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Multi-country comparative analysis of paediatric regulatory frameworks and their impact on access to medicines in times of pandemic and beyond

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Table of Contents

Acronyms 4

Prologue 5

1. Introduction 6

1.1 Health and access to medicines as a human right 6

1.2 The focus on medicines for children 7

1.3 The role of regulatory systems, procedures, and authorities 8

1.3.1 Paediatric regulatory frameworks 10

1.3.2 Access in the absence of regulatory approval 15

1.4 Aim and Objectives 15

2. Theoretical and methodological foundations of the research work 17

2.1 Research context 20

2.2 Summary of the research methodology 21

3. Publications and results 22

3.1 Volodina A, Shah-Rohlfs R, Jahn A. Does EU and US paediatric legislation improve the authorization availability of medicines for children in other countries? 22

3.2 Volodina A, Jahn A, Jahn R. Suitability of paediatric legislation beyond the USA and Europe: a qualitative study on access to paediatric medicines 34

3.3 Volodina A, Jahn A, Jahn R. Public health relevance of medicines developed under paediatric legislation in Europe and the USA: a systematic mapping study 47

4. Discussion 57

4.1 National regulatory frameworks and access to paediatric medicines 57

4.2 Paediatric legislation in the international context 59

4.3 Advancing regulatory frameworks for better child health 60

4.4 Global health efforts beyond regulatory framework 64

4.5. Research limitations 65

5. Conclusions and recommendations 66

6. Summary 68

7. Zusammenfassung 70

8. References 72

9. Declaration of personal contribution to the publications 78

Curriculum vitae 79

Acknowledgements 80

Eidesstattliche Versicherung 81

Acronyms

ART	Antiretroviral Therapy
BPCA	Best Pharmaceuticals for Children Act
COVAX	COVID-19 Vaccines Global Access
COVID-19	COronaVIrus Disease of 2019
EAEU	Eurasian Economic Union
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HICs	High-Income Countries
HIV/AIDS	Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LMICs	Low-and Middle-Income Countries
NCCHPP	National Collaborating Centre for Healthy Public Policy
NRA	National Regulatory Authority
PREA	Paediatric Research Equity Act
R&D	Research and Development
SDGs	Sustainable Development Goals
SRA	Stringent Regulatory Authority
US	United States
WHA	World Health Assembly
WHO	World Health Organisation

Prologue

List of first-author publications relevant to the doctoral topic:

1. Volodina A, Shah-Rohlfs R, Jahn A. Does EU and US paediatric legislation improve the authorization availability of medicines for children in other countries? Br J Clin Pharmacol. 2023;89(3):1056-1066. doi:10.1111/bcp.15553	Chapter 3.1
2. Volodina A, Jahn A, Jahn R. Suitability of paediatric legislation beyond the USA and Europe: a qualitative study on access to paediatric medicines. BMJ Public Health 2024;0:e000264. doi:10.1136/bmjph-2023-000264.	Chapter 3.2
3. Volodina A, Jahn A, Jahn R. Public health relevance of medicines developed under paediatric legislation in Europe and the USA: a systematic mapping study. BMJ Paediatrics Open 2024;8:e002455. doi:10.1136/bmjpo-2023-002455	Chapter 3.3

1. Introduction

1.1 Health and access to medicines as a human right

International human rights documents define health as a universal and irrevocable right. Important examples include the Universal Declaration of Human Rights (Art 25) adopted in 1948, the International Covenant on Economic, Social and Cultural Rights (Art 12) adopted in 1966, and Convention on the Rights of the Child (Art 23-24) adopted in 1989 (United Nations 2023b). Many of them were developed in response to the worst experiences during the Second World War and since then serve as guiding principles for global health institutions and governance.

Amongst many interventions to secure healthy well-being, medicines play a critical if not a decisive role. Access to safe, efficacious, and quality medicines co-defines the right to health and is a part of the United Nations Sustainable Development Goals (SDGs), specifically the SDG target 3.8 (United Nations 2023a). Global health agencies and non-governmental organisations, such as the United Nations Children's Fund, Unitaid, World Bank, work on improving access to medicines in low- and middle-income countries (LMICs). In the last decades the private pharmaceutical sector became actively involved in activities promoting medicines access with more than 70 programs launched in 114 LMICs by the end of 2019 (Access Observatory 2020). Despite these commitments, access remains problematic in many parts of the world. According to the World Health Organization (WHO) about 2,000 million adults and children are deprived from essential medicines in the developing regions (World Health Organisation 2023). The Lancet Commission on Essential Medicines Policies highlighted five core challenges impacting essential medicines access: (1) inadequate financing through universal health coverage, (2) affordability, (3) assuring the quality and safety of medicines, (4) inappropriate use, (5) lack of new medicines that target unmet disease burden or offer more effective outcomes (Wirtz et al. 2017).

Global inequalities in medicines access were highlighted during the dramatic years of the HIV/AIDS pandemic. The discovery of antiretroviral therapy (ART) in the late 1980´s brought the disease largely under control in the high-income countries (HICs) (Broder 2020). However, ART remained inaccessible for most adults and children in the LMICs, to a large extend due to the high prices (Ford et al. 2011, Ojikutu 2007). Compulsory licensing for public health emergencies foreseen under the Agreement on Trade-Related Aspects of Intellectual Property Rights met with objections from several HICs and the pharmaceutical industry (Halbert 2002).

With strong support from human rights and HIV/AIDS activists, public health needs took precedence over profits and generic production expanded (Ford et al. 2011). The Global Fund to Fight AIDS, Tuberculosis and Malaria established in 2002 in response to these dramatic events, remains the largest source of financing for global health initiatives that have helped to save estimated 44 million lives by 2022 (Global Fund 2023).

Almost forty years after the rise of the HIV/AIDS crisis, the world faced a pandemic of severe acute respiratory syndrome coronavirus 2, the virus that causes coronavirus disease COVID-19 and similar access challenges were observed. Despite the rapid development of tests and vaccines, access inequalities led to the large vaccination gap worldwide (Holder 2023), including children (Kampmann et al. 2021). A COVID-19 Vaccines Global Access (COVAX) initiative was established under the WHO leadership to ensure fair distribution of COVID-19 commodities for the LMICs. Notwithstanding some successes, it has faced challenges in achieving vaccine delivery goals and has been criticised for complex processes, and decisions driven by the HICs and the private sector (Usher 2021). The COVID-19 intellectual property rights waiver passed after 18 months of serious negotiations was regarded by many as a half-won battle requiring further improvements (Zarocostas 2022).

The HIV/AIDS and COVID-19 pandemics have shown that access in health crises differs from routine care and brings along unique challenges and opportunities. On the one hand, pandemics mobilise public and industry resources on a global scale, increase public pressure and awareness, foster collaboration, and innovative solutions (Majid et al. 2021). On the other hand, they lead to competition for treatments between the countries, place additional burden on health systems and can exacerbate systemic weaknesses (Babu et al. 2021). This research looks at global access to essential medicines for children in routine and pandemic settings.

1.2 The focus on medicines for children

Improving access to paediatric medicines requires tailored solutions due to the inherent constraints of paediatric drug research and development (R&D) not seen for most adult medicines. Paediatric R&D challenges can be grouped into methodological, ethical, and economic issues. Methodological constraints include difficulties with measuring clinically relevant outcomes in a small patient population and investigating disease processes during periods of rapid growth (Kern 2009). Formulation development is also more complicated for children than for adults (Joseph et al. 2015). Ethical issues relate to obtaining consent, use of

placebo, risk and benefit considerations, particularly for non-therapeutic clinical trials (Joseph et al. 2015). Economic issues occur due to the small market, which makes return of investment rarely possible (Conroy et al. 2000). It is important to note that these R&D challenges do not differentiate between high, middle and low-income countries (Hoppu et al. 2012).

For decades paediatric R&D was progressing slowly, which resulted in the high off label use worldwide (Pandolfini et al. 2005). In 1963 in the wake of thalidomide, sulphanilamide, and other medicines safety issues the Professor of Pharmacology Harry Shirkey from the United States (US) called children "therapeutic orphans" (Shirkey 1968), highlighting the universal scarcity of paediatric labelling and formulations. Healthcare professionals, public health authorities and patient community began to place interest in ensuring that paediatric treatments demonstrate the same level of evidence for safety and efficacy as for adults (Ward 2023). Heterogenicity of patient population and enrolment challenges magnified the need for regulatory harmonisation of requirements for paediatric R&D. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) initiative contributed to gradual increase of experience in developing medicines for children. Established in 1990 with support of the US, European Union (EU) and Japan, the ICH now comprises 20 members and 35 observers including health authorities, and international organisations such as the WHO (International Conference for Harmonisation 2023). The concept behind ICH was to bring experts from public authorities and the pharmaceutical industry together to discuss scientific and technical requirements and jointly develop the R&D guidelines. Key paediatric ICH guidelines issued to date include E11(R1): clinical investigation of medicinal products in the paediatric population, E11(A): draft guideline on paediatric extrapolation, and S11: nonclinical safety testing in support of development of paediatric pharmaceuticals.

1.3 The role of regulatory systems, procedures, and authorities

Regulatory systems represent a set of public health institutions, resources, processes, and regulatory framework with which a government ensures quality, safety and efficacy of medicines in a country (World Health Organization 2003). **Regulatory frameworks** comprise a set of laws, regulations (binding legislation) and guidelines (non-binding legislation), which regulates the entire lifecycle of medicines and other health products (World Health Organisation 2021a). National regulatory authorities (NRAs) are public health institutions responsible for a wide range of activities such as clinical trials, marketing authorisation and post-marketing surveillance, inspections of clinical sites and manufacturers (Khadem Broojerdi et al. 2020).

Marketing authorisation (or registration) is a regulatory process when an NRA assesses quality, non-clinical and clinical data of a medicinal product for the purpose of benefit/risk evaluation. It is a mandatory step before a medicine can legally enter a domestic supply chain (Khadem Broojerdi et al. 2020). Examples of the NRA are the Food and Drug Administration (FDA) in the US, the European Medicines Agency (EMA) in the EU and the Federal Institute for Drugs and Medical Devices in Germany. A pool of stakeholders an NRA interacts with include the pharmaceutical industry, patient community, healthcare professionals, academia, other national and international institutions, such as reimbursement authorities and global health agencies. It is therefore essential to have technical and scientific expertise, robust processes and tools, and an enabling mandate for efficient performance (World Health Organisation 2021a).

The attention to regulatory systems in public health started to gain a momentum in the late nineties when essential health policy functions were defined, and the governance of the pharmaceutical sector became increasingly complex. At that time the WHO began to benchmark national regulatory systems (Khadem Broojerdi et al. 2020) as a part of its efforts to ensure rapid access to high-quality childhood vaccines. It concluded that most countries were lacking efficient systems due to underfunding and weak policies (Khadem Broojerdi et al. 2020). Since then, the WHO systematically introduced global initiatives to facilitate regulatory advancements and improve access to life-saving treatments. An important measure was the introduction of the WHO "stringent regulatory authority" (SRA) concept. It allowed the LMICs to leverage on regulatory expertise of countries with mature systems and stringent review processes. Medicines approved by an SRA were eligible for a collaborative registration procedure in the LMICs and for international procurement. Since its piloting in 2015, more than 50 medicines, primarily antiretroviral and antimalarial treatments, were approved via collaborative registration procedure leading to significant reduction of the review time in the LMICs (Vaz et al. 2022).

The lack of financial and human resources remains a key challenge for NRAs worldwide, and may be partially mitigated by regulatory reliance (World Health Organization 2014). Reliance means that an NRA recognises the validity of the scientific assessment made by other NRAs and takes it into account in the decision-making process (World Health Organization 2014). Although reliance mechanisms have been introduced in most regions (Xu et al. 2022), they have not reached yet the stage of global reliance.

The importance of strong regulatory systems for medicines access is anchored in the key World Health Assembly (WHA) resolutions WHA65.19 *Counterfeit medical products* from 2012, WHA67.20 *Regulatory system strengthening for medical products* from 2014 and WHA67.22 *Access to essential medicines* from 2014. The WHA69.20 *Promoting innovation and access to quality, safe, efficacious and affordable medicines for children* from 2016 is a fundamental document for paediatric medicines. It highlights the importance of child-centred health policies, paediatric drug research, and efforts to increase medicines availability and affordability. Importantly, it emphasises the value of regulatory exchange and supports implementation of best policy practices globally (World Health Organization 2016). Inspired by these WHA resolutions, this research provides a critical review of the national paediatric policies and seeks to obtain data which will help regulatory frameworks to advance globally.

1.3.1 Paediatric regulatory frameworks

1.3.1.1 Paediatric legislation in Europe and the United States

Evolution and achievements of paediatric regulatory framework in the US and the EU deserve special attention. From early 1990´s the US FDA has been actively engaged in the legislative work on paediatric medicines. In 1994 the FDA published Paediatric Labelling Rule encouraging pharmaceutical companies to review available data in children for the purpose of labelling updates. To facilitate paediatric R&D, a set of guidelines on clinical trials and extrapolation in children were issued. However, these efforts were unable to improve the availability of paediatric labelling and formulations, mainly due to their unbinding nature for the pharmaceutical industry (Burckart et al. 2020).

The FDA Modernisation Act adopted in 1997 offered 6 months of additional market exclusivity (also called market protection) for conduct of clinical studies in children requested by the FDA (Sharav, V.H. 2003). Market protection is defined as a period of time during which a generic medicine cannot be placed on the market (European Medicines Agency 2024a). A combination of rewards and obligations turned out to become a breakthrough regulatory mechanism, that manifested itself in two legislative documents, being the Best Pharmaceuticals for Children Act (BPCA) and Paediatric Research Equity Act (PREA) in 2002 and 2003 respectively. BPCA reinforced an exclusivity extension for patented medicines and introduced a state funding of paediatric studies for off-patented medicines through the National Institutes of Health (Burckart et al. 2020). PREA became a legislative “stick” enabling the FDA to require pharmaceutical

companies to conduct paediatric drug development for new regulatory applications, be it a new active substance or indication, new dosage form, regime, or route of administration (Burckart et al. 2020). Paediatric drug development under BPCA and PREA may include non-clinical studies in juvenile animals, clinical studies in children, formulation development and other measures (Vieira et al. 2021).

In parallel to the developing legislation in the US, the EMA in the EU undertook attempts to facilitate industry´s engagement through issuing guidelines on paediatric clinical research and fostering round table stakeholder discussions. At some stage, however, it was recognised that without mandating legislation there was a little hope for progress, as in the US. In 1997 the European Commission initiated legislative endeavour that culminated in the adoption of the Paediatric Regulation N 1901/2006 in 2006 (Rocchi et al. 2020).

The EU Paediatric Regulation N 1901/2006 as amended is essentially based on the same mechanism of rewards and obligations for medicines under patent or similar protection as the US legislation. It deviates slightly from the US in requirements and procedural aspects. Specifically, it foresees an earlier start of interactions between the industry and the EMA on paediatric development. It also mandates launching paediatric medicines in the EU market within two years after regulatory approval. Further, the EU Regulation offers rewards in the form of data and market protection periods for the voluntary development for off-patent medicines. However, this mechanism is largely underutilised (Tomasi et al. 2017).

In both regions there are similar clauses for waiving paediatric R&D requirements: safety or efficacy concerns, no unmet medical need, absence of disease or condition in children or other reasons why paediatric development is not possible (latter specific to the US). Generic companies are exempt from mandatory provisions and are not required to bring a paediatric formulation on the market.

To support implementation of these extensive paediatric regulatory provisions, the EMA and the FDA have allocated substantial human and financial resources, whereas access to relevant expertise remains a priority considering the evolving pharmaceutical science (Chisholm et al. 2023). Industry´s approach in addressing the EU and US paediatric requirements remains to strive for a single paediatric development program that would satisfy both regions. The EMA and FDA recognise the importance of R&D harmonisation and have several supportive initiatives such as regular exchange on paediatric programs, and joint scientific advice

procedure with the manufacturers. Nevertheless, divergent regulatory assessments cannot be avoided, which remains a point of criticism among the expert community (Thomsen 2019).

In summary, the paediatric regulatory mechanism in the EU and the US is a combination of rewards and obligations that secures development and marketing authorisation of medicines from the R&D-based pharmaceutical companies. Although both regions have some legislative particularities, key principles remain the same. Within this research we will use the term "paediatric legislation" to refer to a combination of regulatory rewards and obligations as a backbone of paediatric regulatory framework.

After decades of implementation, paediatric legislation resulted in increased number of clinical trials, labelling and age-appropriate formulations in both regions (European Commission 2017, Field et al. 2012). The policy evaluations conducted in both regions were overall positive with some areas of improvement identified, such as limited impact on medicines used exclusively in children (European Commission 2017). The US Government and the European Commission are working on enhancing the responsiveness of paediatric legislation to children´s needs whist keeping its mandatory nature. In 2023, the European Commission initiated a revision of the EU pharmaceutical legislation. It proposes different periods of market protection depending on select public health criteria. For paediatric medicines, the revision simplifies regulatory procedures and leaves the 6-month paediatric reward unchanged. It also links the scope of mandatory development to a medicine's mechanism of action, which may differ from adult indications (European Commission 2023). A similar requirement was introduced into the US regulatory framework in 2017, allowing a better focus on the unmet needs for treatments developed as an adjunct to adult therapies (Zettler 2022).

The need for industry compliance with paediatric regulatory requirements in two large pharmaceutical markets will inevitably lead to many more medicines for children in future. However, regulatory advances in the EU and the US make less than 9% of children globally (United Nations 2019) into potential beneficiaries of age-appropriate treatments.

In the spirit of the WHA69.20 resolution, this research explores whether paediatric legislation should be considered for global implementation as a means to improve access to medicines for children. Study I examines whether it has an unintended transboundary effect, increasing the number of medicines in other countries without legal enforcement. Study II explores stakeholder opinions on its suitability within their national contexts. Study III assesses

paediatric legislation from public health perspective by investigating the relevance of resulting treatments for health of children.

1.3.1.2 Paediatric regulatory frameworks in the studied countries

In other regions, paediatric regulatory frameworks and their role in access have not been well studied. This research looks at Australia, Brazil, Canada, Kenya, Russia and South Africa (for selection criteria see chapter 2.1). The key paediatric regulatory provisions are discussed below.

Of these countries, Canada has implemented the most detailed paediatric regulatory framework. Similar to the EU and US, it incentivises pharmaceutical companies with a 6-months market protection for paediatric R&D results submitted for marketing authorisation (Health Canada 2021). This reward, however, is not backed up by the mandatory requirements. After more than a decade of implementation this approach has not yet yielded promising results (Gilpin et al. 2022). In 2009 a Paediatric Expert Advisory Committee was established to support the NRA Health Canada in the developing effective paediatric regulatory policies (Government of Canada 2012). In 2020 Health Canada released a Pediatric Drug Action Plan to improve availability of on-label treatments with age-appropriate formulations by stimulating clinical development and regulatory submissions of paediatric data (Government of Canada 2024). In 2021 the Centre for Policy, Pediatrics and International Collaboration at Health Canada was set up to provide policy recommendations on medicines for children (Government of Canada 2024). In 2023 it published a *Draft guidance document on submitting pediatric studies and pediatric development plans* that offers an opportunity to submit either EU/US or Canadian paediatric development plans (Health Canada 2024). This pilot proposal follows regulatory approach in Switzerland, where submission of paediatric data generated upon the request of the EMA and FDA, or the national authority is mandatory (Swissmedic 2022). Although Canadian draft guidance contains voluntary provisions, it demonstrates increased interest in regulatory harmonisation and could be regarded as important step towards strengthening of national paediatric framework.

Other countries covered by this research do not seem to have institutionalised paediatric departments within the NRAs. Australia offers an exemption of annual regulatory fee for medicines that do not generate profit (Therapeutic Goods Administration 2021). Although this provision is not specific to paediatric medicines, it could be regarded as incentivising measure for many of them. The NRAs in Australia and Canada participate in regular teleconferences

with the FDA and the EMA on paediatric drug development programs for the purpose of regulatory exchange and collaboration (European Medicines Agency 2024b). Brazil and Russia offer accelerated regulatory assessment: 120 instead of 365 days in Brazil and 80 instead of 160 days in Russia (National Health Surveillance Agency 2017, Government of the Russian Federation 2023). Since 2014 Russian regulatory framework requires submission of local clinical data except for orphan and generic medicines without providing guidance on its nature and extent (Government of the Russian Federation 2023). It could be seen as a policy measure to attract global clinical research and innovation (Vieira et al 2023).

