaprofen
KETOLAC



CHAPTER 4.2

A systematic review of policies regulating or removing mark-ups in the pharmaceutical supply and distribution chain

I.R. Joosse, H.A. van den Ham, D. Tordrup, J. Glanville, A.K. Mantel-Teeuwisse

Health Policy. 2023 Dec;138:104919.

Abstract

The regulation of mark-ups throughout the pharmaceutical supply and distribution chain may be a valuable approach to control prices of medicines and to achieve broader access to medicines. As part of a wider review, we aimed to systematically determine whether policies regulating mark-ups are effective in managing the prices of pharmaceutical products. We searched for studies published between January 1, 2004 and October 10, 2019, comparing policies on regulating mark-ups against other interventions or a counterfactual. Eligible study designs included randomized trials, and non-randomized or quasi-experimental studies such as interrupted time-series (ITS), repeated measures (RM), and controlled before-after studies. Studies were eligible if they included at least one of the following outcomes: price (or expenditure as a proxy for price and volume), volume, availability or affordability of pharmaceutical products. The quality of the evidence was assessed using the GRADE methodology. A total of 32011 records were retrieved, seven of which were eligible for inclusion for this review. The limited body of evidence cautiously suggests that policies regulating mark-ups may be effective in reducing medicine prices and pharmaceutical expenditures. However, the design of mark-up regulations is a critical factor for their potential success. Additional research is required to confirm the effects of these policies on the availability, affordability or usage patterns of medicines and in low- and middle-income countries.

Introduction

Access to medicines is influenced by several factors such as affordability, rational use, sustainable financing and reliable supply systems [1]. One of the elements currently restricting patients' access to medicines is unaffordable medicine prices [2]. Both high- as well as low- and middle-income countries are challenged by these high prices, whether for innovative medicines or essential (originator or generic) medicines. The regulation of mark-ups throughout the pharmaceutical supply and distribution chain has been proposed as an approach to manage the price of medicines [3, 4].

A mark-up represents the additional charges and costs which are applied to medicines by wholesalers, retailers and pharmacies to cover overhead costs, distribution or dispensing fees, and to provide a profit [5]. Mark-ups are distinct from (profit) margins as the latter only reflect the revenue gained after deduction of costs made. Mark-ups are usually applied as a percentage or a fixed amount on top of the purchase price. Although mark-ups can reflect the dynamics in supply and demand of a medicine in a competitive market [3], a lack of regulation could result in excessive mark-ups. Experiences from medicine price surveys demonstrate that mark-ups can, in extreme cases, account for up to 90% of the final price of a medicine (i.e. consecutive mark-ups together constituting 900% of ex-factory price) [5-9]. It is expected that regulating (maximum) mark-ups throughout the pharmaceutical distribution chain could lead to more affordable medicines. Measures to manage mark-up levels may include fixed percentage mark-ups and regressive mark-ups.

Regulating prices in the distribution chain is not a new approach and is already applied in many countries. A recent (2018) study in 47 high- and upper-middle-income countries demonstrated that wholesale mark-ups were regulated in 32 of these countries and 43 countries reported controlling pharmacy remuneration [10]. Likewise, about 60% of low-income countries regulated wholesale or retail mark-ups in the public and private sector in 2007 [11]. Policies regulating mark-ups were also included in the first World Health Organization (WHO) Guideline on Country Pharmaceutical Pricing Policies [12], which recommended the use of mark-up regulations for wholesalers and retailers, as part of an overall pharmaceutical pricing policy.

A working paper on the regulation of mark-ups by Ball et al. from 2011 noted that, despite the use of mark-up regulations in many countries, there was a lack of evidence on the effects of these regulations [5]. More specifically, the effectiveness of mark-up regulations alone on medicine prices was mostly anecdotal or opinion-based. Furthermore, the authors noted there was no evidence on unintended consequences of mark-up regulations on the availability, sale or consumption patterns of medicines. A third gap in the evidence was the lack of information from low- and middle-income countries.

To reflect the evidence generated since the last systematic literature review in 2010, the 2020 update of the WHO Guideline on Country Pharmaceutical Pricing Policies sought to identify and reassess the available evidence on policies regulating mark-ups, as part of a larger review together with nine other pricing policies [13]. Accordingly, the aim of this systematic review is to determine whether policies regulating mark-ups are effective in managing the prices of pharmaceutical products, and to assess their impact on the volume, availability and affordability of medicines. Additionally, this review describes any reported contextual factors or implementation strategies that may impact the effects of mark-up regulations.

Methods

As part of a broader review on ten pharmaceutical pricing policies (i.e. I) cost-plus pricing, II) policies promoting the use of generic and biosimilar medicines, III) policies regulating mark-ups across the pharmaceutical supply and distribution chain, IV) pooled procurement, V) price discounts for single source pharmaceuticals, VI) (external and internal) reference pricing, VII) tax exemptions or tax reductions for pharmaceuticals, VIII) tendering and negotiation, IX) policies promoting price transparency and X) value-based pricing), this paper only addresses policies regulating mark-ups at any point along the pharmaceutical supply and distribution chain. Within this context, policies could involve the specification of a percentage or fixed mark-up at wholesale or retail level (including a 0% mark-up), as well as pharmaceutical fee-for-service remuneration, in line with the definition used by WHO [12, 13]. This definition does not include policies related to the setting of price thresholds (also referred to as price caps or price ceilings).

This systematic review was undertaken according to the principles of systematic reviewing embodied in the Cochrane Handbook and guidance document published by the Centre for Reviews and Dissemination (CRD) [14, 15]. The methodology and search strategies have been described in detail previously [16], but a summary of key-points is provided below.

Search strategy

An extensive literature search was performed between September 5 and October 10, 2019, for relevant articles published from 2004 to the search date in a large number of databases including but not limited to MEDLINE (Ovid), Embase (Ovid), Social Science Citation Index, EconLit, and the NHS Economic Evaluations Database (NHS EED). A variety of grey literature sources were also searched. The main structure of the search strategy comprised concepts pertaining to 1) non-specific pharmaceutical pricing policies or to 2) pharmaceuticals and one of ten specific pricing policies, among which were policies regulating mark-ups. Supplementary search approaches included reference-list checking and contacting experts. Full details of the search strategy are reported separately [16].

Selection criteria

This systematic review only included studies that used robust experimental or observational study designs comparing policies regulating mark-ups to at least one comparator or counterfactual. Randomized trials and non-randomized or quasi-experimental studies (including interrupted time-series (ITS), repeated measures (RM), panel data analyses, and controlled before-after (CBA) studies) were considered robust designs. Single policies, or combinations of policies, were considered eligible. Studies reporting at least one of the primary outcomes of interest, i.e. price (or expenditure as a proxy), volume, availability or affordability, were eligible for inclusion. Price outcomes were selected to capture the expected, direct effects of policies; volume (e.g. prescription and utilization patterns), availability (at health facility level), and (health system and patient) affordability outcomes were selected to reflect indirect policy effects relevant to patients and society. Definitions of outcome parameters are provided in Appendix 1. Public, private and mixed public-private settings were of interest.

Study selection

A single researcher assessed all titles and abstracts identified from the database searches and removed the obviously irrelevant records based on titles and abstracts. Two reviewers independently screened the titles and abstracts of potentially eligible records, with disagreements adjudicated by a third reviewer. The full texts of studies identified as potentially relevant were then subjected to an eligibility check by two reviewers independently (IJ and HvdH) before data extraction. Disagreements about study selection were resolved by discussion until consensus was reached.

Data extraction and quality assessment

Data from included studies was extracted by one reviewer (IJ) using a standardized data extraction form, including information on study design, setting and subjects, interventions including implementation strategies, outcomes, and results including contextual factors. Extracted data was verified by a second reviewer (HvdH) for accuracy.

The risk of bias in each included study was assessed by the extracting reviewer and checked by a second reviewer. Any disagreements were resolved by discussion until a consensus was reached. The assessment was done according to the Cochrane EPOC (Effective Practice and Organisation of Care) guidelines, in which bias assessment criteria were adapted to study design [17]. Randomized-, non-randomized trials and controlled before-after studies were assessed on nine criteria; ITS and RM studies were assessed on eight criteria; and a set of four assessment criteria applied to all other study types. An explanation of the bias criteria is presented in Appendix 2.

The quality of the evidence was assessed using the GRADE methodology [18]. GRADE evidence levels were determined by considering the body of evidence available for each (sub-) intervention. Domains of scoring were the risk of bias, inconsistency of results, indirectness of

evidence, imprecision of results, and 'other' (Appendix 3). Studies were upgraded in the 'other' domain if strong observational study designs were used (ITS, RM, panel data/regression analysis), according to precedent in literature [19]. The resultant certainty of the evidence was expressed as high, moderate, low or very low.

Data analysis

Substantial expected differences in the characteristics and contexts of included studies meant we did not aim to undertake a meta-analysis. Instead, we provided a narrative summary describing the quality of the studies, the relationship between interventions and patterns discerned in the data.

Results

Published and grey literature searches yielded 43,693 records for the combined review of ten pharmaceutical pricing policies. An additional 2,345 records were identified through the checking of relevant reference lists and other sources. After removal of duplicates, 32,011 records were screened on title and abstract, of which 1,000 articles remained for full-text screening. Thirty-eight of these articles were specific to policies regulating mark-ups. After full-text screening, only seven scientific articles were retained in this section of the systematic review (**Figure 1**). Reasons for exclusion were ineligible study designs (n=25) including four systematic reviews, ineligible interventions (n=3), and primary outcomes not reported (n=3).

Table 1 provides an overview of the characteristics of the included studies, published between 2008 and 2018 [20-26]. Notably, five of the seven studies included [22-26] examined the effects of a single policy in China, known as the 'zero mark-up' drug policy (ZMDP), implemented in different regions and at different times. Reported outcomes in all included studies comprise price (n=3), expenditure (n=4) and volume (n=1) outcomes.

Quality assessment

The results of the risk of bias assessment are presented in **Table 2**. Three studies reporting on price outcomes [20, 21, 25] were each associated with a major limitation, and the overall risk of bias was thus considered to be high across these studies. This led to a downgrading of the certainty of the evidence on price outcomes to low quality.

The controlled before-after study by Cheng et al. [26] was associated with a risk of bias across several domains, which is inherent to its non-randomized study design. The studies by Fu et al., Yang et al., and Zhou et al. [22-24] demonstrated only minor limitations, none of which were considered to have a major influence on the results. Overall, the risk of bias was considered to be low for studies reporting expenditure outcomes. The certainty of the evidence was assessed as low.

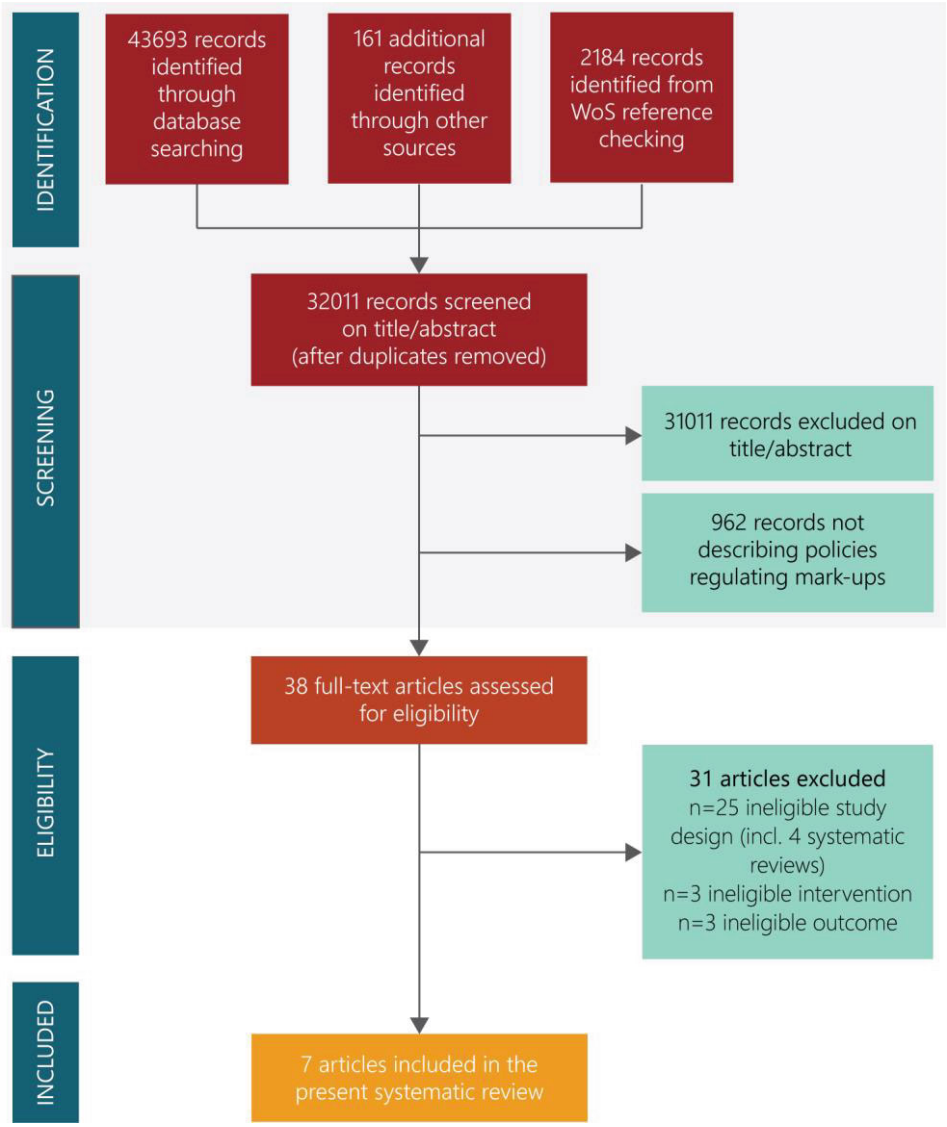


Figure 1 Flow chart of study selection.
The number of articles identified through database searching and screening by title and abstract shown in grey apply to the overall search; as per protocol the database search included search terms for all ten specific pricing policies among which policies regulating mark-ups was one. The lower part of the flow chart shown in white is specific to the selection of studies on policies setting price and mark-up thresholds across the pharmaceutical supply and distribution chain.
WoS = Web of Science.

The study by Moreno-Torres et al. also provided evidence on the outcome volume and was associated with a high risk of bias, as mentioned above [20]. Because the number of prescriptions per capita is considered a proxy for volume, the certainty of the evidence was downgraded to very low due to serious indirectness. Detailed assessments of the overall quality assessment (GRADE) are provided in Appendix 4.

Summary of findings

The summary of findings of policies regulating mark-ups are presented in **Table 3**.

Regressive pharmacy mark-ups

One study by Von der Schulenberg et al. assessed the effects of regressive pharmacy mark-ups [21]. They studied the association between regressive pharmacy mark-ups and originator prices of angiotensin converting enzyme (ACE) inhibitors in a sample of European countries (Denmark, France, Germany, Netherlands, Sweden, United Kingdom). The impact of a mix of other supply- and demand-side measures to reduce pharmaceutical expenditures were studied as well, each included as a dummy variable in the regression model. The estimated coefficients for regressive pharmacy mark-ups were negative (-0.259 to -0.303, $p<0.01$), implying mark-up regulation lowered medicine prices throughout Europe.

The 'zero mark-up' drug policy

Five studies [22-26] each studied the impact of implementing the ZMDP in China. With the ZMDP, public hospitals and primary healthcare centers were required to procure essential medicines via government pooled tendering and dispense these at the procurement price, removing the previously allowed 15% mark-up on dispensed medicines. Previously, hospitals were able to use profits on medicine sales to reward prescribers, thus providing an indirect and perverse incentive to overprescribe drugs [27]. With the ZMDP, the Chinese government aimed to de-couple hospital profits from medicine prescribing, with a view to countering excessive drug use and reducing the financial burden on patients. The ZMDP was piloted and successively implemented across the country in phases between 2007 and 2015. The studies included in this review cover different (pilot) phases of the policy and various strategies to compensate for health centers' losses in revenue.

Li et al. examined the short-term effects of ZMDP implementation on the costs per prescription, in an early pilot of the policy [25]. In this pilot, the community health centers (CHCs) were compensated for their loss in drug revenue by a government subsidy. ZMDP implementation was associated with a negative coefficient estimate (-0.417, $p=0.001$), implying reduced costs for patients. Although volume-related outcomes were only analyzed using descriptive statistics, a reduction in prescription volume was observed.

Table 1 Characteristics of included studies.

Name of study	Study type	Setting	Medicines studied	Intervention	Outcomes
Cheng 2012 [26]	CBA	Beijing, China	All medicines	The ZMDP implemented in 2007, which removed the previously allowed 15% profit margin for drug sales at public hospitals.	Expenditure outcome (cost per outpatient visit)
Fu 2018 [22]	DID	Shaanxi province, China	All medicines	The ZMDP implemented between 2012-2015, which removed the previously allowed 15% profit margin for drug sales at public hospitals.	Expenditure outcomes (cost per outpatient visit; cost per inpatient visit)
Li 2008 [25]	Regression analysis	Chengdu, China	All medicines	The ZMDP implemented in 2007, which removed the previously allowed 15% profit margin for drug sales at public hospitals.	Price outcome (cost per prescription)
Moreno-Torres 2011 [20]	Other	Catalonia, Spain	All medicines	Five reductions of wholesale and retail mark-ups between 1997-2006	Price outcome (price per prescription); volume outcome (number of prescriptions per capita)
Von der Schulenberg 2011 [21]	Panel data analysis	Six European countries[a]	ACE inhibitors	Regressive pharmacy mark-ups, to make dispensing cheaper products more profitable for pharmacists, hence encouraging them to dispense generics rather than originators.	Price outcome (originator price)
Yang 2017 [23]	ITS	Shaanxi province, China	All medicines	The ZMDP implemented in 2010, which removed the previously allowed 15% profit margin for drug sales at public hospitals.	Expenditure outcome (monthly hospitalization expenditure per patient)
Zhou 2015 [24]	DID	China	All medicines	The ZMDP implemented in 2010, which removed the previously allowed 15% profit margin for drug sales at public hospitals.	Expenditure outcomes (cost per outpatient visit; cost per inpatient visit)

ACE = Angiotensin Converting Enzyme; CBA = controlled before-after study; DID = Difference-in-differences; ITS = Interrupted time series; ZMDP = zero mark-up drug policy.

[a] Denmark, France, Germany, Netherlands, Sweden, United Kingdom.

Cheng et al. investigated the effects of ZMDP implementation and three distinct compensation methods for CHCs in a 2007 pilot [26]. A first group of CHCs was compensated through a fixed subsidy, providing full financial support, but these CHCs were not allowed to keep any surplus. The second group relied on an income-linked subsidy that covered staff expenses, but not the full operational costs. The amount of subsidy relied on the revenue of the facility. Within the third group, CHCs were self-financed and were compensated for the mark-up loss based on historical medicines sales.

Large differences were observed between groups. In CHCs receiving a fixed subsidy, medicine costs per visit were reduced by 18.7% ($p<0.001$) in 2007, before increasing again with 17.1% in 2008 and 6.3% in 2009 compared to the year before. The impact of the policy was less pronounced in CHCs receiving an income-linked subsidy, with consecutive relative changes in medicines costs per visit of -1.9% ($p<0.001$), +7.6% and +8.5%. Compensation based on historical medicines sales led to increasingly higher costs despite the implementation of the policy, with a yearly increase between 16.7% to 25.2%. Of note, medicines targeted by the ZMDP were intended to meet the majority of medicine needs, but in reality they accounted for ~75% of total medicine costs per visit in CHCs receiving a fixed subsidy between 2007 and 2009. These proportions were even smaller in the other CHC groups (48.9-60.5%).

The outcomes 'drug expenditure per inpatient admission', and 'per outpatient visit' were included in two studies [22, 24]. Zhou et al. investigated the effects of ZMDP implementation on medical expenses for patients at county hospitals, where the policy had been piloted in most provinces between 2010 and 2011. Data from two county hospitals were analyzed, one functioning as control. Fu et al. examined the effects of ZMDP implementation on medical expenses for patients in a large sample of public general county hospitals in mainland China between 2009 to 2014, where the policy was finally implemented in phases between 2012 and 2015. In the final policy, instead of providing subsidies, the loss of revenue was compensated by the government by raising fees for medical services, which had previously been set far below actual costs of providing the services, resulting in cross-subsidization from revenue generated from dispensed medicines. ZMDP implementation was associated with a -6.3% ($p<0.01$) and -7.4% ($p<0.01$) change in per-visit drug expenditure and a -9.0% ($p<0.01$) and -3.9% ($p<0.01$) change in per-admission drug expenditure [22, 24]. Meanwhile, expenditures on medical services for outpatient visits and inpatient admissions increased by 8.2% ($p<0.01$) and 8.0% ($p<0.01$), respectively. Taken together, total expenditures per visit and admission were lowered only slightly by 2.5% ($p>0.1$) and 1.2% ($p>0.1$). Interestingly, in hospitals with a greater reliance on drug sales before the ZMDP, increased expenditures for diagnostic tests and medical consumables were observed ($p<0.01$).

Table 2 Risk of bias assessment of included studies.

Bias type	Cheng 2012	Fu 2018	Li 2008	Moreno-Torres 2011	Von der Schulenberg 2011	Yang 2017	Zhou 2015
Randomized controlled trials, non-randomized controlled trials and controlled before-after studies							
Random sequence allocation	⊖	-	-	-	-	-	-
Allocation concealment	⊖	-	-	-	-	-	-
Baseline outcome measurements similar	?	-	-	-	-	-	-
Baseline characteristics similar	⊖	-	-	-	-	-	-
Protection against contamination	⊕	-	-	-	-	-	-
Interrupted time series and repeated measures studies							
Intervention independent	-	-	-	-	-	⊕	-
Appropriate analysis	-	-	-	-	-	⊕	-
Pre-specified shape of effect	-	-	-	-	-	⊕	-
Intervention to affect data collection	-	-	-	-	-	⊕	-
All study types							
Incomplete outcome data	?	⊕	?	?	?	?	?
Knowledge of allocated intervention	⊕	⊕	⊕	⊕	⊕	⊕	⊕
Selective outcome reporting	⊖	⊕	⊖	⊕	⊕	⊕	⊕
Other bias	⊖	?	⊖	⊖	⊖	⊕	?

A CBA study by Cheng et al. [26] was associated with a risk of bias across several domains, as is inherent to the study design. Additionally, there seemed to be some selectiveness in the reporting of results and data sources were segmented, possibly leading to differences in data collection. A DID study by Fu et al. presented only minor limitations [22]. It appeared the model used in Li et al. [25] did not take into account several potential confounding factors and did not include volume-related outcomes, regarded as a high risk. Moreno-Torres et al. raised concerns about the independent occurrence of the interventions [20]. There were also doubts about the validity of the model used because assumptions in the model were left untested and sensitivity analyses were not performed. The risk of multicollinearity in the model was assessed as high in Von der Schulenberg et al. [21]. The ITS study by Yang et al. [23] presented only minor limitations, as did the DID study by Zhou et al. [24].

Yang et al. examined the effect of ZMDP implementation in primary health institutions in the rural county of Fufeng, Shaanxi province, on monthly average hospitalization expenditure [23]. Health institutions received subsidies to compensate for their loss of potential drug revenue in this 2010 pilot. In this study with an ITS design, ZMDP implementation was associated with a -6.30 US$ (p=0.366) immediate change in expenditure (reported as change in level) and a -2.58 US$ (p=0.009) change in trend.

Other mark-up regulations

Moreno-Torres et al. examined the impact of five mark-up reductions implemented between 1997 and 2006 in Catalonia, Spain, as well as eleven other interventions to reduce pharmaceutical expenditures [20]. The authors did not describe the scope and extent of the mark-up reductions. Regardless, estimated coefficients were negative for all mark-up reductions for the outcome price per prescription (March 1997 -0.033, p<0.01; June 1999 -0.028, p<0.05; August 2000 -0.023, p<0.01; March 2005 -0.030, p<0.01; March 2006 -0.015, p>0.1). Notably, pharmaceutical expenditure per capita (including costs for the public insurer and respective co-payment by patients) were only (significantly) reduced after implementation of two of the five mark-up reductions. Savings achieved through reduced prices per prescriptions were offset by an increase in the number of prescriptions (March 1997 +0.029, p<0.1; June 1999 +0.031, p>0.1; August 2000 +0.000, p>0.1; March 2005 +0.009, p>0.1, March 2006 +0.025, p>0.1).

Table 3 Summary of findings of policies regulating mark-ups.

Policies regulating mark-ups compared to no policy or fixed mark-ups				
Medicines: ACE inhibitors; all medicines **Settings:** China; Spain; Denmark, France, Germany, Netherlands, Sweden, United Kingdom **Intervention:** Policies regulating mark-ups **Comparison:** No policy or fixed mark-ups				
Outcomes	**Impacts**	**No. of studies**	**Certainty of the evidence (GRADE)**	**Comments**
Price				
Originator drug price	Regressive pharmacy mark-ups may lead to price reductions.	1	Low ⊕⊕◯◯	
Price/cost per prescription	Wholesale and retail mark-up reductions may lead to decreased prices. A zero-mark-up policy[b] may lead to decreased costs.	2		Wholesale and/or retail mark-up reductions as well as the zero-mark-up drug policy were associated with significant negative coefficient estimates, indicating reduced costs.

Drug expenditure per out-patient visit	A zero-mark-up policy[b] may decrease drug expenditure.	3	Low ⊕⊕◯◯	The zero mark-up drug policy was associated with considerable decreases in drug expense per outpatient visit in two studies. In a third study, a small decrease was initially observed before the trend in drug expenditure increased again.
Drug expenditure per inpatient admission	A zero mark-up policy[b] may lead to a reduction in drug expenditure.	2		
Monthly hospitalisation expenditure	A zero mark-up policy[b] may not lead to a difference in expenditure immediately after implementation. It may reduce expenditure long-term.	1		The zero mark-up drug policy was associated with a non-significant decrease in average monthly hospitalisation expenditure immediately after implementation. A significant negative change in trend was observed after the policy, indicating long-term benefits.
Volume				
No. of prescriptions per capita	It is uncertain if mark-up reductions result in a change in utilization, because the certainty of the evidence is very low.	1	Very low ⊕◯◯◯	The reduction of mark-ups was associated with a significant positive coefficient, indicating an increase in the number of prescriptions. Coefficients were positive but not significant for four similar measures that followed.
Availability				
-	No studies meeting the inclusion criteria were found	0	-	-
Affordability				
-	No studies meeting the inclusion criteria were found	0	-	-

[a]GRADE Working Group grades of evidence
High = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different[b] is low.
Moderate = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different[b] is moderate.
Low = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different[b] is high.
Very low = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different[b] is very high.
[b] Substantially different = a large enough difference that it might affect a decision.

