BMJ Paediatrics Open

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

Journal:	*BMJ Paediatrics Open*
Manuscript ID	bmjpo-2023-002455
Article Type:	Original research
Date Submitted by the Author:	21-Dec-2023
Complete List of Authors:	Volodina, Anna; Heidelberg University, Heidelberg Institute of Global Health Jahn, Albrecht; Heidelberg University, Heidelberg Institute of Global Health Jahn, Rosa; University Hospital Heidelberg, Section for Health Equity Studies & Migration
Keywords:	Therapeutics

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Anna Volodina[1], Albrecht Jahn[1], Rosa Jahn[2]

Corresponding author details: Anna Volodina, Heidelberg Institute of Global Health, Heidelberg University, Im Neuenheimer Feld 130.3, 69120 Heidelberg, Germany. Email: anna.volodina@uni-heidelberg.de

[1] *Heidelberg Institute of Global Health, Heidelberg University, Heidelberg, Germany.*
[2]*Section for Health Equity Studies & Migration, University Hospital Heidelberg, Heidelberg, Germany*

Anna.Volodina@uni-heidelberg.de
Albrecht.Jahn@uni-heidelberg.de
RosaHelene.Jahn@med.uni-heidelberg.de

Word count: 2845 out of max 2500

Table count: 6

Abstract – 298 out of max 300 words

Background

Legislation in the European Union (EU) and the United States (US) 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 a wider implementation.

Methods

195 medicines developed under paediatric legislation in the EU and US were sampled from publicly available regulatory databases. Of these, 187 medicines 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). In addition, all medicines were screened for inclusion on the World Health Organisation Model List of Essential Medicines (EML) and the EML for children under 13 years (EMLc).

Results

We found that medicines developed under paediatric legislation 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 DALYs. Neonatal disorders, and malaria were mapped with 2 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 US 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 Europe and the United States has stimulated research and development of medicines for children. According to impact assessments, the availability of paediatric medicines in these countries has benefited. 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

While the resulting treatments are not well aligned with the burden of disease profile globally and in low- and middle-income countries, there is a positive effect for some diseases and a substantial contribution to the WHO essential medicines lists. 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.

Keywords: access to medicines, paediatric legislation, unmet needs, burden of disease

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 United States (US) 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 novel 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 (8-10). These findings suggests 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 in relation to paediatric legislation so far. Addressing this gap, we map the spectrum of novel paediatric medicines developed under paediatric legislation in the EU and US 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 measures 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 (11). In addition, we assess the inclusion of the studied medicines in the World Health Organisation (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. Australia, Brazil, Canada, Kenya, Russia and South Africa were selected for analysis to account for differences in regulatory systems, economic development, and due to data collection considerations as discussed in the previous publication (12).

Sample of medicines developed under paediatric legislation

This study analyses a sample of medicines from the European Medicines Agency (EMA) and Food and Drug Administration (FDA), as described in detail elsewhere (12). In summary, paediatric medicines approved in the EU or US between 2007 and 2018, and not withdrawn for safety reasons were considered for inclusion. For this paper we reviewed 158 paediatric investigation plans (PIPs) from the EU. Deviating from the original sampling process, 22 additional EU PIPs were excluded due to absence of paediatric indication and 9 were aggregated for analysis as they belonged to the same medicine. This resulted in a total of 127 EU medicines sampled. The US sample remained unchanged and included a random sample of 22% of all paediatric labels (12). The total sample was 195 medicines, 127 from the EU and 68 from the US.

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) (13). The GBD results are organised hierarchically with mutually exclusive diseases or conditions that cause death or disability referred to as “DALY cause”. There are 4 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” (14).

The responsiveness to paediatric health needs considering existing treatments was assessed by reviewing medicines´ status in the WHO EML and the and 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 (15).

Data analysis

The sampled medicines were matched to the International Classification of Disease code corresponding to the target diseases using the online electronic International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (16). Code matching was based on the approved indication with the ICD-10 code specification 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 (17). The mapping process is shown in Figure 1. The mapping results to the most detailed DALY causes can be found in supplement 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).

Table 1: Overview of compound level 2 DALYS causes and corresponding Level 3 DALYS causes utilised for mapping

Compound Level 2 DALY causes	Level 3 DALY causes utilised 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 ("EMBI"); hemoglobinopathies & 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

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 INN search of the full sample was performed in the 23rd EML and the 9th EMLc. 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 (18). 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 3 ICD-10 codes no DALY cause could be found in the online DALY tool, and 8 medicines were excluded from the analysis (supplement 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, 9 medicines (5%) were mapped to injuries, which captured 6% (1 783 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 2 medicines, tuberculosis with 311 (1%) global CMNN DALYs and neglected tropical diseases with 290 (1%) global CMNN DALYs was 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, 7 were multicomponent childhood vaccines.