Since 2014 Russia is involved in the development of legislation and processes supporting the single pharmaceutical market of the Eurasian Economic Union (EAEU), which also includes Armenia, Belarus, Kazakhstan, and the Kyrgyz Republic. Several EAEU paediatric guidelines on non-clinical and pharmaceutical R&D aligned with those of the EU have been adopted. The EAEU marketing authorisation legislation published to date (Eurasian Economic Commission 2016) continues to require local clinical data without providing measures to financially incentivise or mandate paediatric R&D.

No paediatric provisions could be identified in the marketing authorisation guidelines in Kenya and South Africa (Pharmacy and Poisons Board 2022, South African Health Products Regulatory Authority 2023). Both countries are engaged in the African Medicines Regulatory Harmonisation initiative. It aims at harmonisation of regulatory requirements across the continent and is a part of a policy framework to contribute to the Sustainable Development Goals (African Union 2017). The African Union Model Law on medicines from 2016 does not include provisions specific to paediatric R&D or registration (African Union 2024).

In summary, the regulatory requirements in the studied countries show varying levels of attention to paediatric medicines and may include procedural or financial incentives. A shared feature in all countries is the voluntary nature of paediatric research and marketing registration for the pharmaceutical industry. The ability of the national frameworks to support access to paediatric medicines was explored in study I. Points analysed included the ability to ensure paediatric labelling, and formulations in a systematic manner. Study II contributed to the analysis by gathering perceptions about medicines access with due attention to the regulatory aspects.

1.3.2 Access in the absence of regulatory approval

The lack of paediatric labelling has been reported in different settings (Castro et al. 2018, Song et al. 2020). In addition to the off-label prescribing, it may prompt the use of alternative access pathways such as importing medicines from abroad (Pati 2016). Different regulatory mechanisms to import unlicensed medicines have been established by the NRAs, termed as "post-approval named patient program", "managed access program", "special access programs". They generally require an application from a healthcare professional justifying the unmet medical need for a patient, and a consent from the pharmaceutical company to supply a requested medicine (Kreeftmeijer-Vegter 2013). These alternative pathways often remain the only way of getting medicines into a country where a company decided not to submit a marketing authorisation or was unsuccessful in doing so (Kreeftmeijer-Vegter 2013).

Scientific evidence suggests that absence of regulatory approval may pose additional barriers for access. In countries where reimbursement is bound to national labelling, the financial burden for off labelling or unlicensed medicines is usually placed on patients (Dooms et al. 2016). Education status of patients as well as parents and caregivers influences health seeking behaviour and is a risk factor for paediatric care (Sanville et al. 2019, Xu et al. 2022). This suggests that families with lower socioeconomic status rely on medicines being easily available to them within the public health system. Other studies report concerns of healthcare professionals and parents about off-label use in children and recommend introduction of specific guidelines to mitigate safety risks (Zhang et al. 2013).

Despite the global reach of the pharmaceutical industry, the regional nature of paediatric legislation may exacerbate inequalities in access. It can be hypothesised that paediatric treatments remain largely unavailable outside of the implementing regions, necessitating the use of alternative access pathways. Before regulatory measures mandating national authorisation can be considered, it is important to explore the role of these alternative pathways. This point was taken in study II and is reported in the second publication.

1.4 Aim and Objectives

The research aims to examine paediatric regulatory frameworks in the selected countries and their impact on access to medicines in routine care and pandemic, such as COVID-19. Specifically, it will evaluate the use of paediatric research results in the absence of regulatory obligations and explore the value of the EU/US paediatric legislation in the international

context. Further aim is to develop regulatory recommendations for better medicines access globally.

Following specific objectives were defined:

1. To examine to what extent paediatric medicines developed under paediatric legislation become authorised in other countries (study I, first publication);
2. To investigate obstacles in access to paediatric medicines used in standard care and in situation of pandemic. As part of this objective the role of marketing authorisation and access mechanisms in its absence receive special attention (study II, second publication);
3. To investigate to what extent medicines developed under paediatric legislation address the paediatric burden of diseases (study III, third publication).

2. Theoretical and methodological foundations of the research work

To synthesise and discuss the research results coherently, several frameworks (Centers for Disease Control and Prevention 2022, World Health Organisation 2022, Morestin et al. 2010) for the analysis of public health policies were reviewed. It was decided to use the analytical framework from the National Collaborating Centre for Healthy Public Policy (NCCHPP) in Canada (Morestin et al. 2010) that analyses policy effect and implementation context. Policy effect is defined as a combination of effectiveness, unintended effects, and equity. Policy implementation relates to acceptability, feasibility, and cost. The NCCHPP framework was chosen for its applicability to analyse both existing and future policies in various contexts. In this research an assessment of national frameworks constitutes analysis of existing policies and the value of paediatric legislation in the international context constitutes prospective policy analysis. Furthermore, the possibility of selecting policy dimensions on the basis of transparent methodological decisions makes this framework highly suitable for this project. A figurative representation of how individual studies were mapped to the NCCHPP analytical framework is provided in Figure 1.

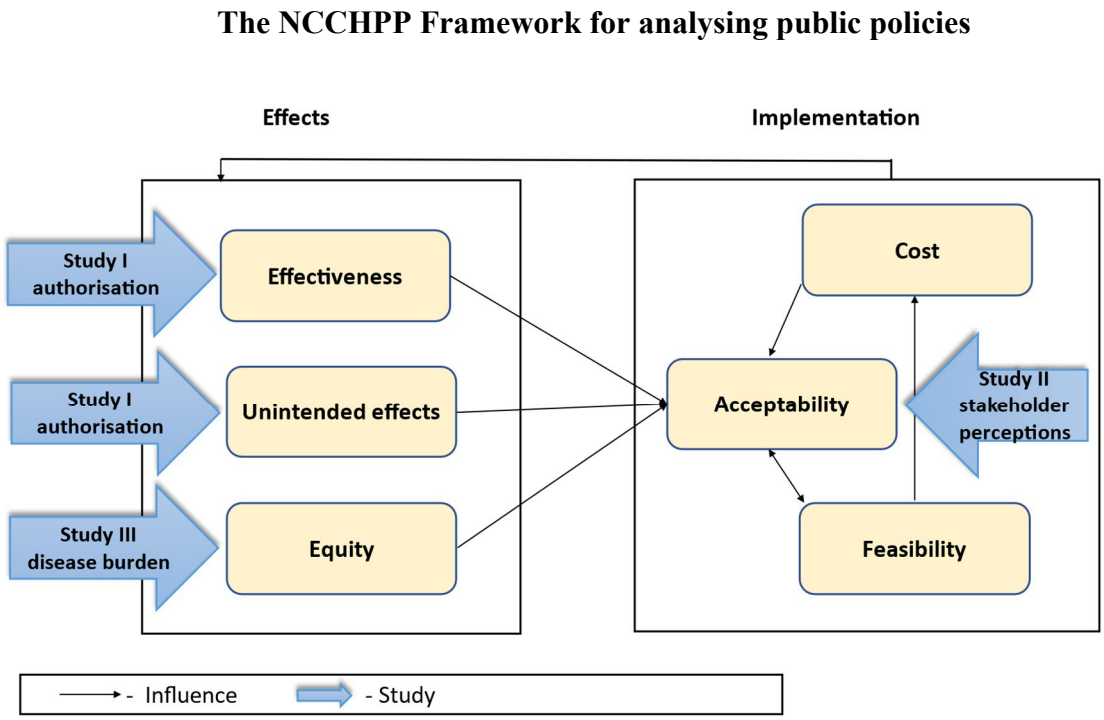

Figure 1. Mapping of thesis studies (in blue) to the NCCHPP framework for analysing public policies (modified from Morestin et al. 2010)

A conceptual model showing NCCHPP analytical framework adapted to synthesise, explain and discuss the research findings is presented in Figure 2. In this model, the Effectiveness, Unintended effects, Equity, and Acceptability are four key elements of analysis.

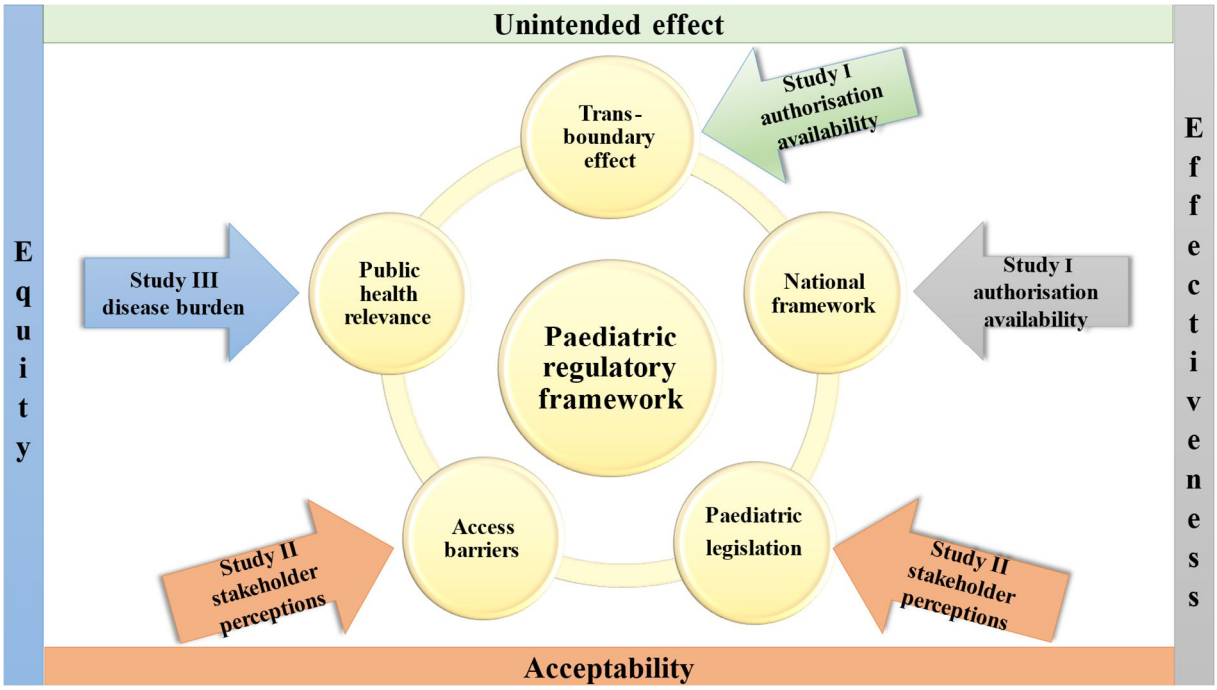

Figure 2. Conceptual framework that synthesises three studies in the research

Definitions of the analytical framework dimensions and their application for this research are as follows:

Effectiveness – policy effectiveness is defined as set of intermediate effects on the causes of the problem and ultimate effect on the problem. To assess ability of a particular policy to achieve its ultimate effect, the NCCHPP framework proposes assembly of a logic model using intermediate policy effects. Figure 3 outlines the logic model developed in the context of this research to illustrate how paediatric regulatory framework improves child health.

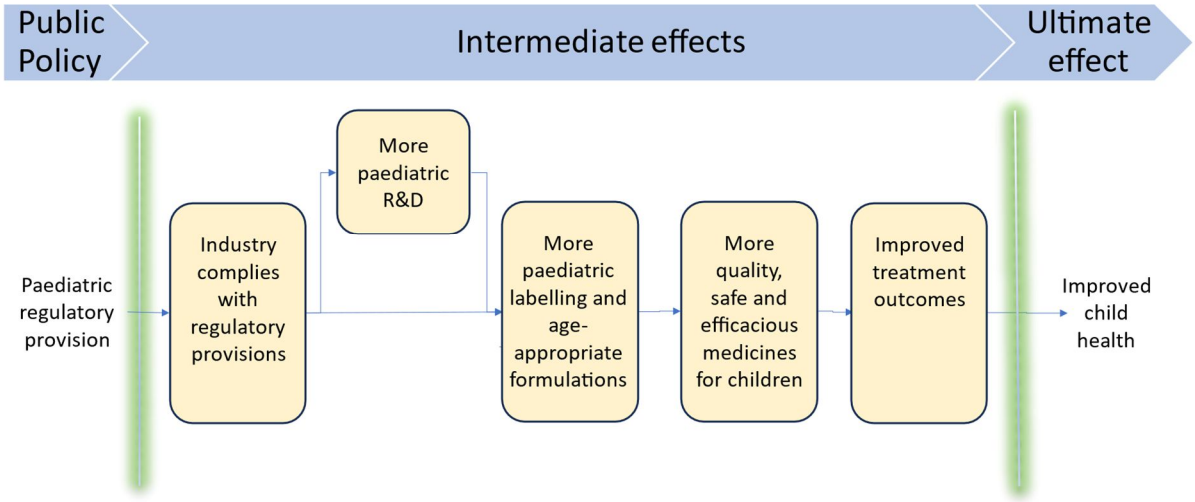

Figure 3. Logic model with intermediate and ultimate effects of paediatric regulatory framework on child health

This logic model shows that paediatric regulatory framework increases availability of on-label medicines and formulations for children by facilitating R&D and regulatory submission of paediatric data. Paediatric labelling and age-appropriate formulations mean that prescribers and caregivers can be supplied with safe, effective and quality medicines for children. The use of such medicines leads to better compliance and better treatment outcomes, thus improving children´s health. This model is applicable to paediatric legislation as well as to national paediatric frameworks in the countries studied. Intermediate effectiveness of national frameworks to secure marketing authorisation of medicines with paediatric labelling and formulations was explored in study I.

Unintended effect - policy evaluation requires attention to effects (neutral, positive, and negative) that go beyond declared objectives. An unintended effect of paediatric legislation was defined as ability to increase paediatric treatments in other countries (positive transboundary effect). It was considered critical to quantify this transboundary effect to draw conclusions on the necessity of introducing regulatory provisions on the national level. Study I therefore allowed a conclusion on effects of health policies in large markets with mature regulatory systems on other countries.

Acceptability – before introducing a policy it is essential to assess whether the topic it addresses is considered a problem that merits public intervention. Then it is necessary to analyse how acceptable a proposed public policy would be for relevant stakeholders. Both aspects of

acceptability were explored in study II analysing perceived access barriers to paediatric medicines. Acceptability of acting on the problem was defined as acceptability that scarcity of paediatric labelling and formulations impedes medicines access and requires policy intervention. Study II therefore investigated in depth stakeholder perceptions about access barriers with due attention to access in the absence of national marketing authorisation. Then stakeholder opinions about feasibility and suitability of paediatric legislation to tackle an accepted problem were explored.

Equity – equity is defined as the extent to which policies benefit groups with greater needs. Equity of paediatric legislation was defined as ability of medicines to address most prominent unmet needs of children. It was analysed in study III by mapping medicines with the paediatric disease burden in the studied countries and globally and reviewing medicines status in the WHO Essential Medicines Lists for adults and children.

Assessment of **feasibility** defined as availability of human, material and technological resources, and **costs** associated with implementation of paediatric legislation in the national frameworks was outside of the research and should be a subject of future studies.

2.1 Research context

A set of countries was purposefully selected to account for different geographical context, economic development, regulatory frameworks, and socio-cultural characteristics to ensure that the study findings and conclusions could be generalised to a broader region. It was decided not to focus on resource-constrained settings, but to include a diverse group of countries since paediatric market exhibits similar challenges globally. Although it is recognised that access barriers to medicines are largely overcome in the HICs, they also experience difficulties in securing access to age-appropriate treatments. The need to mandate paediatric drug development on the legislative level in the EU and the US is a vivid proof of it. Another consideration for inclusion of the HICs in the research was that it should help to develop sustainable policy solutions with global impact. Scientific evidence suggests that several public health initiatives have not received necessary global support because they were unable to demonstrate their value for the HICs (Regmi et al. 2013). In order to avoid focusing policy recommendations on a particular setting when addressing a global issue, countries with all levels of economic development as defined by the World Bank (World Bank 2023) were

considered for inclusion. Based on the research objectives and methodology, following feasibility criteria were applied:

(1) Availability of national regulatory database with medicines labelling in public access
Medicine labelling was defined as a document containing officially approved information for healthcare professionals and/or patients on how to use a medicine safely and effectively.
(2) Availability of national regulatory laws, regulations, and guidelines in public access
(3) Language skills of the researcher (English, German or Russian)

A feasibility study using the ICH and WHO lists of regulatory authorities (International Council for Harmonisation 2023, World Health Organisation 2021b) was performed to identify countries that would fulfil these criteria. The research focuses on two high-income (Australia, Canada) and four middle-income countries (Brazil, Kenya, Russia, South Africa).

2.2 Summary of the research methodology

This is a mixed method research organised in three studies each pertaining to a specific research objective. These studies were undertaken utilising qualitative and quantitative methods to assess existing regulatory frameworks and explore the suitability of paediatric legislation in the international context. Study I and resulting first publication provided first insights regarding effectiveness of national frameworks and unintended transboundary effect of paediatric legislation. Study II investigated contextual characteristics of medicines access in routine and pandemic conditions, and stakeholder acceptability of paediatric legislation in the countries studied. Study III allowed a conclusion on equity of paediatric legislation on national and global scale. Findings from these studies enhance our understanding on the role of regulatory policies in medicines access and help to design effective and sustainable policy solutions for global implementation.

3. Publications and results

3.1 Volodina A, Shah-Rohlfs R, Jahn A. Does EU and US paediatric legislation improve the authorization availability of medicines for children in other countries?

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ORIGINAL ARTICLE

Does EU and US paediatric legislation improve the authorization availability of medicines for children in other countries?

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Aim: For over 15 years, the pharmaceutical industry has been engaged in developing medicines for children to comply with the European Union (EU) and the United States (US) regulatory requirements. We assessed the authorization availability of these medicines in countries without paediatric regulatory obligations. Special attention was given to the authorization availability of paediatric formulations.

Methods: Medicines for children were sampled from the US Food and Drug Administration and European Medicines Agency websites. We carried out systematic content analysis of product information and compared paediatric labelling in Australia, Brazil, Canada, Russia and South Africa with the EU or the US. The authorization availability of paediatric formulations in originator and generic medicines was reviewed. In Kenya, the authorization availability of sampled medicines and paediatric formulations was investigated.

Results: A total of 161 medicines authorized in the EU or the US were sampled. Whilst at least one paediatric indication was found in 70% of the medicines, the EU and US level of authorization was on average 38% in Australia, Brazil, Canada, Russia and South Africa. Paediatric formulations were authorized on average for 40% of originator and 36% of generic medicines. Kenya had the lowest authorization availability of medicines (40%) and formulations (26%).

Conclusions: The authorization availability of novel medicines for children is lower in countries without paediatric regulatory obligations. Paediatric formulations often do not reach other countries if left unregulated, and their generic uptake is low. To increase authorization availability, submission of paediatric development results should become obligatory in each jurisdiction. Policy initiatives to stimulate the introduction of developed formulations should be encouraged.

KEYWORDS
access to medicines, age-appropriate formulations, authorization availability, medicines for children

1 | INTRODUCTION

Access to essential medicines is considered a human right and is a central component of the Sustainable Development Goals to ensure "access to safe, effective, quality and affordable essential medicines and vaccines for all".[1] Unfortunately, the availability of medicines for children is low and this is a significant public health problem, whereby off-label prescribing remains high.[2–6] Several studies have shown that low availability, high prices and poor affordability have kept medicines out of reach for children, as well as lack of age-appropriate formulations, adequate dosing and administration instructions in the product labelling.[7–11]

Over many decades, paediatric drug development has been hindered by various factors. They include a common notion to protect children from research, little appreciation of paediatric pharmacology, recruitment challenges and low market pressure. Whilst considerable improvements have been achieved, the last two factors remain as obstacles in high-, middle- and low-income countries.[12–15] To enhance access to child-appropriate medicines, in 2007 the World Health Assembly unanimously adopted Resolution WHA60.20, "Better Medicines for Children". The World Health Organization (WHO) subsequently launched the campaign "Make Medicines Child Size". Furthermore, the first WHO Model List of Essential Medicines for Children was published in that same year and is updated every 2 years. Equally, there has been an emergence of child-focused nongovernmental organizations, paediatric clinical research consortia and partnerships with the pharmaceutical industry.[16–18]

Among others, one key approach to provide children with better access to safe and effective medicines is through regulatory mechanisms that incentivize and simultaneously mandate paediatric research. Pioneering legislation came into force in the United States (US) in 1997, followed by the European Union (EU) Paediatric Regulation in 2007. Their requirements and limitations are discussed elsewhere.[19–26] Impact assessment carried out in the EU and the US concluded that legislative interventions have been effective and produced a significant increase in clinical studies and evidence-based paediatric labelling of medicines.[27–30] To secure compliance, pharmaceutical companies often need to develop multiple formulations, strengths or administration devices for the EU and the US paediatric markets. Where an adult product is in development or already exists, bridging of a paediatric formulation to the adult one may be utilized to minimize the burden of paediatric drug development.