We considered policies prohibiting mark-ups on medicines (i.e. the ZMDP) to be eligible as the specification of a zero percent mark-up – and thus removing mark-ups – is in line with the definition used in this review. However, we acknowledge that different definitions may be used and controversies on the eligibility of this policy exist. Regardless, this particular type of mark-up regulation – similar to a regulation in South Korea where pharmacies are prohibited from charging mark-ups on essential medicines [28] – should be considered separately from other regulations that do not entirely eliminate mark-ups. Each of the five studies that examined the effects of the Chinese ZMDP support the prior hypothesis that these kind of policies may to some extent be effective in reducing pharmaceutical expenditures [22-26]. However, removing the previously allowed 15% mark-up did not lead to a similar reduction in prices or expenditures. In fact, a decrease of less than 15% implies that hospitals compensated the expected losses in drug revenue by other mechanisms. That facilities sought to offset their losses in drug revenue is probable, as results from the study by Fu et al. have shown that pharmaceutical expenditures were reduced by a greater extent (-6.3% and -9.0% vs. -2.5% and -1.2%) than total expenditures [22]. Similarly, only a modest slowing in growth rate of hospitalization expenditures was observed by Yang et al. (-2.58 US$ per month) [23].

A possible mechanism to compensate for losses in drug revenue is the dispensing of medicines outside of the scope of the ZMDP. Evidence for the use of this compensation mechanism is found in the study by Cheng et al., in which medicines targeted by the policy accounted for only 60% of the total medicine costs [26]. This effect was more distinct in facilities with a stronger incentive to generate revenue, although even facilities on a fixed budget procured medicines outside of the list. The dispensing of medicines outside of the scope of the policy may thus not only be used as a compensation strategy, but could also indicate that medicines targeted by the ZMDP were unable to meet the majority of patients' needs. Along the same line, Li et al. hypothesized that the policy may have restricted patient choices, resulting in fewer patients visiting these health centers and explaining the reduced prescription volumes [25]. A second mechanism is the increased use of medical services or medical consumables. Fu. et al. observed that hospitals showed increased expenditures for medical services and for medical consumables and diagnostics [22]. The increased expenditures for medical services were intended by policy-makers, who raised the fees for medical services as part of the policy that was finally implemented nation-wide, to counterbalance losses in drug revenue and to better reflect actual costs of providing these services. Unintended, however, were the increases in expenditures for diagnostic tests and medical consumables, that imply increased use of these commodities with a higher price-cost margin. This effect was more pronounced in hospitals with a greater reliance on drug revenue before the ZMDP. Overall, reductions in expenditures on medicines achieved by reducing mark-ups were almost completely offset by increases in expenditures on medical services and medical consumables, without any significant changes in total expenditures [22]. A third potential compensation mechanism is the dispensing of larger quantities of medicines, although no specific evidence of that was found in the studies included in this systematic review.

Since the literature search for this systematic review was performed, additional studies meeting the eligibility criteria of this review have been published. In this regard, four studies assessing the impact of the Chinese ZMDP were (not systematically) identified. Three of these studies confirm that drug-related expenses may decrease due to the policy [29-31], although the magnitudes of the effects are probably limited [30]. The fourth study found that drug-related expenses did not change significantly, but the ZMDP did lead to a considerable increase in medical expenditures [32]. By circumventing the ZMDP and providing medicines or services outside of the scope of the policy, the results of the studies included in our review confirm that health system administrations and prescribers by extension act as imperfect agents due to financial incentives, as noted previously [33, 34]. The results of these studies also imply that mark-up control of only selected drugs or medical services is not sufficient to control healthcare expenditures as higher price-cost margins on other medicines and services can indirectly still induce overprescription, despite governments offering subsidies or other compensation strategies. A comprehensive and well-designed approach that takes into account potential undesirable effects is thus expected to achieve better results.

The 2020 WHO Guidelines on Country Pharmaceutical Pricing Policies [13] note that mitigating undesirable effects in the design of policies regulating mark-ups is critical. The guidelines suggest the use of mark-up regulations across the supply and distribution chain, if implemented in conjunction with other pricing policies, and if regressive in structure rather than using a fixed percentage mark-up structure. The results of the present systematic review, although based on a single study that was limited in scope and that provided little detail on the structure of the regulation, confirm that regressive mark-ups may lead to reduced medicine prices [21]. Additionally, it is possible that a policy abolishing all mark-ups may lead to more unintended effects than policies simply reducing them, by eliciting stronger incentives to compensate losses. Overall, mark-up regulation is favored because the policy could facilitate broader access to medicines through incentivizing supply of specific medicines such as lower-priced medicines, generics, low volume medicines and reimbursable medicines [5, 13]. The recommendations on mark-up regulations in the 2020 Guideline on Country Pharmaceutical Pricing Policies are in line with those in the 2015 Guideline [12].

It is remarkable that the evidence gaps noted by Ball et al. in 2011 still remain [5], implying that little new, robust evidence has been produced in recent years, as evidenced by the limited number of studies included in this review despite our wide ranging search of published and grey literature. The relatively large proportion of studies excluded during the review process due to study design and outcomes of interest indicates that there may be a mismatch between the type of evidence needed to inform policy-making through WHO guidelines and the evidence that has been produced. The remaining uncertainties are a clear call for further research, to both researchers and policy-makers. Researchers should better align their research agenda with the needs of policy-makers and in return policy-makers could contribute by planning for the

evaluation of pricing policies and collection of the required data during the design and piloting of policies.

A strength of our systematic review is the use of a rigorous methodology based on the principles described in the Cochrane Handbook and CRD guidance documents [14, 15], including prospective publication of a protocol [16]. Our methodology involved a sensitive search strategy that included a wide range of search terms designed to retrieve both published and grey literature. This was complemented by reference list checking and expert contact to identify any studies potentially missing. The risk of bias and strength of the evidence were assessed in duplicate and following validated guidelines [17, 18], which were adapted to match the study design types encountered in this field of research.

Some limitations of our review are inherent to the nature of policy research. Firstly, although grey literature can be particularly valuable within this field of research, search and exporting functionalities of many grey literature databases are often poor. This demanded a more pragmatic search approach that included a smaller range of search terms than used in the major bibliographic databases. Although this could have resulted in missing potentially relevant literature, this limitation should be regarded within the wider search strategy that was used. Another limitation arises from the incomplete or missing description of the intervention or the context in which it was implemented in several of the studies included in the present review. We did not consult additional resources to clarify any questions, which hampered interpretation of some of the evidence. This is especially true for the studies by Moreno-Torres et al. and Von der Schulenberg et al. [20, 21], as both studies present evidence on policies not encountered elsewhere in the included studies. In contrast, the collective evidence from five publications on the Chinese ZMDP provides a comprehensive overview of the policy. This has aided our interpretation of the results and may also facilitate evidence-informed policy making. Generalizability of our findings on ZMDP implementation is nevertheless limited as it was studied in one country only and study results were not consistent across included and later published studies.

Conclusion

The limited and low-grade evidence identified by this systematic review cautiously suggests that policies regulating mark-ups may be effective in reducing medicine prices and pharmaceutical expenditures. However, the majority of the evidence was on the ZMDP from a single country, further narrowing the applicability of these findings. Nonetheless, the available evidence suggests that the design of mark-up regulations is a critical factor for their potential success, as a supply side driven demand for medicines or services with higher price-cost margins may offset the impact of mark-up regulations. Further studies should include the effects of mark-up

regulations on the availability, affordability or consumption patterns of medicines in countries covering different health care system designs and in resource constrained settings.

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Supplementary materials

Appendix 1: Description and interpretation of primary outcome parameters

Table S1 Description and interpretation of primary outcome parameters.

Term	Operational definition	Measurement unit
Price	Price components, observed or derived, along the value chain from manufacturer, distributor or service providers to patients.	Absolute or percentage changes in reported currency unit(s) or price indices. Expenditure or sales data (aggregate of price and volume) as a proxy for price and volume if these are not individually reported.
Volume	Quantity provided or used.	Number of units sold, supplied, prescribed, dispensed, or consumed.
Availability	A patient is able to obtain when needed, for free or for a fixed fee, a pharmaceutical product which is listed on the national formulary.	Presence-absence binary measurement and qualitative assessment as reported, e.g. a medicine is available when it is found in this facility by the data collector on the day of the visit.
Affordability	"the ability to purchase a necessary quantity of a product or level of a service without suffering undue financial hardship" World Bank cited by Lancet Commission on Essential Medicines [2,3].	For health system: Proportion of spending on medicines compared to historical expenditure on medicines or other health products and services, or as reported in the literature. For individual patients: The number of days' wages needed to pay for the cost of treatment, using wage benchmarks such as salary of the lowest paid government worker and national minimum wage, or as reported in the literature.

Note: adapted from Tordrup et al, 2020 [1].

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Appendix 2: Description and interpretation of risk of bias domains

Table S2 Description and interpretation of risk of bias domains as applied in the systematic review [1].

Bias domain	Explanation
Bias domains specific to interrupted time series and repeated measures studies only	
Intervention independent	Low risk" if there are compelling arguments that the intervention occurred independently of other changes over time and the outcome was not influenced by other confounding variables/historic events during study period. If Events/variables identified, note what they are. "High risk" if reported that intervention was not independent of other changes in time.
Appropriate analysis	"Low risk" if data were analyzed appropriately e.g. if autoregressive integrated moving average (ARIMA) models were used OR time series regression models were used to analyze the data and serial correlation was adjusted/tested for OR reanalysis performed. "High risk" if the outcomes were not analyzed appropriately. "Unclear risk" if not specified in the paper.
Pre-specified shape of effect	"Low risk" if point of analysis is the point of intervention OR a rational explanation for the shape of intervention effect was given by the author(s). Where appropriate, this should include an explanation if the point of analysis is NOT the point of intervention. "High risk" if it is clear that the condition above is not met.
Intervention to affect data collection	"Low risk" if reported that intervention itself was unlikely to affect data collection (for example, sources and methods of data collection were the same before and after the intervention). "High risk" if the intervention itself was likely to affect data collection (for example, any change in source or method of data collection reported).
Bias domains applicable to all study types	
Incomplete outcome data	"Low risk" if missing outcome measures were unlikely to bias the results (e.g. the proportion of missing data was similar in the intervention and control groups/pre- and post-intervention periods or the proportion of missing data was less than the effect size i.e. unlikely to overturn the study result). "High risk" if missing outcome data was likely to bias the results. "Unclear risk" if not specified in the paper (not assuming 100% complete data unless stated explicitly).
Knowledge of allocated intervention	"Low risk" if the authors state explicitly that the primary outcome variables were assessed blindly, or the outcomes are objective. Primary outcomes are those variables that correspond to the primary hypothesis or question as defined by the authors. "High risk" if the outcomes were not assessed blindly. Score "Unclear risk" if not specified in the paper.
Selective outcome reporting	"Low risk" if there is no evidence that outcomes were selectively reported (e.g. all relevant outcomes in the methods section are reported in the results section). "High

	risk" if some important outcomes are subsequently omitted from the results. "Unclear risk" if not specified in the paper.
Other bias	"Low risk" if there is no evidence of other risk of biases.

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Appendix 3: Description and interpretation of GRADE assessment criteria

The Cochrane Effective Practice and Organisation of Care (EPOC) guidance for the development of GRADE and Summary of Findings tables outlines the process of GRADE assessment of observational evidence. The GRADE assessment is based on five domains: risk of bias, inconsistency, indirectness, imprecision, and "other". In this appendix, we clarify the interpretation of these assessment domains.

Table S3 Description and interpretation of GRADE assessment criteria.

Domain	Definition by EPOC [1]	Interpretation and adaptation
Risk of bias	As outlined in appendix 2	
Inconsistency [2]	Inconsistency refers to an unexplained heterogeneity of results. GRADE suggests rating down the quality of evidence if large inconsistency in study results remains after exploration of a priori hypotheses that might explain heterogeneity. Judgment of the extent of heterogeneity is based on similarity of point estimates, extent of overlap of confidence intervals, and statistical criteria including tests of heterogeneity and I^2.	As the study types, outcomes and analyses methods tend to vary, we considered inconsistency to indicate the directionality of evidence. In cases where a point estimate of effect was not statistically significant, the directionality is considered regardless of the precision of the estimate.
Indirectness [3]	Includes consideration of - Indirect (between study) comparisons - Indirect (surrogate) outcomes - Applicability (study populations, interventions or comparisons that are different than those of interest)	The original meaning was consistent with the purposes of the present review.
Imprecision [4]	Includes consideration of whether the recommendation would differ, if the true effect would lie at either extreme of the confidence interval.	Analogously, we considered the precision around the estimate of the effect.
Other	N/A	Other sources of bias may be related to any features of the study not captured by the points above, or by the risk of bias assessment. In particular, we considered external validity (generalisability of the evidence) to be of relevance.

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Appendix 4: Certainty assessment of evidence

Table S4 Certainty assessment (GRADE) of evidence for policies regulating mark-ups.

No of studies	Design (number)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Certainty (overall score)
Outcome: Price							
Price: 3 [1-3]	Panel data (I), regression analysis (I), other (I)	High risk (-1)[a]	No serious inconsistency (0)	No serious indirectness (0)	No serious imprecision (0)	Study design (+1)	Low ⊕⊕◯◯
Expen-diture: 4 [4-7]	CBA (I), DID (II), ITS (I)	Low risk (0)	No serious inconsistency (0)	Serious indirectness (-1)[b]	No serious imprecision (0)	Study design (+1)	Low ⊕⊕◯◯
Outcome: Volume							
1 [1]	Other (I)	High risk (-1)[c]	No serious inconsistency (0)	Serious indirectness (-1)[d]	No serious imprecision (0)	Study design (+1)	Very low ⊕◯◯◯
Outcome: Availability							
Outcome: Affordability							

[a] The overall risk of bias was assessed to be high due to an inappropriate analysis that did not take into account the changes in the number of medicine on a prescription nor time (Li et al.), the examination of a large number of interventions within a short time-window (Moreno-Torres et al.) and the lack of sensitivity analyses (Von der Schulenburg et al.).

[b] Expenditure is a proxy for price, resulting in a downgrade for indirectness.

[c] The overall risk of bias was assessed to be high due to the examination of a large number of interventions within a short time-window (Moreno-Torres et al.).

[d] The study reports on the number of prescriptions per capita, which is a proxy for volume.

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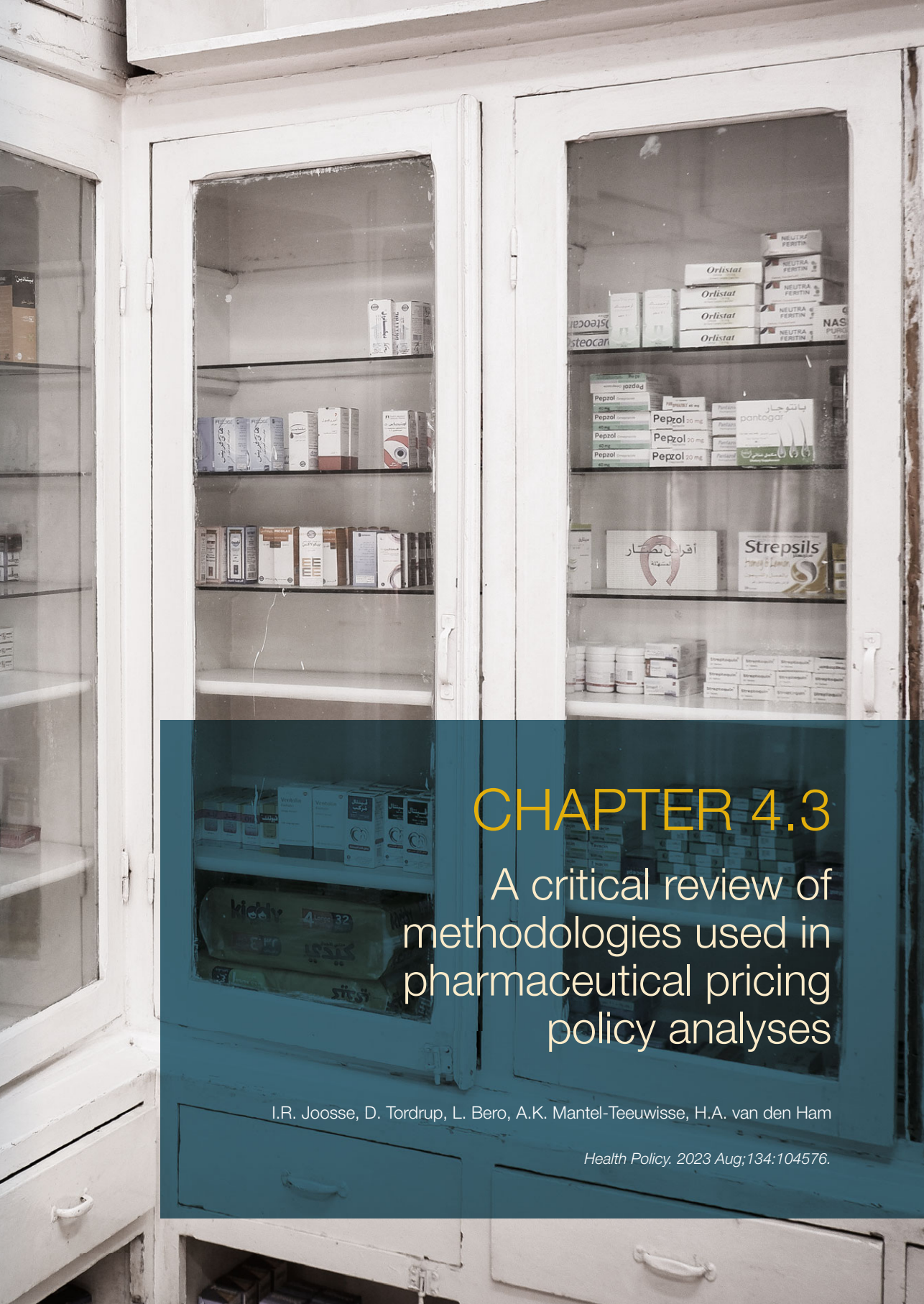
Bivatracin
BETADINE
Kaprofen
KETOLAC



CHAPTER 4.3

A critical review of methodologies used in pharmaceutical pricing policy analyses

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Abstract

Robust evidence from health policy research has the potential to inform policy-making, but studies have suggested that methodological shortcomings are abundant. We aimed to identify common methodological weaknesses in pharmaceutical pricing policy analyses. A systematic review (SR) of studies examining pharmaceutical pricing policies served as basis for the present analysis. We selected all studies that were included in the SR (n=56), and those that were excluded from the SR due to ineligible study designs only (n=101). Risk of bias was assessed and specific study design issues were recorded to identify recurrent methodological issues. Sixty-one percent of studies with a study design eligible for the SR presented with a high risk of bias in at least one domain. Potential interference of co-interventions was a source of possible bias in 53% of interrupted time series studies. Failing to consider potential confounders was the primary cause for potential bias in difference-in-differences, regression, and panel data analyses. In 101 studies with a study design not eligible for the SR, 32% were uncontrolled before-after studies and 23% were studies without pre-intervention data. Some of the methodological issues encountered may be resolved during the design of a study. Awareness amongst researchers on methodological issues will help improve the rigor of health policy research in general.

Introduction

Evidence from health policy research has the potential to be translated into effective and appropriate strategies, policies and interventions [1, 2]. Indeed, health policy research is considered essential in advancing health systems' performances with the ambition of achieving universal health coverage (UHC) and the health-related Sustainable Development Goals (SDG) [2]. Since the 1990s, increased importance has been placed on evidence-based healthcare policy making [3, 4].

Randomized controlled trials (RCTs) remain the gold standard in clinical research for generating robust evidence with a considerable certainty [5]. However, waiting for this same level of certainty in generating evidence on healthcare policies would paralyze the policy-making process [6, 7]. Particularly as conducting RCTs in policy research may be unfeasible or even undesirable [8, 9]. To establish a measure of effect in health policy research that is both unbiased and feasible to produce, certainty of evidence and pragmatism need to be balanced [7]. This is by no means straightforward.

Recognizing this problem, the World Health Organization (WHO) published the *Health Policy and Systems Development: An Agenda for Research* in 1996 [10]. With this technical document the WHO provided researchers with guidance on identifying general research approaches that are potentially appropriate in studying health policies. This document states that, to achieve real advancement in the field of health policy research, policy assessments should move towards measuring the direct and indirect effects of policies on prespecified outcomes. It is emphasized that there is a need for both qualitative and quantitative policy assessments. The need for robust evidence on health policies was further stressed in the *WHO Handbook for Guideline Development* in 2012. This Handbook states that systematic reviews used to inform WHO guidelines are to be developed according to the standards outlined by the Cochrane Collaboration [11]. With that, only RCTs or observational study designs associated with a low risk of bias should qualify for systematic reviews used to support WHO guidelines, besides additional qualitative evidence.

However, little explicit guidance exists on what research designs or methods best inform quantitative health policy analyses and how to perform these [12]. Instead, mostly general recommendations have been presented in the literature over the years [13]. For one, multiple types of outcomes should be adopted in health policy analyses including both unintended and unexpected consequences of a policy intervention [14]. To facilitate the identification of such consequences, the study should encompass a sufficiently long time span [12]. Additionally, an appropriate comparator or counterfactual is necessary to interpret the results [14]. Finally, a comprehensive and well-specified description of the intervention and the contextual factors is

required as it may help to explain the success or failure of an intervention [6, 14]. Although these general recommendations provide some direction, more concrete guidance is lacking.

The present study was inspired by the experiences from an extensive systematic review (SR) of studies evaluating ten pharmaceutical pricing policies, used for the development of the 2020 WHO Guideline on Country Pharmaceutical Pricing Policies [15]. We observed that a large proportion of studies was excluded during the review process due to ineligible study designs [16]. Additionally, we noted that many of the studies that did meet the eligibility criteria had methodological shortcomings. The frequent use of biased or weak study designs in pharmaceutical policy analyses has previously been reported in systematic reviews, each expressing that some of the shortcomings in study design may be preventable [17, 18]. Insight into common weaknesses can provide concrete starting points for improving methodologies used in pharmaceutical pricing policy analyses specifically and health policy research in general. Accordingly, we aimed to identify some of the gaps and methodological weaknesses in pharmaceutical pricing policy analyses.

Methods

We conducted an extensive SR in 2019 that served as the basis for the present study [16]. The SR focused on the effects of ten pharmaceutical pricing policies, with the aim to identify which policies are effective in managing pharmaceutical prices. For the present study, search results of the SR at the full-text level were our primary source of data. Studies were selected if they 1) had been included in the original SR or 2) had been assessed for eligibility on full-text level but had subsequently been excluded from the SR due to an ineligible study design (but met all inclusion criteria otherwise). Studies were excluded from this analysis if there were other reasons for exclusion from the SR, such as an ineligible intervention, ineligible outcomes or an unsuitable publication type.

Description of data source

The original SR was undertaken according to the principles of systematic reviewing embodied in the Cochrane Handbook and guidance document published by the Centre for Reviews and Dissemination (CRD) [19, 20]. A literature search was performed in a number of databases, including but not limited to Ovid MEDLINE, Ovid Embase, Social Science Citation Index, EconLit, and NHS Economic Evaluation Database. Database searches were supplemented by grey literature searches and the reference lists of relevant articles were searched manually.

Studies published after 1 January 2004 and up to October 2019 were eligible for inclusion. Eligible interventions were:

1. Cost-plus pricing
2. Policies promoting the use of generic and biosimilar medicines
3. Policies regulating mark-ups across the pharmaceutical supply and distribution chain
4. Pooled procurement
5. Price discounts for single source pharmaceuticals
6. (External and internal) reference pricing
7. Tax exemptions or tax reductions for pharmaceuticals
8. Tendering and negotiation
9. Policies promoting price transparency
10. Value-based pricing

Studies were eligible if they included at least one of the following outcomes: price (or expenditure as a proxy), volume, availability or affordability of pharmaceuticals. Studies that compared interventions to at least one comparator or counterfactual and that included pre-intervention data were eligible for inclusion in the SR. Eligible study designs were: randomized trials and non-randomized or quasi-experimental designs, e.g. controlled before-after studies, difference-in-differences (DID), interrupted time series (ITS), non-randomized controlled trials (nRCT), and repeated measures (RM). As the study label did not always represent the actual study design, studies were classified according to the features of a study's design rather than the label mentioned in the paper by the authors. Besides study types primarily aiming to prevent confounding at the design level, studies using techniques intended to correct for confounding during analysis (e.g. regression analyses, panel data analyses) were also eligible. All eligible study types either included a direct control or were able to correct for absence of a control, increasing the certainty of the evidence. Definitions and categorizations of study designs and analysis techniques as applied in the SR are shown in **Table 1**. Searches were conducted without language restriction.

Two reviewers independently assessed study eligibility and possible types of bias based on risk bias criteria as suggested by Cochrane Effective Practice and Organisation of Care (EPOC) [21]. The quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. We did a narrative summary of the evidence describing the relationship between studies and patterns discerned in the data. The methodology and detailed search strategies have been published elsewhere [22].

Data extraction and analysis

For the present study the following information was extracted for all studies: inclusion status in the SR, type of publication, WHO region of study location, and type of intervention (according to one of ten pharmaceutical pricing policies as used in the SR). The year of publication and

income setting of the study location (as designated by the World Bank for 2019–20) were extracted to test the hypothesis that there could be a relationship between these features and the studies with an ineligible study design.

