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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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