EU and US paediatric legislation continues to evolve.[31] Whilst changes are to come, its compulsory nature is expected to stay and will lead to the emergence of many more medicines in the coming decades. The only other countries requiring evidence-based paediatric labelling and age-appropriate formulations for novel medicines are the United Kingdom and Switzerland.[32,33] At the same time, more than 90% of the world's children reside outside of these four high-income regions. Several publications suggest only limited benefit from conducted research for other countries and call for a more active position of local regulators.[34–42] Among the six countries selected for this study, Canada is currently in the forefront of paediatric regulatory initiatives (Table 1).

What is already known about this subject

- Many medicines are not approved for paediatric use.
- Paediatric legislation in the European Union (EU) and the United States (US) has improved the authorization availability of medicines for children in both regions.

What this study adds

- The results of conducted paediatric development are underutilized in other countries.
- Paediatric formulations developed for the EU or US markets do not often reach other countries; when they do, their generic uptake is low.
- Policy initiatives are needed to increase the utilization of paediatric data and formulations.

Generic medicines, those where the original patent has expired, may be produced by manufacturers other than the originator (patent-holding) company. The introduction of a generic paediatric formulation is an important step to expand access because it reduces costs and makes supply systems robust. In the absence of facilitating regulatory mechanisms, simple economic considerations may determine the decision of generic companies to engage with paediatric formulations. However, there is a little reason to believe that they would be considered commercially attractive.

This study investigates the influence of EU and US paediatric legislation on countries where provision of evidence-based paediatric labelling and age-appropriate formulations is not mandated by national legislation. To contribute to this understanding, we investigated the authorization availability of EU- or US-driven paediatric medicines in Australia, Brazil, Canada, Kenya, Russia and South Africa. Special attention was given to age-appropriate formulations: we investigated their authorization availability in originator medicines and their generic equivalents. Authorization availability was defined as the presence of paediatric indication(s) and, if applicable, age-appropriate formulation(s) in local product information (PI) and was chosen as a proxy indicator because it is an essential milestone towards access to medicines in the studied countries.

2 | METHODS

2.1 | Study context

We carried out a systematic content analysis of PI for medicines from the National Medicines Regulatory Agencies (NMRA) websites in

TABLE 1 Key paediatric regulatory features in Australia, Brazil, Canada, Kenya, Russia and South Africa

Type of legislation	Australia	Brazil	Canada	Kenya	Russian Federation	South Africa
Legislation to provide financial incentive for the development of medicines for children	No	No	In effect from 2006	No	No	No
Legislation mandating the development of medicines for children	No	No	No	No	No	No
Other regulatory measures to support medicines for children	Regulatory fee waiver for low-volume products	Expedited regulatory review	Paediatric Medicines Advisory Committee as external advisory body to Health Canada	No	Expedited regulatory review	No
Regulatory cooperation on harmonization and standardization in paediatric research	Regulatory cluster calls on paediatrics with EMA and FDA ICH observer	No ICH member	Regulatory cluster calls on paediatrics with EMA and FDA ICH member	No No[a]	No ICH observer	No ICH observer
Geographic region	East Asia and Pacific	Latin America and the Caribbean	North America	Sub-Saharan Africa	Europe and Central Asia	Sub-Saharan Africa
Country classification by income level	High-income	Upper- middle-income	High-income	Lower-middle income	Upper- middle income	Upper- middle income

Abbreviation: ICH, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.

[a]As part of East African Community.

Source: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups.

Australia, Brazil, Canada, Kenya, Russia and South Africa. The term "product information" refers to a document that describes the pharmacological properties and approved indications of use of a medicine. In countries where PI is available separately for patients and healthcare professionals, the latter version was used. The study countries were purposely selected with the following criteria: (i) different geographic contexts; (ii) economic development; (iii) drug regulatory systems; and (iv) the presence of an open-access database with approved PI. Kenya and South Africa were selected to give representation of the African context and were found to have the most comprehensive databases on medicines among African NMRAs.

2.2 | Reference data source: EU and the US

We first selected the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) websites to identify medicines subject to paediatric legislation. The EMA List of Paediatric Investigation Plans (PIPs) was downloaded from the EMA website on 17 May 2021. The EMA defines a PIP as "a development plan aimed at ensuring that the necessary data are obtained through studies in children, to support the authorisation of a medicine for children".[43] The US Paediatric Labelling and Studies Report was downloaded from the FDA website on 21 September 2021. Medicines subject to written requests and paediatric study plans were considered for inclusion. Information in the EU and US lists was verified and substantiated by cross-checking the approved EU or US PIs, EMA public assessment reports on paediatric submissions and FDA approval letters from the EMA and FDA websites.

Medicines with paediatric developments completed by the end of 2018 were selected for inclusion. The end of 2018 was chosen as a cut-off point to consider the time required for the preparation of matching regulatory submission and update of the NMRA database. Medicines were excluded if at the time of study conduct (i) they were withdrawn from the market due to safety concerns or authorization rejected either in the EU or the US; (ii) they were not registered in all EU countries; (iii) studies in children did not result in a paediatric indication; and (iv) entries were duplicate copies of the same product. For the US list, a random sampling step was done in addition. The sampling steps are outlined in detail in Figures 1 and 2.

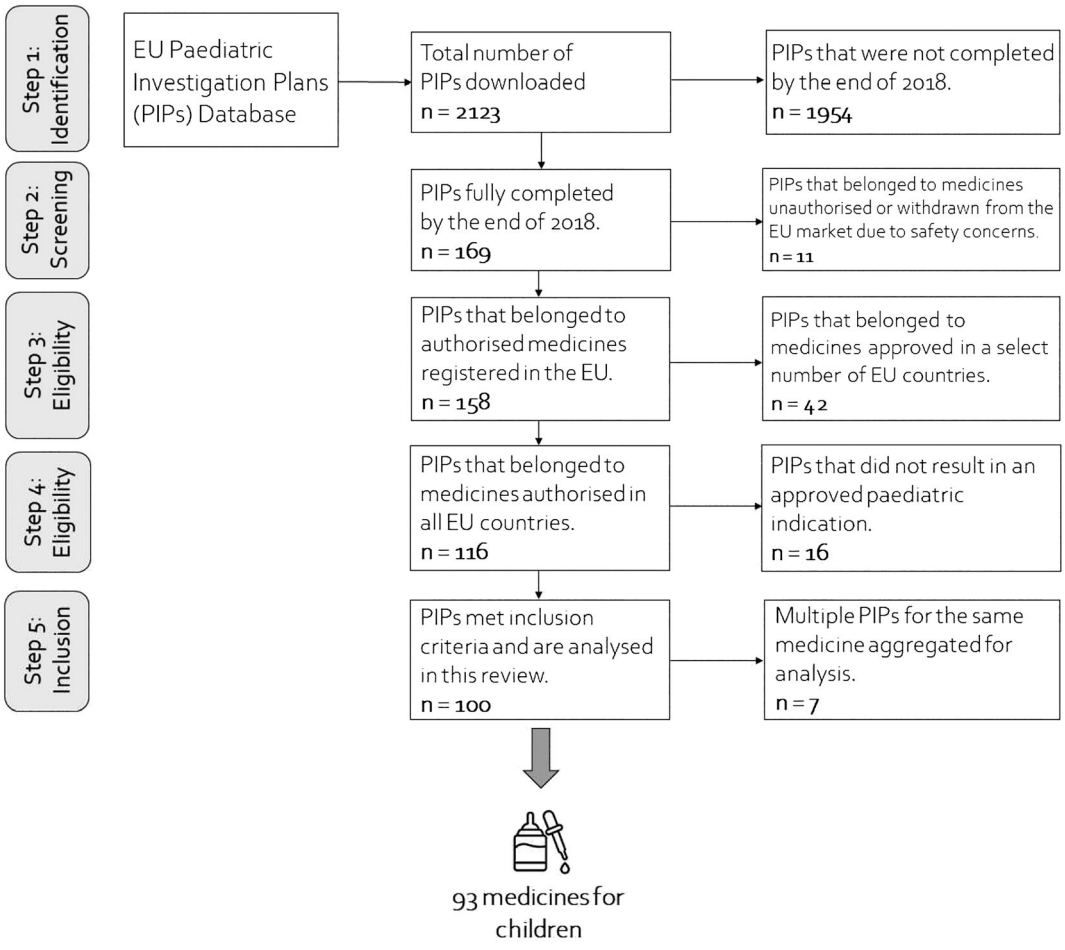

FIGURE 1 Selection of medicines with approved paediatric indications in the EU

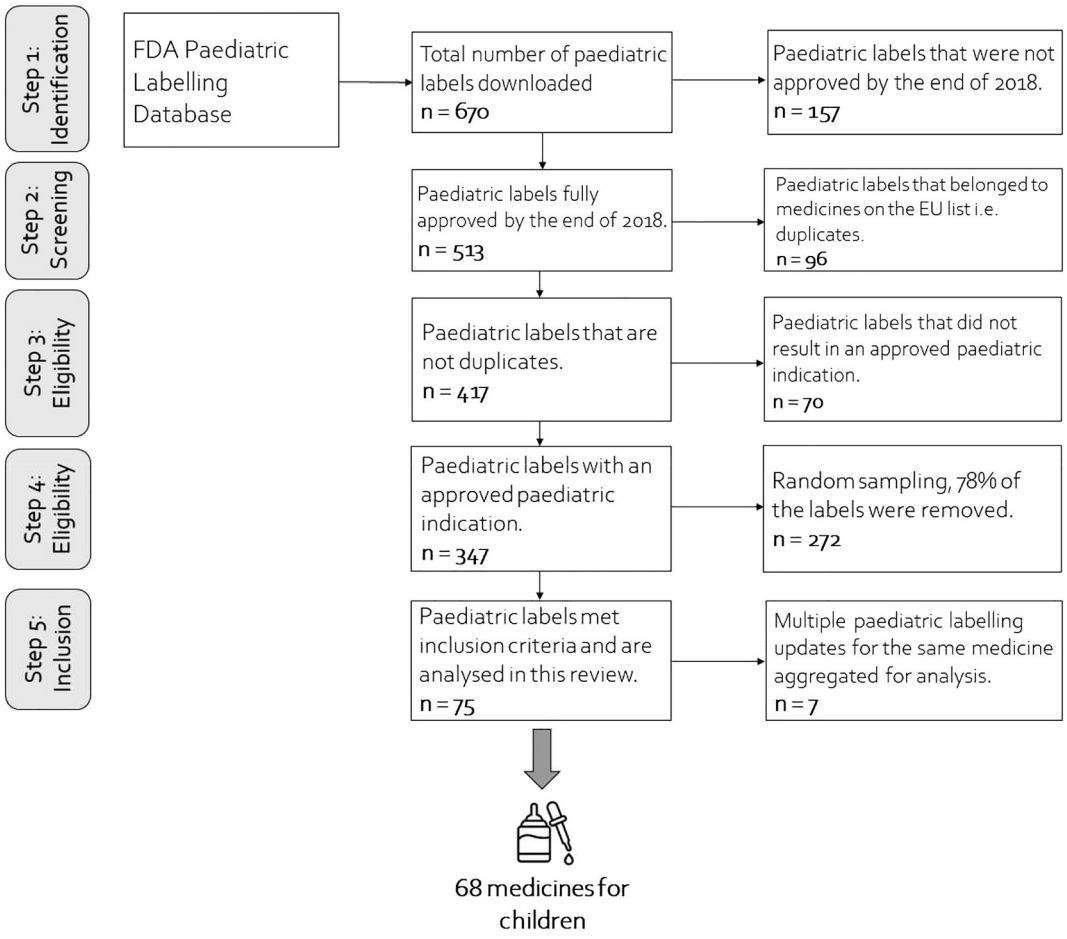

FIGURE 2 Selection of medicines with approved paediatric indications in the US

In total, we sampled 161 out of 352 medicines (42%) with identified paediatric indications developed between 2007 and 2018.

Sampled medicines were classified into two groups: (1) medicines that did not require age-appropriate formulation and (2) medicines that had at least one age-appropriate formulation. An age-appropriate formulation was defined following the main considerations of the EMA guideline on the pharmaceutical development of medicines[44] as a formulation or presentation developed in addition to the adult one to facilitate administration and acceptance in a targeted paediatric subset.

2.3 | National Medicines Regulatory Agencies: local PI

Local PI for the sampled medicines was collected from the NMRA databases: Roszdravnadzor in Russia, the Brazilian Health Regulatory Agency, Therapeutic Goods Administration in Australia, Health Canada and the South African Health Products Regulatory Authority. The databases were searched by selecting the combination of the active substance and/or the brand name and/or MAH with the same strength and formulation matching the reference products. If no PI was available in the NMRA database, we searched the national MAH website. If PI was not found there either, the medicine was excluded from the content analysis.

Prior to the analysis, local guidance and templates for the industry were consulted to identify the paediatric labelling rules. The PI sections "indication", "posology and method of administration", "contraindications", "summary of clinical trials" and "pharmacokinetics in special population – children" were reviewed. If there was insufficient information to allocate an appropriate category (described below), the key words "children", "paediatric", "adolescents", "newborn" and "neonates" were searched throughout the document. PI in Portuguese was translated into English using Google Translate.

Thematic categories were developed to reflect the nature of paediatric information available to local prescribers. The aspects compared to the reference PI were (i) the number of approved paediatric indications; (ii) approved paediatric age cohort; and (iii) approved age-appropriate formulations. As shown in Table 2, medicines found in the NMRA databases were coded into four mutually exclusive categories. The process steps taken for the systematic content analysis are shown in Figure 3.

The authorization availability of age-appropriate formulations was reviewed in the sampled medicines and their generic equivalents. The authorization availability of an age-appropriate formulation for at least

one generic was judged sufficient for the categorization of "medicine with generic age-appropriate formulation".

In Kenya, PI is not available in the NMRA database. Regulatory information such as "approval status", "formulation", "strength" and "presentation" was collected via the Kenyan Board Registry. Assessment was done at the active ingredient level because it was not possible to consistently distinguish between originator and generic products. We reviewed whether a medicine and age-appropriate formulation, if applicable, was listed in the registry.

2.4 | Data analysis

Results were calculated as percentages (proportions) of the products which were approved. Data are presented both in terms of the sum of all countries and separately for each country. Distributions between different therapeutic areas were identified according to the Anatomical Therapeutic Chemical code provided in the EMA List of PIPs, and the FDA Paediatric Labelling and Studies Report. Descriptive tables, figures and statistics were created using MS Excel.

TABLE 2 Categories reflecting the nature of paediatric labelling in local PI

Category	Definition
Full match to EU/US reference PI	Local PI contained all paediatric indications for the same age cohort and with the same number of age-appropriate formulations
Incomplete match to EU/US reference PI	Local PI did not contain all the paediatric indications, and/or all age-appropriate formulations, and/or age cohort was reduced
Not approved for children	Medicine approved for adult use only
Not retrievable	Local PI not found

3 | RESULTS

Out of the 161 sampled medicines, over one-fifth (37/161) were used to treat infectious diseases, followed by neurological disorders (17/161), cancer medicines (14/161) and vaccines (13/161) (Figure 4).

Of the sample, 110 medicines (68%) were identified in the state database of Russia, 118 (73%) in Australia, 134 (83%) in Canada, 113 (70%) in Brazil and 90 (56%) in South Africa. In Brazil and South Africa, PI for four and 32 medicines, respectively, were not found (category "not retrievable") and were excluded from further calculations. Kenya had the lowest number of medicines in the state database: 64 (40%) out of 161.

3.1 | Content analysis of local PI: Australia, Brazil, Canada, Russia and South Africa

Figure 5 presents the results of content analysis of local PI on the use in children. At least one paediatric indication (categories "full match" plus "incomplete match") was found in 83 medicines (70%) in Australia, 81 (74%) in Brazil, 89 (66%) in Canada, 88 (80%) in Russia and 33 (60%) in South Africa, which results in an average 70% rate. On average, 45 local products "fully matched" the EU/US

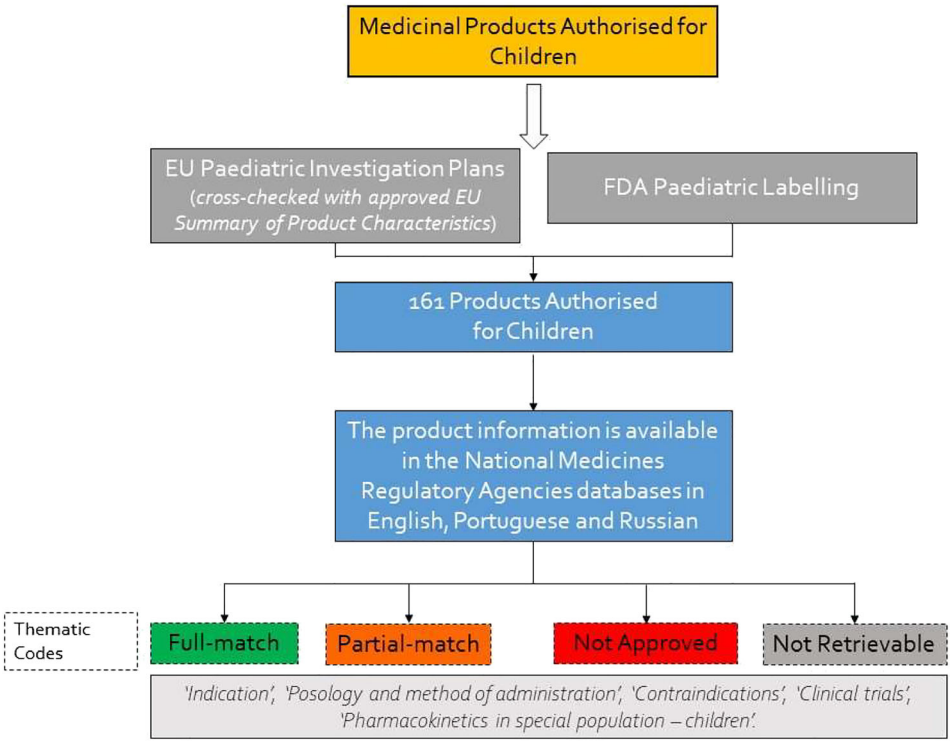

FIGURE 3 Steps taken in the systematic content analysis of product information

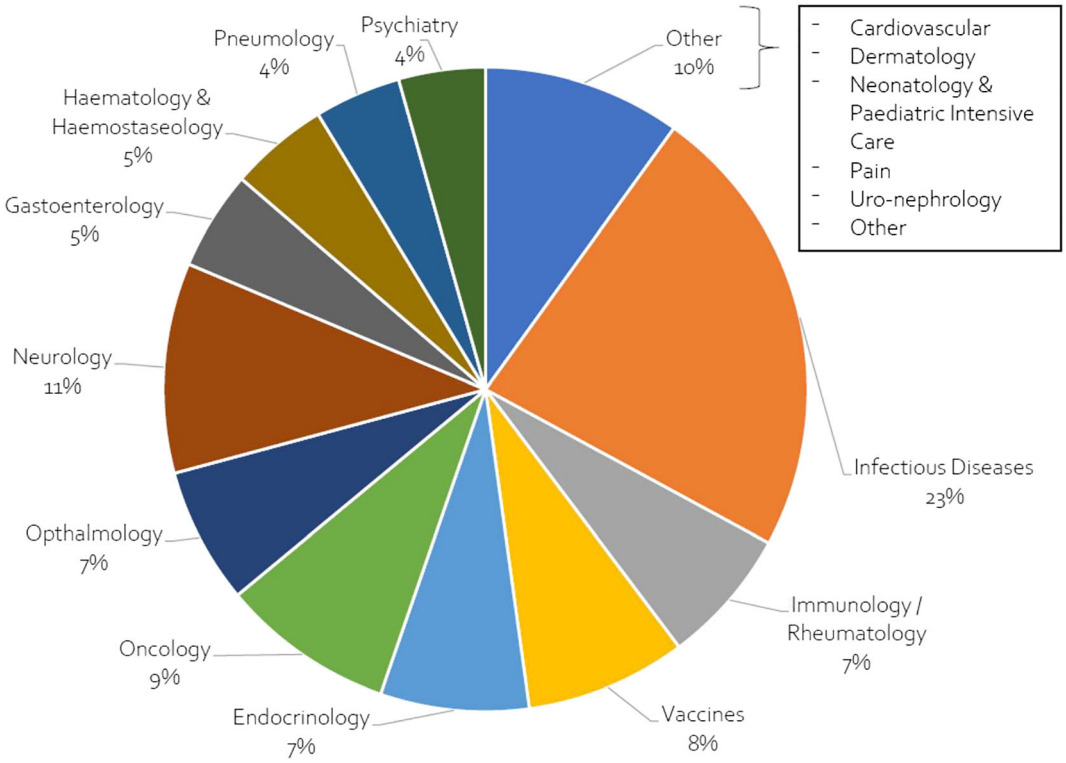

FIGURE 4 Reference medicines for children per therapeutic area (N = 161)