For studies that had been included in the SR information on study design features and risk of bias as extracted for the SR was used. Risk of bias assessment criteria as suggested by EPOC had been adapted to study design (randomized trials, non-randomized trials and controlled before-after studies were assessed on nine criteria; ITS and RM studies were assessed on eight criteria; and a set of four assessment criteria applied to all other study types; Appendix 1). For articles not included in the SR the specific design issues were recorded. The risk of bias was not assessed for this group.

We used descriptive statistics to identify recurrent methodological issues per type of study design. Some examples from the SR were selected to illustrate the issues encountered.

Results

We identified 32011 publications in our initial literature search for the SR. After removal of the obviously irrelevant records we assessed 1000 records for eligibility at full-text level [16]. Only 56 studies were deemed eligible at the time, meeting all requirements including an eligible study design (hereafter called 'eligible study designs group', Appendix 2). Important reasons for exclusion from the review were study design issues (n=316), ineligible interventions (n=241), ineligible outcomes (n=181), and insufficient data (n=161). Upon re-inspection of the 316 records that had been excluded for design issues, 215 studies were also ineligible for reasons other than design issues. This left 101 studies for the current analysis (hereafter called 'ineligible study designs group', Appendix 3). With that, 157 studies fulfilled the inclusion criteria of the present study (**Figure 1**). The general characteristics of the studies are shown in **Table 2**. A total of 144 (92**%**) of 157 included studies were published as an original research article and 102 (65%) were published in the past eight years (2012-19) (**Table 2**). Additionally, most studies were conducted in European countries (39**%**), followed by a fair number of studies originating in the WHO region for the Americas (15**%**, mainly the United States) and the WHO region for the Western Pacific (22**%**, mainly the China). This distribution is also reflected in the income setting with very little evidence from low-income countries (<1**%**). Internal reference pricing was the most researched pricing policy (24%), whilst cost-plus pricing and tax reductions were not the subject of any studies. Overall, the distribution of both groups of studies follows a similar pattern for all characteristics.

Studies with an eligible study design

When focusing on the eligible study designs group only, these applied different designs with the majority being ITS (n=17) and DID studies (n=13) (**Table 3**). There is no apparent association between the type of intervention and the study designs that are used to study them (Appendix 4). Most studies reported on multiple types of outcomes related to drug pricing and expenditure but none reported on the outcomes availability and affordability. Information on contextual factors or on the implementation of the intervention, both of which could help explain the failure or success of an intervention, was provided in 57% and 45% of the eligible studies, respectively. Thirty-four (61%) studies scored high risk of bias in at least one domain (**Table 3**). Only four studies (7%) were associated with a low risk of bias across all domains. Notably, 86% of the studies were considered to have an unclear risk of bias in the domain 'incomplete outcome data' (**Figure 2a**).

Fifty-three percent (53%, n=17) of ITS studies were associated with a risk of bias due to potential interference from co-interventions (see Figure 2b), the effects of which could not always be discerned from the intervention of interest. Although the short time between successive interventions was often acknowledged but did not allow for a satisfactory separate analysis [23-27], several other studies disregarded the influence of co-interventions completely within their analysis. An example is the study by Kwon et al. [28]. The authors noted the possible impact of two co-interventions that were implemented 17 and 21 months after the main intervention of equal medicine pricing (EMP), but did not introduce these as separate segments in their regression analysis. Additionally, a third co-intervention 18 months before the intervention was not mentioned in this publication but was described in another study examining the EMP [29]. The immediate effect of the intervention (presented as the change of intercept in an ITS analysis) and the long-term effects (presented as a change in slope) may thus have been influenced by co-interventions. In contrast, in the study by Langley et al. [30] the effects of the introduction of new treatment guidelines 6 months after the implementation of a transparency measure was separated using a different segment.

Sixty-six percent (66%, n=29) of DID studies, regression analyses and panel data analyses were associated with a high or unclear risk of bias in the domain 'other bias' (**Figures 2c-2e**). In the majority of cases the lack of relevant confounding factors in the empirical model resulted in this assessment. In some of these studies the authors described several factors as potential confounders, but were unable to control for these elements because the data was unavailable to them [31-34]. In other studies potential explanatory factors did not seem to have been considered at all. For example, in the study by Wu et al. [35] the characteristics of the medicines included in the study were not described. Because interventions are often specific for certain products, factors such as formulation and pack size may have influenced the results and could have been taken into account.

Table 1 Definitions of study designs and analysis techniques as applied in the systematic review.

Design strategies	Characteristics	Results of analysis	Example[a]
Randomized designs			
Randomized trial	An experimental study in which subjects are allocated to different interventions using methods that are random [19].	Generally represented by an absolute or relative difference compared to the pre-intervention time period, usually corrected for the effect in the control group	Bhargava 2010 [55]
Non-randomized and quasi-experimental designs			
Controlled before-after	An observational study that uses observations from few time points (<3) before and after the implementation of an intervention, both in a group that receives the intervention and in a control group that does not [19].	Generally represented by an absolute or relative difference compared to the pre-intervention time period, usually corrected for the effect in the control group.	Adesina 2019 [51]
Difference-in-Differences	Quasi-experimental design and analysis technique in which observations are made at multiple time points before and after an intervention, both in a group that receives the intervention and in a control group that does not.	An estimate for a regression coefficient, that signifies a difference in changes over time between the intervention and control group. May also be presented as a percentage difference.	Ghislandi 2013 [52]
Interrupted Time Series	A quasi-experimental study designs that uses observations at multiple time points (≥3) before and after an intervention (the 'interruption'). The design attempts to detect whether the intervention has had an effect greater than any underlying trend over time [19].	Estimates for regression coefficients corresponding to two effects: a change in level (the difference between the observed level at the first post-intervention time point and that predicted by the pre-intervention time trend) and a change in trend (the difference between pre- and post-intervention slopes) before and after the intervention.	Yoo 2015 [53]
Non-randomized trial[b]	An experimental study in which subjects are allocated to different interventions using methods that are not random [19].	Generally represented by an absolute or relative difference compared to the pre-intervention time period, usually corrected for the effect in the control group.	NA
Repeated Measures	An interrupted time series design where measurements are made in the same individuals at each time point [19].	Dependent upon analysis method, the results may be represented as estimates for regression coefficients	Ben-Aharon 2017 [36]

		(e.g. regression methods) or F-ratios (repeated measures ANOVA).	
Analytic strategies			
Conventional confounding correction methods			
Regression analysis	An analysis technique that examines the influence of one or more independent variables on a dependent variable. In (health) policy analysis, the technique usually uses longitudinal data.	Estimates for regression coefficients, representing the isolated effect of each independent variable on the dependent variable.	Kaiser 2014 [56]
Confounding correction methods for multidimensional data			
Panel data analysis	Analysis technique that uses multidimensional data (cross-sectional time-series data) and allows for variation along individual and time dimensions[c].	Estimates for regression coefficients, representing the isolated effect of each independent variable on the dependent variable.	Von der Schulenburg 2011 [54]

[a] Examples as encountered in the systematic review. Please note that these examples are not necessarily free of bias, see systematic review for details [16].

[b] Non-randomized trials were not encountered in the systematic review.

[c] If there are only two groups and two measurements, this model is equivalent to the difference-in-differences design.

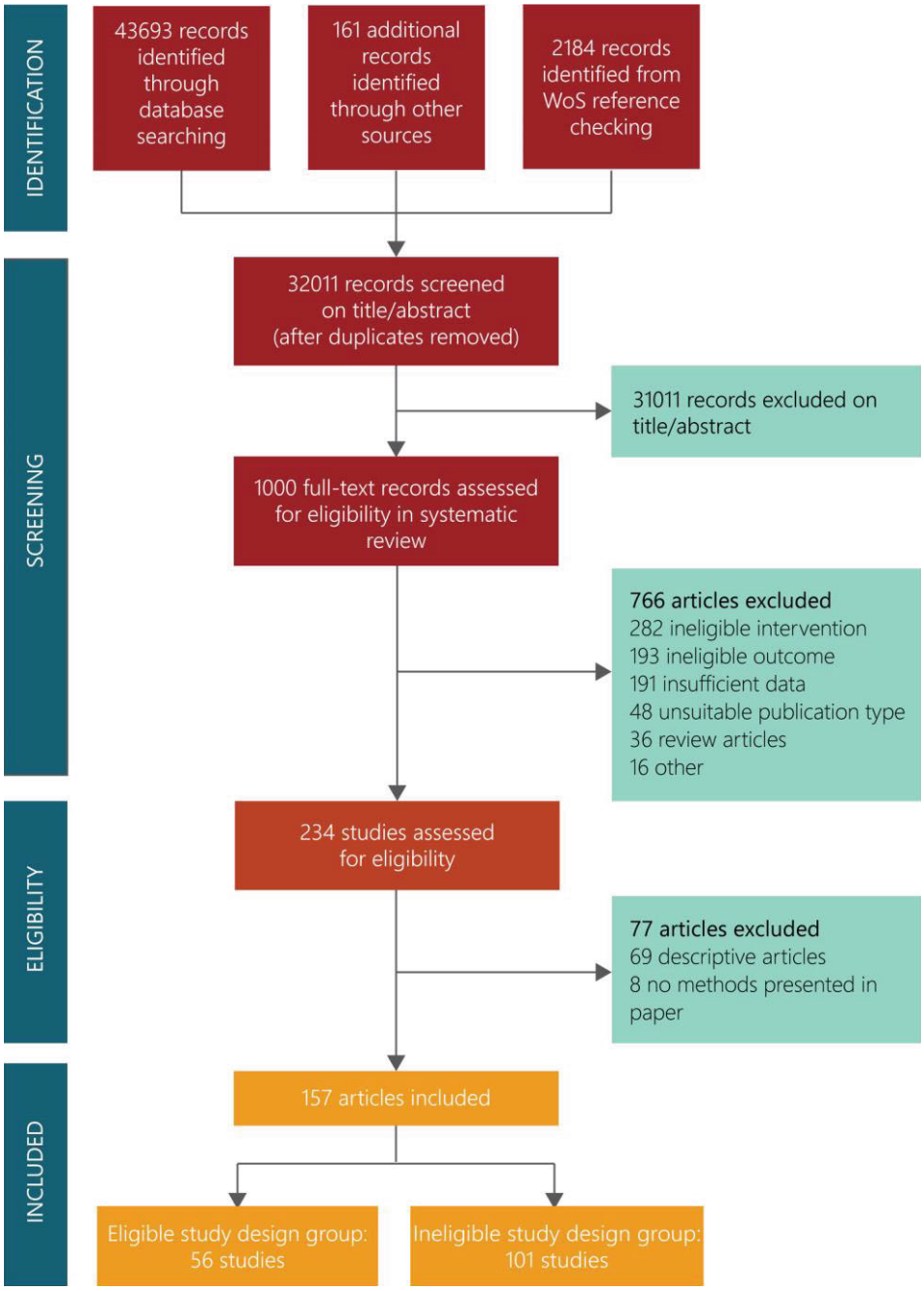


Figure 1 Flowchart of study selection.
WoS = Web of Science.

Table 2 General characteristics of included studies.

	Eligible study designs	Ineligible study designs
n (%)	56	101
Year of publication		
2004-2007	7 (13)	12 (12)
2008-2011	9 (16)	27 (27)
2012-2015	21 (38)	36 (36)
2016-2019[a]	19 (34)	26 (26)
WHO Region		
Africa	2 (4)	5 (5)
Americas	9 (16)	14 (14)
South-East Asia	2 (4)	4 (4)
Europe	23 (41)	38 (38)
Eastern Mediterranean	0 (0)	6 (6)
Western Pacific	15 (27)	20 (20)
Global	5 (9)	14 (14)
Setting		
Low-income	0 (0)	1 (1)
Lower-middle income	2 (4)	7 (7)
Upper-middle income	11 (20)	28 (28)
High-income	39 (70)	49 (49)
Multiple income settings	4 (7)	16 (16)
Publication type		
Dissertation	0 (0)	1 (1)
Guidelines	0 (0)	1 (1)
Original research article	49 (88)	95 (94)
Report	7 (13)	3 (3)
Other	0 (0)	1 (1)
Type of intervention		
Cost-plus pricing	0 (0)	0 (0)
Promoted use of generic and biosimilar medicines	10 (18)	15 (15)
Price setting and mark-up thresholds	10 (18)	15 (15)
Pooled procurement	6 (11)	12 (12)
Price discounts for single source pharmaceuticals	0 (0)	0 (0)
External reference pricing	0 (0)	6 (6)
Internal reference pricing	18 (32)	19 (19)
Tax exemptions or tax reductions	0 (0)	0 (0)
Tendering and negotiation	1 (2)	12 (12)
Policies promoting price transparency	3 (5)	2 (2)
Value-based pricing	2 (4)	2 (2)
Multiple interventions	6 (11)	18 (18)

[a] Data was included until October 2019.

Table 3 Additional characteristics for studies with an eligible study design (n=56).

Eligible study design group	n (%)
Study design	
Design strategies	
Controlled before-after	2 (4)
Difference-in-differences	13 (23)
Interrupted time series	17 (30)
Randomised trial	1 (2)
Repeated measures	1 (2)
Other	6 (11)
Analytic strategies	
Regression analysis	8 (14)
Panel data analysis	8 (14)
Information on contextual factors provided	32 (57)
Information on implementation method provided	25 (45)
Risk of bias	
No domains with a risk of bias	4 (7)
≥1 domain with a high risk of bias	34 (61)

A problem observed across study designs is related to the timing of the intervention. As time is an important co-variate in all longitudinal policy analyses in which one expects to see changes over time, an exact definition of the timing and the correct analysis thereof is crucial. However, in several studies the exact timing of the intervention was either not described [36] or difficult to establish [37-39]. In two other studies the authors did not apply the point of intervention as point of analysis [23, 40]. To illustrate, in an ITS study by Hsiao et al. [40] the quarter in which the intervention occurred (Jan-Mar 2003) was regarded in the analysis as 'pre-intervention' even though the policy was implemented in March 2003. This makes interpretation of immediate changes in usage patterns difficult.

Instead, authors should consider the use of a phase-in period, also when the implementation of an intervention has been gradual or when there may have been an anticipatory response to implementation of a policy. To allow for this possibility, Leopold et al. [26] considered a four-month transition period prior to implementation of the policy and excluded these data points from analysis.

Studies with an ineligible study design

Studies that were ineligible for the original SR due to design issues can be subdivided in roughly six categories, among which four ineligible study designs and two design issues: 1) cross-sectional study, 2) descriptive study without statistical analysis, 3) theoretical study, 4)

uncontrolled before-after study, 5) lack of pre-intervention data, 6) other design issue (see table 4). Although a study design that is prone to bias, uncontrolled before-after studies were nonetheless abundant (32 of 101 ineligible studies). This design's sensitivity to bias becomes clear in the study by Law et al. [41] in which quarterly data from 2010 was used to estimate the potential savings of a policy reducing generic drug prices. Data from quarters 1 and 2 was used to derive a counterfactual, which was then compared to the observed data from quarters 3 and 4. An analysis based on so few datapoints risks seasonal variation or randomly deviating datapoints being incorporated and leading to biased conclusions. This is likely the case in this example: an aberrant datapoint in quarter 2 resulted in an upward counterfactual trend pre-policy that was not prolonged in the observed data post-policy. The inclusion of either a control group or more timepoints before and after the intervention would allow correction for random or seasonal variations.

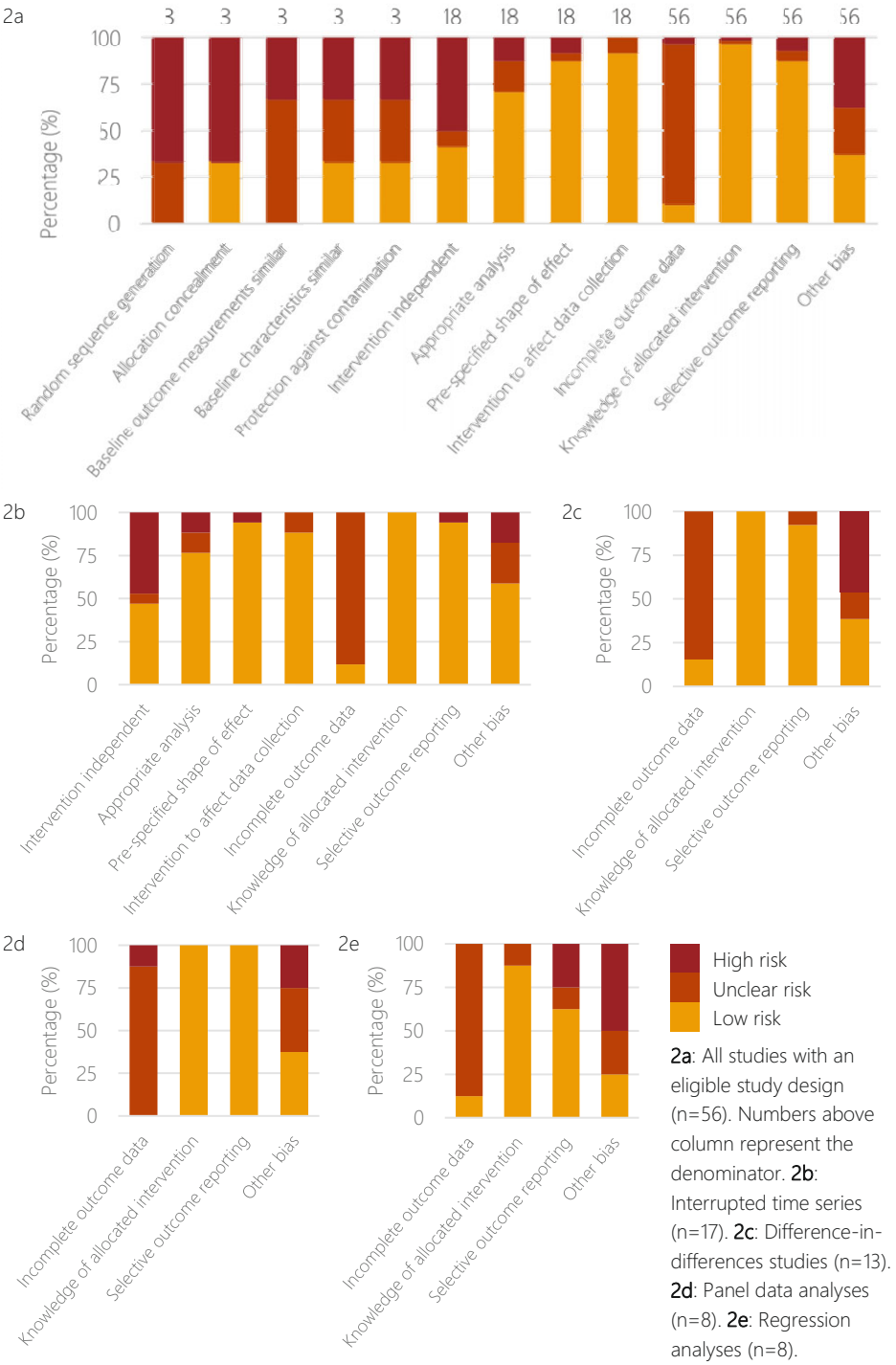
Studies without pre-intervention data were also encountered frequently (23 of 101 ineligible studies). Without a pre-policy baseline the effectiveness of an intervention cannot be determined, as any trend could be pre-existing and not due to the intervention. To illustrate, Adriaen et al. [42] aimed to examine pricing strategies in Belgium, including internal reference pricing. The Belgian reference-pricing system itself was introduced in June 2001, yet data was collected beginning at July 2001. With that, the authors were able to report on factors that influence pricing strategies, but not on the effectiveness of the pricing strategy. Inclusion of data from before the intervention would have allowed for this.

No apparent association between the design issues and the interventions of interest was found (Appendix 4).

Table 4 Issues with studies with an ineligible study design (n=101).

Ineligible designs and design issues	n (%)
Ineligible study designs	
Cross-sectional studies	12 (12)
Descriptive study without statistical analysis	17 (17)
Theoretical study	16 (16)
Uncontrolled before-after study	32 (32)
Design issue	
Lack of pre-intervention data	23 (23)
Other design issue	1 (1)

Figure 2 The risk of bias of studies in the eligible study design group.



2a: All studies with an eligible study design (n=56). Numbers above column represent the denominator. **2b**: Interrupted time series (n=17). **2c**: Difference-in-differences studies (n=13). **2d**: Panel data analyses (n=8). **2e**: Regression analyses (n=8).

Discussion

We found that methodological weaknesses in pharmaceutical pricing policy analyses were multifold. Our results show that three out of five studies that met the eligibility criteria of the original SR were associated with a high risk of bias in at least one domain. In ITS studies this was predominantly due to the potential effects of co-occurring interventions. In DID studies, regression analyses, and panel data analyses, the failure to account for potential confounders often resulted in a high or unclear risk of bias. Establishing an exact timing of a policy intervention was problematic across all study designs, and information on contextual factors or implementation methods of the policy was often limited. Finally, a large absolute number of studies was excluded from the original SR for study design issues alone.

The large proportion of studies ineligible due to design issues suggests that there is a mismatch between the type of evidence generated by researchers and that required to make evidence-informed decisions. It is worth noting, however, that research evidence is not the only input that is considered in policy-making. Other components such as politics, social culture, financial concerns and timing impact policy decisions as well, as suggested by the term 'evidence-informed' rather than 'evidence-based' policy-making [43]. Understanding the motives and perspectives of researchers on one hand and policy-makers on the other may be an important step in aligning evidence generation with policy-making in practice. Nonetheless, the prevalent use of study designs that are highly vulnerable to bias, and the limited attention in scientific research to specific pricing policy topics creates an important evidence gap. The building of an encyclopedia to map evidence and impacts has been proposed as a way to identify such gaps, with the ultimate goal of enhancing current efforts and furthering future research [44].

Some of the methodological issues that we encountered could probably be resolved without much difficulty. For instance, the analysis of co-interventions as separate segments in ITS should be considered when the time of implementation of co-interventions is known. Likewise, careful selection of potential confounders in empirical models could markedly reduce the risk of confounding bias in pharmaceutical pricing policy analyses. And although not considered a methodological flaw, the reporting of contextual information on interventions can often be improved to facilitate interpretation of results. Lastly, we acknowledge that some of the issues may be borne from a lack of data and require a more fundamental solution. Both researchers and policy-makers could play an important role in collecting the required data for adequate monitoring of implemented policies.

Similarly, some methodologies with high associated risks of bias that were not eligible for inclusion in the SR can be modified in such a way to make them more rigorous. To illustrate, uncontrolled before-after studies are very sensitive to bias, because the number of datapoints before and after the intervention is insufficient to distinguish an effect that is different from

random variations or a preexisting trend [45, 46]. The addition of another intervention group and multiple control groups could tackle this flaw [21, 46]. However, including a suitable control is complicated by variations in health systems, disease burden or demographics that may result in different effects in different countries or regions following implementation of the same intervention. Due to these complications, the use of a control alone is oftentimes insufficient unless a highly similar setting can be identified or a control from within the same setting (such as a different medication group). Yet a control group still does not address the issue of preexisting trends, which can only be elucidated if historical data is available. Including data from before the intervention is therefore imperative in these policy analyses, but we often observed it to be missing. When including pre-intervention data, the study should preferably include multiple timepoints before and after the intervention to permit correction for preexisting trends [47].

Not only do our results indicate a relatively low awareness of more robust observational study designs, it is also suggested that pharmaceutical pricing policy analyses have remained challenging even in recent years and that these challenges are experienced in all regions of the world. Concretely, we hypothesized that there would be a relationship between the studies with an ineligible study design and the year of publication or income-setting of the country, but substantial differences between studies with eligible and ineligible study designs were not found. In addition to this, studies from low-income settings were widely missing. More awareness on rigorous study designs among both researchers, journal editors and policy makers could help encourage the generation of higher quality evidence that can be used to inform policy-making, as noted by others [17, 44]. This also provides opportunities for capacity-building in low-income economies, which could further contribute to strengthening methods used in the field.

Our results also indicate that the Cochrane tool for grading the risk of bias may not be sufficiently tailored to the study types that we see in the field of pharmaceutical policy evaluation [48]. For one, the large number of studies that were associated with an unclear risk of bias in the domain 'incomplete outcome data' is striking. According to the tool, complete data should not be assumed unless specifically stated. However, where missing data may suggest a problem in a randomized drug trial, the study designs that we encounter here mostly use periodically collected and validated data from databases. Hence, it is reasonable that most of the studies did not specify whether data was missing. Along the same lines, the domain 'Knowledge of allocated intervention' is in clinical randomized trials related to the blinding of researchers, but in this context regarded as the objectivity of outcomes. This may be a less relevant sign of bias in this field of study because pharmaceutical pricing policy analyses are predominantly based on objective outcomes such as unit prices. Thirdly, the large proportion of studies associated with a high risk of bias in the domains 'random sequence generation', 'allocation concealment' and 'random sequence generation' is misleading. Not only does the

small denominator overstate the pattern, but more importantly is the use of non-randomized studies penalized. Indeed, non-randomized or controlled before-after studies are always scored as high risk according to the EPOC guidelines, even if performed well. The pattern that is now shown in **Figure 2a** is thus the result of the choice for these study design themselves and not the methodological choices within these studies. Fourthly, the domain 'other bias' was often assessed to have an unclear or high risk of bias because relevant and common issues could not be captured under the other domains. A simpler, empirically based tool could possibly provide more accurate measures of risk of bias and study quality in pharmaceutical pricing policy analysis [49]. As many tools for assessing risk of bias already exist [50], the pros and cons of these tools can be assessed to guide development of an empirical tool. Furthermore, we encourage the modification of existing tools in the development of empirically based tools that match the specific characteristics of health policy research. Particularly, biases that are typically found in policy research – such as confounding bias – should be addressed in a new tool. Joint efforts of the research community and the Cochrane Collaboration should be made to develop a tool appropriate for assessing bias in health policy analyses.

This study maps the methodological weaknesses of studies that have been published in the field of pharmaceutical pricing policies, and intends to encourage researchers, journal editors, policy makers and other relevant stakeholders to increase both the supply of and demand for high quality observational research on pharmaceutical and other health policies. A strength of this study is that it includes a representative sample of studies, not only due to an extensive literature search for the original SR but also the inclusion of multiple interventions within one field of study. Another strength is that gaps in reporting could be identified through literature complementing each other. We encountered several cases in which the exact same intervention was studied in different settings or focusing on different outcomes. Information in one study then enabled us to make better assessments in another study.

Our study has several limitations. The first limitation is that generalizability to other fields of study may be limited. The present study only included evidence from a SR on ten pharmaceutical pricing policies and may not accurately reflect the issues that are encountered in other areas of health policy. However, the methodological designs that were identified in this study are not unique to this field of study and issues identified are equally important to consider in other areas of health policy analysis. Additionally, the purpose of the present work is to illustrate some of the gaps and methodological weaknesses, which could be informative for researchers outside of pharmaceutical pricing policy analysis. Another limitation is the inconsistent naming of the study design used in included studies, if declared at all. In many cases, the method of analysis was presented as a study design. In others, neither the analysis nor design method was described in the paper. Both instances required the classification of study designs to be made based on the methods as presented. This could have introduced misclassification in the present work. A third limitation is the small number of studies that was included per study type.

Saturation of possible recurrent methodological shortcomings may not have been achieved with this sample.

Conclusion

We have described that study design issues occur often in pharmaceutical pricing policy analyses and lead to a reduction in the volume of evidence that can be effectively used for policy-making. The common issues identified in the present study might be indicative of similar issues within other fields of health policy analysis and should be used as starting point for improving commonly applied methodologies in the field. Our results also indicate that a more tailored tool is needed for the assessment of the quality and risk of bias of health policy analyses. Ultimately, the generation of more robust evidence should go hand in hand with aligning the efforts of researchers and policy-makers to bridge the existing gap between generating evidence and policy-making in practice.

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Supplementary materials

Appendix 1: Description and interpretation of risk of bias domains

Table S1 Description and interpretation of risk of bias domains as applied in the systematic review [1].

Bias domain	Explanation
Bias domains specific to interrupted time series and repeated measures studies only	
Intervention independent	Low risk" if there are compelling arguments that the intervention occurred independently of other changes over time and the outcome was not influenced by other confounding variables/historic events during study period. If Events/variables identified, note what they are. "High risk" if reported that intervention was not independent of other changes in time.
Appropriate analysis	"Low risk" if data were analyzed appropriately e.g. if autoregressive integrated moving average (ARIMA) models were used OR time series regression models were used to analyze the data and serial correlation was adjusted/tested for OR reanalysis performed. "High risk" if the outcomes were not analyzed appropriately. "Unclear risk" if not specified in the paper.
Pre-specified shape of effect	"Low risk" if point of analysis is the point of intervention OR a rational explanation for the shape of intervention effect was given by the author(s). Where appropriate, this should include an explanation if the point of analysis is NOT the point of intervention. "High risk" if it is clear that the condition above is not met.
Intervention to affect data collection	"Low risk" if reported that intervention itself was unlikely to affect data collection (for example, sources and methods of data collection were the same before and after the intervention). "High risk" if the intervention itself was likely to affect data collection (for example, any change in source or method of data collection reported).
Bias domains applicable to all study types	
Incomplete outcome data	"Low risk" if missing outcome measures were unlikely to bias the results (e.g. the proportion of missing data was similar in the intervention and control groups/pre- and post-intervention periods or the proportion of missing data was less than the effect size i.e. unlikely to overturn the study result). "High risk" if missing outcome data was likely to bias the results. "Unclear risk" if not specified in the paper (not assuming 100% complete data unless stated explicitly).
Knowledge of allocated intervention	"Low risk" if the authors state explicitly that the primary outcome variables were assessed blindly, or the outcomes are objective. Primary outcomes are those variables that correspond to the primary hypothesis or question as defined by the authors. "High risk" if the outcomes were not assessed blindly. Score "Unclear risk" if not specified in the paper.

Selective outcome reporting	"Low risk" if there is no evidence that outcomes were selectively reported (e.g. all relevant outcomes in the methods section are reported in the results section). "High risk" if some important outcomes are subsequently omitted from the results. "Unclear risk" if not specified in the paper.
Other bias	"Low risk" if there is no evidence of other risk of biases.

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Appendix 2: List of studies with an eligible study design

Table S2 Studies with an eligible study design.

Reference	Study design[a]
Adesina A, Wirtz VJ, Dratler S. Reforming antiretroviral price negotiations and public procurement: the Mexican experience. Health Policy Plan. 2013;28(1):1-10.	Controlled before-after study
Andersson K, Bergstrom G, Petzold MG, Carlsten A. Impact of a generic substitution reform on patients' and society's expenditure for pharmaceuticals. Health Policy. 2007;81(2-3):376-84.	Other
Andersson K, Petzold MG, Sonesson C, Lonnroth K, Carlsten A. Do policy changes in the pharmaceutical reimbursement schedule affect drug expenditures? Interrupted time series analysis of cost, volume and cost per volume trends in Sweden 1986-2002. Health Policy. 2006;79(2-3):231-43.	Other
Armeni P, Jommi C, Otto M. The simultaneous effects of pharmaceutical policies from payers' and patients' perspectives: Italy as a case study. Eur J Health Econ. 2016;17(8):963-77.	Difference-in-differences
Baldi S, Vannoni D. The impact of centralization on pharmaceutical procurement prices: the role of institutional quality and corruption. Reg. Stud. 2017;51(3):426-38.	Regression analysis
Balmaceda C, Espinoza MA, Diaz J. Impacto de una Política de Equivalencia Terapéutica en el Precio de Medicamentos en Chile. Value Heal Reg Issues. 2015 Dec 1;8C:43–8.	Difference-in-differences
Barbosa K, Fiuza EPS. Demand aggregation and credit risk effects in pooled procurement: evidence from the Brazilian public purchases of pharmaceuticals and medical supplies. Escola Econ São Paulo. 2012:1-46.	Panel data analysis
Ben-Aharon O, Shavit O, Magnezi R. Does drug price-regulation affect healthcare expenditures? Eur J Health Econ. 2017;18(7):859-67.	Repeated measures
Bergman MA, Granlund D, Rudholm N. Reforming the Swedish pharmaceuticals market: consequences for costs per defined daily dose. Int J Health Econ Manag. 2016;16(3):201-14.	Panel data analysis
Bhargava V. Addition of Generic Medication Vouchers to a Pharmacist Academic Detailing Program: Effects on the Generic Dispensing Ratio in a Physician-Hospital Organization. 2010;16(6).	Randomised trial
Bhaskarabhatla A, Chatterjee C, Anurag P, Pennings E. Mitigating regulatory impact: the case of partial price controls on metformin in India. Health Policy Plan. 2017;32(2):194-204.	Difference-in-differences
Brekke KR, Grasdal AL, Helge Holmås T. Regulation and pricing of pharmaceuticals: Reference pricing or price cap regulation? Eur Econ Rev. 2009;53(2):170–85.	Panel data analysis
Brekke KR, Canta C, Straume OR. Does reference pricing drive out generic competition in pharmaceutical markets? Evidence from a policy reform. NHH Dept Econ. 2015(11)	Panel data analysis

Buzzelli C, Kangasharju A, Linnosmaa I, Valtonen H. Impact of generic substitution on pharmaceutical prices and expenditures in OECD countries. J Pharma Finance Econ Policy. 2006;15(1):41-63.	Difference-in-differences
Chen CL, Chen L, Yang WC. The influences of Taiwan's generic grouping price policy on drug prices and expenditures: evidence from analysing the consumption of the three most-used classes of cardiovascular drugs. BMC Public Health. 2008;8:118.	Panel data analysis
Cheng W, Fang Y, Fan D, Sun J, Shi X, Li J. Study on the effect of «zero mark-up» policy on medicines in Beijing community health facilities. Pharma Policy Law. 2012;14(2-4):177-86.	Controlled before-after
Chu HL, Liu SZ, Romeis JC. Assessing the effects of drug price reduction policies on older people in Taiwan. Health Serv Manage Res. 2011;24(1):1-7.	Regression analysis
Clark B, DuChane J, Hou J, Rubinstein E, McMurray J, Duncan I. Evaluation of increased adherence and cost savings of an employer value-based benefits program targeting generic antihyperlipidemic and antidiabetic medications. J Manag Care Pharm. 2014;20(2):141-50.	Difference-in-differences
Danzon PM, Furukawa MF. Cross-national evidence on generic pharmaceuticals: pharmacy vs. Physician-driven markets. National Bureau of Economic Research, Inc, NBER Working Papers: 17226. 2011. Available from: https://www.nber.org/papers/w17226.	Regression analysis
Dubois P, Lefouili Y, Straub S. Pooled procurement of drugs in low and middle income countries. 2019. Available from: https://www.cgdev.org/publication/pooled-procurement-drugs-low-and-middle-income-countries.	Panel data analysis
Ferraresi M, Gucciardi G, Rizzo L. Does purchase centralization reduce public expenditure? evidence from the Italian healthcare system. 2017.	Difference-in-differences
Fraeyman J, Verbelen M, Hens N, Van Hal G, De Loof H, Beutels P. Evolutions in both co-payment and generic market share for common medication in the Belgian reference pricing system. Appl Health Econ Health Policy. 2013;11(5):543-52.	Other
Fu H, Li L, Yip W. Intended and unintended impacts of price changes for drugs and medical services: evidence from China. Soc Sci Med. 2018;211:114-22.	Difference-in-differences
Ghislandi S, Armeni P, Jommi C. The impact of generic reference pricing in Italy, a decade on. Eur J Health Econ. 2013;14(6):959-69.	Difference-in-differences
Godman B, Wettermark B, Miranda J, Bennie M, Martin A, Malmstrom RE. Influence of multiple initiatives in Sweden to enhance ARB prescribing efficiency following generic losartan; findings and implications for other countries. Int J Clin Pract. 2013;67(9):853–62.	Interrupted time series
Grootendorst P, Stewart D. A re-examination of the impact of reference pricing on anti-hypertensive drug plan expenditures in British Columbia. Health Econ. 2006;15(7):735-42.	Difference-in-differences
Grootendorst PV, Marshall JK, Holbrook AM, Dolovich LR, O'Brien BJ, Levy AR. The impact of reference pricing of nonsteroidal anti-inflammatory agents on the use and costs of analgesic drugs. Health Serv Res. 2005;40(5 Pt 1):1297-317.	Regression analysis

Hsiao FY, Tsai YW, Huang WF. Price regulation, new entry, and information shock on pharmaceutical market in Taiwan: a nationwide data-based study from 2001 to 2004. BMC Health Serv Res. 2010;10:218.	Interrupted time series
Kaiser U, Mendez SJ, Ronde T, Ullrich H. Regulation of pharmaceutical prices: evidence from a reference price reform in Denmark. J Health Econ. 2014;36:174-87.	Regression analysis
Kaiser U, Méndez SJ. How do drug prices respond to a change from external to internal reference pricing? evidence from a Danish regulatory reform. ZEW Discussion Papers. 2015:1-13.	Regression analysis
Kim SW, Skordis-Worrall J. Can voluntary pooled procurement reduce the price of antiretroviral drugs? a case study of Efavirenz. Health Policy Plan. 2017;32(4):516-26.	Difference-in-differences
Koskinen H, Ahola E, Saastamoinen LK, Mikkola H, Martikainen JE. The impact of reference pricing and extension of generic substitution on the daily cost of antipsychotic medication in Finland. Health Econ Rev. 2014;4(1):9.	Interrupted time series
Koskinen H, Mikkola H, Saastamoinen LK, Ahola E, Martikainen JE. Time series analysis on the impact of generic substitution and reference pricing on antipsychotic costs in Finland. Value Health. 2015;18(8):1105-12.	Interrupted time series
Kwon HY, Bae S, Choi SE, Park S, Lee EK, Park S, et al. Easy cuts, easy rebound: drug expenditures with massive price cuts in Korea. Health Policy. 2019;123(4):388-92.	Interrupted time series
Kwon HY, Hong JM, Godman B, Yang BM. Price cuts and drug spending in South Korea: the case of antihyperlipidemic agents. Health Policy. 2013;112(3):217-26.	Interrupted time series
Langley T, Lacey J, Johnson A, Newman C, Subramanian D, Khare M, et al. An evaluation of a price transparency intervention for two commonly prescribed medications on total institutional expenditure: a prospective study. Future Healthc J. 2018;5(3):198-202.	Interrupted time series
Lee IH, Bloor K, Hewitt C, Maynard A. The effects of new pricing and copayment schemes for pharmaceuticals in South Korea. Health Policy. 2012;104(1):40-9.	Interrupted time series
Leopold C, Zhang F, Mantel-Teeuwisse AK, Vogler S, Valkova S, Ross-Degnan D, et al. Impact of pharmaceutical policy interventions on utilization of antipsychotic medicines in Finland and Portugal in times of economic recession: Interrupted time series analyses. Int J Equity Health. 2014;13(1).	Interrupted time series
Li L, Chen Y, Yao L, Li Y. Evaluation of the effects of implementing the policy "Without Added Profit" to sale drug in community health service institutions of Chengdu. Chinese J New Drugs. 2008;17(21):1820-1822+1842.	Regression analysis
Lu CY, Ross-Degnan D, Stephens P, Liu B, Wagner AK. Changes in use of antidiabetic medications following price regulations in China (1999-2009). J Pharm Health Serv Res. 2013;4(1):3-11.	Interrupted time series
Mardetko N, Kos M. Introduction of therapeutic reference pricing in Slovenia and its economic consequences. Eur J Heal Econ. 2018;19(4):571–84.	Interrupted time series
Moodley R, Suleman F. The impact of the single exit price policy on a basket of generic medicines in South Africa, using a time series analysis from 1999 to 2014. PLoS ONE [Electronic Resourse]. 2019;14(7):e0219690.	Interrupted time series

Moodley R, Suleman F. Evaluating the impact of the single exit price policy on a basket of originator medicines in South Africa from 1999 to 2014 using a time series analysis. BMC Health Serv Res. 2019;19(1):576.	Interrupted time series
Moreno-Torres I, Puig-Junoy J, Raya JM. The impact of repeated cost containment policies on pharmaceutical expenditure: experience in Spain. Eur J Health Econ. 2011;12(6):563-73.	Other
Puig-Junoy J. The impact of generic reference pricing interventions in the statin market. Health Policy. 2007;84(1):14-29.	Interrupted time series
Sahay A, Jaikumar S. Does pharmaceutical price regulation result in greater access to essential medicines? Study of the impact of drug price control order on sales volume of drugs in India. Indian Institute of Management Ahmedabad 2016. 1-28.	Other
Schneeweiss S, Dormuth C, Grootendorst P, Soumerai SB, Maclure M. Net health plan savings from reference pricing for angiotensin-converting enzyme inhibitors in elderly British Columbia residents. Med Care. 2004;42(7):653-60.	Other
Stargardt T. The impact of reference pricing on switching behaviour and healthcare utilisation: the case of statins in Germany. Eur J Health Econ. 2010;11(3):267-77.	Difference-in-differences
Suh HS, Kim JA, Lee IH. Effects of a price cut reform on the cost and utilization of antidiabetic drugs in Korea: a national health insurance database study. BMC Health Serv Res. 2018;18(1):429.	Interrupted time series
Toulemon L. The effect of group purchasing on prices hospitals pay for medicines. Health Econ. 2018;19:19.	Panel data analysis
von der Schulenburg F, Vandoros S, Kanavos P. The effects of drug market regulation on pharmaceutical prices in Europe: overview and evidence from the market of ACE inhibitors. Health Econ Rev. 2011;1(1):18.	Panel data analysis
Wu BZ, Zhang Q, Qiao X. Effects of pharmaceutical price regulation: China's evidence between 1997 and 2008. J. Asia. Pac. Econ. 2015;20(2):290-329.	Regression analysis
Yang C, Shen Q, Cai W, Zhu W, Li Z, Wu L, et al. Impact of the zero-markup drug policy on hospitalisation expenditure in western rural China: an interrupted time series analysis. Trop Med Int Health. 2017;22(2):180-86.	Interrupted time series
Yasaitis L, Gupta A, Newcomb C, Kim E, Newcomer L, Bekelman J. An insurer's program to incentivize generic oncology drugs did not alter treatment patterns or spending on care. Health Aff. 2019;38(5):812-19.	Difference-in-differences
Yoo KB, Lee SG, Park S, Kim TH, Ahn J, Cho MH, et al. Effects of drug price reduction and prescribing restrictions on expenditures and utilisation of antihypertensive drugs in Korea. BMJ Open. 2015;5(7):1-10.	Interrupted time series
Zhou Z, Su Y, Campbell B, Zhou Z, Gao J, Yu Q, et al. The financial impact of the 'zero-markup policy for essential drugs' on patients in county hospitals in western rural China. PLoS ONE. 2015;10(3):1-17.	Difference-in-differences

[a] based on methods presented.

Appendix 3: List of studies with an ineligible study design

Table S3 Studies with an ineligible study design.

Reference	Study design issue
Aalto-Setala V. The impact of generic substitution on price competition in Finland. Eur J Health Econ. 2008;9(2):185-91.	Uncontrolled before-after study
Abramson RG, Harrington CA, Missmar R, Li SP, Mendelson DN. Generic drug cost containment in medicaid: lessons from five state MAC programs. Health Care Financ Rev. 2004;25(3):25-34.	Cross-sectional study
Abuelkhair M, Abdu S, Godman B, Fahmy S, Malmstrm RE, Gustafsson LL. Imperative to consider multiple initiatives to maximize prescribing efficiency from generic availability: Case history from Abu Dhabi. Expert Rev Pharmacoeconomics Outcomes Res. 2012;12(1):115-24.	Uncontrolled before-after study
Adriaen M, De Witte K, Simoens S. Pricing strategies of originator and generic medicines following patent expiry in Belgium. Journal of Generic Medicines. 2008;5(3):175-187.	Studies without pre-intervention data
Ahmad NS, Hatah E, Makmor-Bakry M. Association between medicine price declaration by pharmaceutical industries and retail prices in Malaysia's private healthcare sector. J Pharm Policy Pract. 2019;12:15.	Studies without pre-intervention data
Alabbadi I, Hammad EA. The impact of generic entry and price competition in Jordanian public health sector. J Generic Med. 2014;11(3-4):123-28.	Uncontrolled before-after study
Al-Abbadi I, Qawwas A, Jaafreh M, Abosamen T, Saket M. One-year assessment of joint procurement of pharmaceuticals in the public health sector in Jordan. Clin Ther. 2009;31(6):1335-44.	Uncontrolled before-after study
Ali GK, Yahia Y. Controlling medicine prices in Sudan: the challenge of the recently established medicines regulatory authority. East Mediterr Health J. 2012;18(8):811-20.	Studies without pre-intervention data
Amaral SM, Blatt CR. Municipal consortia for medicine procurement: impact on the stock-out and budget. Rev Saude Publica. 2011;45(4):799-801.	Uncontrolled before-after study
Anggriani Y, Ibrahim MIM, Suryawati S, Shafie AA. The impact of Indonesian generic medicine pricing policy on medicine prices. J Generic Med. 2013;10(3-4):219-29.	Cross-sectional study
Arinaminpathy N, Cordier-Lassalle T, Lunte K, Dye C. The global drug facility as an intervention in the market for tuberculosis drugs. Bull World Health Organ. 2015;93(4):237-48A.	Descriptive results without statistical analysis
Avdi E. The effect of pricing policies and cost-containment measures in Albanian health insurance scheme. Romanian Econ Bus Rev. 2013;8(3):61-78.	Descriptive results without statistical analysis
Bardey D, Bommier A, Jullien B. Retail price regulation and innovation: reference pricing in the pharmaceutical industry. J Health Econ. 2010;29(2):303-16.	Theoretical study

Bastani P, Imanieh MH, Dorosti H, Abbasi R, Dashti SA, Keshavarz K. Lessons from one year experience of pooled procurement of pharmaceuticals: exploration of indicators and assessing pharmacies` performance. DARU. 2018;12:12.	Uncontrolled before-after study
Becker B, Kruppert S, Kostev K. Economic prescribing of corticosteroid nasal sprays in Germany: comparison of mometasone and budesonide nasal sprays on the basis of the DDD, the PDD and reference prices. Int J Clin Pharmacol Ther. 2013;51(1):12-8.	Studies without pre-intervention data
Bocquet F, Loubiere A, Fusier I, Cordonnier AL, Paubel P. Competition between biosimilars and patented biologics: learning from European and Japanese experience. Pharmacoeconomics. 2016;34(11):1173-86.	Studies without pre-intervention data
Brekke KR, Canta C, Straume OR. Reference pricing with endogenous generic entry. J Health Econ. 2016;50:312-29.	Theoretical study
Brekke KR, Holmas TH, Straume OR. Margins and market shares: pharmacy incentives for generic substitution. Eur. Econ. Rev. 2013;61:116-31.	Theoretical study
Casanova-Juanes J, Mestre-Ferrandiz J, Espin-Balbino J. Competition in the off-patent medicine market in Spain: The national reference pricing system versus the regional system of tendering for outpatient prescription medicines in Andalusia. Health Policy. 2018;122(12):1310-15.	Descriptive results without statistical analysis
Chan A, Kitchen J, Scott A, Pollock D, Marshall R, Herdman L. Implementing and delivering a successful biosimilar switch programme - the Berkshire West experience. Future Healthc J. 2019;6(2):143-45.	Uncontrolled before-after study
Chaves GC, Castro C, Oliveira MA. Public procurement of hepatitis C medicines in Brazil from 2005 to 2015. Cienc. 2017;22(8):2527-38.	Descriptive results without statistical analysis
Cho MH, Yoo KB, Lee HY, Lee KS, Kwon JA, Han KT, et al. The effect of new drug pricing systems and new reimbursement guidelines on pharmaceutical expenditures and prescribing behavior among hypertensive patients in Korea. Health Policy. 2015;119(5):604-11.	Uncontrolled before-after study
Chokshi M, Farooqui HH, Selvaraj S, Kumar P. A cross-sectional survey of the models in Bihar and Tamil Nadu, India for pooled procurement of medicines. WHO South-East Asia j. 2015;4(1):78-85.	Cross-sectional study
Coma A, Zara C, Godman B, Agusti A, Diogene E, Wettermark B, et al. Policies to enhance the efficiency of prescribing in the Spanish Catalan region: impact and future direction. Expert Rev Pharmacoecon Outcomes Res. 2009;9(6):569-81.	Uncontrolled before-after study
Csanádi M, Kaló Z, Prins CPJ, Grélinger E, Menczelné Kiss A, Fricke FU, et al. The implications of external price referencing on pharmaceutical list prices in Europe. Health Policy Technol. 2018;7(3):243-50.	Cross-sectional study
Curto S, Ghislandi S, van de Vooren K, Duranti S, Garattini L. Regional tenders on biosimilars in Italy: an empirical analysis of awarded prices. Health Policy. 2014;116(2-3):182-7.	Studies without pre-intervention data

Danzon PM, Epstein AJ. Effects of regulation on drug launch and pricing in interdependent markets (No. w14041). National Bureau of Economic Research. 2008.	Theoretical study
Danzon PM, Mulcahy AW, Towse AK. Pharmaceutical pricing in emerging markets: effects of income, competition and procurement. Health Econ. 2015;24(2):238-52.	Other design issue
de Jager H, Suleman F. The impact of generics and generic reference pricing on candesartan and rosuvastatin utilisation, price and expenditure in South Africa. Int J Clin Pharm. 2019;41(1):81-87.	Descriptive results without statistical analysis
Degrassat-Theas A, Bensadon M, Rieu C, Angalakuditi M, Le Pen C, Paubel P. Hospital reimbursement price cap for cancer drugs: the French experience in controlling hospital drug expenditures. Pharmacoeconomics. 2012;30(7):565-73.	Uncontrolled before-after study
Díaz-Rojas JA, Rodríguez-Márceles M, Rodríguez-Romero A, Brown P. Impact of group purchasing in cooperative of hospital in Colombia, using a price index from 1999 to 2012. Rev. colomb. ciencias quim. farm. 2013;42(1):80-102.	Descriptive results without statistical analysis
DoHA. The Impacts of Pharmaceutical Benefits Scheme Reform. Department of Health and Ageing: 2010. Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/4BC52286D3009386CA257BF000209AD5/$File/PwC%20The%20Impacts%20of%20PBS%20Reform.pdf.	Theoretical study
Drummond M, Jonsson B, Rutten F, Stargardt T. Reimbursement of pharmaceuticals: reference pricing versus health technology assessment. Eur J Health Econ. 2011;12(3):263-71.	Cross-sectional study
Dutta A, Bandyopadhyay S. Policy intervention for access to medicine: does it work similarly for poor and non-poor? Int J Health Plann Manage. 2019;34(1):e557-e68.	Studies without pre-intervention data
Fang Y, Wagner AK, Yang S, Jiang M, Zhang F, Ross-Degnan D. Access to affordable medicines after health reform: evidence from two cross-sectional surveys in Shaanxi Province, western China. Lancet Glob. Health. 2013;1(4):e227-37.	Studies without pre-intervention data
Fraeyman J, Van Hal G, De Loof H, Remmen R, De Meyer GR, Beutels P. Potential impact of policy regulation and generic competition on sales of cholesterol lowering medication, antidepressants and acid blocking agents in Belgium. Acta Clin Belg. 2012;67(3):160-71.	Descriptive results without statistical analysis
Garuoliene K, Godman B, Gulbinovic J, Wettermark B, Haycox A. European countries with small populations can obtain low prices for drugs: Lithuania as a case history. Expert Rev Pharmacoecon Outcomes Res. 2011;11(3):343-9.	Uncontrolled before-after study
Geng DF, Saggi K. International effects of national regulations: external reference pricing and price controls. J. Int. Econ. 2017;109:68-84.	Theoretical study
Gilman BH, Kautter J. Consumer response to dual incentives under multitiered prescription drug formularies. Am J Manag Care. 2007;13(6 II):353-59.	Cross-sectional study
Gilman BH, Kautter J. Impact of multitiered copayments on the use and cost of prescription drugs among Medicare beneficiaries. Health Serv Res. 2008;43(2):478-95.	Cross-sectional study