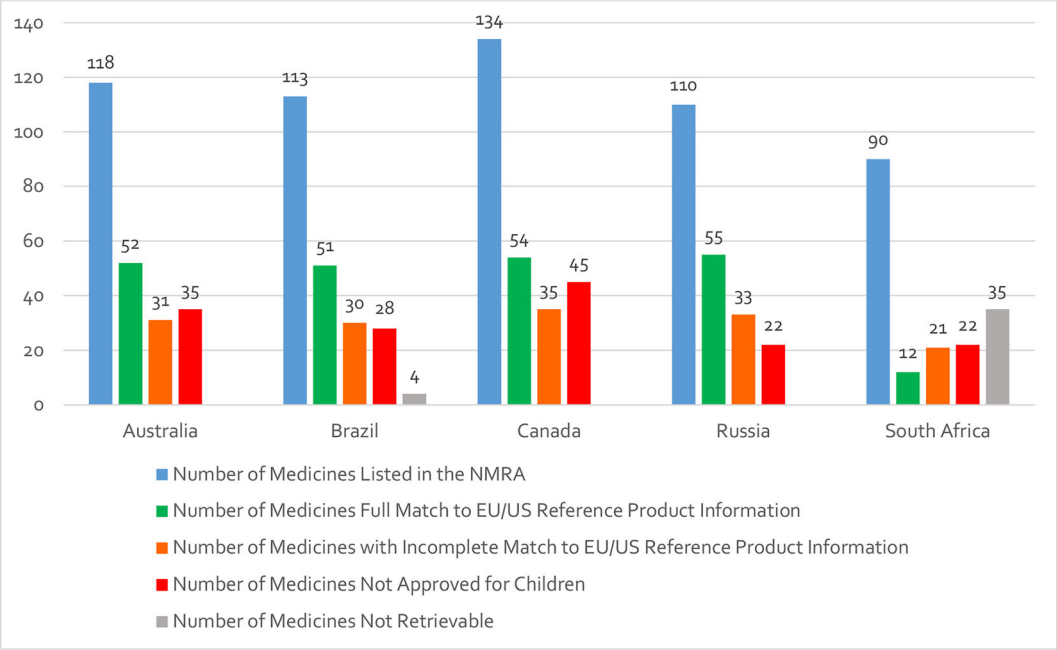

FIGURE 5 Systematic content analysis of local product information in five selected countries (N = 161)

reference PI in all countries with Russia having the highest proportion (50%) (Figure 5). The majority of medicines within this labelling category did not require age-appropriate formulations (81% in Australia and Russia, 84% in Brazil, 80% in Canada and 83% in South Africa).

3.2 | Not approved for use in children: what information is available to prescribers?

Most medicines not approved for use in children did not contain any paediatric information in the local PI but had a standard text such as:

"Use in children is not recommended, no data is available" and "Safety and efficacy in patients below the age of 18 have not been studied". Since November 2020, the regulatory guidelines in Canada require the MAH to state whether paediatric data were submitted for regulatory review and whether approval was granted.[45] At the time of this study, three medicines approved for use in children in the EU or the US contained a statement: "No data were made available to Health Canada; therefore, Health Canada has not authorized an indication for paediatric use."

A small number of medicines had at least partial information on conducted development in "Pharmacokinetics", "Summary of Clinical Studies" or "Safety Warnings" sections: four (18%) in Russia, 12 (27%) in Canada, seven (25%) in Brazil, 10 (29%) in Australia and one (5%) in South Africa.

3.3 | Age-appropriate formulations: Canada, Russia, Brazil, Australia, South Africa and Kenya

Out of the 161 sampled medicines, 55 (34%) had at least one age-appropriate formulation approved in the EU or the US. The majority of these medicines were found in Australia, Brazil, Canada, Russia and South Africa. However, the authorization availability of age-appropriate formulations was low, ranging from 34% to 44%. For medicines that experienced generic penetration, it was further reduced. The results are summarized in Table 3. In Kenya, paediatric formulations were found for nine (26%) out of 34 possible medicines.

4 | DISCUSSION

Our study demonstrates that EU and US paediatric legislation has provided a measurable but limited benefit to Australia, Brazil, Canada, Russia and South Africa. Content analysis showed that on average, only 38% of local PI with paediatric labelling fully matched the reference PI. Thus, the high number of medicines only partly or not-at-all approved for use in children indicates that none of these countries fully utilize the results of paediatric development imposed on the pharmaceutical industry.

Analysis of a local PI helps to reveal reasons why a medicine has not been approved for use in children in a given jurisdiction. As seen in our study, for PI with statements "no data on use in children is available/was provided", it is most likely that paediatric indications were never submitted for local regulatory review. For PIs with paediatric information only in sections such as "Clinical Trials", paediatric indications were most likely rejected by the local regulatory authorities. We observed the latter for medicines where paediatric developments were based on nonrandomized clinical trials, compassionate use programmes or supported by extrapolation from older age groups.

4.1 | Country-specific considerations

4.1.1 | Canada

Our data show no apparent difference in the number of approved paediatric medicines in Canada compared to Russia, Brazil and Australia. This could imply that in small markets, regulatory systems based on incentives may not be effective.

4.1.2 | Russia

The requirement for local clinical development did not seem to have a negative impact on paediatric authorizations in Russia, despite this being reported as a regulatory barrier for emerging markets.[46] One explanation could be the common inclusion of Russian sites to support clinical developments for the reference countries,[47,48] which results in the fulfilment of the national registration requirements. However, in other settings, mandatory local clinical studies, if not supported by scientific rationale, may present a regulatory hurdle for anyway unattractive paediatric market and negatively impact patient access.

4.1.3 | Kenya and South Africa

Kenya and South Africa demonstrate substantial disadvantage in the authorization availability of medicines for children as well as age-appropriate formulations. Although pharmaceutical products are manufactured in certain African countries, including South Africa and Kenya,[49,50] for a long while the African region has not been in the spotlight for the pharmaceutical industry due to low market

TABLE 3 Authorization availability of age-appropriate formulations in originator and generic medicines (N = 55)

	Originator medicine listed in the NMRA		Originator medicine with generic equivalents listed in NMRA	
Country	Total	With age-appropriate formulation	Total	With generic age-appropriate formulation
Australia	48	20 (42%)	18	5 (28%)
Brazil	50	17 (34%)	15	5 (33%)
Canada	52	23 (44%)	14	5 (35%)
Russia	50	20 (40%)	25	7 (28%)
South Africa	42	16 (38%)	11	6 (55%)

attractivity, fragmented regulatory systems and political instability. In recent years, the healthcare landscape has undergone substantial changes such as pursuance of regulatory harmonization initiatives and efforts to achieve universal health coverage. We believe that the expected growth of child population[51] and maturation of healthcare systems will stimulate momentum in the development of strong paediatric policies. The WHO Paediatric Regulatory Network and similar initiatives will continue to play leading roles in shaping effective regulatory interventions in low- and middle-income countries, and facilitating international cooperation among regulators.

Over the course of this study, the importance of a comprehensive database that allows public access to information on medicines became apparent. It proved challenging to find comparable databases among African NMRAs and this is an important finding highlighting the need for improved information technology infrastructure in healthcare.

4.2 | Consideration on age-appropriate formulations

The study results demonstrate that age-appropriate formulations have a tendency not to become authorized in other countries, if left unregulated. Marginal expected revenues, logistical complexity and additional development efforts could be some of the key reasons for the lack of age-appropriate formulations in originator medicines and generic counterparts.[52,53]

It is fair to deduce that utilization of EU/US-mandated paediatric research in other regions depends a great deal on (a) the goodwill of the pharmaceutical industry and (b) the data submitted by pharmaceutical companies to convince local regulatory authorities. However, there may be other reasons why medicines remain unapproved for use in children that could not be identified in this study.

4.3 | A way forward

Authorization gaps as well as possible causes identified in the study encourage efforts by both the pharmaceutical industry and regulators to increase access to paediatric medicines. The results of paediatric development should be systematically submitted to regulatory authorities in countries where adult registration is sought. We believe that exclusion of paediatric studies from the registration dossier and hence from the PI is not justifiable from scientific, ethical and regulatory points of view. At the same time, a precondition of a requirement towards mandatory paediatric submissions is the presence of relevant expertise and capacity on an authority level. In resource-constrained settings, regulatory reliance mechanisms should be considered to alleviate constraints.

Furthermore, industry and regulators should aim to minimize divergent assessment outcomes over paediatric development. The complexity of paediatric research and low incremental revenues make industry's development efforts beyond the EMA and FDA-agreed programs unlikely. Embracement of global harmonization initiatives such as ICH[54] has the potential to substantially reduce divergent regulatory decisions on the same dataset.

Sustainable country-specific measures to stimulate the introduction of both originator and at least first-on-the market generic formulation in high-interest paediatric indications should be considered. However, we acknowledge that many health systems in low- and middle-income countries have technical, financial and political constraints which may hinder effective medicines regulation.

Finally, further steps beyond authorization availability, such as market availability and financial access, are needed to make access to medicines for children a reality.

In conclusion, this study confirms that countries without paediatric regulatory obligations have limited authorization availability of novel medicines. Furthermore, EU- or FDA-approved paediatric formulations often do not reach other countries if left unregulated, and their generic uptake is low. Essentially, access to medicines for children is still limited in countries outside of the EU and the US.

4.4 | Study limitations and further research

Some limitations were identified for the source data, as the nationally authorized products were reported on a voluntary basis by NMRAs and thus may not be complete. Nevertheless, the listed products are expected to represent most of the relevant ones authorized.

Access determinants beyond authorization such as marketing or reimbursement status were outside of the study scope. This study provides a snapshot of the real-world situation, which may change over time and will not fully reflect all the dynamic factors related to authorization availability.

Analysis of unmet medical needs addressed by paediatric medicines is required to further inform policymakers in the studied countries.

Our findings refer to a selective group of countries and as such may not be representative for all markets, therefore similar data from other countries, for example China and India, would be needed to create a better picture of the overall situation.

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COMPETING INTEREST

Authors have no conflict of interest.

PATIENT CONSENT STATEMENT

Not applicable.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

CLINICAL TRIAL REGISTRATION

Not applicable.

DATA AVAILABILITY STATEMENT

Data are available on file upon reasonable request.

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3.2 Volodina A, Jahn A, Jahn R. Suitability of paediatric legislation beyond the USA and Europe: a qualitative study on access to paediatric medicines

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Suitability of paediatric legislation beyond the USA and Europe: a qualitative study on access to paediatric medicines

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ABSTRACT

Background Paediatric legislation has contributed to better access to appropriate treatments in the European Union and the USA by requiring paediatric research in return for financial incentives. This study explored whether similar policies could improve access to medicines in other countries.

Methods We conducted 46 interviews with representatives from healthcare practice, patient organisations and health authorities from six countries (Australia, Brazil, Canada, Kenya, Russia and South Africa) as well as multinational pharmaceutical companies exploring their views regarding access barriers to paediatric medicines. Emphasis was placed on regulation-related barriers and the effect of the COVID-19 pandemic. Where participants were familiar with paediatric legislation, views regarding its relevance for domestic context were explored in depth.

Results Insufficient paediatric research and development, regulatory hurdles and reimbursement constraints were reported to be relevant access barriers in all studied settings. In the absence of marketing registration or reimbursement, access to paediatric medicines was associated with increased legal, financial and informational barriers. Brazil, Kenya, Russia and South Africa additionally described overarching deficiencies in medicines provision systems, particularly in procurement and supply. The COVID-19 pandemic was said to have reduced regulatory hurdles while further heightening global access inequalities.

Views regarding paediatric legislation were mixed. Concerns regarding the implementation of such policies focused on regulatory resource constraints, enforceability and potential reduction of industry activity.

Conclusions The study findings suggest that paediatric legislation may be most impactful in mature health systems and should be accompanied by measures addressing access barriers beyond marketing registration. This could include strengthening domestic manufacturing capacities and technology transfer for medicines with high public health relevance. Ideally, legislative changes would build on global harmonisation of paediatric legislation, which could be achieved through existing WHO structures.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Availability of appropriate treatments for children has increased in Europe and the USA since the introduction of paediatric legislation, but whether such policies could improve access in other regions remains unclear.

WHAT THIS STUDY ADDS

⇒ Regulation-related barriers to paediatric medicines are relevant across different countries and could be reduced by globally harmonised paediatric legislation. Supporting measures are required to alleviate remaining system-level access barriers, particularly in resource-constrained settings. The COVID-19 pandemic highlighted the limitations of regulatory actions when paired with a reliance on international manufacturers.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study supports efforts to introduce paediatric legislation beyond the European Union and USA, highlighting the necessity of global regulatory harmonisation, robust medicines provision systems and increased domestic manufacturing capacities.

INTRODUCTION

Child health has been a focus of the global health community for many decades and features prominently in the Sustainable Development Goals.[1] Despite these commitments, there were an estimated five million deaths among children under 5 in 2021, most of which would have been preventable with essential health services.[2] Access to paediatric medicines is a particular challenge. Appropriate treatments are often either lacking entirely, not registered domestically or only available in adult formulations, thus severely limiting access for children.[3 4] It also makes paediatric care particularly reliant on off-label use, which is associated with poor treatment adherence and medication errors.[5–7]

Among all health system determinants, the critical role of regulatory processes in defining access to medicines is widely recognised.[8 9] Since beginning to benchmark regulatory systems in 1997, the WHO has strived to strengthen regulatory systems for medical products.[10] These efforts include Stringent Regulatory Authorities, which work with the WHO's prequalification programme, and a WHO collaborative registration procedure that leverages prequalification results to speed up national registration.[11]

In the context of paediatric medicines, the USA, European Union (EU) and, more recently, Switzerland have implemented dedicated regulatory legislation to tackle persistent deficiencies in paediatric research and development (R&D) and labelling. Prior efforts to encourage paediatric R&D only using financial incentives had not yielded the intended results. The EU/US paediatric legislation, therefore, additionally introduced obligations to the drug manufacturers.[12–14] Pharmaceutical manufacturers applying for marketing registration of a new product, indication, formulation or administration route for adults are now required to conduct paediatric investigations as a part of their application. In return for these paediatric investigations, the legislation provides a 6-month patent extension for the respective medicine as a financial incentive. Exceptions from these mandatory investigations can be granted on a case-by-case basis, that is, due to safety or efficacy concerns, or lack of medical needs in children. For off-patent medicines, paediatric regulatory provisions remain voluntary and may include incentives such as extending data protection.[15–17]

The EU/US paediatric legislation primarily aimed to reduce access barriers by increasing paediatric R&D, reducing off-label use and improving the availability of child-friendly formulations.[18–21] Evaluations of the policy's success found that these parameters have improved in both regions, particularly for patented drugs.[22 23] During the COVID-19 pandemic, paediatric legislation also ensured early consideration of paediatric vaccine development, supporting inclusion of children in the crisis response.[24 25]

However, available evidence suggests that the paediatric use knowledge generated under the mandatory paediatric investigation in the EU and USA is rarely used outside of these regions,[26–28] thus exacerbating global access inequalities. Such inequalities could be reduced if the geographical coverage of paediatric legislation increased, potentially strengthening access to appropriate treatments in regions beyond the USA and Europe.[29] The WHO recognises the benefits of leveraging policy experiences and encourages the transfer of successful regulatory policies to other countries.[30] However, regulatory policy implementation must account for a wide range of contextual factors, including the national health system infrastructure, local and regional access barriers, socioeconomic and cultural aspects.[31–34] Understanding stakeholders' perceptions and expectations towards access helps to ensure that policies remain meaningful and attainable. The value of legislation in the implementing regions has been a subject of considerable study,[35–40] however, little is known about views regarding its suitability outside of Europe and the USA.

The study aimed to explore the potential of transferring paediatric legislation to selected countries outside of Europe and the USA. To this end, the study collected views of relevant stakeholders regarding paediatric access barriers, particularly relating to R&D, marketing registration and formulation issues, as well as any perceived changes during the COVID-19 pandemic.

METHODS

Study design

We conducted a qualitative study investigating the perceptions of key stakeholders on access barriers for paediatric medicines in two high-income countries (HICs), Australia and Canada, and four middle-income countries (MICs), Brazil, Kenya, Russia and South Africa. This study is a part of a larger study on the role of paediatric policies on medicines access in these areas. The country selection aimed at capturing countries of varying income levels,[41] geographical contexts, as well as regulatory and health systems (for more information, see Volodina *et al*[26]). Selection was limited by the availability of open-access regulatory databases and the language skills of the first author (English, German and Russian). Online supplemental 1 provides an overview of the regulatory system of each of the studied countries. For data collection, we adopted a qualitative semistructured in-depth interview methodology to allow for a wide range of opinions.

Instrument development

The interview guide was developed using open-access templates,[42] relevant literature on the EU/US paediatric legislation[18–22 43] and evidence from earlier stages of the research.[26] It included open-ended questions on three main topics:

1. Access barriers to paediatric medicines.
2. Role of marketing registration and access mechanisms in its absence.
3. Access barriers to paediatric COVID-19 vaccines compared with routine care.

Where paediatric policies based on incentives and obligations for the industry were mentioned by the participants, their opinions regarding such policies were also explored. The interview guide contained two sets of questions, one for interviewees from national contexts (health authorities, patient organisations and healthcare professionals) and one for participants from pharmaceutical companies. It was tested in four pilot interviews and subsequently revised (see online supplemental attachment 1).

Sampling and recruitment

Interviews were conducted with representatives from patient organisations, healthcare professionals, national health authorities (ministry of health or regulatory

agency) and global R&D pharmaceutical companies. This allowed us to gain perspectives on access issues from those shaping national medicines policies and those affected by them. Inclusion criteria were as follows: (1) affiliation with a stakeholder group that develops, governs or uses paediatric medicines and,(2) fluency in English, German or Russian. Potential participants were identified from relevant websites in each country as well as by scanning publications on child health for authors with relevant affiliations. In some cases, approached individuals referred to other experts deemed more knowledgeable about the study subject. To supplement our findings, we also interviewed one expert involved in implementing paediatric legislation in the EU and one expert from a non-governmental organisation working on access to medicines in low-income and middle-income countries (LMICs).

All participants were contacted with a standard email containing information about the purpose and methods of the study and were asked for their voluntary participation. Of 132 individuals approached for the study, 49 agreed to participate, and 3 interviewees later withdrew consent.

Interview conduct and analysis

AV conducted 46 interviews between June 2021 and December 2022. 12 interviews were carried out face-to-face under adherence to applicable COVID-19 restrictions; 34 were conducted virtually or over the telephone. The average interview duration was 35 min, ranging from 20 min to 81 min; other persons were not present during the interview. 11 interviews were recorded and transcribed verbatim, and 35 interviews were protocolled, depending on the interviewees' preferences. All transcripts and protocols were checked by the participants to ensure the correctness of captured data and translated, if necessary, into English by AV.

Data analysis was carried out by two researchers based on the thematic analysis method.[44] After familiarisation with the data, AV conducted an initial open coding of the interview material using the NVivo V.12 software. Interviews were conducted until saturation was reached and further interviews did not result in the generation of new codes.

Subsequently, AV and RJ reviewed the initial coding for emerging themes. With these themes, the data were recoded, and the themes further refined. This iterative process was repeated until further reviews did not lead to any more changes, indicating that the themes were well-defined and clearly distinguished. The themes that emerged regarding access barriers were found to cover a wide variety of aspects along the entire medicine life cycle. To facilitate the interpretation of access-related aspects, these themes were subsequently mapped onto the pharmaceutical value chain.[45] This model divides the medicine life cycle into the following distinct stages: R&D and Innovation, Manufacturing, Marketing registration, Selection, Pricing and Reimbursement, Procurement, Supply, Prescribing, Dispensing, and Use. Following this step, the coding tree was finalised. Study findings were not discussed with the interviewees.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Characterisation of the study participants

Of the 46 study participants, 20 were healthcare professionals, 11 were from patient organisations, 9 from national health authorities, 5 from pharmaceutical companies and 1 from a non-governmental organisation (for geographical distribution, see table 1). Interviewees representing the pharmaceutical industry belonged to four companies.