Godman B, Burkhardt T, Bucsics A, Wettermark B, Wieninger P. Impact of recent reforms in Austria on utilization and expenditure of PPIs and lipid-lowering drugs: implications for the future. Expert Rev Pharmacoecon Outcomes Res. 2009;9(5):475-84.	Descriptive results without statistical analysis
Godman B, Shrank W, Andersen M, Berg C, Bishop I, Burkhardt T, et al. Policies to enhance prescribing efficiency in europe: findings and future implications. Front Pharmacol. 2010;1:141.	Uncontrolled before-after study
Godman B, Shrank W, Andersen M, Berg C, Bishop I, Burkhardt T, et al. Comparing policies to enhance prescribing efficiency in Europe through increasing generic utilization: changes seen and global implications. Expert Rev Pharmacoecon Outcomes Res. 2010;10(6):707-22.	Uncontrolled before-after study
Godman B, Wettermark B, van Woerkom M, Fraeyman J, Alvarez-Madrazo S, Berg C, et al. Multiple policies to enhance prescribing efficiency for established medicines in Europe with a particular focus on demand-side measures: findings and future implications. Front Pharmacol. 2014;5:106.	Descriptive results without statistical analysis
Goncalves R, Rodrigues V, Vasconcelos H. Reference pricing in the presence of pseudo-generics. Int J Health Econ Manag. 2015;15(3):281-305.	Theoretical study
Gouya G, Reichardt B, Bidner A, Weissenfels R, Wolzt M. Eine differenzierte Rezeptgebühr für Generika erzielt Einsparungen für Kostenträger und Patienten. Wiener klinische Wochenschrift. 2008;120(3-4):89-95.	Uncontrolled before-after study
Habl C, Schneider P, Németh G, Šebesta R. Euripid guidance document on external reference pricing (ERP). European Commission, Consumer, Health and Food Executive Agency 2018.	Theoretical study
Hammerschmidt T. Analysis of German new drug prices after AMNOG in relation to European prices. Gesundheitswesen. 2017;22(1):43-53.	Studies without pre-intervention data
Han S, Feng L, Zhang YY. Study of settling differential margin mode for hospital medicine selling in China. Chinese Pharmaceutical Journal. 2011;46(9):710-13.	Theoretical study
Han S, Liang H, Su W, Xue Y, Shi L. Can price controls reduce pharmaceutical expenses? a case study of antibacterial expenditures in 12 Chinese hospitals from 1996 to 2005. Int J Health Serv. 2013;43(1):91-103.	Studies without pre-intervention data
Heo JH, Rascati KL, Lee EK. Prediction of change in prescription ingredient costs and co-payment rates under a reference pricing system in South Korea. Value Health Reg Issues. 2017;12:7-19.	Theoretical study
Herr A, Stühmeier T, Wenzel T. Reference pricing and cost-sharing: theory and evidence on German off-patent drugs. Beiträge zur Jahrestagung des Vereins für Socialpolitik. 2014:1-30.	Theoretical study
Herruzo Ferrer M. Reference pricing system in Spain: Period 2000 - 2008. Ars Pharm. 2010;51(SUPPL. 3):641-56.	Descriptive results without statistical analysis

Hoffmann F, Glaeske G, Pfannkuche MS. The effect of introducing rebate contracts to promote generic drug substitution, on doctors' prescribing practices. Dtsch Arztebl Int. 2009;106(48):783-8.	Uncontrolled before-after study
Hornyak L, Nagy Z, Ilku L, Talos Z, Endrei D, Agoston I, et al. Price competition and reimbursement of biosimilar granulocyte-colony stimulating factor in Hungary. Expert Rev Pharmacoecon Outcomes Res. 2019:1-7.	Uncontrolled before-after study
Hornyak L, Nagy Z, Talos Z, Endrei D, Agoston I, Csakvari T, et al. [Experiences with price competition of biosimilar drugs in Hungary]. Acta Pharm Hung. 2014;84(2):83-7.	Uncontrolled before-after study
Huang JL, Tang ZJ. Investigation of the present situation and tendency of Shanghai Municipal Medical Institution Central Bidding and Procurement of Pharmaceuticals. Pharm Care Res. 2006;6(4):257-59.	Theoretical study
Jiang ST, Yin XZ, Wang WH, Liu YP. Relationship between price regulation and the sale volume of 146 kinds of medicines. Pharm Care Res. 2004;4(3):267-68.	Uncontrolled before-after study
Jin C, Chen Z, He L. The study on zero profit drug supply and the corresponding reimbursement policy in medical institutions in Shanghai. Chinese Journal of Health Policy. 2010;3(10):24-28.	Uncontrolled before-after study
Johnson J. Five-year examination of utilization and drug cost outcomes associated with benefit design changes including reference pricing for proton pump inhibitors in a state employee health plan. Journal of Managed Care Pharmacy. 2011;17(3):200-212.	Descriptive results without statistical analysis
Kajdiž R, Bojnec S. Do the price regulation and reimbursement affect public expenditures for medicinal products? Zdr Vestn. 2012;81(9):618-25.	Uncontrolled before-after study
Kajdiž R, Bojnec Š. Price developments of the first level of anatomic-therapeutic-chemical classification of regulated medicines. Zdr Vestn. 2013;82(9):564-72.	Uncontrolled before-after study
Kim Gustavsen, Ole Henriksen, Rasmus Fynbo-Aagaard Jensen, Vasegaard K. Analyse af indkøb af lægemidler i primærsektoren. COWI.: 2014.	Descriptive results without statistical analysis
Kohler JC, Mitsakakis N, Saadat F, Byng D, Martinez MG. Proofs for PLOS ONE paper : Does pharmaceutical pricing transparency matter? examining Brazil's public procurement system. Global Health. 2015;11:13.	Studies without pre-intervention data
Law MR, Ystma A, Morgan SG. The short-term impact of Ontario's generic pricing reforms. PLoS ONE. 2011;6(7):e23030.	Uncontrolled before-after study
Lee YC, Yang MC, Huang YT, Liu CH, Chen SB. Impacts of cost containment strategies on pharmaceutical expenditures of the national health insurance in Taiwan, 1996-2003. Pharmacoeconomics. 2006;24(9):891-902.	Studies without pre-intervention data
Leopold C, Mantel-Teeuwisse AK, Seyfang L, Vogler S, de Joncheere K, Laing RO, Leufkens H. Impact of external price referencing on medicine prices–a price comparison among 14 European countries. Southern med review. 2012;5(2):34.	Cross-sectional study

Li Y, Ying C, Sufang G, Brant P, Bin L, Hipgrave D. Evaluation, in three provinces, of the introduction and impact of China's national essential medicines scheme. Bull World Health Organ. 2013;91(3):184-94.	Uncontrolled before-after study
Maiga D, Williams-Jones B. Assessment of the impact of market regulation in Mali on the price of essential medicines provided through the private sector. Health Policy. 2010;97(2-3):130-5.	Uncontrolled before-after study
Marđetko N, Kos M. Influence of generic reference pricing on medicine cost in Slovenia: a retrospective study. Croatian medical journal. 2018;59(2):79-89.	Studies without pre-intervention data
Mardetko N, Rijavec N, Kos M. Development and performance of the external reference pricing system in Slovenia from 2007 to 2012. Health Policy Technol. 2017;6(3):348-57.	Descriptive results without statistical analysis
Martich EV. A política de medicamentos genéricos e o mercado farmacêutico na Argentina e no Brasil. 2013:50-50.	Studies without pre-intervention data
Miraldo M. Reference pricing versus co-payment in the pharmaceutical industry: price, quality and market coverage. CHE. 2007:1-45.	Theoretical study
Mohamed O, Kreling DH. The impact of a pricing policy change on retail prices of medicines in Egypt. Value Health Reg Issues. 2016;10:14-18.	Uncontrolled before-after study
Moorkens E, Simoens S, Troein P, Declerck P, Vulto AG, Huys I. Different policy measures and practices between swedish counties influence market dynamics: part 2-biosimilar and originator etanercept in the outpatient setting. BioDrugs. 2019;33(3):299-306.	Descriptive results without statistical analysis
Moye-Holz D, van Dijk JP, Reijneveld SA, Hogerzeil HV. The impact of price negotiations on public procurement prices and access to 8 innovative cancer medicines in a middle-income country-the case of Mexico. Value Health Reg Issues. 2019;20:129-35.	Descriptive results without statistical analysis
Olga SC, Daphne KC, Panagiota LS, Georgia GS, Helen AA, Panagiotis PG, et al. Investigating the economic impacts of new public pharmaceutical policies in greece: focusing on price reductions and cost-sharing rates. Value Health Reg Issues. 2014;4:107-14.	Uncontrolled before-after study
Pan YH, Cui MD, Li XH. Study on effect of zero-profit medicine policy on medical expenses and compensation mechanisms. Shanghai Jiao Tong Da Xue Xue Bao Yi Xue Ban. 2015;35(11):1696-701.	Uncontrolled before-after study
Patel HK, Dwibedi N, Omojasola A, Sansgiry SS. Impact of generic drug discount programs on managed care organizations. Am J Pharm Benefits. 2011;3(1):45-53.	Cross-sectional study
Petrou P. Long-term effect of tendering on prices of branded pharmaceutical products. Health Policy Technol. 2016;5(1):40-46.	Studies without pre-intervention data
Petrou P, Talias MA. Tendering for pharmaceuticals as a reimbursement tool in the Cyprus public health sector. Health Policy Technol. 2014;3(3):167-75.	Cross-sectional study

Prada SI, Soto VE, Andia TS, Vaca CP, Morales AA, Marquez SR, et al. Higher pharmaceutical public expenditure after direct price control: improved access or induced demand? the Colombian case. Cost Eff Resour Alloc. 2018;16:8.	Studies without pre-intervention data
Puig-Junoy J, Moreno-Torres I. Do generic firms and the Spanish public purchaser respond to consumer price differences of generics under reference pricing? Health Policy. 2010;98(2-3):186-94.	Descriptive results without statistical analysis
Qendri V, Bogaards JA, Berkhof J. Pricing of HPV vaccines in European tender-based settings. Eur J Health Econ. 2019;20(2):271-80.	Studies without pre-intervention data
Rothberg AD, Blignault J, Serfontein CB, Valodia B, Eekhout S, Pels LM. Experience of a medicines reference-pricing model. S Afr Med J. 2004;94(3):183-8.	Descriptive results without statistical analysis
Roy V. A way to low cost, quality medicines: Implementation of an essential medicines policy in public health facilities in Delhi (India). IJPSR. 2013;4(3):397-410.	Studies without pre-intervention data
Sakshaug S, Furu K, Karlstad O, Ronning M, Skurtveit S. Switching statins in Norway after new reimbursement policy: a nationwide prescription study. Br J Clin Pharmacol. 2007;64(4):476-81.	Uncontrolled before-after study
Sarol Jesus N. Effect of government-mediated access pricing on availability of directly affected drugs in retail drug stores in the Philippines from 2009 to 2011. Acta Medica Philippina. 2014:9-17.	Uncontrolled before-after study
Sigulem F, Zucchi P. E-procurement in the Brazilian healthcare system: the impact of joint drug purchases by a hospital network. Rev Panam Salud Publ. 2009;26(5):429-34.	Studies without pre-intervention data
Steyn R, Burger JR, Serfontein JHP, Lubbe MS. Influence of a new reference-based pricing system in South Africa on the prevalence and cost of antidiabetic medicine: a pilot study. Int J Pharm Pract. 2007;15(4):307-11.	Uncontrolled before-after study
Timonen J, Heikkilä R, Ahonen R. Generic substitution in Finland: lessons learned during 2003-2008. J Pharm Health Serv Res. 2013;4(3):165-72.	Studies without pre-intervention data
Tordoff JM, Norris PT, Reith DM. Managing prices for hospital pharmaceuticals: a successful strategy for New Zealand? Value Health. 2005;8(3):201-8.	Theoretical study
Tordoff JM, Norris PT, Reith DM. "Price management" and its impact on hospital pharmaceutical expenditure and the availability of medicines in New Zealand hospitals. Value Health. 2008;11(7):1214-26.	Theoretical study
Ubeda A, Cardo E, Selles N, Broseta R, Trillo JL, Fernandez-Llimos F. Antidepressant utilization in primary care in a Spanish region: impact of generic and reference-based pricing policy (2000-2004). Soc Psychiatry Psychiatr Epidemiol. 2007;42(3):181-8.	Studies without pre-intervention data
Unsorg M. Reference pricing systems on the pharmaceutical market. Digital Economy. 2018	Theoretical studies

Wang J, Liu X, Wang S, Chen H, Wang X, Zhou W, et al. Short-term differences in drug prices after implementation of the national essential medicines system: a case study in rural Jiangxi Province, China. Indian J Pharmacol. 2015;47(5):535-9.	Uncontrolled before-after study
Waning B, Kaplan W, King AC, Lawrence DA, Leufkens HG, Fox MP. Global strategies to reduce the price of antiretroviral medicines: evidence from transactional databases. Bull World Health Organ. 2009;87(7):520-8.	Studies without pre-intervention data
Wouters OJ, Sandberg DM, Pillay A, Kanavos PG. The impact of pharmaceutical tendering on prices and market concentration in South Africa over a 14-year period. Soc Sci Med. 2019;220:362-70.	Studies without pre-intervention data
Yin T, Jiang B. Effects of drug procurement under cap price policy in Sanming. J Chinese Pharma Sci. 2018;27(11):799-804.	Cross-sectional study
Ying L, Lingui LI. The Effect Analysis of the Procurement System in Ningxia Rural Areas. China Pharmacy. 2005	Cross-sectional study
Zhang H, Hu H, Wu C, Yu H, Dong H. Impact of china's public hospital reform on healthcare expenditures and utilization: a case study in ZJ province. PLoS ONE. 2015;10(11):1-19.	Uncontrolled before-after study

Appendix 4: Association between methodological issues and studies intervention

Figure S1 Study designs used per intervention for studies in the eligible study design group.

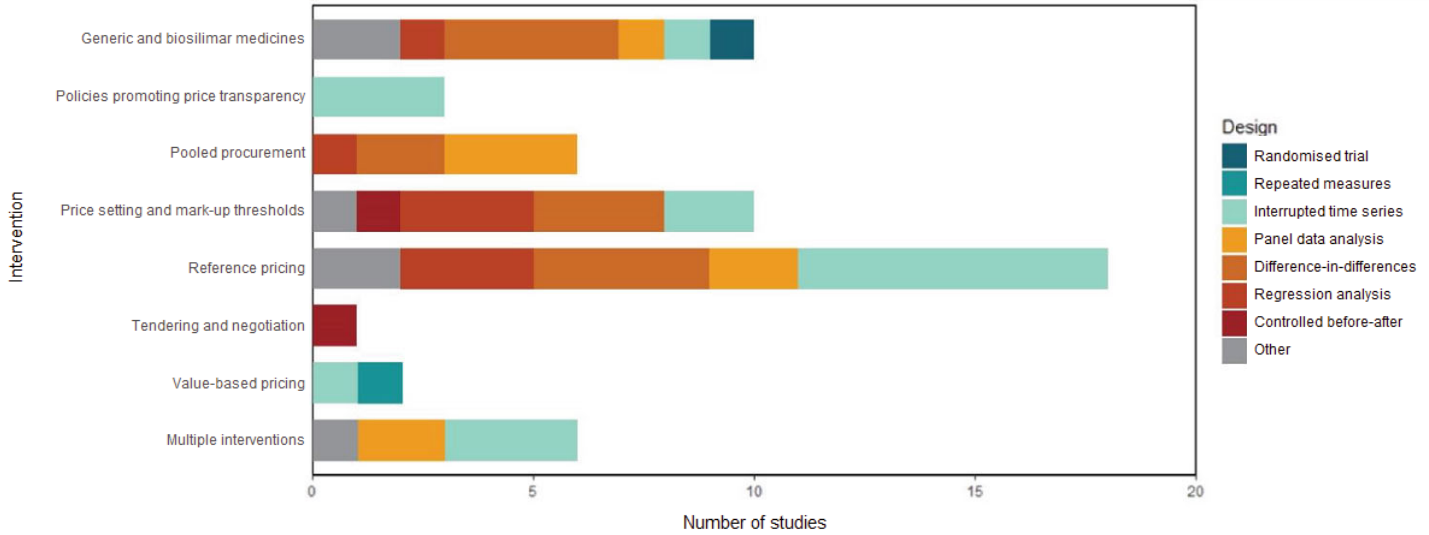
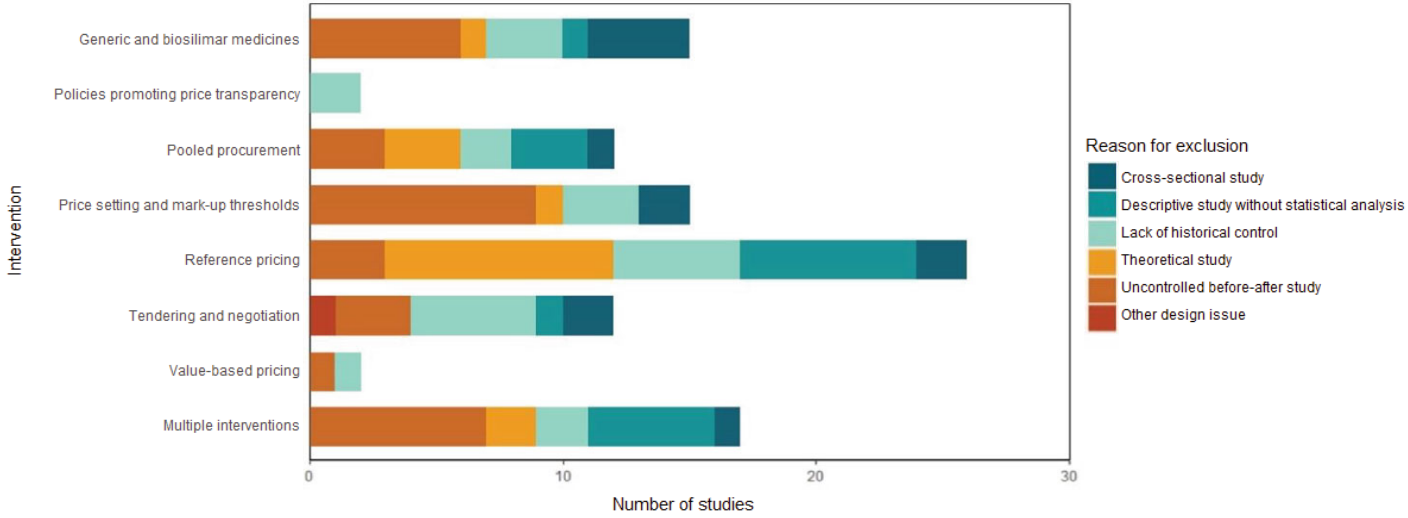


Figure S2 Designs issues per intervention in studies with an ineligible study design.




Bivatracin
BETADINE
Kaprofen
KETOLAC

CHAPTER 5

General discussion

Paths forged in access to medicines research

Despite the established significance of medicines in the attainment of the highest possible level of health, an estimated 2 billion people worldwide still lack regular access to essential medicines [1]. Efforts to bridge these persistent access gaps and reduce global inequities hinge on monitoring and evaluation of access, forming an essential part of the continuous cycle of problem identification, policy formulation, implementation, and evaluation [2]. Particularly, performance monitoring, health systems analysis and pharmaceutical policy analysis constitute three important assessment methods in the evaluation of health systems and policies in providing access to medicine (**Figure 1**); evidence generated through these research activities contribute to effective national political priority setting, to the development of targeted policy interventions, and to refinement of existing strategies to local inefficiencies [3, 4]. Nonetheless, monitoring and evaluation efforts have not reached their full potential in the past decade due to minimal innovation in methodological tools and approaches and limited generation of evidence on access to medicines, leaving methodological and informational deficiencies unresolved. This dissertation aimed to bring advancement and innovation to access to medicines research, and to these three evidence-generation mechanisms specifically.

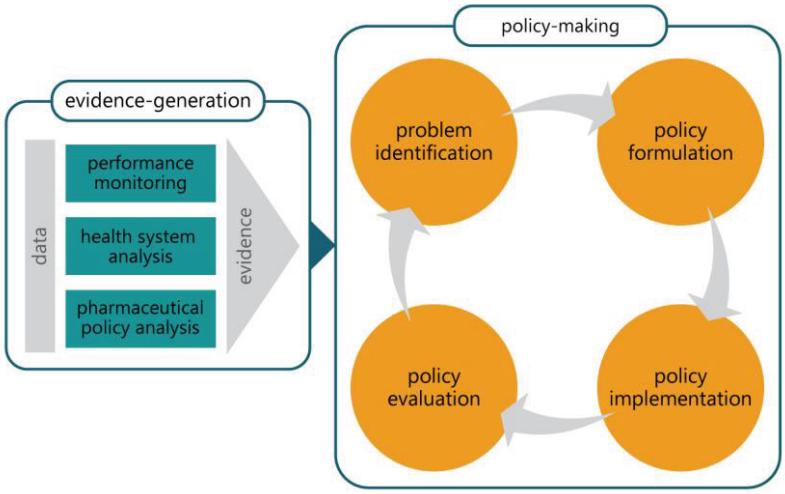


Figure 1 From evidence-generation to policy-making.

Evidence from performance monitoring, health systems analyses and pharmaceutical policy analyses feed into the policy cycle: through problem identification, performance monitoring has the potential to steer the political agenda; health systems analyses help identify root causes of problems, contribute to agenda-setting, and offer insight into the reasons for policy successes

or failures; pharmaceutical policy analyses can inform which interventions to implement and how, and evaluate whether existing or future policies have achieved their objectives.

Performance monitoring

As the most important performance monitoring tool for measuring access to medicine, we brought advancement to Sustainable Development Goal (SDG) indicator 3.b.3 by expanding its scope to include the much neglected population of children in **Chapter 2**. SDG indicator 3.b.3 – the United Nation's (UN) core indicator to measure access to medicines – was adapted to better reflect the needs of children. To this end, two core sets of tracer age-appropriate essential medicines were established for different age groups in **Chapter 2.4**. To permit technical calculation of the indicator for children, a novel parameter, labeled the *Number of Units Needed for Treatment* (NUNT), was developed. Proof-of-concept of the adaptations was provided in **Chapter 2.2**, and further validation was undertaken in **Chapter 2.3**.

Health systems analysis

Novel approaches to evaluate health systems and their capacity to provide access to medicines were introduced and tested in **Chapter 3**, in a case study of access to childhood cancer medicines in South Africa. The alignment between fundamental pharmaceutical processes was studied in **Chapter 3.1**, integrating multiple data sources to study operationalization of policies in their practical setting. Further innovation was brought through the formulation of a novel analytical framework for the study of determinants of access to medicines from a health system perspective in **Chapter 3.2**, which was then applied to the case study of childhood cancer in **Chapter 3.3**. Barriers and facilitators as perceived by stakeholders were verified through the lived experiences of caregivers of children affected by cancer in **Chapter 3.4**. Further triangulation of methods and synthesis of findings in **Chapter 3.5** enabled the identification of areas for potential policy development in the field of cancer care.

Pharmaceutical policy analysis

Insight was offered in the present landscape of pharmaceutical pricing policy research and methodologies employed in **Chapter 4**. **Chapters 4.1** and **4.2** outlined the existing body of evidence regarding policies promoting price transparency and policies regulating mark-ups, whilst inherently mapping the evidence gaps within these topics. An overview of common methodological weaknesses in pharmaceutical pricing policy analyses was provided in **Chapter 4.3**. This chapter highlighted opportunities for alternative methodological approaches in these type of studies, and emphasized the need for additional information on the specifics of implemented policies and their local context.

In pursuit of bringing advancement to three distinct monitoring and evaluation methods, our efforts revealed two pivotal challenges that transcend the individual chapters, methodologies and tools. Firstly, we encountered a myriad of complexities that are inherent to conducting

evaluations of access to medicines. Secondly, the absence of critical data further compounds the complexity and impedes generation of the evidence required for decision-making. These transcendent challenges will be discussed in-depth in the remainder of this chapter, followed by recommendations that could aid in bridging the current gap between evidence-generation and policy-making.

Complexities are inherent to monitoring and evaluating access to medicines

Complexity is construed in healthcare literature as a state of non-linearity, unpredictability, multiplicity and interactivity [5-11]. Inherently, access to medicines embodies this complexity as a multidimensional concept, encompassing both demand- and supply-side aspects of access within the context of a health system, while also considering national and international factors [12, 13]. Beyond conceptual complexity, other complexities were evident throughout the studies in this thesis at multiple levels – methodological, systemic, and interventional. This section unpacks different types of complexities that were encountered in monitoring and evaluating access to medicines.

Conceptual complexity – operationalizing theoretical principles

To facilitate performance monitoring through SDG indicator 3.b.3, the theoretical principles of access to medicines had to be operationalized into a practical and measurable evaluation tool. Fundamental to this operationalization was concretization and simplification of two abstract and complex input dimensions of SDG indicator 3.b.3: availability and affordability of medicines. In adapting SDG indicator 3.b.3 to children in **Chapter 2,** it was revealed how the complexity of these theoretical concepts affects SDG indicator 3.b.3, and how their operationalization has shaped the appropriateness of the main indicator and its child-appropriate equivalent.

The indicator, rooted in the World Health Organization (WHO)/Health Action International (HAI) methodology for collecting data and measuring components of access to medicines, defines availability as the presence of a medicine on the day of data collection [14], therein mirroring the WHO/HAI methodology [15]. This entailed considerable simplification of the concept into a binary variable without making any quantifications of availability. With that, this metric fails to capture the relationship between the quantity needed by users and the quantity available [12]. Furthermore, the cross-sectional measurement does not reflect availability over time: what is available today might be out of stock tomorrow, and vice versa. Consequently, the simplification of this metric somewhat compromises its relevance. To enhance its relevance and reflect availability over an extended period of time, the mapping of stock-out duration has been employed [16], but experts caution about the difficulties in accurately measuring this [3]. Despite

the limitations, the current – simplified but reasonably feasible – measure remains widely accepted.