In the following, we present the themes developed from the data through thematic analysis. A table showing

Table 1 Study participants by geographical region and stakeholder group

Geographical region	Stakeholder group				
	Healthcare professional	Patient organisation	Health authority*	Non-governmental organisation	Pharmaceutical industry
Australia	2	1	1	–	–
Brazil	3	1	2	–	–
Canada	2	2	1	–	–
Kenya	3	2	2	–	–
Russia	7	2	1	–	–
South Africa	3	3	1	–	–
Europe	–	–	1	–	–
Multinational	–	–	–	1	5

*Ministry of Health or Regulatory Agency.

themes distribution across interviewees from different national and institutional backgrounds can be found in online supplemental 2.

Access barriers in the studied countries

R&D and innovation

The interview participants generally agreed that current levels of paediatric R&D were insufficient. This was attributed to the small market size and marginal revenues, making paediatric R&D commercially unattractive. It was also pointed out that national regulations may further disincentivise paediatric R&D through divergent regulatory requirements, such as clinical data thresholds, or by requesting price reductions as a condition for reimbursement.

> I think the overall issue is that paediatric regulations are different in different countries, even between the EU and the US. There are different data requirements, and they require different responses from the industry. [Industry-36]

Furthermore, paediatric R&D was described as resource-intensive and complex. Parental hesitancy, uneven distribution of research infrastructure and lengthy approval processes were said to complicate research in the MICs such as Brazil.

> Sometimes pharmaceutical industry does not like to do local clinical trials in Brazil because of bureaucracy. If they do clinical trials that are very fast, they do not put centres in Brazil. [Brazil, healthcare professional-29]

Manufacturing

Access challenges associated with the lack or type of manufacturer were reported in all MICs. Basic off-patent medicines were reported to have no or very few manufacturers due to profitability risks. For on-patent medicines, concerns were raised about a reliance on foreign companies and international supply chains, which had proven vulnerable during the COVID-19 pandemic. Some participants believed that strengthening local manufacturing capabilities would alleviate these issues. Examples of efforts to achieve this included a domestic manufacturing transfer for a low-priced paediatric formulation in Kenya and policies to support the domestic industry in Russia. Furthermore, it was suggested that local companies would be more interested in manufacturing medicines relevant to the domestic context.

> I really think that we can only be strong in access to medicines if we have a strong domestic industry. Industry that would be interested in our local market, in responding to the true patients' needs in our country, in having our patients, our children as its main priority. [South Africa, patient organization-37]

> Many distributors have a license to manufacture foreign medicines. […]. Here we have a hope that even if the borders get closed, they will not run away and certain amount of medicines will be accessible to Russian patients. [Russia, health authority-08]

Issues relating to medicines that are only manufactured as adult formulations emerged in all studies countries. Interviewees described that paediatric formulations are often compounded in healthcare facilities. Hospital compounding was criticised in Brazil and Canada due to perceived issues with standardisation and quality control, whereas in Russia, it was seen as a reasonable alternative to commercial formulations.

> …in Brazil hospitals sometimes have to change the dosage form when an appropriate one is not available […] For example, they dissolve tablets in the water before giving them to children. As pharmacists specialized in pharmaceutical technology, we know that we cannot always proceed like this. [Brazil, health authority—23]

> There is an initiative to restore pharmacies with manufacturing facilities in order to make paediatric formulations. [Russia, healthcare professional—07]

Marketing registration

A lack of registered paediatric medicines was described by participants from all countries. Some perceived the marketing registration process itself as unduly lengthy or expensive, discouraging industry applications. Participants from pharmaceutical companies highlighted the lack of regulatory support for paediatric applications. In contrast, increased regulatory flexibility and cooperation during the COVID-19 pandemic were said to have expedited vaccine development and registration.

> In many cases the backlog [at the regulatory authority] is huge. […] Just trying to get [a paediatric formulation] approved has been taking years. It offers much better quality of life, less side effects, but getting something like that just has been impossible. (South Africa, patient organization-41)

> Currently we have two [COVID-19] vaccines for children […]. In both cases [the regulatory agency] established a close relation with regulatory agencies of countries that have already approved them, exchanging experience, information, and I think it was a very collaborative way to do assessment, in order not to lose time. (Brazil, health authority-33)

Access was described as particularly challenging for medicines that are registered abroad but lack national marketing registration. Across all interviews, we identified five access avenues to such no-label medicines: special access programmes (SAPs), lawsuits, participation in clinical trials, industry donations and health tourism. Of these, SAPs and lawsuits were most widely discussed.

SAPs are regulatory mechanisms to access medicines from abroad and they were reported in all countries. Lawsuits were more common in Brazil and Russia, where access to medicines can be legally enforced. Both pathways were described as lengthy, and often inaccessible to the most disadvantaged populations who may lack the necessary knowledge and support.

> But who are the people that are going to sue? They should have some knowledge about medicines, at least to know how to write and read or know somebody who can help them. [Brazil, healthcare professional-24]

Industry participants described SAPs as 'messy' [Industry—18] due to divergent requirements across the world. It was suggested that SAPs could serve as an excuse not to engage with larger access issues, particularly in LMICs.

> I think that the non-routine supply channels are used sometimes by the industry to pat themselves on the back and say: "This medicine is available for children in Africa, they can buy it via International Pharmacy". I think these routes are sometimes perceived by the industry as an easy way out in access discussions. [Industry—14]

Selection, pricing and reimbursement

Reimbursement emerged as an important access determinant across all interviews. Without reimbursement, medicines must be paid out-of-pocket, but particularly novel medicines are often unaffordable to the general population.

> Price remains a big problem, especially if a medicine from the public health [system] you rely on is missing, then you have to pay for another medicine that is not [reimbursed]. This is an issue for all Brazilians, they rely on the free medicine that they get [Brazil, healthcare professional-24]

Participants from Australia, Brazil, Canada and Russia stated that paediatric use labelling is a prerequisite for reimbursement negotiations. Pharmaceutical companies were described as reluctant to apply for reimbursement due to cumbersome processes, or the inability to meet reimbursement data thresholds.

> In order to get a paediatric indication reimbursed, you would need to demonstrate a comparative efficacy of your product vs standard of care, […] but for children this standard of care may not exist. [Australia, patient organization-17]

For COVID-19 vaccines, the reimbursement procedures were streamlined, which reportedly facilitated rapid access in the HICs.

> Canada is a federated nation, and […] decisions on funding of medicines are being done by 13 provinces and territories through separate negotiations. To have to negotiate a price with 13 separate bodies scares pharmaceutical companies away. In this case [of COVID-19] reimbursement was taken up to the federal level and so this issue did not exist. [Canada, health authority-22]

National pricing policies were reported to shape the prices of medicines, particularly in the public sector, but there appeared to be different approaches in the studied countries. Participants from Russia and South Africa, for example, described a fixed list price which regulates medicines purchases in the public sector. In Kenya, interviewees described a lack of a national pricing policy or negotiation. This reportedly led to pricing differences within the country, which was viewed as detrimental to access.

> There is a list price, and that listed price has to be what is charged. [South Africa, patient organization-46]

> You can get all types of price ranges on the market for children, so there is poor control. [Kenya, healthcare professional-32]

Procurement and supply

Procurement systems were perceived to affect pricing, availability, and quality of paediatric medicines. Central or hospital-based procurement using tender systems was described in Brazil and Russia, where the selection is primarily based on the lowest price. There were concerns in both countries that this leads to the purchase of cheaper medicines regardless of their quality.

> We are buying less expensive drugs and at the end we may be buying drugs that are ineffective. This worries me a lot. [Brazil, healthcare professional-30]

Medicine shortages in the public sector were considered most common in Brazil, Kenya and South Africa. The underlying reasons included underfinancing, failures in demand forecasting and organisational supply chain shortcomings. The depot system for medicines distribution in South Africa was described as cumbersome leading hospitals to use by-path routes and exacerbating supply problems.

> South Africa has a system of drug depots in each province and hospitals have to order medicines from these depos. […] It is easier for doctors to go directly to the drug companies to get these essential drugs instead of using the depot system. [South Africa, healthcare professional—organization-39]

The supply of paediatric COVID-19 vaccines was described as better compared with medicines in routine care in Australia, Brazil, Canada and Russia. Interviewees in Kenya and South Africa expressed mixed opinions and recognised the global inequity of vaccine delivery. Most industry interviewees claimed no hesitancy to supply paediatric COVID-19 vaccines globally, but it was also suggested that profit-driven practices prevailed.

> With the COVID-19 I do not see a lot of changed behaviour, you should just look at the vaccination rates in the US and in Africa. Industry goes to the regions where the big money is. [Industry-14]

Prescribing

Interview participants highlighted differences between off-label and on-label prescribing. For off-label use knowledge and acceptance of overseas labelling among health professionals were reported to shape prescription behaviour. In Russia, overseas labelling was reportedly largely unknown and liability concerns were said to further discourage off-labelling and no-labelling prescribing. On the other hand, interviewees from Canada reported

a high awareness and utilisation of scientific evidence beyond the information on the label.

> [Prescription] relates more to the rigour and robustness of the evidence, as opposed to anything having to do with the label. [Canada, healthcare professional-28]

> Based on legal considerations and in the opinion of insurance companies we must strictly follow approved [labelling] when using drugs in children. [Russia, healthcare professional-01]

Other issues affecting prescribing behaviour were staff training and qualification, limited choice of medicines and lobbying by pharmaceutical companies.

Dispensing and use

Challenges regarding trust in generic medicines were reported to reduce the acceptability of cheaper medicines among patients and healthcare professionals in the MICs. Mistrust to generics was based on the perceived poor manufacturing standards and ineffective quality control. In Russia, children were reported to preferentially receive originator brands, generic substitutes often being declined by the parents.

> These are our domestic brands; they are absolutely useless. [Russia, patient organization-09]

This attitude was known to health authorities but perceived as baseless and reduced treatment effects claimed by patients were said to be rarely medically confirmed.

> People are spoiled, plus our mentality: when a medicine is for free, they start to be picky [Russia, health authority-08].

Regarding COVID-19 vaccines, hesitancy due to personal beliefs and information overflow was reported to slow down vaccine uptake in all countries. An overburdening of the health system was reported in Kenya and South Africa.

Strengths and weaknesses of paediatric legislation

Regulatory policies were discussed by 21 study participants, 12 of whom seemed to be well familiar with EU/US legislation. Most of them perceived the legislation as successful in stimulating paediatric R&D and on-label use. The active position of the EU and US regulators was viewed positively since *'the industry would not look into [paediatric R&D] on its own' [Industry-13]*. However, it was said that many of the developed medicines address conditions uncommon in children and the lack of comparable incentives for generics was criticised. One participant in particular did not find paediatric legislation effective and described it as 'window dressing'. Others suggested that it could lead to a delay in the initiation of paediatric studies and to a focus on securing EU and US-endorsed investigation plans at the expense of alternative paediatric research. There were also concerns regarding unethical patient recruitment practices to secure compliance, delayed publication of results and lobbying.

> There is sometimes a bit of a misalignment when companies need to do the paediatric studies, very often they tend to follow […] the European Medicines Agency's Paediatric investigation plan or an equivalent in the US. […] What we see sometimes is that what these plans require or what a company has committed to do is not what is needed at the global level. [non-governmental organization-47]

Interviewees in Canada, Russia and South Africa mentioned that negotiations for similar policies were ongoing, although in Russia, they would apply only to domestic manufacturers. At the same time, several implementation concerns emerged from the interviews. First, it was stated that paediatric legislation would require substantial regulatory resources and training that are currently unavailable. Second, we found concerns regarding enforceability of requirements because companies could '*always provide arguments why it did not work' [Australia, healthcare professional-40]'*. Third, interviewees in Canada, Brazil and Russia feared that introducing requirements could make smaller markets unattractive to global companies.

> …they do not have a manpower right now at Health Canada to start looking, to take care of children. Maybe they have 2 persons in the office. There would be a major investment of resources. [Canada, patient organization-44]

> In my opinion, we cannot introduce obligatory paediatric registration for medicines since this requirement can close our market for the drugs. We also have adult patients. [Russia, health authority-08]

Most industry interviewees highlighted that appealing financial rewards were key to policy success in other regions. Some suggested that countries unable to offer rewards should limit their efforts to advocacy initiatives. Overall, a reduction of business activity due to unattractive paediatric provisions was considered possible, unless they become a global standard. However, it was also expressed that EU/US rewards were sufficient and negotiating additional incentives would be commercially advisable only in a few other markets.

> I do not think we need more rewards in other countries. […] From pure industry perspective China and Japan are the only two countries where it would be attractive to do a bit of a lobbying for paediatric legislation with rewards. The rest of the world, including Canada, Australia, and other countries you research on—it does not really matter. [Industry-18]

It emerged from the interviews that harmonisation could play a positive role in policy implementation in other regions. Some interviewees suggested national regulatory negotiations should be moved under the umbrella of a global organisation. It was discussed that this could harmonise clinical data thresholds and increase regulatory reliance.

> …what could help is perhaps a process under the umbrella of the WHO. When the WHO would take over the task of reviewing regulatory package, taking into account a reference label, and would have a central task for regulatory

review of paediatric submissions. This would also take off a financial burden locally. [Industry-15]

In my ideal world there would be a global [paediatric investigation plan] that would contain minimum set of requirements where each jurisdiction could add a separate requirement. [Canada, health authority-22]

DISCUSSION

Paediatric access barriers relating to lack of R&D, marketing registration and reimbursement were reported by interviewees from all countries as well as pharmaceutical companies. Participants from MICs additionally described more system-level access barriers. These included insufficient procurement and supply systems, limited domestic manufacturing, lack of pricing regulations and mistrust towards generics. Resulting access inequalities were considered exacerbated for off-label or no-label use, which require significant resources, knowledge and support. The COVID-19 pandemic was said to have reduced regulatory hurdles while further heightening inequalities between countries. Opinions about the EU/US paediatric legislation were mixed. Regulatory resource constraints and fears of discouraging industry activity in smaller markets were reported to deter policy implementation.

Our study results and the scientific literature show that access barriers in HICs are related to regulatory systems, including marketing registration, R&D and reimbursement.[46–49] In these countries, paediatric legislation could alleviate widely reported off-label and formulation issues while relying on strong medicines provision systems.[50 51] Hence, the transfer of paediatric legislation to HICs could be particularly impactful, although some high-priced medicines may remain inaccessible.

The access barriers identified in MICs were broader and more closely linked to underlying, system-level shortcomings.[52 53] This suggests that pairing regulatory policies with supportive measures strengthening the health system would be vital to improving access. For example, governments should implement policies aimed at reducing the prices of medicines, which remain a significant barrier.[54] This could include extending regulatory provisions to generic formulations that remain largely unavailable.[55] However, a negative attitude to generics found in our study and other healthcare contexts[56–58] may threaten the success of such policies. Strengthening public confidence in generic manufacturing standards should be considered alongside regulatory changes.[59]

The role of national regulatory frameworks in determining medicines access has been highlighted by the results of this study and the wider literature.[60 61] In addition to the inherent characteristics of the paediatric market, policies of individual states have been shown to further reduce the attractiveness of paediatric R&D. Specifically, the study results underpin the negative impact of divergent regulatory and reimbursement requirements that have been discussed in other publications.[62–65] For example, Health Technology Assessment (HTA) agencies providing the basis for reimbursement decisions in the HICs have been criticised for not being transparent enough[66] and lacking regionally harmonised requirements.[67 68] Moreover, methodologies routinely applied in reimbursement evaluations were found to be less suitable for paediatric populations.[69 70] Harmonisation of requirements could support access globally including the LMICs where the HTA agencies may face lack of capacity or technical expertise.[71 72] Available regulatory initiatives, such as the WHO Collaborative Registration Procedure, increase standardisation and reliance[73] and should be further pursued for paediatric medicines. Similar harmonisation efforts are required between national regulatory and reimbursement authorities.[67 74]

The transfer of paediatric legislation to other settings requires attention to the global legislative framework as well as a robust tailoring to national contexts. The challenge of designing appropriate national rewards was widely discussed in the interviews. Combined with the existing rewards under the EU/US legislation, additional national rewards for regulatory utilisation of paediatric data could lead to an overincentivisation of the pharmaceutical industry and a duplication of spending. Debates such as these highlight the relevance of regulatory cooperation via international platforms such as the WHO Paediatric Regulatory Network[75] and suggest that engaging in a dialogue with the pharmaceutical industry would be beneficial. While tailored paediatric policies are still under development, governments should focus on strengthening regulatory mechanisms governing no-label and off-label use of medicines as well as stringent compounding standards.[76] Ensuring that such mechanisms are well known and readily available could be an effective, if limited, contribution to patient welfare.

Additionally, the lessons from the COVID-19 pandemic highlighted the limitations of regulatory actions when paired with a reliance on international manufacturers of patented medicines.[77] Despite the efforts to expedite the marketing registration in LMICs,[78 79] vaccines were primarily supplied to HICs able to afford securing doses at competitive prices, contributing to the extreme inequality of the global vaccine access.[80] The small number of manufacturers and lack of generic products has been acknowledged to contribute to the shortage of COVID-19 vaccine doses.[81 82] The shortage of domestic manufacturing capacities and the lack of technology transfer have proven problematic beyond crises situation like COVID-19.[83 84] Accordingly, international recommendations routinely highlight the necessity of strengthening domestic R&D and manufacturing capacities as well as facilitating access to intellectual property.[85]

CONCLUSIONS AND RECOMMENDATIONS

The study findings suggest that paediatric legislation may be most impactful in countries with mature health systems and should be accompanied by measures addressing access barriers beyond marketing registration. Ideally, legislative changes would build on a harmonisation of paediatric drug research and regulatory processes, that could be achieved through WHO structures, such as the WHO Paediatric Regulatory Network. For medicines with high public health relevance strengthening domestic manufacturing capacities and technology transfer is recommended.

STUDY LIMITATIONS AND FURTHER RESEARCH

This study benefited from the inclusion of various stakeholders in six countries of diverse income levels. While we are unaware of a similarly comprehensive study in this area, our analysis is still limited by the purposive country selection, possible selection bias in the participants' recruitment, and the predefined semistructured interview guide. Specifically, fluency in German, English or Russian as one of the selection criteria may have limited the scope of possible participants for Brazil, Kenya and South Africa. We made our best effort to include interview participants with diverse backgrounds to arrive at a balanced representation of the relevant perspectives, but our list of stakeholder groups may be not fully exhaustive. Further research in other geographical regions and the involvement of domestic manufacturers and reimbursement authorities is recommended to further refine policy recommendations. Finally, implementation challenges of paediatric legislation and ways to overcome them require further study.

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Supplement 1. Select categories of the paediatric regulatory framework in Australia, Brazil, Canada, Kenya, Russia, South Africa.

Category	Australia	Brazil	Canada	Kenya	Russian Federation	South Africa
National regulatory framework						
Legislation to provide financial incentive for development of medicines for children.	No	No	In effect from 2006	No	No	No
Legislation mandating development of medicines for children.	No	No	No	No	No	No
Legislation mandating placing medicines for children on the market	No	No	No	No	No	No
Guidelines on product information include section on paediatric use	Yes	Yes	Yes	Yes	Yes	Yes
Other regulatory measures to support medicines for children.	Regulatory fee waiver for low volume products	Expedited regulatory review	Paediatric Expert Advisory Committee	No	Expedited regulatory review	No
International regulatory collaboration						
Paediatric cluster calls with EMA and FDA	Yes	No	Yes	No	No	No
ICH affiliation	Observer	Member	Member	None*	Observer	Observer
ACCESS Consortium member	Yes	No	Yes	No	No	No
Global Collaborative Oncology Review Program member	Yes	Yes	Yes	No	No	No
WHO Collaborative Registration procedure participant	No	No	No	Yes	No	Yes

* Only within East African Community

EMA – European Medicines Agency

FDA – Food and Drug Administration

ICH – International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

WHO – World Health Organization

Paediatric cluster calls - monthly teleconferences between regulatory authorities on paediatric drug development

ACCESS Consortium – collaboration of regulatory authorities to promote harmonization of regulatory requirements.

Global Collaborative Oncology Review Program – collaboration of regulatory authorities to facilitate approvals of oncology medicines.

Collaborative Registration procedure – aims to accelerate national marketing registration through information sharing

Supplement 2. Pharmaceutical value chain: main themes in access to medicines for children

Pharmaceutical value chain stage	Main themes						
	Pharmaceutical Industry	Australia	Canada	Russian Federation	Brazil	Kenya	South Africa
R&D and Innovation	Financial and operational hurdles						
	Divergent national regulations						
Manufacturing	Lack of paediatric formulations						
			Hospital compounding sub-optimal	Hospital compounding as alternative	Hospital compounding sub-optimal		
				Lack of domestic manufacture			
Marketing registration	Lack of on-label medicines						
	Need for support beyond EU/US						
	Flexibility in pandemic						
	Cumbursome special access programms						
Selection, Pricing and Reimbursement		Price as access barrier					
				State price regulations		Lack of pricing policy	State price regulations
	No reimbursement for off-label						
	Discouraging reimbursement practices						
	Flexibility in pandemic						
Procurement, Supply				Quality concerns for tenders			
					Medicine shortages		
	Global supply in pandemic	Better supply in pandemic				Supply inequity in pandemic	
Prescribing	Off-label prescription routine			Off-label discouraged			
				Staff qualification		Staff qualification	
Dispensing and Use		Vaccine hesitancy despite pandemic					
				Mistrust in generics			
						Health system overburden in pandemic	

3.3 Volodina A, Jahn A, Jahn R. Public health relevance of medicines developed under paediatric legislation in Europe and the USA: a systematic mapping study

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Public health relevance of medicines developed under paediatric legislation in Europe and the USA: a systematic mapping study

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ABSTRACT

Background Legislation in the European Union (EU) and the USA promoting the development of paediatric medicines has contributed to new treatments for children. This study explores how such legislation responds to paediatric health needs in different country settings and globally, and whether it should be considered for wider implementation.

Methods We searched EU and US regulatory databases for medicines with approved indications resulting from completed paediatric development between 2007 and 2018. Of 195 medicines identified, 187 could be systematically mapped to the burden of the target disease for six study countries (Australia, Brazil, Canada, Kenya, Russia, South Africa) and globally, using disability-adjusted life years (DALYs). All medicines were also screened for inclusion on the WHO Model List of Essential Medicines (EML) and the EML for children under 13 years (EMLc).

Results The studied medicines were disproportionately focused on non-communicable diseases, which represented 68% of medicines and 21% of global paediatric DALYs. On the other hand, we found 28% of medicines for communicable, maternal, neonatal and nutritional disorders, representing 73% of global paediatric DALYs. Neonatal disorders and malaria were mapped with two medicines, tuberculosis and neglected tropical diseases with none. The gap between medicines and paediatric DALYs was greater in countries with lower income. Still, 34% of medicines are included in the EMLc and 48% in the EML.

Conclusions Paediatric policies in the EU and the USA are only partially responsive to paediatric health needs. To be considered for wider implementation, paediatric incentives and obligations should be more targeted towards paediatric health needs. International harmonisation of legislation and alignment with global research priorities could further strengthen its impact on child health and support ongoing efforts to improve access to medicines. Furthermore, efforts should be made to ensure global access to authorised paediatric medicines.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Paediatric legislation in the European countries and the USA has stimulated research and development of medicines for children. According to impact assessments, the number of paediatric medicines in these has increased. However, there are no studies to assess the potential impact on the childhood burden of disease beyond these countries and globally.

WHAT THIS STUDY ADDS

⇒ Emerging treatments do not reflect the disease burden in high-income countries and diverge even further from the needs in resource-constrained settings. Nevertheless, they offer more treatment options for select high-burden conditions, such as universally occurring infections and debilitating non-communicable diseases. They are also important contributors to the WHO lists of essential medicines. To achieve a better public health impact paediatric legislation should be expanded internationally, harmonised and tailored to global research priorities in children.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study informs ongoing and future regulatory reform processes and especially the current revision of the EU Paediatric Legislation, to support the development of more impactful policies.

INTRODUCTION

Access to medicines remains a key priority of the United Nations Sustainable Development Goals (SDGs) aiming to secure healthy well-being.[1] The SDGs recognise the need to promote research and development (R&D) of missing medicines and vaccines, especially for low- and middle-income countries (LMICs).[2] Children are particularly affected by the continuing lack of R&D and quality, safe and effective medicines globally.[3–5] To improve paediatric care, the European Union (EU) and the USA introduced paediatric medicines legislation in 2007 and 1997, respectively. This legislation is based on a combination of obligations and incentives. Pharmaceutical companies are required to conduct paediatric investigations for new medicines including those intended for use in adults, receiving patent extensions in

return.[6 7] Research has shown that there has been an increase in paediatric labelling and formulations in both regions since the legislation was introduced.[8–11] These findings suggest that similar legislation may be used to improve paediatric medicines availability and access in other regions.

However, one concern regarding EU/US paediatric legislation is that the paediatric R&D it encourages may not meet paediatric needs, thus limiting its practical benefits for paediatric care.[9] Exploring the responsiveness of paediatric legislation to the health needs of children globally and in different countries is therefore crucial for understanding its potential for wider implementation. To our knowledge, there have been no systematic comparisons between paediatric medicines and paediatric needs beyond the implementing regions in relation to paediatric legislation so far. Addressing this gap, we map the spectrum of new paediatric medicines developed under paediatric legislation in the EU and USA to the burden of the target diseases in six countries of diverse income levels (Australia, Brazil, Canada, Kenya, Russia, South Africa) and globally. As a measure of disease burden, we use disability-adjusted life years (DALYs), which quantify the loss of health by combining years of life lost plus years lived with disability.[12] In addition, we assess the inclusion of the studied medicines in the WHO Model List of Essential Medicines (EML) as an indicator of their relevance to paediatric health needs relative to existing medical products. Based on this assessment, the paper examines the role of paediatric legislation for paediatric care in the international context.

METHODS

Study context

This analysis is part of a larger study of paediatric regulatory policies and their implications for universal access. The selection of countries aimed for variability in geographical context, economic development, as well as regulatory and health systems. The selection was constrained by data collection considerations of the wider project, such as the availability of open-access data on medicine labelling (for more information, see Volodina *et al*[13]). After an initial assessment, Australia, Brazil, Canada, Kenya, Russia and South Africa were selected for analysis. For the present paper, we applied a systematic mapping approach to ensure rigour, reduce bias and gain a comprehensive overview over the medicine development landscape under the EU/US legislation.

Sample of medicines developed under paediatric legislation

The medicines included in this review were identified from the open-access databases of medicines maintained by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[14 15] The databases were downloaded and filtered for all medicines with approved indications resulting from paediatric development completed between 1 January 2007 and 31 December 2018. Paediatric development was indicated by completed Paediatric Investigation Plans (EMA) or approved paediatric labelling (FDA). The variables required for this study (approved indications, approved formulations) were included in the FDA database, so no additional data extraction was necessary. For the EMA database, information regarding these variables had to be extracted by hand from the individual medicine's entry on the EMA website.[16] Data used for this analysis were cross-checked with other sources to ensure reliability. Lastly, medicines withdrawn for safety reasons, duplicates and medicines without an approved indication were excluded, and database entries that belonged to the same medicine were consolidated (for more information, see Volodina *et al*[13]). For the present analysis, the sampling included medicines authorised in any EU country as opposed to only those approved in all EU countries, resulting in a larger sample than in Volodina *et al*.[13] For the included medicines from the FDA, a random sample of 22% was drawn. The total sample comprised 195 medicines, 127 from the EU and 68 from the USA.

Indicators of the public health relevance

To assess the responsiveness of the EU/US paediatric legislation to paediatric health needs, we (1) mapped the sampled medicines to the DALYs of the target condition(s) and (2) reviewed their EML status.

The burden of disease assessment was based on DALY data from the 2019 Global Burden of Diseases (GBD) results published by the Institute for Health Metrics and Evaluation (IHME).[17] The GBD results are organised hierarchically with mutually exclusive diseases or conditions that cause death or disability referred to as 'DALY cause'. There are four hierarchical levels of DALY causes, starting with three categories at the first level: (1) communicable, maternal, neonatal and nutritional causes (CMNN); (2) non-communicable diseases (NCDs) and (3) injuries. The fourth level includes individual conditions or pooled categories as the most detailed causes. As example, see the levels for 'typhoid fever' provided in the 'GBD concepts and terms defined': 'level 1: CMNN; level 2: enteric infections; level 3: typhoid and paratyphoid; level 4: typhoid fever'.[18]

The responsiveness to paediatric health needs considering existing treatments was assessed by reviewing medicines' status in the WHO EML and the EML for children under 13 years of age (EMLc). Both EMLs have a core and a complementary list, representing the needs of basic and specialised healthcare systems, respectively.[19]

Data analysis

The sampled medicines were matched to the International Classification of Disease code corresponding to the target diseases using the open-access online electronic International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10).[20] Code matching was based on the target disease in the approved indication with the ICD-10 code specification

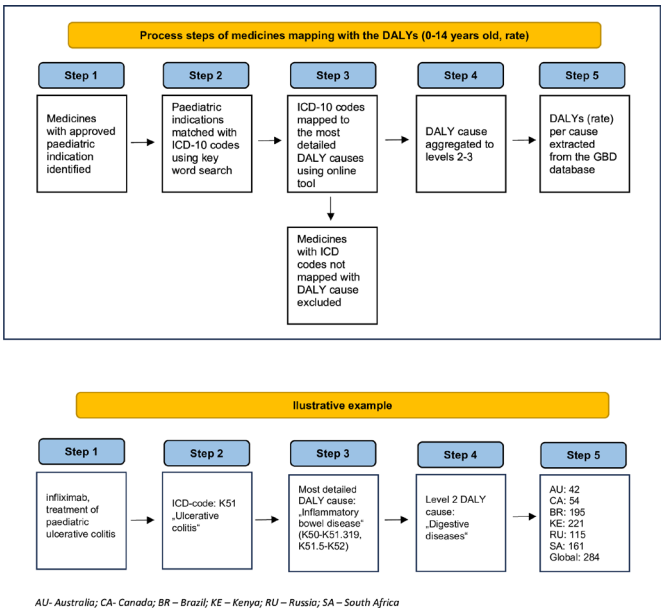


Figure 1 Process steps of medicines mapping to the disability-adjusted life years (DALYs) with an illustrative example. GBD, Global Burden of Diseases; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision.

up to the first three or four characters. Medicines with more than one indication were matched with multiple ICD-10 codes.

The codes obtained were mapped to the most detailed DALY causes in children (0–14 years, total DALYs and rate) for each country and globally. Mapping was done using the online IHME tool.[21] The mapping process is shown in figure 1. The mapping results to the most detailed DALY causes can be found in online supplemental file 1).

For analysis and reporting, the mapping results were aggregated to DALY cause level 2. For relevant compound level 2 categories, level 3 DALY causes were used instead to ensure sufficient detail (see table 1).

Results were calculated as percentages (proportions) according to the rounding rules and organised according to the level 1 DALY causes (tables 2–4). The colour code was generated automatically using the XLS function of conditional formatting.

Mutually exclusive thematic categories were developed for medicines mapped with <0.05 DALYs to distinguish between global or national lack of measurable burden (table 5).

The international nonproprietary name search of the full sample was performed in the 23rd EML and the 9th EMLc from 2023. To account for the difference in the paediatric population between the EMLc (up to 13 years) and paediatric legislation (up to 18 years), and to capture essential medicines for adolescents, we included the EML in our review. When the EMLs included the Anatomical Therapeutic Chemical (ATC) subgroup as a therapeutic alternative, it was searched using the online ATC database.[22] Assignment to the core or the complementary list was recorded.

Descriptive tables, figures and statistics were generated using MS Excel.

PATIENT AND PUBLIC INVOLVEMENT

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Burden of disease mapping

The 195 medicines were matched with 101 ICD-10 codes, allowing a DALY mapping for 187 medicines. For three ICD-10 codes, no DALY cause could be found in the online DALY tool, and eight medicines were excluded from the analysis (online supplemental file 2). In total, 61 (21%) of the 293 most detailed DALY causes were mapped to at least one medicine in the sample. A total of 128 medicines (68%) were mapped to NCDs which captured 21% of the global disease burden (30 031 DALYs). 52 medicines (28%) were mapped to CMNN diseases, which captured 73% of the global disease burden (21 915 DALYs). Two medicines with multiple indications were mapped to both, communicable and non-communicable disease groups. And lastly, nine medicines (5%) were mapped to

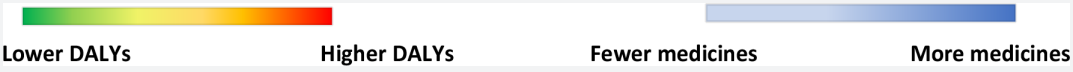
Table 1 Overview of compound level 2 DALY causes and corresponding level 3 DALY causes used for mapping

Compound level 2 DALY causes	Level 3 DALY causes used for mapping
Other non-communicable diseases	Congenital birth defects; urinary diseases and male infertility; gynaecological diseases; sudden infant death syndrome; oral disorders; endocrine, metabolic, blood and immune disorders; haemoglobinopathies and haemolytic anaemias
Respiratory infections and tuberculosis (TB)	Respiratory infections excl. TB; tuberculosis
Neglected tropical diseases (NTDs) and malaria	NTDs excl. malaria; malaria
HIV/AIDS and other sexually transmitted diseases (STDs)	STDs excl. HIV/AIDS; HIV/AIDS
Maternal and neonatal disorders	Maternal disorders; neonatal disorders

DALY, disability-adjusted life year.

Table 2 Medicines for children (N=52) mapped to communicable diseases, maternal, neonatal disorders and nutritional (CMNN) diseases, with corresponding disease burden ranked by global burden

DALY cause	DALYs per 100 000, 0–14 years, 2019 (% of total burden of DALYs attributed to CMNN diseases)							Mapped medicines, n (% of CMNN mapped medicines)
	AU	BR	CA	KE	RU	SA	Global	
Neonatal disorders*	1139 (69)	5907 (66)	1543 (76)	9000 (34)	1456 (52)	10 669 (45)	8883 (41)	2 (4)
Respiratory infections excl. TB	221 (13)	1199 (13)	226 (11)	3330 (13)	543 (20)	2687 (11)	3360 (15)	16 (31)
Enteric infections	76 (5)	566 (6)	139 (7)	5238 (20)	228 (8)	2550 (11)	3241 (15)	6 (12)
Other infectious diseases	81 (5)	300 (3)	71 (3)	1856 (7)	231 (8)	1474 (6)	1952 (9)	19 (37)
Malaria*	<0.05 (0)	7 (0)	<0.05 (0)	2450 (9)	<0.05 (0)	40 (0)	1820 (8)	2 (4)
Nutritional deficiencies	117 (7)	601 (7)	53 (3)	1705 (6)	135 (5)	1155 (5)	1344 (6)	1 (2)
STDs excl. HIV	1 (0)	37 (0)	<0.05 (0)	420 (2)	2 (0)	1321 (6)	371 (2)	2 (2)
HIV/AIDS*	2 (0)	79 (1)	4 (0)	1875 (7)	150 (5)	3072 (13)	338 (2)	15 (29)
Tuberculosis*	1 (0)	26 (0)	1 (0)	220 (1)	16 (1)	621 (3)	311 (1)	0 (0)
NTDs excl. malaria	13 (1)	171 (2)	4 (0)	241 (1)	16 (1)	96 (0)	290 (1)	0 (0)
Maternal disorders	<0.05 (0)	3 (0)	<0.05 (0)	5 (0)	<0.05 (0)	<0.05 (0)	4 (0)	0 (0)
Total burden	1651	8897	2041	26 340	2777	23 685	21 915	



All DALY causes aggregated at the second level unless marked with *.
DALY source: Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.
*DALY causes aggregated to the third level.
AU, Australia; BR, Brazil; CA, Canada; DALY, disability-adjusted life year; KE, Kenya; NTD, neglected tropical disease; RU, Russia; SA, South Africa; STD, sexually transmitted disease; TB, tuberculosis.

injuries, which captured 6% (1783 DALYs) of the global disease burden.

In the following, we present the results of the systematic mapping of medicines to GBD DALYs by the three level 1 causes CMNN, NCDs and injuries in order of global disease burden (see tables 2–4).

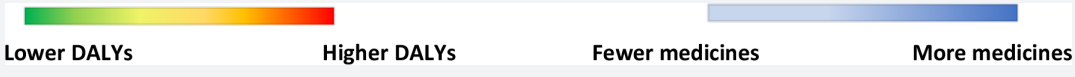
Table 2 presents the mapping results for CMNN diseases and includes 52 medicines (28%) of all mapped medicines, of which 7 were mapped to more than one cause. The CMNN DALY cause with the highest burden across all countries and globally was 'neonatal disorders' with 8883 global CMNN DALYs (41% of all respective DALYs). It was mapped to 2 (2%) CMNN medicines, both *Streptococcus pneumoniae* vaccines. Malaria with 1820 (8%) global CMNN DALYs was mapped to two medicines, tuberculosis with 311 (1%) global CMNN DALYs and neglected tropical diseases with 290 (1%) global CMNN DALYs were mapped to none. Overall, 'other infectious diseases', 'HIV/AIDS' and 'respiratory infections excl. TB' were each mapped to 15 or more medicines, by far the highest number. 'Other infectious diseases' with 1952 (9%) global CMNN DALYs was mapped to 19 (37%) CMNN medicines. 12 of them were for hepatitis B or C, bacteraemia, cytomegalovirus and invasive fungal infections, and 7 were multicomponent childhood vaccines.

Table 2 also shows that middle-income countries bear a higher burden of infectious diseases, nutritional deficiencies and neonatal disorders.

Table 3 presents the DALY mapping for NCDs, which includes 128 (68%) of medicines, of which 9 are mapped to more than one cause. The burden of disease distribution did not reveal striking differences between the countries or globally. The DALY cause with the highest burden was 'congenital birth defects' with 2394 (38%)

Table 3 Medicines for children mapped to non-communicable diseases (NCDs; N=128) with corresponding disease burden ranked by global burden

	DALYs per 100 000, 0–14 years, 2019 (% of total burden of DALYs attributed to NCD)							Mapped medicines, n (% of mapped NCD medicines)
DALY cause	AU	BR	CA	KE	RU	SA	Global	
Congenital birth defects*	720 (18)	3077 (41)	809 (21)	1734 (34)	1108 (27)	1653 (35)	2394 (38)	2 (2)
Skin and subcutaneous diseases	715 (18)	735 (10)	759 (20)	601 (12)	768 (19)	504 (11)	627 (10)	13 (10)
Mental disorders	822 (21)	766 (10)	625 (16)	512 (10)	491 (10)	516 (11)	587 (9)	8 (6)
Neurological disorders	317 (8)	685 (9)	330 (8)	382 (8)	314 (8)	391 (8)	433 (7)	15 (12)
Neoplasms	220 (6)	484 (7)	251 (6)	295 (6)	308 (8)	173 (4)	426 (7)	10 (8)
Digestive diseases	42 (1)	195 (3)	54 (1)	221 (4)	115 (3)	161 (3)	284 (4)	10 (8)
Haemoglobinopathies and haemolytic anaemias*	12 (0)	79 (1)	8 (0)	189 (4)	22 (1)	34 (1)	280 (4)	3 (2)
Chronic respiratory disease	479 (12)	461 (6)	326 (8)	273 (5)	173 (4)	340 (7)	267 (4)	13 (10)
Cardiovascular diseases	46 (1)	222 (3)	59 (2)	187 (4)	76 (2)	159 (3)	233 (4)	7 (5)
Endocrine, metabolic, blood, immune disorders*	167 (4)	161 (2)	134 (3)	79 (2)	154 (4)	186 (4)	159 (3)	29 (23)
Sense organ diseases	104 (3)	147 (2)	72 (2)	196 (4)	133 (3)	197 (4)	157 (2)	12 (9)
Sudden infant death syndrome*	102 (3)	45 (1)	68 (2)	87 (2)	102 (3)	135 (3)	125 (2)	0 (0)
Musculoskeletal disorders	126 (3)	161 (2)	218 (6)	80 (2)	160 (4)	74 (2)	123 (2)	8 (6)
Diabetes and kidney disease	25 (1)	92 (1)	39 (1)	79 (2)	61 (2)	93 (2)	122 (2)	5 (4)
Oral disorders*	50 (1)	55 (1)	50 (1)	52 (1)	57 (1)	52 (1)	54 (1)	1 (1)
Urinary diseases and male infertility*	8 (0)	52 (1)	9 (0)	24 (0)	14 (0)	11 (0)	35 (0.5)	1 (1)
Gynaecological diseases*	22 (1)	24 (0)	23 (1)	25 (0)	22 (1)	22 (1)	24 (0.3)	1 (1)
Substance use disorders	8 (0)	5 (0)	13 (0)	2 (0)	4 0)	2 (0)	3 (0)	0 (0)
Total burden	3985	7446	3847	5018	4082	4704	6333	



All DALY causes aggregated at the second level unless marked with *.
DALY source: Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.
*DALY causes aggregated to the third level.
AU, Australia; BR, Brazil; CA, Canada; DALY, daily-adjusted life year; KE, Kenya; RU, Russia; SA, South Africa.