The concept of affordability is defined in literature as the relationship between the price of a medicines and a user's ability to pay [12]. Operationalization of this definition required concretization and quantification of a subjective ability. Previously, the WHO/HAI methodology used the number of day's wages of the lowest-paid unskilled government worked (LPGW) required to purchase a course of treatment [15] to quantify this ability. Notably, this methodology did not apply a threshold and emphasized that the LPGW wage must be positioned in relation to the local context, for a considerable part of the population may earn less (or more) than the LPGW or may be unemployed [15]. Nonetheless, a threshold of one day's wages to determine affordability is often used when applying this methodology [16-18], likely based on the handbook's observation that medicines are *generally* considered affordable if they cost less than a day's wage [15]. Although setting such a threshold facilitates interpretation of the concept, applying a normative choice also significantly impacts the outcome [19].

A known limitation of the WHO/HAI definition of affordability is that other non-discretionary expenditures such as food and housing are not taken into account when reporting on the number of days of work required to pay for the medicine [20]. SDG indicator 3.b.3 therefore introduced a novel approach to express affordability, in which the cost for a medicines should not exceed the wage of the LPGW, after reduction of non-discretionary spending (i.e. the National Poverty Line, NPL) [14]. This definition too involves a normative choice, and continues to overlook that multiple dependents may live on a single wage [20]. This is particularly relevant for children, who depend on a caregiver. Additionally, a part of the population may be covered by health insurance. With a global ambition to achieve Universal Health Coverage (UHC) by 2030, there is also a growing need for an affordability measure that incorporates this aspect [21]. Other proposed approaches to measure affordability, including the impoverishment approach (considering a household's absolute financial resources before and after payment for a medicine) and catastrophic spending approach (cost of a medicine relative to a household's financial resources) [19, 22], face similar shortcomings.

Beyond concretization and simplification of availability and affordability as core input components of SDG 3.b.3 indicator, further operationalization of the theoretical principles of access to medicines was needed to obtain a practical tool. This involved the consolidation of several other input components, including a core set of essential medicines and proportional weights based on disease burden (discussed in detail in **Chapter 2.2**). The appropriateness of the resultant SDG indicator 3.b.3 might be most fittingly appraised through the lens of a set of criteria for selecting indicators. In February 2019, a panel consisting of 40 experts from around the globe convened and identified a number of criteria to guide indicator selection for access to medicines [3]. These criteria stipulate that an indicator should be:

1) *outcome-focused*, measuring concrete outcomes rather than processes;
2) *universal*, applying to all contexts;
3) *feasible*, allowing practical measurement;
4) *established*, based on existing and easy-to-use data sources;
5) *actionable*, being easy to understand and resonating with policy-makers;
6) *reflect change*, capturing changes over time and between context;
7) *relevant*, providing insight into performance and informing decision-making.

Upon applying these criteria to SDG indicator 3.b.3 and its child-appropriate equivalent, several concerns in their operationalization become apparent:

Outcome-focused

SDG indicator 3.b.3 focuses on measuring tangible outcomes, aligning with the criterion.

Universal and relevant

Efforts were made to ensure universal relevance of the indicator by selecting a core set of essential medicines with global relevance, and additional core sets of child-appropriate medicines as detailed in **Chapter 2.4**. At the same time attempting to enable national applicability of these medicines, proportional weights representing local importance were introduced based on burden of disease. However, **Chapter 2.3** highlights considerable disproportionality in the child-specific indicator due to this component. This disproportionality presumably extends to the original indicator. In addition to this, the relevance of core input component affordability in particular is questionable (see above) and calls for fundamental rethinking rather than mere refinement.

Feasible and established

Although intended to facilitate practical measurement of access to medicines, the many input variables and computational steps in the indicator compromises its feasibility. While preconfigured tools – such as the core sets of age-appropriate medicines and associated NUNT that are described in **Chapter 2.4** offer some simplification, the number of other input variables from multiple data sources required to calculate the indicator is still considerable (as discussed under 'methodological complexity').

Actionable

In order for an indicator to resonate with policy-makers, it must be easy to interpret. The considerable number of input variables and steps not only make computation of the indicator complex, the outcomes are also less intuitive. Additionally, **Chapter 2.3**

reveals that applying proportional weights based on disease burden makes the indicator unpredictable and consequently non-actionable.

Reflect change

For an indicator to effectively inform decision-making, it should reflect modest changes in access. However, computation of the indicator twice involves the transformation of continuous data into binary data using defined thresholds, before obtaining a final score. This is of particular relevance for the 80% threshold that is applied to determine whether a health facility provides sufficient access to medicines. Any improvement below this threshold may still embody relevant change, but would not be reflected in a change of the outcome. To bypass this limitation, results in **Chapter 2.2** and **Chapter 2.3** were reported as mean facility scores, without applying the final conversion step. In addition to this, disaggregate availability and affordability outcomes were still required.

The conceptual complexity of operationalizing access to medicines through SDG indicator 3.b.3, including its child-specific counterpart, resides in the need to transform a complex theoretical construct into a practical tool, and ensuring its feasibility without compromising relevance. This process inevitably involves simplification, resulting in a trade-off between relevance and practicality, requiring a delicate balance. Furthermore, whilst the multidimensional approach of the indicator is theoretically preferred, it introduces practical challenges, questioning the desirability of having a single indicator to embody such a complex concept.

The complexities and limitations of this indicator call for further refinement and simplification. Future validation steps should involve prospectively collected data in a case study country, with the ultimate objective to obtain a ready-to-use tool that is both practical and actionable. Until such a time, the indicator in its current form can offer some insight into access to medicines according to its intended purpose.

Methodological complexity – linking multiple data sources

The potential of leveraging multiple data sources has previously been well-documented in the context of health services research [23-25]. This potential extends into the domain of health policy research [26], as demonstrated in **Chapter 3.1**. In this chapter the operationalization of pharmaceutical policies was assessed through a joint analysis of Essential Medicines Lists (EMLs), a registration database, medicine formularies, tender documents and a price registry, allowing us to study alignment of core pharmaceutical processes and identify bottlenecks in access. However, the potential of leveraging the multiple data sources is contingent upon achieving interoperability of data collected from the different sources, and the type of information recorded in each source [23-25]. It is within these aspects that complexity arises. In **Chapter 3.1** challenges particularly arose in assessing alignment of medicine finished pharmaceutical preparations, as this information was not available across all sources.

Similar potential and complexity were encountered in another domain of access to medicines research. SDG indicator 3.b.3 was constructed as a monitoring tool for countries to evaluate their performance in ensuring access to medicines. Within this indicator, the dimension of affordability is not solely determined by one's ability to pay (as discussed under 'conceptual complexity'), but also by the cost of treatment, in which the price of a course treatment is used as the unit of analysis [14]. This composite parameter relies on the price of a single medicine unit, the dosage required by a patient, the duration of treatment, and the dosage strength of the medicine. Defined-Daily-Dosages (DDDs) were used as a ready-to-use measure to inform required dosing, but the use of this metric does not extend to children. To enable calculation of SDG indicator 3.b.3 and improve feasibility of the methodology for children, the NUNT was established as child-appropriate equivalent in **Chapter 2.4**. The development of this measure alone required the gathering of information from multiple different data sources, which included the WHO Essential Medicines List for Children (EMLc), eleven clinical treatment guidelines or equivalents, and three types of weight-for-age charts to assure interoperability. The subsequent integration process involved distilling large amounts of data, and multiple conversion and validation steps to establish a NUNT for each of the eligible age-appropriate formulations. This process demonstrates the complexity inherent to extending what seems like a straightforward measure to a previously overlooked group – particularly such a heterogeneous one as children – highlighting the need to predetermine ready-to-use measures to ensure broader utilization of available tools.

Systemic complexity – unpacking intricate systems

Health systems are inherently internally complex; each health system component interacts with other components in the system, and their collective performance influences one another [9]. Externally, the health system operates within national and international political, economical and social dynamics. A health system perspective embraces this interconnectedness and the complexity that it entails [9]. To improve access to medicines and guide its activities, the WHO adopted this perspective in their 2019 roadmap [26].

However, in evaluating access to medicines this complex system needs to be unpacked in order to provide an understanding of where barriers and facilitators occur and how this affects other components and processes. To facilitate the study of determinants of access to medicines from a health system perspective, **Chapter 3.2** introduced a framework that aids in unpacking key pharmaceutical processes, while still recognizing their interconnectedness with other components. Critical health system building blocks were integrated in the pharmaceutical value chain, and further contextualized within the broader national political context. This approach proved worthwhile, enabling us to dissect the complex processes and pathways that hinder or enable access to pediatric oncology medicines in the South African case study in **Chapter 3.3**. At the same time, it should be clear that there is no one-size-fits-all approach to ensuring a well-functioning health system, nor is there a universal framework that accommodates all

contexts [7, 26]. Therefore, the proposed framework offers a basic structure for conducting a health systems analysis of access to medicines, while maintaining flexibility.

In addition, to obtain a full understanding of a complex system, consolidation of different perspectives is required. Hence, mixed-method case studies have been proposed as an important tool in constructing a complete narrative [7]. Indeed, the triangulation of methods, and the data they yield, is believed to enhance the value of research through further positioning of the data and verification of data accuracy [3, 27]. This integration holds significance whether it occurs at the study design, methods, or interpretation and reporting level [27]. The triangulation of quantitative and qualitative data in **Chapter 3.5** exemplifies the value of a mixed-method approach in health systems analyses; for example, the bottlenecks in procurement identified in **Chapter 3.1** were contextualized through stakeholder perspectives gathered in **Chapter 3.3**.

While some contend that a mixed-methods approach mainly benefits from integrating different data types (quantitative and qualitative data) [27], the merit of triangulating qualitative methods only should not be overlooked. Indeed, the mixing of individual interviews and focus group discussions allows for different perspectives that might otherwise go unidentified [28]. This was confirmed in **Chapter 3.4**, where the user perspective was used to confirm the viewpoint of other stakeholders while also providing additional insights related to financial and emotional experiences from caregivers' perspectives.

Taken together, **Chapter 3** demonstrates that – amidst the inherent complexity of the health system – triangulation of different methods and data, in addition to utilizing an analytical framework that embraces the complexity of national pharmaceutical systems, is instrumental in unpacking the intricacies of the health system.

Interventional complexity – reviewing complex interventions

The fourth layer of complexity encountered in the monitoring and evaluation of access to medicines pertains to the complexity of interventions, particularly that of pharmaceutical policies. However, this complexity cannot be regarded in isolation from where the intervention takes place; some argue that the complexity is actually a property of the system in which an intervention is implemented rather than of the intervention itself [6, 29], while others consider it to be a feature of both the system and the intervention [11]. In both definitions, the impact of pharmaceutical pricing policies is – at least partially – determined by the characteristics of a multi-component health system that behaves non-linearly to change.

In reviewing complex interventions, even defining the intervention itself may be challenging, given the absence of a standardized definition and that it may be implemented in varying settings, and along with other policies [9, 29]. Similarly, the study designs and outcome measures used to assess and measure these interventions may vary considerably across studies,

as observed in **Chapter 4.3**. Using overly restrictive selection criteria to manage this heterogeneity could yield a very limited number of eligible studies, possibly even resulting in no studies meeting the selection criteria [9]. Although we established broad definitions for pharmaceutical pricing policies and eligible settings in **Chapter 4**, our selection criteria required studies with robust experimental or observational designs. This stringent criterium may explain the limited number of studies included in **Chapter 4.1** and, in some instances, may have resulted in empty reviews within the wider review of ten pharmaceutical pricing policies [30].

Beyond working from an assumption of expected heterogeneity in establishing selection criteria, account should also be taken in the analysis and synthesis of heterogeneous evidence; due to the variability in data, pooling may not be feasible [9]. Instead, employing a structured, narrative synthesis offers greater flexibility to explain differences in outcomes in a way that produces meaningful results for decision-makers [8, 9]. Critical therein is contextualization; nuanced variations in the intervention, implementation strategy or setting are not merely footnotes to the story but key to understanding the process and outcomes [7]. The central role of contextual information in health policy analysis was demonstrated in **Chapter 4.2**, in which each of five studies reporting on the Chinese 'zero mark-up drug policy' (ZMDP) contributed different explanations for the policy's smaller-than-expected effect.

However, even when yielding few or no eligible studies, empty reviews of complex interventions can be valuable. Despite inconclusive findings regarding the effects of an intervention, the body of evidence assessed for potential inclusion can offer important insights, exposing research gaps and revealing the state of the evidence [31]. Neglecting to share the valuable observations and experiences gained from the assessment of retrieved records for inclusion with the research community would squander the considerable time and effort invested in this process [31]. That valuable knowledge can indeed be distilled from (almost) empty reviews is showcased in **Chapter 4.3**: in an effort to guide future analyses and systematic reviews on this topic, we shared our observations on the study designs used in pharmaceutical pricing policy analyses and recurrent sources of bias, even if studies did not meet all eligibility criteria for inclusion in the systematic review. The importance of including a control group and pre-intervention data were identified as key recommendations for researchers of policy interventions, as well as the need for providing detailed contextual information on the specifics and implementation of policies.

In summary, in employing different monitoring and evaluation methods in access to medicines, we encountered a myriad of conceptual, methodological, systemic and interventional complexities that determine the research landscape. Whilst these inherent complexities pose significant challenges, embracing them also opens up new pathways for research and evidence generation.

A data gap complicates all monitoring and evaluation efforts

Data form the backbone of all monitoring and evaluation efforts, playing an indirect yet pivotal role in policy decisions [32]. The availability of (reliable) data is thus fundamental. However, a considerable information gap was identified as a transcendent challenge in our efforts to advance access to medicines research, adding a further layer of complexity. Although literature uses terminology interchangeably to describe informational gaps and a clear classification for missing information is lacking [33, 34], it is imperative to distinguish data deficits from data voids. In the former, some data exist but they are insufficient or inadequate to address a research question; in the latter, there is an absolute gap and there are no data available. This section explores the information gaps that shaped our research activities, in which we will differentiate between the nature of missing information, and the reasons behind their occurrence.

Gaps in core data

Data on the availability and prices of essential medicines are the core inputs for measuring access to medicines, usually collected in health care facility surveys of medicines [14, 15]. However, in adapting SGD indicator 3.b.3 to benefit children as well, a substantial gap in these data regarding age-appropriate medicines was observed in both scientific literature and other data sources. This gap, described in **Chapter 2.1**, manifested in three ways: 1) medicine surveys targeting the general population omitted most of the medicines relevant for children, 2) there was a lack of surveys specifically dedicated to age-appropriate medicines, and 3) those surveys that were dedicated to children were often limited in their scope or failed to consider age-appropriate formulations. This large data deficiency necessitated us to pool data from ten historical datasets in **Chapter 2.3**, to ensure sufficient data to conduct meaning sensitivity analyses with.

The significant gap in availability and pricing data for age-appropriate medicines can be attributed to the shortcomings of existing survey tools in addressing the particular needs of children. However, this explanation only partially accounts for the data gap, which exists not just for age-appropriate medicines but extends to the general population as well. This widespread deficiency was noted even before initiation of this dissertation's research [35], but little progress has been made despite repeated calls to address it [3, 36-38]. In fact, up until this point no medicine surveys have been conducted specifically to report on SDG indicator 3.b.3. Because the SDG indicators rely heavily on the availability of data [39], this data void means that SDG indicator 3.b.3 is categorized as a tier II indicator within the Global Indicator Framework. This classification signifies that the "indicator is conceptually clear, has an internationally established methodology and standards are available, but data are not regularly produced by countries" [40].

The lack of efforts to collect the data needed for reporting on SDG 3.b.3 is likely due to the laborious nature of medicine surveys. It is widely acknowledged that conducting medicine surveys demands significant resources and time, which may particularly affect the ability of low- and middle-income countries (LMIC) to prioritize these surveys and allocate adequate budgets to [41]. As a result, these surveys have in recent years predominantly been undertaken by academic research groups and non-governmental organizations (NGOs) [42-46]. To mitigate the time and costs associated with undertaking medicine surveys and streamline data collection for SDG indicator 3.b.3 in particular, the WHO developed the Essential Medicines and Health Products Price and Availability Monitoring Mobile Application (EMP MedMon) in 2016 [47]. Similar mobile applications for collecting availability and pricing data have already demonstrated their utility [16, 41]. However, despite the potential of the EMP MedMon application, it is still pending official launch.

To overcome the data void for SDG indicator 3.b.3, the WHO has been exploring the use of more routine data collection systems to feed into this indicator [47]. This is in line with the expert panel's recommendation that indicators should build on existing data and rely on established data sources (see 'Conceptual complexity') [3], a criterion that is currently not met. The WHO identified medicine surveys recorded in the HAI database and using the WHO/HAI methodology as a potential source of data [48], as well as Service Availability and Readiness Assessment (SARA) surveys [14, 49]. Yet, the HAI database has not been regularly updated, including no medicine surveys conducted in full accordance with the WHO/HAI methodology, and only eight surveys with adaptations to the methodology, since 2015. It is unclear to which extent SARA surveys have been conducted in recent years. Nevertheless, despite the availability of potential data sources, access to medicines has not been reported on since inception of the SDGs [50-57].

As an alternative to these existing data collection surveys, the possibilities offered by sentinel-site based monitoring are worth considering. This monitoring approach, based on a number of selected health facilities that collect and report data, has been used previously in health surveillance [58] and pharmacovigilance [59], but remains unexplored as an option in monitoring access to medicines. Despite potential limitations in data, this approach offers a potential solution for the laborious and resource-intensive nature of existing medicine surveys and presents an opportunity for more frequent data collection. In addition to this, this approach could possibly mobilize healthcare professionals, especially pharmacists, as data collectors.

Besides opportunities for innovative data collection systems, existing data collected by academic research groups and NGOs remain an untapped resource and provide an important opportunity to start reporting on SDG indicator 3.b.3 immediately. Critical availability and pricing data are being collected in some of the poorest countries worldwide [42-45], but the UN has yet to leverage these data effectively. More widespread utilization of the core baskets of

medicines as defined for the indicator in surveys conducted by research groups could facilitate the reuse of their data for this indicator and enhance reporting on this particular target. However, even partial datasets hold the potential to start reporting on access to medicines [3, 14]. Exploring the application of data science tools such as web scraping [60], could aid in leveraging existing data, provided ethical and methodological concerns are addressed.

As long as no consistent efforts are being made to collect the required availability and pricing data on essential medicines and not all available data sources are being effectively leveraged, indicator 3.b.3 will remain a tier II indicator and risks removal and replacement in the 2025 planned review of indicators [61]. Despite the technical limitations of the indicator, an immediate removal of this indicator would be detrimental and cause further delays in achieving the important target of access to medicines for all; not only would development of a replacement indicator require substantial time, it would also impede any ongoing efforts to collect the required data in the meantime. Given that development of the present indicator required more than three years (and adapting it for children another two years), it would be highly unlikely that any data – whether for this indicator or its replacement – will have been collected by 2030. With that, the global community is at risk of yet again failing to report on this vital aspect. As not to jeopardize sustainable development efforts for access to medicines [39], SDG indicator 3.b.3 should be retained and data collection efforts intensified until a replacement has been developed and extensively validated.

Gaps in supportive data

In addition to the core input variables on which monitoring and evaluating access to medicines relies, a range of supportive input parameters and associated data sources are needed to conduct effective analyses. Besides methodological complexities associated with integrating multiple sources of data, more fundamental complications were encountered in gathering the required data. The underlying causes for these supportive data gaps were diverse and manifested differently across topics.

In adapting SGD indicator 3.b.3 to accommodate the needs of children, we encountered several gaps: not only were we unable to obtain National Poverty Line (NPL) values – required to compute affordability – for all countries in our dataset (**Chapter 2.3**), we were also confronted with gaps in basic tools such as standardized age-appropriate tracer sets, child-appropriate DDDs and international weight-for-age charts applicable to children aged 10-12 years (**Chapter 2.4**). Although we managed to navigate these gaps and address some by introducing two age-appropriate core sets and the NUNT, the unresolved lack of data on utilization of medicines in primary care by neonates led to their exclusion from our studies (**Chapter 2.4**).

The gaps described here constitute a population gap; a certain population – children in this instance – are not adequately represented or under-researched [62]. This fits with the observation that this group has historically been subject to neglect across various

pharmaceutical domains, and there is still much catching up to do (see **Chapter 1**). However, part of this gap may be borne out of a lack of documented information, rather than out of a lack of information per se [34]; primary care physicians, neonatologists or other clinicians may well be aware of medicine use in neonates in primary care, but this has not been documented in research. In other instances, the research and policy-making community may have been unaware of some of these gaps and constitute previously unidentified gaps [33]. Simply identifying and mapping these research gaps is valuable and could inform effective research prioritization [33, 34].

In other cases, the required data may exist but prove inaccessible for research purposes. In the study of alignment of pharmaceutical processes in the South African case study in **Chapter 3.1**, national clinical guidelines on childhood cancer could not be accessed and necessitated the use of a regional guideline instead. Although this lack of specificity did likely not affect the representativeness of the outcomes, this issue might have been avoided. Similarly, ambiguous reimbursement lists from private sector medical insurance schemes impeded more conclusive findings.

These documents were inaccessible despite recognition of the pivotal role of such documents in studying operationalization of policies in health systems, which is considered key in improving access to medicines [63]. Beyond their research utility, public availability of standards and commitments is crucial for ensuring government institutions' and other stakeholders' transparency and accountability. This too contributes to improved access to medicines [64]. Although South Africa is among a few countries with transparency in medicine prices (**Chapter 2.1**), further transparency could benefit research endeavors, bolster public trust and improve access to medicines.

In a methodological review of pharmaceutical pricing policy analyses in **Chapter 4.3**, findings revealed that studies were associated with a high risk of bias due to oversight of potential confounding factors in their models. Although we were unable to pinpoint the root causes of these omissions in most studies, the authors of several studies pointed to the unavailability of crucial data as the main impediment. These data gaps might be attributed to inadequacies in data sources used for pricing policy analyses, which fail to record supportive data on potential confounders. This would also suggest that in other cases, the absence of core or supportive data could have rendered the intended study design unfeasible, compelling researchers to compromise on their preferred approach or forego studying the policy altogether.

Research gaps

The gaps observed in core and supportive data within access to medicines research efforts have – in some instances – compromised the certainty and quality of the evidence, thereby contributing to research gaps [34]. These gaps – sometimes referred to as an evidence or knowledge gap – refer to missing information that could otherwise potentially address a key

question of decision-makers [33]. Analogously to data gaps, research gaps may refer to a deficient evidence base that is inadequate to draw conclusions from [62], or desired research findings do not exist at all, constituting a knowledge void [65]. **Chapter 4.1** and **Chapter 4.2** showcase instances where our conclusions remained cautious due to limited and inadequate evidence. Drawn conclusions primarily regarded pricing outcomes, and evidence on the availability or affordability of medicines was completely lacking, as well as evidence from LMIC contexts. Notably, contextual information was very limited in all of the included studies, despite it being central to the success or failure of complex interventions [7]. Absolute voids were observed for cost-plus pricing policies, price discounting policies for single source pharmaceuticals as well as tax exemptions or reductions in **Chapter 4.3**; our search strategy failed to yield any eligible – or even ineligible – studies on these policies, leaving an extensive knowledge void within this domains.

Considering the information gaps collectively, not all data necessary for effective monitoring and evaluation of access to medicines is currently being collected or accessible, contributing to significant knowledge gaps within access to medicines. Those data that are collected are not always leveraged to the full extent in decision-making. All three of these components – data collection, access and use – are required for data equity [66], which in turn could help in bridging the access gap between high-income economies and LMIC. The identification and mapping of these information gaps is critical in informing effective prioritization of future research efforts [33, 34].

Bridging the gap between evidence-generation and policy-making

Contingent upon the successful navigation of the complexities and information gaps discussed previously, scientific evidence holds immense potential in shaping health policy-making and being translated into effective, efficient and equitable interventions [67]. Not only can monitoring and evaluation of access to medicines inform the policy agenda and answer concrete policy questions, it also exposes policy-makers to a broader scope of concepts and policy options than otherwise available to them, and can offer the perspectives and preferences of those not routinely included in the decision-making process [68, 69]. In addition to providing a well-informed foundation for policies, scientific evidence can also make connections between seemingly separate factors and provides explanations for why some policies succeed and others fail [69].

The concept of evidence guiding decision-making is rooted in 'evidence-based medicine' [70], which has since moved beyond clinical care to include health systems and policies. However, the idea that policy decisions should rely on the best possible evidence generates tension within

health policy-making, for the concept presumes the availability of the required evidence [70]. This presumption is challenged in LMIC, where the evidence gap has been well-documented [71]. Moreover, scientific evidence is not the only asset that informs the policy process. A variety of other sources of knowledge informs policy, such as histories and experiential knowledge, beliefs, values, skills, legislation, politics, and protocols [72, 73]. This understanding is embodied within the concept of 'evidence-informed decision-making', which emphasizes the role of various sources of knowledge in policy-making and recognizes that research findings often need to compete with these other sources [67]. As an example, the WHO considers the required human and financial resources, acceptability and feasibility of pharmaceutical pricing interventions – besides scientific evidence on their intended and unintended effects – using Evidence to Decision (EtD) frameworks [74, 75]. With that, evidence-informed decision-making is now considered the standard [67].

In spite of this, literature suggests that research evidence uptake in policy-making is suboptimal [76-78], including in the domain of access to medicines for children [79]. This translation deficit presents a multifactorial issue. On the one hand, research topics chosen by researchers tend to be of academic interest but of limited practical relevance to decision-makers [71, 80, 81]. This mismatch may be attributed to the tendency of researchers to select topics and methods based on data availability. Ironically, the availability of data needed for policy evaluation may be increased through collaborative engagement of policy-makers and researchers, by means of early planning of policy evaluations in policy development (as also suggested in **Chapter 4.1** and **Chapter 4.2**). Besides research topics of limited interest to policy-makers, research timelines often do not align with the more immediate needs of policy-makers, and dissemination of research findings is primarily among other researchers [71, 81]. Policy-makers, on the other hand, lack training in and understanding of the nuances and limitations of research, hindering their ability to effectively commission, interpret and utilize research findings [81]. A paradox thus exists where policy-makers encounter knowledge gaps in certain areas, while simultaneously facing a surplus of irrelevant scientific literature that, while informative, does not address their needs [71]. In addressing these barriers, research networks such as the Dutch Research Network HTA (Health Technology Assessment) have emerged as a successful model for research-policy interaction [82], providing a platform for local stakeholders to collaboratively set research agendas, discuss, and disseminate research findings.