Table 4 Medicines for children (N=9) mapped to injuries with corresponding disease burden ranked by global burden

DALY cause	DALYs per 100 000, 0–14 years, 2019 (% of total burden of DALYs attributed to injuries)							Mapped medicines, n (% of injury mapped medicines)
	AU	BR	CA	KE	RU	SA	Global	
Unintentional injuries	574 (74)	838 (56)	308 (57)	659 (65)	851 (67)	923 (51)	1107 (62)	8 (89)
Transport injuries	130 (17)	371 (25)	143 (26)	217 (22)	258 (20)	555 (31)	437 (25)	0 (0)
Self-harm and interpersonal violence	70 (9)	279 (19)	90 (17)	133 (13)	171 (13)	321 (18)	240 (13)	1 (11)
Total burden	774	1488	541	1009	1280	1799	1783	

Lower DALYs — Higher DALYs — Fewer medicines — More medicines

All DALY causes aggregated at the second level.
DALY source: Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.
AU, Australia; BR, Brazil; CA, Canada; DALY, daily-adjusted life year; KE, Kenya; RU, Russia; SA, South Africa.

NCD DALYs globally. It was mapped to two medicines for paediatric glaucoma. Several high-burden DALY causes were well represented in the sample, such as 'skin and subcutaneous diseases' with 627 (10%) global NCD DALYs and 13 (10%) NCD treatments, 'neurological disorders' with 443 (7%) global NCD DALYs and 15 (12%) NCD treatments. However, most NCD medicines (23%) were mapped to the DALY cause of endocrine, metabolic, blood and immune disorders ('EMBI'), which accounted for 3% of NCD DALYs globally. The most targeted 'EMBI' indications were anaemia, rare coagulation and metabolic disorders.

For several NCD DALY causes at levels 2 and 3, medicines were indicated for a few conditions. For example, in 'musculoskeletal disorders', seven out of eight medicines were for juvenile arthritis. In 'chronic respiratory diseases', eight medicines were for allergic rhinitis and the remaining five for asthma. 'Diabetes and kidney diseases' was mapped exclusively to insulins.

Table 4 shows the mapping results for the level 1 DALY group 'Injuries', which was mapped with 9 (5%) of all mapped medicines. Eight medicines addressed complications of medical treatment and were mapped to 'unintentional injuries'. One medicine in the 'self-harm and interpersonal violence' was indicated to prevent organ transplant rejection. The DALY distribution for injuries was higher in the middle-income countries.

In total, 28 medicines were mapped to DALY causes at the most detailed level that had a negligible burden of disease (<0.05 DALYs) (see table 5). 18 of these medicines targeted conditions uncommon in children in all studied countries and globally. These were either generally rare diseases (eg, rare tumour), diseases that primarily affect the adult population but are uncommon in children (eg, hypertension), or human papillomavirus vaccines.

10 medicines were mapped to diseases with a lack of measurable burden in some countries, namely in Australia and Canada.

Table 5 Medicines (N=28) for conditions with <0.05 DALYs (0–14 years) with thematic categories

Thematic category	Paediatric indication	Medicines with respective indication, n
No measurable burden in all studied countries	Hypertension	6
	Type II diabetes mellitus	5
	HPV infection	2
	Immediate reduction of blood pressure in hypertensive crisis	1
	Multiple sclerosis	1
	Subependymal giant cell astrocytoma	1
	Infantile haemangioma	1
	Heavy menstrual bleeding	1
No measurable burden in some studied countries	Poliomyelitis	4
	Diphtheria	4
	Tetanus	4
	Treatment or prevention of hepatitis B	6
	Malaria	2
	Chronic hepatitis C	1

DALY, daily-adjusted life year; HPV, human papillomavirus.

WHO EMLs review results

Of all 195 sampled medicines, 67 (34%) were found in the EMLc and 93 (48%) in the WHO EML (see table 6), with most medicines included in the core lists. The largest groups were childhood and influenza vaccines, antivirals and antifungals, human immunoglobulins, medicines for blood disorders and antiretrovirals. Of the 26 medicines included only in the EML, 7 were for adolescent use for

Table 6 WHO essential medicines list inclusion of sampled medicines for children (N=195)

WHO list inclusion	Number of medicines, n (%)
Medicines included in the EMLc, 2023	**67 (34)**
Out of them:	
Medicines in the core list	45
Of these, included as therapeutic alternatives	11
Medicines in the complementary list	22
Of these, included as therapeutic alternatives	5
Medicines included in the EML, 2023	**93 (48)**
Out of them:	
Medicines in the core list	67
Of these, included as therapeutic alternatives	22
Medicines in the complementary list	26
Of these, included as therapeutic alternatives	7

EML, Essential Medicines List; EMLc, Essential Medicines List for children.

mental disorders, emergency contraception or HIV/AIDS pre-exposure prophylaxis.

DISCUSSION

Our study shows that the sampled medicines developed under paediatric legislation in the EU and USA are a heterogeneous group with limited responsiveness to children's health needs. Overall, we found a disproportionate focus on NCDs, many of which have a high burden on adults but not on children. Conversely, we found few medicines that address high-burden paediatric diseases, particularly childhood infections. Still, the inclusion of about a third of the sampled medicines in the WHO EMLc suggests that there has been a relevant contribution to paediatric care. Finally, the study identified high-burden diseases with available treatments where access remains limited.

Mismatch between disease burden and spectrum of medicines

Our findings support previous evidence on the limited alignment between R&D and paediatric needs in the EU and the USA itself, including the bias towards therapeutic areas with relevant adult indications.[23] Studies conducted after the adoption of the EU/US legislation have shown persisting off-labelling prescribing across therapeutic areas.[24 25] This evidence, together with our study, suggests that while paediatric legislation may have addressed the needs of children to some extent, significant gaps remain. The lack of paediatric treatments for poverty-related diseases shows that the gap between the needs and research efforts is most pronounced for children in LMICs.

The focus on areas with adult indications found in our study echoes the fact that paediatric legislation requires developers to assess the potential of medicines primarily developed for adults for their use in children. However, this policy approach is limited by the lack of alignment between research efforts and health needs of children and adults in general. A study by the US Congressional Budget Office suggested that instead of health needs, R&D investment decisions are based on expected sales, R&D costs and local policies.[26] A study analysing the pharmaceutical pipeline from 2006 to 2011 found that 26% of 2477 medicines were indicated for neoplasms, followed by diseases of the nervous system and sense organs (13%), infectious and parasitic diseases (11%) and EMBI disorders (9%).[27] These figures are echoed in the distribution of medicines in our study and do not reflect the spectrum of the global burden of disease, in adults or children.[28]

Advancing regulatory policies for children

Our results show that there have been some relevant contributions to paediatric care since the implementation of the EU/US paediatric policies. As such, paediatric policies may be a promising policy tool to improve availability of appropriate paediatric medicines, provided they are modified to be more needs-oriented. Such changes would also be beneficial in regions where paediatric legislation is already in place. For example, the European Commission has recently proposed variable data protection periods depending on the unmet needs addressed by the medicine.[29] Such measures could strengthen the responsiveness of paediatric legislation to paediatric health needs and encourage research into conditions relevant to children. Ideally, the assessment of unmet needs underlying variable protection periods or other measures tied to paediatric needs should be based on a global assessment of paediatric needs. In addition, the introduction of paediatric legislation in countries outside of the EU and USA should include the harmonisation of regulatory obligations and rewards to enhance compliance and impact.[30] Nonetheless, fostering needs-driven R&D for paediatric medicines requires complementary financing mechanisms directed at the development of original paediatric medicines beyond the scope of paediatric legislation. This could be particularly relevant for off-patent medicines where the incentives of the EU legislation were shown to be insufficient.[23] Efforts to define missing medicines were undertaken in the past[31 32] and could serve as a sound basis for policy development in this area. Finally, alongside with regulatory policies, global initiatives and research collaborations such as the Global Accelerator for Paediatric Formulations Network and the

International Neonatal Consortium will continue to play a critical role in facilitating development and access to paediatric medicines.[33 34]

Our study also highlights that successful drug development does not always result in practical use. For example, Australia and Canada were the only countries with a negligible burden of vaccine-preventable diseases in our study. These findings underscore the relevance of health system and other barriers that affect access to existing medicines, particularly in LMICs.[35] Reducing access barriers and increasing coverage of approved medicines is therefore critical. The same applies to access to surgery, mental health services and other non-pharmacological interventions, which may be required to address some of the included paediatric conditions, such as injuries, congenital birth defects or mental disorders. Our findings also underscore the relevance of diseases related to poor living conditions and unhealthy environments, including enteric infections and nutritional deficiencies. Addressing these requires the provision of access to safe water and sanitation, food security and health education. Public health interventions beyond pharmaceutical policies thus remain indispensable in reducing paediatric disease burden and need to continue.[36 37]

Strengths and limitations

Our study provides important insights into the responsiveness of paediatric legislation to paediatric health needs in countries with diverse disease burden and globally. The study is the first to systematically compare paediatric R&D to paediatric health needs, despite more than a decade since the implementation of paediatric legislation. It offers relevant and novel insights into the potential gains and limitations of paediatric legislation and can support policy-making decisions in the EU and beyond.

This study has several limitations. The exclusion of contraceptives and symptomatic treatments, that is, pain killers, and the paediatric age group from 15 to 18 years of age from the DALYs mapping may have underestimated the responsiveness of the studied medicines sample to paediatric needs. Some DALY causes, such as injuries, frequently require non-pharmaceutical interventions or surgeries, which may explain the small number of medicines in the sample for such causes. Medicines approved after 2018 were not analysed. The EU/US orphan drug legislation[38] may have contributed to the high number of medicines for low-burden diseases, obscuring the relationship to paediatric legislation. Moreover, while our results examine the scope of medicines developed under the paediatric legislation, the lack of a comparison to paediatric R&D before policy implementation limits our ability to assess the direct effect of the legislation. Finally, limitations associated with the use of DALYs apply.[39] Research in other geographical regions is recommended to further refine policy recommendations.

CONCLUSION

Medicines developed under the paediatric legislation in the EU and USA are only partially responsive to paediatric health needs and exhibit a disproportionate focus on NCDs. To be considered for wider implementation, paediatric incentives and obligations should therefore be more targeted towards paediatric health needs. International harmonisation of legislation and alignment with global research priorities could further strengthen its impact on child health and support ongoing efforts to improve access to authorised treatments. Finally, health interventions beyond improving access to medicines are needed to achieve a global reduction of paediatric disease burden.

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4. Discussion

The aim of the present research was to examine the role of regulatory frameworks in access to paediatric medicines in different country settings and to develop regulatory recommendations for better access globally. The results highlight a critical role of marketing authorisation and define the benefits and limitations of paediatric legislation in the international context. The key findings include:

1. Authorisation availability of paediatric medicines and formulations was lower in the countries studied compared to the EU and the US. Generic medicines generally did not contain age-appropriate formulations even when they were available from the originator (study I, first publication).
2. The lack of paediatric labelling and formulations and absence of regulatory harmonisation in paediatric drug research were reported as barriers to access in all countries. Middle-income countries additionally described overarching health system barriers, such as poor health financing and supply (study II, second publication).
3. The COVID-19 pandemic has temporarily reduced regulatory barriers, but the benefits for access were perceived mainly in Australia and Canada (study II, second publication).
4. Acceptance of paediatric legislation was hampered by concerns about equity and feasibility (study II, second publication).
5. Medicines developed under paediatric legislation ranged from common childhood vaccines to highly specialised treatments, some of which were later included in the WHO lists of Essential Medicines. The spectrum of addressed diseases was not fully in line with the needs, as evidenced by the burden of disease. Among others, neonatal and poverty-related diseases were substantially underrepresented (study III, third publication).

The following discussion will focus on these key findings and close with the reflection on policy and practice implications, study limitations and future research perspectives.

4.1 National regulatory frameworks and access to paediatric medicines

The national regulatory frameworks and their impact on access to medicines for children were analysed in study I in terms of authorisation availability of paediatric indications and

formulations. Study I identified authorisation gaps across all studied countries. These gaps could be attributed, at least in part, to the lack of regulatory submissions or negative authority evaluations. Most striking was the absence of substantial difference in the number of treatments between Canada as the only country offering 6-months protection and other countries that do not offer it. Another interesting finding was a low uptake of paediatric formulations by generic companies in all countries. These findings suggest that existing regulatory provisions do not ensure the availability of age-appropriate treatments in a systematic manner.

The quantitative findings of study I were confirmed by the qualitative findings of study II. Regulatory barriers such as lack of guidance and harmonisation, paediatric labelling and formulations were reported in all countries. The availability of regulatory processes and expertise to advise on paediatric studies was considered critical by the industry but perceived as insufficient. These regulatory barriers combined with conflicting reimbursement policies were found to discourage domestic R&D and regulatory submission of paediatric research data. Study II confirmed that off-label and unlicensed medicines cannot be regarded as a sustainable alternative to nationally authorised medicines. Information barriers, out of pocket payments, and restrictive national policies make them less accessible, particularly in the LMICs.

Taken together, these findings suggest that paediatric regulatory framework should include mandatory requirements for the industry and should be extended to generic manufacturers. Mandatory global submission of paediatric data would ensure that treatment decisions are based on the same level of evidence in all countries and thus contribute to access to effective treatments. Regulatory cooperation and reliance should be further strengthened. Across the countries studied reliance procedures are currently established within geographically and politically determined alliances: Russia within the EAEU, Kenya, and South Africa within African Economic Communities, Australia and Canada with the mature regulators from the North. Strengthening of cooperation outside of these clusters could promote global equality in medicines access. Development of global paediatric reliance procedures, for example, global regulatory consultations on clinical and formulation development, systematic sharing of regulatory assessments, could facilitate access to medicines for children.

To summarise, the regulatory frameworks in the studied countries do not secure national paediatric labelling and formulations in a systematic manner. The lack of technical harmonisation and support for paediatric R&D discourages industry and strains public health resources. Together with the barriers to off-label and unlicensed use these findings provide a

compelling case for an internationally harmonised paediatric framework mandating and rewarding paediatric R&D, which should be preferably hosted by the WHO.

4.2 Paediatric legislation in the international context

Paediatric legislation in the EU and the US was analysed in studies I, II and III in terms of its unintended transboundary effects, equity, and acceptability in other countries. The key finding of study I was that this legislation had a measurable effect beyond the countries in which it was implemented. It may be taken to indicate that health policy decisions in leading jurisdictions affect the availability of medical treatments in other countries. This finding further supports the need to strengthen multi-country regulatory platforms such as the WHO Paediatric Regulatory Network to enable international policy negotiations and agreements.

The magnitude of the transboundary policy effect observed in study I was not satisfactory, with most treatments remaining confined to Europe and the US. Paediatric legislation was perceived by the industry interviewees in study II as a policy benchmark and a financial reward was seen as pre-requisite for industry involvement. These findings may suggest that future policies should be developed in the light of experience with paediatric legislation and are likely to be appraised against it in terms of acceptability and effectiveness.

When analysing policy equity defined as the ability of paediatric legislation to benefit groups with greater needs, the research confirmed a positive policy impact on some therapeutic areas that remain burdensome in children. However, it was less successful in areas routinely neglected by the drug research, such as neonatal care, malaria or neglected tropical diseases. These findings complement available regional assessments by looking at the legislation from the global perspective. The results of study III suggest that paediatric legislation increases health inequalities by not sufficiently promoting research for most vulnerable paediatric groups. If adopted globally without modification, it may lead to a widening of socioeconomic inequalities between and within the countries.

Stakeholders´ acceptance of paediatric legislation was explored in study II and revealed a mixed picture. Alongside the support and advocacy, concerns about enforcement, resources and policy effectiveness were identified, which may prevent its adoption in other countries. Indeed, an establishment of a comprehensive regulatory framework, such as the EU/US paediatric legislation, would require administrative procedures, technical guidelines, and training. Supervision of such legislation would fall within the remit of NRAs, but their structures and

functions would need to be expanded. Although the need for public funding to support implementation needs to be acknowledged, some regulatory tasks could be accommodated within the reliance mechanisms discussed above. Enforcement in smaller markets could be ensured by adopting paediatric requirements globally. This would remove the ability of pharmaceutical companies to make business decisions on the basis of paediatric requirements.

Compliance with paediatric provisions would require investment from local pharmaceutical companies that may be unfamiliar with paediatric research and formulation manufacture. Global companies would have an advantage as they could leverage on expertise gained from the EU/US. To mitigate the differences in industry readiness, paediatric provisions could have a delayed implementation deadline for domestic companies allowing them to gain experience in pilot programmes and build up an expertise.

The perception that paediatric drug development was driven by adult health issues was an important reason for effectiveness concerns among many stakeholders in study II. The fact that some medicines indeed address diseases that constitute a primary burden in adults, such as hypertension, was confirmed by study III, but these were a small proportion. It may be concluded that although it would not be entirely accurate to describe the legislation as futile, addressing the limitations identified in this research may lead to better impact and acceptance.

4.3 Advancing regulatory frameworks for better child health

The research findings suggest the directions for improvement of paediatric frameworks and implementation issues that may arise. Taken together, they confirm that the regulatory mechanism of rewards and obligations is more effective than non-binging measures, which is consistent with legislative experience in the EU and the US. The findings support the work of the WHO in promoting harmonisation and cooperation in medicines regulation. By pointing out the limitations of paediatric legislation, the obtained results indicate that changes are needed to improve equity and acceptability before it could be considered for global implementation. Approaches to advance paediatric regulatory framework for better child health globally are discussed below.

To increase policy equity, it seems necessary to link paediatric requirements to the unmet needs. The 2023 legislative proposal from the European Commission may indeed bring improvements in therapeutic areas with adult development, for example, in oncology. However, it does not contain specific measures to promote R&D for paediatric-only diseases. Nor it provides a strong

incentive for pharmaceutical companies to purposefully direct the R&D pipelines towards paediatric disease burden. Other regulatory measures and perhaps alternative funding may be needed to stimulate the development of relevant medicines.

One approach could be to link paediatric reward to the disease burden in children. Medicines that address high unmet needs in children would be subject to a 6-months global market protection and other medicines, whilst still mandatory for development, would not receive a reward. A global alignment on missing essential medicines could serve as a tool to support the regulatory evaluation of high unmet needs and transparency in decision-making. Medicines eligible for a global reward could include treatments for neonatal conditions, antimicrobials including antiparasitic treatments, antivirals, gene and cancer therapy.

To further improve acceptance, paediatric reward should be internationally aligned. Although industry interviewees in study II highlighted the lack of financial incentives as a key reason for not launching EU/US-developed medicines in other countries, receiving paediatric reward in each market could lead to over-incentivisation. The intention of the rewards was to compensate companies for paediatric R&D efforts in the absence of a return on investment, not to secure profits. The mere regulatory utilisation of paediatric data already rewarded in other jurisdiction does not justify new incentives as there is no new R&D effort to reward. However, a country-specific development effort undertaken in consultation with the national NRA should be rewarded. Furthermore, generic manufacturers should be rewarded for bringing age-appropriate formulations on the market. Based on the above and the EU proposal for varying market protection, the following rewards and obligations scheme could be considered for global legislative discussion.

Table 1. Global paediatric rewards scheme linked to the unmet needs in children

<table>
<tr><th colspan="5">R&D-based companies</th></tr>
<tr><td colspan="5">Market protection at the time of initial registration:
• for medicines with high unmet needs – 8 years
• for other medicines – 6 years</td></tr>
<tr><td rowspan="4"></td><td colspan="4">Paediatric obligation</td></tr>
<tr><td colspan="2">EITHER</td><td colspan="2">OR</td></tr>
<tr><td colspan="2">paediatric development completed in compliance with national development plan</td><td colspan="2">paediatric development completed in compliance with foreign development plan</td></tr>
<tr><td>and</td><td>or</td><td>and</td><td>or</td></tr>
<tr><td>Paediatric reward</td><td>+ 6 months market protection</td><td>paediatric development addresses high unmet needs</td><td>paediatric development does not address high unmet needs</td><td>no reward</td><td>no reward</td><td>no additional development conducted</td><td>additional development conducted</td><td>+ 6 months market protection</td></tr>
<tr><td colspan="5"></td></tr>
<tr><td colspan="5">Generic manufacturers</td></tr>
<tr><td>Paediatric obligation</td><td colspan="4">generic medicine contains all age-appropriate formulations from innovator product</td></tr>
<tr><td>Paediatric reward</td><td colspan="4">Advanced market commitment, preferential state procurement, or other reward</td></tr>
</table>

To illustrate the application of this progressive system, three hypothetical scenarios for R&D companies are described:

Scenario 1:

A company develops a medicine that meets the classification of high unmet need in adults but not in children. Paediatric drug development follows the requirements of the EU regulatory authority. Regulatory submissions are planned globally, with no further development required.