In addition to policy-makers, healthcare providers constitute another critical yet often overlooked group of health research users that have a stake in which research activities are prioritized on research agendas [83, 84]. A subgroup of healthcare providers that merits special consideration in discussions on access to medicines is pharmacists. Although notoriously absent from decision-making processes [85, 86], they could play a crucial role in informing the research agenda for access to medicines [86, 87]. The significance of healthcare providers extends beyond

problem signaling and health advocacy; they also possess a unique perspective on policy interventions that are most responsive and sensitive to their concerns [88, 89].

In discussions on research agendas for global health and access to medicines, the perverse power dynamics that currently dictate which topics are put on the research agendas must be acknowledged. Described as neo-colonialism, there are issues of dependency because funding decisions and subsequent research priorities are dictated by external actors and institutions from high-income and historically privileged countries [90]. This can result in misaligned agendas that do not address local needs, as well as exploitation of LMIC partners in evidence generation [91, 92]. In pursuit of decolonizing global health research, authorship and target audiences must also be considered: the standpoint from which publications are written, who they should benefit, and to whom they are – and should be – disseminated affect the message and impact of the research [93]. It is evident that the studies in **Chapter 3** of this dissertation are also implied in this, in which I, as researcher from a high-income country, acknowledge my privileged position and part in an inequitable system that perpetuates them. While recognizing the limits of what I can understand and contribute as an 'outsider' to a local issue, being an 'outsider' may also have some advantages: an unbiased perspective on the unfamiliar, and an ability to persuade interviewees fuller explanations than they might have given an 'insider' [94]. By combining the 'outsider' perspective with that of an 'insider' – in this case co-author FS – a rich and comprehensive understanding of the access determinants at play has been achieved [94]. Additionally, the findings of these studies were disseminated both locally and internationally [93], ensuring that they could benefit both local policy dialogue as well as international research efforts.

To resolve the evidence translation deficit in access to medicines, we must prioritize those research activities that have the highest potential to inform policy-making. Identifying these activities requires active engagement of all relevant stakeholders, particularly local policy-makers and healthcare professionals, and rectification of the prevailing power dynamics that currently influence research prioritization.

Key recommendations

To bridge the current gap between evidence-generation and policy-making in access to medicines, the following three key areas for improvement were identified in this dissertation:

Actionable evidence for decision-makers

To ensure that monitoring and evaluation activities yield actionable evidence for policy-makers, it must be of good quality and presented in a format that is comprehensible to policy-makers, and not solely intended for other researchers. Feasible and relevant indicators are pivotal in this regard. While this dissertation has made notable progress therein, further refinements are needed to ensure that developed tools are validated and ready-to-use. This should encompass finding innovative approaches to measure affordability. Beyond that, the systemic and

interventional complexity inherent to access to medicines should be embraced, through the employment of methods that yield comprehensive, integrated and context-specific evidence in access to medicines. Additionally, systematic reviews are indispensable tools in aiding policy-makers to identify, appraise and synthesize at times contradictory research findings.

Addressing data and knowledge gaps

Addressing persistent knowledge gaps in access to medicines, particularly concerning LMIC and vulnerable populations such as children, is necessary to ensure the availability of the evidence needed for policy-making. Identifying research gaps plays a critical role therein, to which this dissertation has contributed. However, on a more fundamental level, gaps in core or supportive data that preclude monitoring and evaluation activities from taking place must be addressed. This should involve making data accessible for research purposes by both public and private parties and leveraging all available data sources, even those that are suboptimal. Most urgently, medicine availability and pricing data must be collected, for both the general population and children, to enable performance monitoring through SDG indicator 3.b.3. until 2030.

Evidence-generation driven by information needs

To ensure that monitoring and evaluation efforts generate relevant evidence for policy-makers, it is crucial to align research activities with the specific information needs of decision-makers as well as prioritize those monitoring and evaluation activities that are most likely to inform local policy-making. Proactive engagement between researchers, policy-makers and health professionals is pivotal in setting the research agenda. Vice versa, engagement with researchers and healthcare professionals in policy formulation by planning for policy evaluations is necessary to facilitate the collection of pertinent data.

Conclusion

Amidst the inherent complexities of monitoring and evaluating access to medicines and the information gaps that define the current evidence landscape, this dissertation nonetheless shows the potential for innovation in a field that had lost some of its momentum. Forged paths include the enhancement of existing methodological instruments, the introduction of novel approaches in the monitoring and evaluation of health systems, and the expansion of their scope to typically understudied populations and health conditions. While these advancements embody important mechanisms in bridging the persistent evidence-to-policy gap, further concerted efforts from national and international researchers, policy-makers and healthcare professionals are needed to maintain access to medicines as a priority on the research and policy agendas and ultimately achieve equitable access for all.

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CHAPTER 6

Summaries


Bivatracin
BETADINE
Kaprofen
KETOLAC

CHAPTER 6.1

Summary

Significant disparities in access to medicines persist, with an estimated two billion people still lacking regular access to essential medicines. To guide effective pharmaceutical policy development for improved access to medicines, evidence from monitoring and evaluation activities is key. However, recent years have only seen minimal innovation in access to medicines research, as well as limited evidence generation on this topic. To bridge this gap between evidence-generation and policy-making, this thesis aimed to explore advancements to three key evidence-generation mechanisms for formulating and evaluating pharmaceutical policies: performance monitoring, health systems analysis and pharmaceutical policy analysis. It intended to do so by reviewing and identifying gaps in the evidence landscape and methodologies used, by enhancing existing methodological instruments, by introducing novel approaches in the monitoring and evaluation of access to medicines within health systems, and by expanding their scope to typically understudied populations and diseases.

Monitoring access to medicines for children

Chapter 2 focused on monitoring performance in access to medicines for children by modifying Sustainable Development Goal (SDG) indicator 3.b.3, the most important performance monitoring tool for measuring access at this time.

In **Chapter 2.1**, we explored the large gap in performance data on child-appropriate medicines, required for monitoring of access. To this end, we examined data on the availability and pricing of child- appropriate medicines across 50 cross-sectional medicine surveys. This revealed that child-appropriate medicines needed for the management of nine out of 12 priority diseases affecting children were infrequently surveyed or not at all. A similar data deficit on age-appropriate medicines was detectable in the broader scientific literature. We also noted that existing instruments for collecting data on the availability or prices of medicines were limited in their ability to generate the required data for children. We identified four priorities for improved monitoring of access to child medicines as part of the sustainable development goal agenda for 2030: (I) dedicated child medicine surveys are needed on availability and prices of child-appropriate medicines; (II) standardized survey instruments should include age-appropriate medicines and dosages; (III) health facility service readiness survey tools should include the collection of data on the price of child-appropriate medicines in addition to the availability of medicines; and (IV) SDG indicator 3.b.3 should be modified to enable the monitoring of access to medicines for children.

In **Chapter 2.2**, we presented a complementary indicator for children based on the existing SDG indicator 3.b.3, enabling the monitoring of access to child-appropriate medicines. Adaptations to the indicator included the selection of two core sets of child-appropriate medicines, for young children aged 1 to 59 months and for school-aged children aged 5 to 12 years. With the objective to enable calculation of affordability of medicines for children, the number of units needed for treatment (NUNT) was created. We provided proof-of concept of the adapted

methodology by successfully applying it to three historical datasets: Burundi (2013), China (2012) and Haiti (2011). However, further proposed validation steps included sensitivity analyses to help determine the robustness of the methodology and the novel measures introduced, as well as expert validation of the two core sets of child-appropriate medicines.

Proof of the robustness of the child-specific SDG indicator 3.b.3 methodology was provided in **Chapter 2.3**. Data on availability and prices of child-appropriate medicines from ten historical datasets were combined to create two datasets for analysis: dataset 1, in which medicines were selected at random, and dataset 2 in which preference was given to available medicines, to better capture affordability of medicines. A base case scenario and univariate sensitivity analyses were performed to test critical components of the methodology, including the new variable NUNT and its lower and upper limits, various disease burden (DB) weighting approaches, and several National Poverty Line (NPL) values. Different NUNT scenarios led to minor variations in both datasets in mean facility scores of <1%, and mild variation (<5%) at a more critical value of the NPL. Different approaches for weighting for DB induced considerable changes of 9.0% and 11.2%, respectively. Additional analyses were run on a continuously smaller basket of medicines to explore the minimum number of medicines required for analysis. Stable outcomes with <5% change in mean facility score were observed if the medicine basket included at least 12 medicines. For smaller baskets, scores increased more rapidly with a widening range. Through these sensitivity analyses, this study confirmed that the proposed adaptations to make SDG indicator 3.b.3 appropriate for children were robust, but general concerns remained about the weighting of medicines for DB and the NPL.

The development of the two tracer sets of child-appropriate medicines and their validation was described in **Chapter 2.4**. Firstly, priority diseases affecting children were selected based on global burden of disease and linked to active ingredients of first-choice according to treatment guidelines and the World Health Organization (WHO) model list of essential medicines for children (EMLc). To ensure clinical relevance, the Delphi technique was employed to identify areas of (dis)agreement among clinical pediatric experts. During two consultation rounds, experts were invited to indicate (dis)agreement. Five experts per each age group were largely in agreement with initial selections, but various therapeutic alternatives were suggested for addition. A second consultation round with five experts did not lead to major adjustments. The final sets included 26 treatment options at active ingredient level for both groups. Specific age-appropriate formulations of selected active ingredients were selected from the WHO EMLc 2023. These two globally representative tracer sets of medicines for children can be used in conjunction with SDG indicator 3.b.3 or other methodologies for monitoring access.

Collectively, this chapter introduced a modified indicator for measuring access to medicines for children, provided proof-of-concept and evidence of its rigor. Despite remaining concerns about some of the unchanged parameters of the methodology, the child-specific indicator could be a valuable addition to the official Global Indicator Framework and aid countries in the monitoring of accessibility to pediatric medicines. However, this chapter also reveals that

deficiencies in data and data collection tools need to be addressed urgently to ensure monitoring of access to child-appropriate medicines as part of the SDG agenda for 2030.

A health systems analysis of access to pediatric oncology medicines – the South African case study

Chapter 3 focused on novel approaches in health systems analyses of access to medicines. These approaches were applied to a case study of access to childhood oncology medicines in South Africa, with the objective to identify sources of access constraint to pediatric cancer medicines.

The alignment of several linked pharmaceutical processes – rather than in isolation from related processes – was studied in **Chapter 3.1**, given that the effectiveness of a health system in providing access to medicines is in part determined by the alignment of multiple pharmaceutical processes. For South Africa's public health sector these included the registration of medicines, their selection on a National Essential Medicines List (NEML) and their subsequent procurement through national tenders. Registration, formulary selection and reimbursement were identified as key processes in the private sector. Within this context, a selection of priority chemotherapeutics, anti-emetics and analgesics in the treatment of five prevalent childhood cancers in South Africa was compared to those listed on 1) the World Health Organization Essential Medicines List for Children (WHO EMLc) 2021, 2) the registered health products database of South Africa, 3) the relevant South African NEMLs, 4) bid packs and awarded tenders for oncology medicines for 2020 and 2022, and 5) oncology formularies from the leading Independent Clinical Oncology Network (ICON) and two private sector medical aid schemes. We found full alignment for 25 priority chemotherapeutics for children between the NEML, the products registered in South Africa and those included on tender. However, due to unsuccessful procurement, access to seven essential chemotherapeutics for children was potentially constrained in the public sector. An exploratory assessment of private sector formularies showed recurrent gaps in formularies and possibly limited insurance coverage.

This study of core pharmaceutical processes was complemented with a more comprehensive analysis of perceived determinants of access to medicines from a health systems perspective. Although access to medicines is shaped by various interacting processes within a health system, a suitable analytical framework for such an analysis was lacking. To this end, a novel analytical framework facilitating the identification and structuring of barriers and enablers in access was proposed in **Chapter 3.2**. Identified from existing frameworks in the field, this framework incorporated eight core (pharmaceutical) functional processes: I) medicine regulation, III) financing and pricing, II) selection, IV) reimbursement, V) supply and procurement, VI) healthcare delivery, VII) dispensing and VIII) use. National contextual components included

policy and legislation and monitoring and surveillance. To emphasize the interlinkage of processes, the proposed framework was structured as a pharmaceutical value chain.

This framework was applied to the case study of childhood cancer medicines in South Africa in **Chapter 3.3**, where we sought to identify drivers of access from the perspective of different stakeholders in the pharmaceutical value chain. Qualitative semi-structured interviews were conducted with 29 key health system stakeholders, including policy makers and regulators, medical insurance scheme informants, medicine suppliers, healthcare providers and civil society stakeholders. Barriers and facilitators were identified across all components of the pharmaceutical value chain. Key barriers included 1) a lack of political commitment to childhood cancers, 2) the lack of registration of new medicines and discontinuation of essential chemotherapeutics, 3) incomplete insurance coverage for childhood cancers, 4) stock-outs of essential medicines, 5) the inability to access care including travel to healthcare facilities, and 6) low awareness on childhood cancers among primary healthcare workers. This analysis confirmed that the proposed framework could facilitate systematic evaluation of access in a country, and provided context-specific evidence of access constraints within the broader context of the healthcare sector.

Besides the perspectives of professional stakeholders in the pharmaceutical value chain, the perspectives and experiences of caregivers of children with cancer were presented in **Chapter 3.4**. Specifically, this chapter explored the treatment-related, financial and psychological experiences of caregivers during cancer treatment of their children in South Africa's public and private sectors. Three focus groups were conducted with caregivers of children undergoing cancer treatment in the public healthcare sector, and a fourth small focus group with two parents in the private sector was conducted online. Of the 20 public sector caregivers, many expressed frustration at the number of visits to primary healthcare clinics before being referred. Caregivers also had difficulties coping with and accepting the diagnosis, alongside managing continued care for the child and other children at home. Support received by family and community members varied. Financial strain was an important concern for all caregivers. The two private sector parents indicated greater levels of support and no financial hardship, but expressed similar levels of emotional stress. These caregiver experiences allowed us to confirm barriers previously identified by professional stakeholders. Beyond that, it also shed more light on the emotional and psychological impact of childhood cancer on caregivers and provided a more nuanced insight into the extent of financial strain experienced by caregivers.

The appropriateness of South Africa's National Cancer Strategic Framework in addressing barriers to childhood cancer medicines identified in previous chapters was examined in **Chapter 3.5**. Identified barriers were compared to the limitations and interventions as discussed in the current strategic framework, to identify areas for strengthening. We identified three recurrent gaps in the strategic framework in relation to childhood cancers, representing a range of issues throughout the pharmaceutical value chain: 1) childhood cancers are neglected compared to adult cancers, in both the policy arena and the organization of healthcare services, 2) there are

particular challenges for childhood cancers due to their rarity, thus requiring targeted interventions (e.g. regulatory incentives, tailored pricing solutions and customized evidence requirements by decision-making bodies), and 3) children must be accompanied by a caregiver during treatment, causing several social and financial issues for their families. This analysis underscored that the areas in which childhood cancers are different from adult cancers should be acknowledged and given particular consideration in national policies, as not to neglect the needs of a vulnerable population.

Altogether, this chapter described a comprehensive analysis of access to childhood cancer medicines within the South African context, employing a range of complementary approaches that could aid the systematic evaluation of access across other countries, disease areas and populations. The approaches used acknowledge that access to medicines is shaped by various interacting processes within a health system, and that each contributes a distinct piece of the complex puzzle. The improved understanding of drivers of access and shortcomings of existing policy documents in the South African context could aid the country in their objective of reducing the burden of cancer.

The evidence landscape for pharmaceutical pricing policies

Chapter 4 examined the pharmaceutical policy analysis landscape through the lens of pharmaceutical pricing policies. This work was part of a wider systematic review in which ten pharmaceutical pricing policies were systematically evaluated for their effectiveness in managing the prices of pharmaceutical products.

Chapter 4.1 presented the evidence on policies promoting price transparency, as an important approach to control medicine prices and achieve better access to medicines. Policies promoting price transparency were compared against other interventions or a counterfactual. Eligible study designs included randomized trials, and non-randomized or quasi-experimental studies such as interrupted time-series, repeated measures, and controlled before-after studies. The quality of the evidence was assessed using the GRADE methodology. A total of 32011 records were retrieved, of which two studies were eligible for inclusion. The available evidence suggested that – although based on evidence from a single study – public disclosure of medicine prices may be effective in reducing prices of medicines short-term, with benefits possibly sustained long-term. Evidence on the impact of a cost-feedback approach to prescribers was inconclusive. No evidence was found for impact on the outcomes volume, availability or affordability.

Existing literature on policies regulating or removing mark-ups in the pharmaceutical supply and distribution chain was reviewed in **Chapter 4.2**. Following a similar methodology as the previous chapter, seven of the 32011 records retrieved were eligible for inclusion. The limited body of evidence cautiously suggested that policies regulating mark-ups may be effective in

reducing medicine prices and pharmaceutical expenditures. However, the design of mark-up regulations was a critical factor in their potential success.

In these systematic review of policies promoting price transparency, policies regulating mark-ups and eight other pharmaceutical pricing policies, a large number of studies had been excluded during the review process due to ineligible study designs. Additionally, methodological shortcomings had been observed in many of the studies that did meet the eligibility criteria. In **Chapter 4.3**, the common weaknesses in studies of pharmaceutical pricing policies were therefore identified, and methodologies used were critically reviewed for their value in providing robust evidence. All 56 studies that had been included in the wider systematic review were selected, as well as those that had been excluded from the review due to ineligible study designs. The latter group consisted of 101 records. Risk of bias was assessed and specific study design issues were recorded to identify recurrent methodological issues. Sixty-one percent of studies with a study design eligible for the systematic review presented with a high risk of bias in at least one domain. Potential interference of co-interventions was a source of possible bias in 53% of interrupted time series studies. Failing to consider potential confounders was the primary cause for potential bias in difference-in-differences, regression, and panel data analyses. In 101 studies with a study design not eligible for the review, 32% were uncontrolled before-after studies and 23% were studies without pre-intervention data.

Taken together, this chapter highlighted the gaps in evidence on pharmaceutical pricing policies, particularly on outcomes such as volume, availability or affordability, and on their effectiveness in low- and middle-income countries. The frequently encountered methodological issues – some of which may be resolved during the design of a study – provide opportunities for an increased volume of evidence that could be effectively used for policy-making in the future.

Recommendations and conclusion

Scientific evidence holds immense potential in shaping health policy-making and being translated into effective, efficient and equitable interventions. However, in conducting evaluations of access to medicines, we encountered a myriad of complexities that are inherent to this field of study. Besides the different conceptual, methodological systemic and interventional complexities, the absence of core and supportive data further impeded evidence generation. Of the research evidence that was generated upon successful navigation of the complexities and information gaps, uptake in policy-making was suboptimal and constituted an evidence-to-policy gap in the field of access to medicines. To bridge the gap between evidence-generation and policy-making, the following three key areas for improvement were identified in this dissertation:

Actionable evidence for decision-makers

To ensure that monitoring and evaluation activities yield actionable evidence for policy-makers, it must be of good quality and presented in a format that is comprehensible to policy-makers, and not solely intended for other researchers. Feasible and relevant indicators are pivotal therein, as well as systematic reviews, which are indispensable tools in aiding policy-makers to identify, appraise and synthesize at times contradictory research findings. Further refinements are needed to ensure that developed tools and indicators are validated and ready-to-use. Beyond that, the systemic and interventional complexity inherent to access to medicines should be embraced, by employing methods that yield comprehensive, integrated and context-specific evidence in access to medicines.

Addressing data and knowledge gaps

Addressing persistent knowledge gaps in access to medicines is necessary to ensure the availability of the evidence needed for policy-making. Identifying research gaps plays a critical role therein. On a more fundamental level, gaps in core or supportive data which deter monitoring and evaluation activities from taking place must be addressed. This should involve making data accessible for research purposes by both public and private parties and leveraging all available data sources, even those that are suboptimal. Most urgently, medicine availability and pricing data must be collected for both the general population and children, to enable performance monitoring through SDG indicator 3.b.3. until 2030.

Evidence-generation driven by information needs

To ensure that monitoring and evaluation efforts generate relevant evidence for policy-makers, research activities must be aligned with the information needs of decision-makers, those monitoring and evaluation activities that are most likely to inform local policy-making must be prioritized. Proactive engagement between researchers, policy-makers and health professionals is pivotal in setting the research agenda. Vice versa, engagement with researchers and healthcare professionals in policy formulation by planning for policy evaluations is necessary to facilitate the collection of pertinent data.

Amidst the complexities and information gaps that define the current access to medicines evidence landscape, this dissertation nonetheless showed the potential for innovation in a field that had lost some of its momentum. While these advancements embody important mechanisms in bridging the persistent evidence-to-policy gap, further concerted efforts from national and international researchers, policy-makers and healthcare professionals are needed to maintain access to medicines as a priority on the research and policy agendas and ultimately achieve equitable access for all.


Bivatracin
BETADINE
Kaprofen
KETOLAC

CHAPTER 6.2

Samenvatting

Wereldwijd bestaan nog steeds grote verschillen in de toegankelijkheid van geneesmiddelen; naar schatting hebben twee miljard mensen geen structurele toegang tot essentiële geneesmiddelen. Om de toegang wereldwijd te vergroten is effectief farmaceutisch beleid nodig, waar monitorings- en evaluatiestudies een fundamentele rol in spelen. Echter, in recente jaren is er slechts minimale innovatie geweest in de onderzoeksmethoden die binnen het veld worden toegepast. Ook zijn er weinig studies uitgevoerd naar toegankelijkheid, waardoor bewijsvorming beperkt is gebleven. Dit proefschrift had als doel de kloof tussen bewijsvorming en beleidsontwikkeling te overbruggen. Daartoe richtte het zich op het innoveren van drie belangrijke onderzoeksmechanismen voor de formulering en evaluatie van farmaceutisch beleid: prestatiemeting van toegankelijkheid, analyse van toegang vanuit een systeem-perspectief en evaluatie van farmaceutische beleidsinterventies. Dit werd gedaan door hiaten in het bewijs en gebruikte methodologieën te identificeren en te beoordelen, door bestaande methodologische instrumenten te verbeteren, door nieuwe benaderingen te introduceren in het monitoren en evalueren van toegang tot geneesmiddelen vanuit een systeemperspectief en door hun reikwijdte uit te breiden naar doorgaans weinig bestudeerde patiëntengroepen en aandoeningen.

Monitoren van toegang tot geneesmiddelen voor kinderen

Hoofdstuk 2 richtte zich op prestatiemeting van toegang tot geneesmiddelen voor kinderen. Hierbij werd *Sustainable Development Goal* (SDG) indicator 3.b.3 – op dit moment het belangrijkste instrument voor prestatiemeting van toegankelijkheid – gemodificeerd om de indicator geschikt te maken voor toepassing bij kinderen.

In **Hoofdstuk 2.1** werd het aanzienlijke tekort aan data over beschikbare en betaalbare geneesmiddelen voor kinderen – benodigd voor prestatiemeting en monitoring van toegankelijkheid – in kaart gebracht. Rapportages van vijftig onderzoeken naar toegankelijkheid van geneesmiddelen in geselecteerde zorgfaciliteiten werden beoordeeld op hun inclusie van data over de beschikbaarheid en prijzen van geneesmiddelen voor kinderen. Dit liet zien dat geneesmiddelen die nodig zijn in de behandeling van negen van de in totaal twaalf belangrijkste ziekten die kinderen treffen, zelden of helemaal niet werden onderzocht. Daarnaast werd vastgesteld dat bestaande instrumenten voor het verzamelen van data over de beschikbaarheid of prijzen van geneesmiddelen beperkt waren in hun vermogen om de vereiste gegevens voor kinderen te genereren. We identificeerden vier prioriteiten voor verbeterde monitoring van toegang tot geneesmiddelen voor kinderen, als onderdeel van de ontwikkelingsdoelen voor 2030: (I) er zijn meer onderzoeken nodig naar de beschikbaarheid en prijzen van geneesmiddelen die speciaal op kinderen gericht zijn; (II) gestandaardiseerde onderzoeks-instrumenten moeten geneesmiddelen, toedieningsvormen en doseringen bevatten die voor kinderen geschikt zijn; (III) instrumenten voor het beoordelen van de gereedheid van

zorgfaciliteiten moeten, naast data over beschikbaarheid, ook data verzamelen over de prijzen van geneesmiddelen; en (IV) SDG indicator 3.b.3 dient te worden aangepast om monitoring van toegang tot geneesmiddelen voor kinderen mogelijk te maken.

Hoofdstuk 2.2 introduceerde een aangepaste SDG indicator 3.b.3 voor kinderen waarmee monitoring van toegang tot geneesmiddelen voor kinderen technisch mogelijk werd, ter aanvulling op de bestaande indicator voor de algemene populatie. Aanpassingen aan de indicator omvatten de selectie van twee sets geneesmiddelen die een indicatie geven van toegankelijkheid, waarbij de eerste set middelen voor jonge kinderen met een leeftijd van 1 tot 59 maanden bevat en de tweede medicijnen voor schoolgaande kinderen van 5 tot 12 jaar. Om de berekening van betaalbaarheid van geneesmiddelen voor kinderen mogelijk te maken, werd de nieuwe parameter NUNT, ofwel het aantal benodigde eenheden voor behandeling, gecreëerd. We bewezen de technische haalbaarheid van de aangepaste methodologie door deze met succes toe te passen op historische datasets van drie landen: Burundi (2013), China (2012) en Haïti (2011). Ondanks dit bewijs werden verdere validatiestappen voorgesteld, waaronder gevoeligheidsanalyses om de robuustheid van de methodologie en de nieuw geïntroduceerde parameters te helpen bepalen, evenals expertvalidatie van de twee geneesmiddelsets.

Bewijs van de robuustheid van de aangepaste indicator voor kinderen werd geleverd in **Hoofdstuk 2.3**. Gegevens over de beschikbaarheid en prijzen van geneesmiddelen voor kinderen uit tien historische datasets werden gecombineerd om twee datasets voor analyse te creëren: een eerste dataset waarbij medicijnen willekeurig werden geselecteerd en een tweede waarbij voorkeur werd gegeven aan beschikbare medicijnen, om zo de betaalbaarheid van medicijnen beter te kunnen onderzoeken. Verschillende univariate gevoeligheidsanalyses werden uitgevoerd om kritieke componenten van de methodologie te testen. Zo werden onder andere de nieuwe parameter NUNT, inclusief onder- en bovengrenzen, verschillende benaderingen voor het wegen van ziektelast en verschillende waarden voor de nationale armoedegrens getest. Deze scenario's werden vergeleken met een basisscenario op basis van gemiddelde prestatiescores van zorgfaciliteiten. De verschillende NUNT-scenario's leidden in beide datasets tot minimale variatie in scores van <1%, en milde variatie (<5%) bij een kritischere waarde van de armoedegrens. Alternatieve benaderingen voor het wegen van ziektelast veroorzaakten meer significante variaties, met respectievelijk 9% en 11% verschil tussen de verschillende benaderingen. Een extra analyse werd uitgevoerd op een voortdurend kleiner wordende set geneesmiddelen, om het minimaal aantal benodigde medicijnen voor betrouwbare analyse te verkennen. Stabiele resultaten met minder dan 5% variatie in prestatiescore werden waargenomen wanneer ten minste 12 geneesmiddelen werden meegenomen in de berekening. Bij kleinere aantallen nam de variatie snel toe, met toenemende standaarddeviaties. Gezamenlijk bevestigden deze gevoeligheidsanalyses dat de voorgestelde aanpassingen aan SDG indicator 3.b.3 robuust zijn, maar algemene zorgen bleven bestaan over het wegen van ziektelast en het gebruik van de nationale armoedegrens.

De ontwikkeling van de twee sets met geneesmiddelen voor kinderen en hun validatie werd beschreven in **Hoofdstuk 2.4**. Aanvankelijk werden de belangrijkste ziekten die kinderen treffen geselecteerd op basis van wereldwijde ziektelast. Vervolgens werden deze ziekten gekoppeld aan eerste keus werkzame stoffen op basis van behandelrichtlijnen en de modellijst van essentiële geneesmiddelen voor kinderen (EMLc) van de Wereldgezondheidsorganisatie (WHO). Om klinische relevantie van deze selecties te waarborgen, werd de Delphi-techniek gebruikt om overeenstemming en verdeeldheid onder klinische experts in kaart te brengen. Gedurende twee consultatierondes werd experts gevraagd aan te geven of ze het eens of oneens waren met de door ons geselecteerde werkzame stoffen. De vijf experts per leeftijdsgroep stemden grotendeels in met de initiële selecties in de eerste ronde, maar stelden verschillende therapeutische alternatieven voor als toevoeging aan de sets. Een tweede consultatieronde met vijf experts in totaal leidde niet tot significante aanpassingen. De uiteindelijke sets omvatten elk 26 behandelopties inclusief therapeutische alternatieven. Specifieke formuleringen van deze werkzame stoffen werden vervolgens pragmatisch geselecteerd uit de WHO EMLc van 2023. De twee verkregen sets zijn wereldwijd representatief voor toegang tot geneesmiddelen voor kinderen en kunnen worden gebruikt in combinatie met SDG indicator 3.b.3 of andere methodologieën voor het monitoren van toegang.

In zijn geheel introduceerde dit hoofdstuk een aangepaste indicator voor prestatiemeting van toegang tot geneesmiddelen voor kinderen en leverde het bewijs van zijn robuustheid en waarde. Ondanks blijvende zorgen over sommige onaangepaste parameters in de methodologie, kan deze kind-specifieke indicator een waardevolle toevoeging zijn aan het officiële pakket van indicatoren van de Verenigde Naties en landen helpen bij het monitoren van de toegankelijkheid van geneesmiddelen voor kinderen. Dit hoofdstuk onthulde echter ook urgente datatekorten en beperkingen van bestaande meetinstrumenten, welke dringend moeten worden aangepakt om te waarborgen dat het monitoren van toegang tot geneesmiddelen voor kinderen deel blijft uitmaken van de SDG agenda voor 2030.

Analyse van toegang tot kinderoncologische geneesmiddelen vanuit een systeemperspectief – het voorbeeld van Zuid-Afrika

Hoofdstuk 3 richtte zich op nieuwe benaderingen in de analyse van gezondheidssystemen en hun vermogen toegang tot geneesmiddelen te borgen. Deze benaderingen werden toegepast op kinderoncologische geneesmiddelen in Zuid-Afrika, met als doel oorzaken van beperkte toegang tot deze middelen in kaart te brengen.

Het vermogen van een gezondheidssysteem tot het garanderen van toegang tot geneesmiddelen wordt bepaald door de onderlinge afstemming van meerdere gerelateerde

farmaceutische processen. Deze afstemming werd bestudeerd in **Hoofdstuk 3.1**. Cruciale processen in de publieke gezondheidssector van Zuid-Afrika zijn onder andere de registratie van geneesmiddelen, hun selectie in een nationale lijst van essentiële geneesmiddelen (NEML) en hun daaropvolgende inkoop via nationale aanbestedingen. Registratie, selectie in vergoedingsformularia en positieve vergoedingslijsten werden geïdentificeerd als cruciale mechanismen in de private sector. In deze context werd een selectie van de belangrijkste chemotherapeutica, anti-emetica en analgetica voor de behandeling van vijf veelvoorkomende kinderkankers in Zuid-Afrika vergeleken met de geneesmiddelen vermeld in 1) de WHO EMLc van 2021, 2) de database van geregistreerde gezondheidsproducten van Zuid-Afrika, 3) de Zuid-Afrikaanse NEML, 4) nationale biedingspakketten en toegekende aanbestedingen voor oncologische geneesmiddelen voor 2020 en 2022, en 5) oncologieformularia van het toonaangevende Independent Clinical Oncology Network (ICON) en de positieve vergoedingslijsten van twee zorgverzekeraars in de private sector. Voor 25 belangrijke chemotherapeutica voor kinderen vonden we volledige afstemming tussen de NEML, de in Zuid-Afrika geregistreerde producten en de biedingspakketten. Echter, onsuccesvolle inkoop van zeven essentiële chemotherapeutica werd geïdentificeerd als barrière tot toegang in de publieke sector. Een verkennende beoordeling van formularia in de private sector toonde omvangrijke hiaten en mogelijk beperkte verzekeringsdekking.

Bovenstaande studie werd aangevuld met een uitgebreidere analyse van determinanten van toegang vanuit een gezondheidssysteemperspectief. Hoewel toegang tot geneesmiddelen wordt beïnvloed door de interactie tussen farmaceutische processen en andere componenten in het gezondheidssysteem, ontbrak een geschikt analytisch kader voor een dergelijke kwalitatieve analyse. Daartoe werd in **Hoofdstuk 3.2** een aangepast analytisch kader voorgesteld om de identificatie en structurering van determinanten in de toegang te vergemakkelijken. Op basis van bestaande raamwerken en structuren werden acht functionele kernprocessen geïdentificeerd: I) medicijnregulatie, III) financiering en prijsstelling, II) selectie, IV) vergoeding, V) inkoop en distributie, VI) levering van zorg, VII) verstrekking van geneesmiddelen en VIII) gebruik. Contextuele componenten op nationaal niveau omvatten wetgeving en beleid, en gezondheidsinformatiesystemen. Om de onderlinge samenhang tussen deze processen te benadrukken, werd het voorgestelde kader als een farmaceutische waardeketen geordend.

Dit analytische kader werd toegepast op het voorbeeld van toegang tot kinderoncologische geneesmiddelen in Zuid-Afrika in **Hoofdstuk 3.3**, waarbij determinanten van toegang werden geïdentificeerd vanuit het perspectief van verschillende belanghebbenden in de farmaceutische waardeketen. Semigestructureerde interviews werden gehouden met 29 belanghebbenden in het gezondheidssysteem, waaronder beleidsmakers en toezichthouders, informanten van medische verzekeraars, geneesmiddelleveranciers, zorgprofessionals en maatschappelijke organisaties. Barrières en bevorderende factoren werden geïdentificeerd in alle componenten van de farmaceutische waardeketen. Belangrijke barrières in toegang tot kinderoncologische zorg waren onder meer 1) een gebrek aan politieke prioriteit, 2) het ontbreken van registratie

voor nieuwe geneesmiddelen terwijl essentiële chemotherapeutica worden teruggetrokken van de markt, 3) onvolledige verzekeringsdekking voor kinderkanker, 4) tekorten aan essentiële medicijnen, 5) het onvermogen om gebruik te maken van zorg, onder andere door transportkosten naar gezondheidsfaciliteiten, en 6) onvoldoende kennis van kinderkanker onder eerstelijnsgezondheidswerkers. Deze analyse bevestigde dat het in **Hoofdstuk 3.2** voorgestelde kader een systematische evaluatie van toegang in een land kan vergemakkelijken, context-specifiek bewijs van toegangsbeperkingen kan leveren binnen de bredere context van de zorgsector en kan helpen bij het identificeren van concrete aanbevelingen voor verbeterde toegang en beleidsontwikkeling vanuit het perspectief van belanghebbenden.

Naast de perspectieven van professionele belanghebbenden in de farmaceutische waardeketen, werden de perspectieven en ervaringen van ouders en verzorgers van kinderen met kanker gepresenteerd in **Hoofdstuk 3.4**. Specifiek onderzocht dit hoofdstuk de zorggerelateerde, financiële en psychologische ervaringen van verzorgers tijdens de kankerbehandeling van hun kinderen in de publieke en private sectoren van Zuid-Afrika. Drie focusgroepen werden georganiseerd met verzorgers van kinderen die een kankerbehandeling ondergingen in de publieke gezondheidszorgsector. Een vierde kleinere focusgroep met twee ouders uit de private sector werd online georganiseerd. Van de 20 verzorgers uit de publieke sector uitten velen frustratie over het aantal bezoeken aan eerstelijnsgezondheidsklinieken dat nodig was voordat ze werden doorverwezen naar een ziekenhuis voor adequate diagnostiek. Daarnaast hadden verzorgers moeite de diagnose te verwerken en te accepteren en woog de gelijktijdige zorg voor het betreffende kind en andere kinderen thuis zwaar. De steun vanuit familieleden en de bredere gemeenschap varieerde. Alle verzorgers ervaarden financiële problemen door de behandeling. De twee ouders in de private sector gaven aan meer ondersteuning te krijgen en geen financiële problemen te ondervinden, maar vergelijkbare emotionele stress te ervaren. De perspectieven van ouders en verzorgers stelden ons in staat om de barrières die eerder door professionele belanghebbenden geïdentificeerd waren te bevestigen. Daarnaast wierp het meer licht op de emotionele en psychologische impact van kinderkanker op ouders en verzorgers en gaf het een genuanceerder inzicht in de financiële problemen die worden ervaren.

De doelmatigheid van het Nationale Strategisch Plan voor Kanker van Zuid-Afrika in het aanpakken van barrières in toegang tot kinderoncologische geneesmiddelen werd bestudeerd in **Hoofdstuk 3.5**. Barrières geïdentificeerd in eerdere hoofdstukken werden vergeleken met de obstakels en interventies zoals beschreven in het strategische plan, om op deze wijze domeinen voor verbetering te kunnen identificeren. Deze waren terug te leiden tot drie hiaten in het strategische plan met betrekking tot kinderkanker, die tot een reeks aan tekortkomingen leiden in de farmaceutische waardeketen: 1) kinderkankers worden herhaaldelijk verwaarloosd ten opzichte van kankers die vooral volwassenen treffen, zowel op beleidsniveau als in de organisatie van gezondheidsdiensten; 2) er zijn specifieke uitdagingen voor kinderkankers vanwege hun zeldzaamheid en dat vereist daarom gerichte beleidsinterventies (bijvoorbeeld regulatoire prikkels, flexibele prijsoplossingen en aangepaste bewijsvereisten door besluit-vormende organen); en 3) kinderen moeten tijdens de behandeling worden begeleid door een

ouder of verzorger, wat tot verschillende sociale en financiële problemen leidt. Deze analyse benadrukte dat de domeinen waarin kinderkankers verschillen van kankers die volwassenen treffen moeten worden erkend en dat zij aandacht verdienen in nationale beleidsdocumenten, om de behoeften van een kwetsbare bevolkingsgroep niet te verwaarlozen.

Collectief beschreef dit hoofdstuk een uitgebreide analyse van de toegang tot kinderoncologische geneesmiddelen binnen de Zuid-Afrikaanse context. De gebruikte reeks complementaire onderzoeksmethoden – welke onderschrijven dat toegang tot geneesmiddelen wordt gevormd door onderling gerelateerde processen binnen een gezondheidssysteem – zou ook de systematische evaluatie van toegang in andere landen, therapeutische gebieden en bevolkingsgroepen kunnen faciliteren. Het verbeterde begrip van de determinanten van toegang en de tekortkomingen van bestaande beleidsdocumenten in de Zuid-Afrikaanse context kan de Zuid-Afrikaanse overheid helpen bij hun doelstelling om de ziektelast van kinderkanker te verminderen.

Het bewijslandschap voor farmaceutisch prijsbeleid

Hoofdstuk 4 onderzocht de impact van farmaceutisch prijsbeleid of toegang tot geneesmiddelen, om inzicht te krijgen in de omvang en kwaliteit van farmaceutische beleidsanalyses. Dit werk maakte deel uit van een bredere systematische review waarin de effectiviteit van tien farmaceutische prijsbeleidsmaatregelen systematisch werd geëvalueerd.

Een overzicht van het bestaande bewijsmateriaal over beleidsmaatregelen die prijstransparantie bevorderen werd gepresenteerd in **Hoofdstuk 4.1**, wat mogelijk een belangrijk mechanisme voor het beheersen van prijzen van geneesmiddelen en verbeterde toegang tot geneesmiddelen is. Beleidsmaatregelen die prijstransparantie bevorderden werden vergeleken met andere interventies of ongereguleerde omstandigheden. Onderzoeksmethoden die in aanmerking kwamen voor inclusie waren gerandomiseerde onderzoeken en niet-gerandomiseerde of quasi-experimentele studies zoals *interrupted time series* (ITS), *repeated measures* en gecontroleerde voor-en-na studies. De kwaliteit van het bewijs werd beoordeeld met behulp van de GRADE-methodologie. In totaal werden 32.011 mogelijke bronnen geïdentificeerd voor de bredere systematische review, waarvan twee studies werden geïncludeerd voor dit onderwerp. Het beschikbare bewijs suggereerde dat – hoewel gebaseerd op bewijs uit één enkele studie – het publiekelijk beschikbaar maken van nationale geneesmiddelenprijzen mogelijk effectief kan zijn in het direct verminderen van prijzen, met mogelijk ook meer langdurige voordelen. Bewijs over de impact van het terugkoppelen van prijzen aan voorschrijvers gaf geen uitsluitsel over de effectiviteit van deze vorm van prijstransparantie. Er werd geen bewijs gevonden over de impact van deze maatregelen op de uitkomsten geneesmiddelvolume, -beschikbaarheid of betaalbaarheid.

Literatuur over maatregelen die de marges in de farmaceutische distributieketen reguleren werd geëvalueerd in **Hoofdstuk 4.2**. Via een vergelijkbare methodologie als in het voorgaande hoofdstuk kwamen zeven van de in totaal 32.011 artikelen in aanmerking voor inclusie. Het beperkte bewijs suggereerde voorzichtig dat beleidsmaatregelen ter regulering van marges effectief zijn in het verminderen van geneesmiddelenprijzen en farmaceutische uitgaven. De samenstelling van de regulering bleek hierbij een cruciale factor te zijn in hun mogelijke effectiviteit.

In de systematische review van beleidsmaatregelen die prijstransparantie bevorderen, interventies die marges in de farmaceutische distributieketen reguleren en acht andere farmaceutische prijsbeleidsmaatregelen werd een groot aantal studies uitgesloten tijdens het beoordelingsproces vanwege onbruikbare onderzoeksmethoden. Daarnaast werden met regelmaat methodologische tekortkomingen waargenomen in studies die wel aan de inclusiecriteria voldeden. In **Hoofdstuk 4.3** werden daarom de veelvoorkomende zwakheden in studies naar farmaceutische prijsbeleidsmaatregelen geïdentificeerd en werden onderzoeksmethoden kritisch beoordeeld op hun waarde in het leveren van robuust bewijs. Alle 56 studies die aan de inclusiecriteria van de bredere systematische review voldeden werden hiervoor geselecteerd, evenals 101 studies die waren uitgesloten vanwege onbruikbare onderzoeksmethoden. Het risico op vertekening van resultaten werd beoordeeld en methodologische problemen werden geregistreerd om vaker voorkomende zwakheden te identificeren. Van de 56 studies die geïncludeerd waren in de systematische review vertoonde 51% een hoog risico op vertekening in ten minste één domein. Mogelijke interferentie van co-interventies was een bron van mogelijke vertekening in 53% van de ITS studies. Het niet meewegen van mogelijke verstorende factoren was de belangrijkste oorzaak van mogelijke vertekening in *difference-in-differences* studies en regressie- en paneldata-analyses. Van de 101 studies met een methodologie die niet voldeden aan de selectiecriteria van de review was 32% een ongecontroleerde voor-en-na studie en 23% een studie zonder pre-interventiedata.

In zijn geheel liet dit hoofdstuk de hiaten in het bewijs over farmaceutische prijsbeleidsmaatregelen zien, met name met betrekking tot uitkomsten zoals geneesmiddelvolume, beschikbaarheid of betaalbaarheid en tot hun effectiviteit in lage- en middeninkomenslanden. De vaker waargenomen methodologische problemen – waarvan sommige kunnen worden opgelost tijdens het ontwerp van een studie – bieden mogelijkheden voor een grotere hoeveelheid bewijs die effectief kan worden gebruikt voor beleidsontwikkeling in de toekomst.

Aanbevelingen en conclusie

Wetenschappelijk bewijs heeft de potentie om gezondheidsbeleidsontwikkeling te sturen en te worden vertaald in effectieve en rechtvaardige interventies. Echter, bij het uitvoeren van monitorings- en evaluatiestudies naar de toegang tot geneesmiddelen stuitten we op een verscheidenheid aan complexiteiten die inherent zijn aan dit onderwerp. Naast de verschillende

conceptuele, methodologische, systemische en interventionele complexiteiten belemmerde het ontbreken van cruciale en ondersteunende data verdere bewijsvorming. Het onderzoeksbewijs dat wel werd gegenereerd na succesvolle inachtneming van de complexiteiten en datatekorten wordt nog onvoldoende benut in beleidsontwikkeling. Hiermee blijft de kloof tussen bewijsvorming en beleidsontwikkeling op het gebied van toegang tot geneesmiddelen voortbestaan. Om deze kloof in de toekomst te kunnen overbruggen, werden in dit proefschrift de volgende drie kerngebieden voor verbetering geïdentificeerd:

Bruikbaar bewijs voor beleidsmakers

Om ervoor te zorgen dat monitorings- en evaluatiestudies bruikbaar bewijs opleveren voor beleidsmakers, moet het van goede kwaliteit zijn en gepresenteerd worden op een manier die begrijpelijk is voor beleidsmakers en niet slechts gericht op andere onderzoekers. Praktisch haalbare en relevante indicatoren zijn daarbij cruciaal. Ook systematische reviews zijn een onmisbaar instrument, doordat ze beleidsmakers helpen bij het identificeren, beoordelen en synthetiseren van soms tegenstrijdige onderzoeksresultaten. Verdere verfijning is nodig om ervoor te zorgen dat ontwikkelde instrumenten en indicatoren gevalideerd zijn en klaar voor gebruik. Daarnaast moeten de systemische en interventionele complexiteiten die inherent zijn aan toegang tot geneesmiddelen worden omarmd. Dit wordt mogelijk door het toepassen van methoden die toegang tot geneesmiddelen integreren in het bredere gezondheidssysteem.

Tegengaan van hiaten in kennis en datatekorten

Het vullen van aanhoudende kennishiaten met betrekking tot de toegang tot geneesmiddelen is noodzakelijk voor effectieve beleidsontwikkeling. Allereerst is daarbij het identificeren van deze hiaten cruciaal. Tekorten in cruciale of ondersteunende data die op dit moment effectieve monitoring en evaluatie belemmeren moeten op een meer fundamenteel niveau worden aangepakt. Hiertoe zouden data van zowel publieke als private belanghebbenden toegankelijk moeten zijn voor onderzoeksdoeleinden. Ook dienen alle beschikbare databronnen in het wetenschappelijke domein te worden benut, zelfs wanneer deze suboptimaal zijn. Data over de beschikbaarheid en prijzen van geneesmiddelen voor kinderen en de algemene bevolking moeten urgent worden verzameld om prestatiemeting van toegankelijkheid mogelijk te maken voor 2030.

Bewijsvorming gestuurd door informatiebehoeften

Om ervoor te zorgen dat monitorings- en evaluatiestudies relevant bewijs genereren voor beleidsmakers, moeten onderzoeksactiviteiten worden afgestemd op hun informatiebehoeften. De activiteiten met de meeste potentie om lokale beleidsontwikkeling te sturen moeten worden geprioriteerd. Proactieve betrokkenheid tussen onderzoekers, beleidsmakers en gezondheids-professionals is cruciaal bij het bepalen van een passende onderzoeksagenda. Tegelijkertijd is betrokkenheid van onderzoekers en zorgprofessionals bij beleidsontwikkeling eveneens vereist, waarbij beleidsevaluaties vroegtijdig moet worden gepland om de data die noodzakelijk zijn voor zulke evaluaties ook te kunnen verzamelen.

Te midden van de complexiteiten en informatietekorten die het huidige onderzoeksveld kernmerken, bracht dit proefschrift desondanks innovatie waar dit eerder beperkt was. Hoewel deze innovaties belangrijke mechanismen belichamen in het overbruggen van de aanhoudende kloof tussen bewijsvorming en beleidsontwikkeling, zijn verdere, vereende inspanningen noodzakelijk. Nationale en internationale onderzoekers, beleidsmakers en gezondheids-professionals moeten de handen ineen slaan om toegang tot geneesmiddelen als prioriteit te handhaven op onderzoeks- en beleidsagenda's, met als ultiem doel rechtvaardige toegang tot geneesmiddelen voor iedereen te realiseren.


Bivatracin
BETADINE
Kaprofen
KETOLAC

CHAPTER 7

Addendum

Chapter 7.1
Acknowledgements (dankwoord)

I am deeply grateful to the individuals who have guided and supported me these past four years.

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Chapter 7.2

About the author

Iris Joosse, born in 1995 in Eindhoven, the Netherlands, obtained her Bachelor of Science in Pharmacy from Utrecht University in 2016, where she developed a keen interest in access to medicines and international health systems during her Master's program. After graduating in 2019, Iris began her professional journey as a research associate at the Division of Pharmacoepidemiology and Clinical Pharmacology of Utrecht University. During this time, she contributed to a project commissioned by the World Health Organization (WHO) focusing on country pharmaceutical pricing policies, further fueling her interest in addressing global health challenges.

In 2020, she started her PhD at Utrecht University in the Division of Pharmacoepidemiology and Clinical Pharmacology, under the supervision of prof. dr. Aukje Mantel-Teeuwisse, prof. dr. Fatima Suleman and dr. Rianne van den Ham. She was given the opportunity to conduct part of her research activities in Durban, South Africa, hosted by prof. dr. Fatima Suleman at the University of KwaZulu-Natal, broadening her perspective on health systems and local access challenges.

As part of her doctoral training, Iris has showcased her research at national and international conferences and participated in a number of training courses, allowing her to expand her knowledge across several domains (including epidemiology, global health and pharmacy systems). Additionally, having attained her University Teaching Qualification, she has been actively involved in Utrecht University's Pharmacy Curriculum as a teacher. Beyond her involvement in several core courses, she has contributed to the elective courses 'Access to medicines' and 'Pharmaceutical Policy Analysis', as well as an annual Summer School program of similar focus.

Iris is eager to continue her career dedicated to overcoming the challenges in access to medicines worldwide.

Chapter 7.3

List of publications

Joosse IR, Mantel-Teeuwisse AK, Wirtz VJ, Suleman F, van den Ham HA. Missing data on accessibility of children's medicines. Bull World Health Organ. 2022 Oct;100(10):636-642.

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Chapter 7.4
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Chapter 7.5
Author contribution statements

Chapter 1 IRJ conceptualized and wrote the general introduction of this dissertation. Minor revisions were made upon feedback of her supervisors.

Chapter 2.1 IRJ contributed to the conceptualization and data interpretation of this study. She collected and analyzed the data, visualized the findings and wrote the initial draft of the manuscript. IRJ revised the manuscript based on her co-authors' feedback.

Chapter 2.2 IRJ contributed to the conceptualization of this study. She developed the methodology, collected and analyzed the data, and conducted initial interpretation of the findings, receiving guidance from her supervisors. She visualized the findings and wrote the initial draft of the manuscript. IRJ revised the manuscript based on her co-authors' feedback.

Chapter 2.3 IRJ conceptualized this study, developed the methodology, and collected, analyzed and interpreted the data with assistance from co-authors. She visualized the findings and wrote the initial draft of the manuscript. IRJ revised the manuscript based on her co-authors' feedback.

Chapter 2.4 IRJ contributed to conceptualization of this study and its design. She collected, analyzed and interpretated the data with assistance from her supervisors. She visualized the findings and wrote the initial draft of the manuscript. IRJ revised the manuscript based on her co-authors' feedback.

Chapter 3.1 IRJ contributed to the conceptualization of this study and its design. She collected, analyzed and interpretated the data with assistance of her supervisors, and wrote the initial draft of the manuscript. IRJ revised the manuscript based on her co-authors' feedback.

Chapter 3.2 IRJ contributed to the conceptualization of this study. She developed and visualized the analytical framework with assistance of her supervisors, and wrote the initial draft of the manuscript. IRJ revised the manuscript based on her co-authors' feedback.

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Chapter 5 Following initial discussion with one of her supervisors, IRJ further conceptualized and wrote the general discussion of this thesis. Minor revisions were made after feedback of her supervisors.