Duration of market protection: 8 years

Duration of global paediatric reward: 0 months in the EU and the rest of the world

Scenario 2:

A company develops a high unmet needs medicine exclusively for paediatric use. Paediatric drug development follows the requirements of the US regulatory authority. Regulatory submissions are planned globally. The NRA in Canada requires more patients in the dose-finding study. All other countries pose no additional requirements.

Duration of market protection: 8 years

Duration of global paediatric reward: 6 months in the US, 6 months in Canada and 0 months in the rest of the world

Scenario 3:

A company develops a medicine that does not meet the classification of high unmet needs in adults but does in children. Paediatric drug development follows the requirements of the NRA in Kenya. Regulatory submissions are planned in Kenya and Brazil. The NRA in Brazil requests additional safety study.

Duration of market protection: 6 years

Duration of global paediatric reward: 6 months in Kenya and 6 months Brazil

These examples show that such a progressive system of rewards provides higher rewards for medicines with high unmet needs in adults and children and mandates but does not reward the use of the same paediatric data in other countries.

One criticism of this proposal could be that it requires paediatric development for medicines outside of the definition of high unmet need, which may still lead to the development of paediatric treatments for “adult” indications. However, ethical concerns could be raised if mandatory paediatric R&D is only applied to high unmet needs diseases, for example in regions where paediatric legislation is already in place. This consideration supports the notion that regulatory policies cannot be an absolute guarantee of a needs-driven drug development. Another point of criticism could be that paediatric R&D outside of high unmet needs is not rewarded, although it necessitates industry investment. It would be a point of negotiation to decide on alternatives, e.g. whether a paediatric reward of 3 months and less would satisfy public health and industry stakeholders.

Regardless of the exact provisions, a global progressive reward scheme would encourage global companies to invest in paediatric diseases that offer the prospects of profit generation in most markets. A global progressive reward scheme is unlikely to direct global companies into R&D for endemic infections in resource-constrained settings, such as neglected tropical diseases.

This is because an extended market protection is unlikely to be a sufficient incentive for global companies in the absence of global sales. This policy limitation needs to be recognised. To promote R&D for endemic infections in LMICs, regulatory reforms must be accompanied by policies to strengthen domestic pharmaceutical industry.

The outlined rewards scheme is only one possible scenario. Other alternative approaches such as transferable voucher, have been proposed in the past and could be considered for global applicability. Further, direct R&D funding may still be required as a complimentary measure to regulatory policies, for example to facilitate paediatric R&D with off-patented medicines.

Decision-making bodies in all countries need to be fully informed about the benefits and limitations of paediatric legislation and consequences of not having a mandatory paediatric framework. Advocacy and awareness-raising for paediatric policies could be supported by the WHO Paediatric Regulatory Network and similar platforms.

4.4 Global health efforts beyond regulatory framework

This research provides important findings on child health and medicines access issues that go beyond the merit of regulatory frameworks. It has demonstrated that sustainable medicines procurement and supply are essential for regulatory policies to be impactful. As observed in study II, medicines affordability and availability in public sector remain the key access barriers in the middle-income countries. It is therefore likely that regulatory changes without improved national medicines provision system would be less effective and receive lower acceptance.

While in the context of the COVID-19 regulatory barriers have been reduced globally, weak medicines provision system and lack of domestic manufacture continued to hinder access in the middle-income countries. This finding suggests that domestic manufacturing capacity is indispensable for securing essential needs. Finally, substantial part of the global disease burden in children observed in study III comes from conditions not or only partly mitigated by medicines. Particularly this is evident for countries where lack of access to safe water or malnutrition remain public health threats. Public health interventions that tackle socioeconomic determinant of health should be routinely included in child health policies and, in situations of severe resource constraints, may be prioritised over regulatory advances.

4.5. Research limitations

This research is limited by the fact that it only surveyed high- and middle-income countries hence generalisability of the results to the least developed regions should be taken with caution. The research did not evaluate perceptions of all health stakeholders affected by or involved in regulatory frameworks for children and those who were interviewed were purposefully selected. In addition to the EU/US paediatric legislation, there may be other policies with demonstrated effectiveness that merit an analysis of their international applicability. Despite these limitations, this research certainly adds to our understanding of the impact of paediatric regulatory frameworks on medicines access and suggests directions for paediatric regulatory reforms in the international context.

5. Conclusions and recommendations

This research has been one of the first attempts to analyse paediatric regulatory frameworks in different countries and assess their impact on access to medicines. It shows that access to age-appropriate treatments remains a challenge in both mature and developing markets and that paediatric regulatory policies are limited and not internationally harmonised. It also confirms that marketing authorisation makes access more sustainable through the removal of barriers to off-label and unlicensed use. Overall, this research highlights a clear need to set up a global paediatric regulatory framework that would make paediatric R&D and the use of foreign data for registration mandatory.

The research findings have several practical and policy implications. They suggest that changes are necessary before the EU/US regulatory mechanism could be recommended for global implementation. Encouraging paediatric R&D in areas of greatest need, while minimising over-incentivisation of private sector, should be a key policy priority. This could be achieved by revisiting the current system of rewards and obligations and extending it to generic companies. A shift towards a needs-based remuneration system has been initiated at the EU level, which could be a first step towards the improvement of equity and acceptability of paediatric legislation. On a global scale, the precise mechanism of needs-driven rewards remains to be elaborated.

Efforts to facilitate the harmonisation of regulatory requirements for paediatric R&D need to be strengthened. A reasonable approach to tackle this task could be to promote the ICH guidelines using the existing WHO structures. In addition, the possibility of divergent regulatory decisions on the same data set should be minimised. This could be achieved through the inclusion of many more regions in the regulatory reliance procedures that are currently established in the form of disengaged clusters. Increased reliance and harmonisation are expected to help overcome concerns about enforcing obligations to global pharmaceutical industry in smaller markets, alleviate regulatory resource constraints and facilitate industry compliance.

An important practical implication of the research results is the definition of the limitations of the paediatric legislation that should be considered when deciding on its implementation or comparing with other policy proposals. These limitations include reliance on patent and market protection, pharmaceutical industry activity and strong health system. Without a sustainable health system, paediatric medicines will be authorised but remain largely inaccessible.

Therefore, measures to enhance paediatric R&D and marketing authorisation need to go hand in hand with efforts to ensure access to resulting treatments by the end-users. For medicines with high public health impact such as pandemic vaccines strengthening domestic manufacturing capacity is recommended. Finally, continued public health efforts to reach all SDGs are required to effectively reduce the disease burden in children, particularly in the LMICs.

Taken together, the research findings provide strong evidence for the establishment of a globally harmonised regulatory framework for children with needs-based rewards and obligations for innovative and generic companies. Combined with the efforts to strengthen health systems and interventions beyond public access to medicines, it is expected to make a significant contribution to child health around the world.

A natural progression of this work would be to analyse feasibility and costs of implementing harmonised paediatric regulatory framework globally. Future studies should consider other geographical regions and involve other relevant stakeholders to further guide policy design and implementation.

6. Summary

In the field of public health, the importance of access to essential medicines has been a focus of attention. For children, improving access is even more urgent as the lack of medicines with paediatric labelling and age-appropriate formulations is a global health problem. The European Union and the United States have adopted paediatric regulatory framework more than 15 years ago, that requires and rewards paediatric pharmaceutical research (hereafter referred to as paediatric legislation). In this way, both regions have been able to stimulate the research and marketing authorisation of medicines for children and thus to improve access to age-appropriate treatments.

Paediatric legislation becomes an indispensable commodity in times of health crisis. It ensures that the medical needs of this vulnerable population are addressed without undue delay. For example, vaccines against Coronavirus disease COVID-19 have been rapidly developed for paediatric use. From 2023, the European pharmaceutical legislation is under review with the aim of further strengthening paediatric research. However, the vast majority of children live outside of Europe and the United States where the role of regulatory frameworks in access to paediatric medicines is not well understood.

This research aimed to examine regulatory frameworks in six countries with different health and economic status and to develop regulatory recommendations for better access globally. Countries selected for analysis were Australia, Brazil, Canada, Kenya, Russia, and South Africa. The research employed a mixed-method design with qualitative and quantitative methods and included three studies each pertaining to a research objective. The analytical framework from the National Collaborating Centre for Healthy Public Policy in Canada was used to synthesise and interpret the results obtained.

Results: Authorisation availability of paediatric medicines and formulations in the studied countries was lower compared to Europe and the United States. Generic medicines generally did not contain age-appropriate formulations even when they were available from the originator. Regulatory barriers to access were identified in all countries. These included a lack of harmonisation of paediatric research requirements, poor availability of medicines with paediatric use information and formulations. Brazil, Kenya, Russia, and South Africa additionally described overarching health system barriers, such as poor financing and supply. Children in these countries continue to suffer from the diseases well-saturated with novel treatments, which indicates barriers to access at the health system level. The COVID-19

pandemic temporarily reduced regulatory barriers. In middle-income countries, however, the impact on access to medicines has been limited due to weak health systems. Medicines developed under paediatric legislation ranged from common childhood vaccines to highly specialised treatments, some of which were later included in the World Health Organisation´s lists of Essential Medicines. However, the spectrum of addressed diseases was not fully in line with the needs, as evidenced by the burden of disease. Among others, medicines for neonatal and poverty-related diseases were substantially underrepresented. Acceptance of paediatric legislation was hampered by concerns about its equity and feasibility.

Conclusions: Regulatory frameworks in the studied countries remain unable to support access to paediatric medicines and formulations in a systematic manner. National marketing authorisation is essential for equitable access but in case of paediatric medicines it cannot be achieved without binding regulatory measures. Overall, the research highlights the need for a globally harmonised paediatric regulatory framework that would contain needs-based rewards and obligations for pharmaceutical companies. While regional legislative efforts are underway, they should become global. The impact of regulatory measures may be limited if not combined with a robust system to deliver medicines to patients and industry activity in a country. Therefore, efforts to strengthen the health system and support for the domestic manufacturing sector remain necessary elements of access to medicines. Finally, continued public health efforts to reach all Sustainable Development Goals are required to effectively reduce the disease burden in children, particularly in the low-and middle-income countries.

7. Zusammenfassung

Im Bereich der öffentlichen Gesundheit steht der Zugang zu unentbehrlichen Arzneimitteln im Mittelpunkt. Dennoch ist der Mangel an Arzneimitteln für Kinder ein weltweites Gesundheitsproblem. Die Europäische Union und die Vereinigten Staaten von Amerika haben vor mehr als 15 Jahren gesetzliche Maßnahmen ergriffen, die die pharmazeutische Industrie verpflichten und gleichzeitig finanziell belohnen, Arzneimittel für Kinder zu entwickeln (im Folgenden Kindergesetzgebung genannt). In beiden Regionen ist es gelungen, die Erforschung und Zulassung von Arzneimitteln für Kinder zu fördern und damit den Zugang zu verbessern.

Bei Gesundheitskrisen wie Pandemien wird eine solche Gesetzgebung zu einem unverzichtbaren Instrument. Sie gewährleistet, dass die Gesundheitsbedürfnisse dieser vulnerablen Bevölkerungsgruppe unverzüglich berücksichtigt werden. So wurden beispielweise Impfstoffe gegen die Coronavirus Erkrankung COVID-19 zügig für die pädiatrische Anwendung entwickelt. Seit 2023 wurden auf europäischer Ebene weitere legislative Anstrengungen unternommen, um die pädiatrische Forschung zu stärken. Die überwiegende Mehrheit der Kinder lebt jedoch außerhalb der Europäischen Union und der Vereinigten Staaten. Es gibt nur wenige Erkenntnisse darüber, wie sich die gesetzlichen Rahmenbedingungen in anderen Ländern auf den Zugang zu Kinderarzneimitteln auswirken.

Ziel der Studie war es, die regulatorischen Anforderungen und ihre Auswirkungen auf den Zugang zu Arzneimitteln für Kinder in sechs verschiedenen Ländern zu untersuchen und zu prüfen, inwiefern sich die Kindergesetzgebung in den internationalen Kontext einfügt. Ein weiteres Ziel war, regulatorische Empfehlungen zu entwickeln, um den weltweiten Arzneimittelzugang weiter zu verbessern. Die für die Forschung ausgewählte Länder waren Australien, Brasilien, Kanada, Kenia, Russland und Süd Afrika. Die Studie wurde als Mixed-Methods-Studie durchgeführt. Dabei wurden sowohl qualitative als auch quantitative Methoden eingesetzt, die sich jeweils auf ein Forschungsziel bezogen. Der Rahmenkonzept des National Collaborating Centre for Health Public Policy in Kanada wurde für die Zusammenfassung und Interpretation der Ergebnisse verwendet.

Ergebnisse: Im Vergleich zu Europa und den Vereinigten Staaten werden in allen untersuchten Ländern weniger Kinderarzneimittel zugelassen. Generikahersteller produzieren in der Regel keine pädiatrischen Darreichungsformen, auch wenn diese bei den Originalpräparaten vorhanden sind. In allen Ländern wurden regulatorische Barrieren festgestellt. Dazu gehörten die fehlende Harmonisierung der pädiatrischen Forschungsanforderungen und der Mangel an

Arzneimitteln mit pädiatrischen Indikationen und Darreichungsformen. In Ländern mit mittlerem Einkommen wie Brasilien, Kenia, Russland und Südafrika wird der Zugang zu Arzneimitteln jedoch auch durch systemische Probleme wie die unzureichende Finanzierung des Gesundheitssystems erschwert. Dort leiden Kinder weiterhin an Krankheiten, gegen die es bereits Medikamente gibt. Im Rahmen der COVID-19-Pandemie wurden einige regulatorische Barrieren vorübergehend verringert. Die Auswirkungen auf den Arzneimittelzugang waren jedoch in den Ländern mit mittlerem Einkommen aufgrund der Schwächen des Gesundheitssystems kaum spürbar. Die im Rahmen der Kindergesetzgebung entwickelten Arzneimittel reichen von allgemeinen Impfstoffen bis hin zu hochspezialisierten Therapien. Einige dieser Medikamente wurden in die Liste der unentbehrlichen Arzneimittel der Weltgesundheitsorganisation aufgenommen. Allerdings besteht eine Diskrepanz zwischen dem globalen Bedarf, der sich aus der Krankheitslast ergibt, und dem Krankheitsspektrum, für das neu entwickelte Arzneimittel verfügbar sind. Vor allem Arzneimittel zur Behandlung von Erkrankungen bei Neugeborenen und von armutsbedingten Krankheiten sind stark unterrepräsentiert. Bedenken hinsichtlich der Gerechtigkeit und Durchführbarkeit haben die Akzeptanz der Kindergesetzgebung behindert.

Schlussfolgerungen: Die regulatorischen Anforderungen in den untersuchten Ländern sind noch nicht darauf ausgerichtet, den Zugang zu Kinderarzneimitteln systematisch zu unterstützen. Nationale Zulassungen spielen eine wichtige Rolle für den Zugang zu Arzneimitteln, jedoch werden pädiatrische Indikationen und Darreichungsformen ohne verbindliche regulatorische Maßnahmen nur vereinzelt zugelassen. Die Studie unterstreicht die Notwendigkeit einer weltweit harmonisierten Kindergesetzgebung, die sowohl verpflichtende als auch belohnende Maßnahmen für die pharmazeutische Industrie vorsieht und den Gesundheitsbedürfnissen von Kindern gerecht wird. Die regionalen Bemühungen im Bereich der Gesetzgebung für Kinder sollten auf globaler Ebene erfolgen. Regulatorische Reformen setzen jedoch ein funktionierendes System der Arzneimittelversorgung voraus. Anstrengungen zur Stärkung des Gesundheitssystems und Unterstützung der lokalen Pharmaproduktion bleiben notwendig. Schließlich muss der gesamte Bereich der öffentlichen Gesundheit gestärkt werden, um alle Ziele für eine nachhaltige Entwicklung zu erreichen und die Krankheitslast bei Kindern, insbesondere in Ländern mit mittlerem und geringem Einkommen, wirksam zu verringern.

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9. Declaration of personal contribution to the publications

The results of this research were published in the following articles:

1. Volodina A, Shah-Rohlfs R, Jahn A. Does EU and US paediatric legislation improve the authorization availability of medicines for children in other countries? Br J Clin Pharmacol. 2023;89(3):1056-1066. doi:10.1111/bcp.15553

2. Volodina A, Jahn A, Jahn R. Suitability of paediatric legislation beyond the USA and Europe: a qualitative study on access to paediatric medicines. BMJ Public Health 2024;0:e000264. doi:10.1136/bmjph-2023-000264

3. Volodina A, Jahn A, Jahn R. Public health relevance of medicines developed under paediatric legislation in Europe and the USA: a systematic mapping study. BMJ Paediatrics Open 2024;8:e002455. doi:10.1136/bmjpo-2023-002455

For the first publication, I carried out the literature review, data collection and analysis. Data interpretation, and manuscript writing were done in collaboration with the other authors.

For the second publication, I carried out the literature review, developed the interview guide and conducted all the interviews. Data analysis, interpretation, and manuscript writing were done in collaboration with the other authors.

For the third publication, I contributed to the conceptualisation, conducted the literature review and data collection. Data analysis, interpretation, and manuscript writing were carried out in collaboration with the other authors. For more details on the personal contribution, see Table 2.

Table 2. Details on personal contribution to the publications listed above

Procedure	1st Publication	2nd Publication	3rd Publication
Conception (%)	60	60	60
Literature research (%)	100	100	100
Ethics request (%)	not applicable	60	not applicable
Data collection (%)	100	100	100
Data evaluation (%)	100	80	80
Interpretation of results (%)	70	60	65
Writing of the Manuscript texts (%)	75	70	70
Review (%)	60	50	60

Curriculum vitae

Educational background:

Jun 2021 – to date Doctoral Student, Institute of Global Health, Heidelberg University

Sep 2008 – Oct 2010 Master course in Drug Regulatory Affairs, German Society for Regulatory Affairs, University of Bonn, Germany;

Sep 2007 – Sep 2008 Master of Science in International Health, University of Heidelberg Germany. DAAD Scholarship

Sep 2002 – Jun 2007 Diploma cum laude in Pharmacy, Voronezh State University, Russia

Professional experience:

Oct 2019 – Jun 2021 Regional Regulatory Affairs Manager, Boehringer Ingelheim, Germany.

- Lead EU major indication extensions and scientific advice
- Perform regulatory due diligence evaluation
- Mentor junior colleagues

Sept 2014 – Sept 2019 - Global Regulatory Affairs Manager focus CMC, Boehringer Ingelheim, Germany (internal job rotation)

- Provide global regulatory oversight of manufacturing site transfer
- Lead global response to regulatory quality requests
- Review registration withdrawal requests worldwide under consideration of public health impact

Jan 2011 – Aug 2014 Global Regulatory Affairs Manager, Boehringer Ingelheim, Germany.

- Provide regulatory input in cross-functional teams, accountable for development and implementation of global regulatory strategy for assigned products
- Review core documentation for development (phase I - phase II) and maintenance products to ensure compliance with international regulatory requirements.
- Liaise with local regulatory affairs colleagues to develop best response strategy to authority questions, including the EMA, FDA and PMDA
- Lead core teams in authority interactions on national level

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Eidesstattliche Versicherung

1. Bei der eingereichten Dissertation zu dem Thema „Multi-country comparative analysis of paediatric regulatory frameworks and their impact on access to medicines in times of pandemic and beyond“ handelt es sich um meine eigenständig erbrachte Leistung.

2. Ich habe nur die angegebenen Quellen und Hilfsmittel benutzt und mich keiner unzulässigen Hilfe Dritter bedient. Insbesondere habe ich wörtlich oder sinngemäß aus anderen Werken übernommene Inhalte als solche kenntlich gemacht.

3. Die Arbeit oder Teile davon habe ich bislang nicht an einer Hochschule des In- oder Auslands als Bestandteil einer Prüfungs- oder Qualifikationsleistung vorgelegt.

4. Die Richtigkeit der vorstehenden Erklärungen bestätige ich.

5. Die Bedeutung der eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unrichtigen oder unvollständigen eidesstattlichen Versicherung sind mir bekannt.
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