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

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.

	DALYs per 100 000, 0-14 years, 2019 (% of total burden of DALYS attributed to CMNN diseases)							Mapped Medicines, n (% of CMNN mapped medicines)
DALY cause	AU	BR	CA	KE	RU	SA	Global	
Neonatal disorders*	1139 (69)	5907 (66)	1543 (76)	9000 (34)	1456 (52)	10669 (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	8 897	2 041	26 340	2 777	23 685	21 915	

Lower DALYs **Higher DALYs** **Fewer medicines** **More medicines**

All DALY causes aggregated at the second level unless marked with *
* - DALY causes aggregated to the third level

DALY Source: Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.

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%) NCD DALYs globally. It was mapped to 2 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 "EMBI", which accounted for 3% NCD DALYs globally. The most targeted "EMBI" indications were anaemia, rare coagulation and metabolic disorders.

For several NCD DALY causes at level 2 and 3, medicines were indicated for a few conditions. For example, in "musculoskeletal disorders" 7 out of 8 medicines were for juvenile arthritis. In "chronic respiratory diseases" 8 medicines were for allergic rhinitis and the remaining 5 for asthma. "Diabetes and kidney diseases" was mapped exclusively to insulins.

Table 3. Medicines for children mapped to non-communicable diseases (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 & 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)
Hemoglobinopathies & hemolytic anemias*	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)
Gynecological 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	3 985	7 446	3 847	5 018	4 082	4 704	6 333	

Lower DALYs **Higher DALYs**

Fewer medicines **More medicines**

All DALY causes aggregated at the second level unless marked with *
* - DALY causes aggregated to the third level

DALY Source: Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.

Table 4 shows the mapping results for the level 1 DALY group "Injuries", which was mapped with 9 (5%) of all mapped medicines. 8 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.

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

	DALYs per 100 000, 0-14 years, 2019 (% of total burden of DALYS attributed to Injuries)							Mapped Medicines, n (% of injury mapped medicines)
DALY cause	**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.

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 (e.g., rare tumour), diseases that primarily affect the adult population but are uncommon in children (e.g., hypertension), and human papilloma virus 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
	Diphteria	4
	Tetanus	4
	Treatment or prevention of hepatitis B	6
	Malaria	2
	Chronic hepatitis C	1

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

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	**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	**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

Discussion

Our study shows that the sampled medicines developed under paediatric legislation in the EU and US are a heterogeneous group with a limited responsiveness to children´s health needs. Overall, we found a disproportionate focus on NCDs, many of which have a high burden in adults but not in 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 US itself, including the bias towards therapeutic areas with relevant adult indications (19). Studies conducted after the adoption of the EU/US legislation have shown persisting off-labelling prescribing across therapeutic areas (20-21). 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 show 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 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 (22). 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%) (23). 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 (24).

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 (25). 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 US should include the harmonisation of regulatory obligations and rewards to enhance compliance and impact (26). 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. Efforts to define missing medicines were undertaken in the past (27-28) and could serve as a sound basis for policy development in this area.

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 (29). Public health efforts aimed at securing access to available treatments need to continue.

Strengths and limitations

Our study provides important insights into the responsiveness of paediatric legislation to paediatric health needs 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, i.e. pain killers, 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 (30-31) may have contributed to the high number 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 (32).

Conclusion

Medicines developed under the paediatric legislation in the EU and US 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 medicines. Furthermore, efforts should be made to ensure global access to authorised paediatric medicines.

Authorship:

AV carried out data collection, analysis, and interpretation, drafted the initial paper, reviewed, and agreed on the final version.

RJ contributed to the data interpretation, reviewed, revised the manuscript, and agreed on the final version.

AJ conceptualised the work, reviewed, commented, and agreed on the final version of the manuscript.

Funding Information:

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Research Ethics Approval:

No Ethics Approval

Competing Interests

The authors declare no competing interests.

Acknowledgements

Not applicable

Abbreviations

ATC – Anatomic Therapeutic Chemical

CMNN – Communicable, Maternal, Neonatal And Nutritional

DALYs – Disability Adjusted Life Years

EMA – European Medicines Agency

EMBI – Endocrine, metabolic, blood and immune

EML – Essential Medicines List

EMLc – Essential Medicines List for children

EU – European Union

FDA – Food and Drug Administration

HIV/AIDS – Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome

HPV – Human Papilloma Virus

LMICs – Low- and Middle-Income Countries

NCDs – Non-Communicable Diseases

NTDs – Neglected Tropical Diseases

R&D – Research and Development

SDG – Sustainable Development Goals

STDs – Sexually Transmitted Diseases

US – United States

WHO – World Health Organization

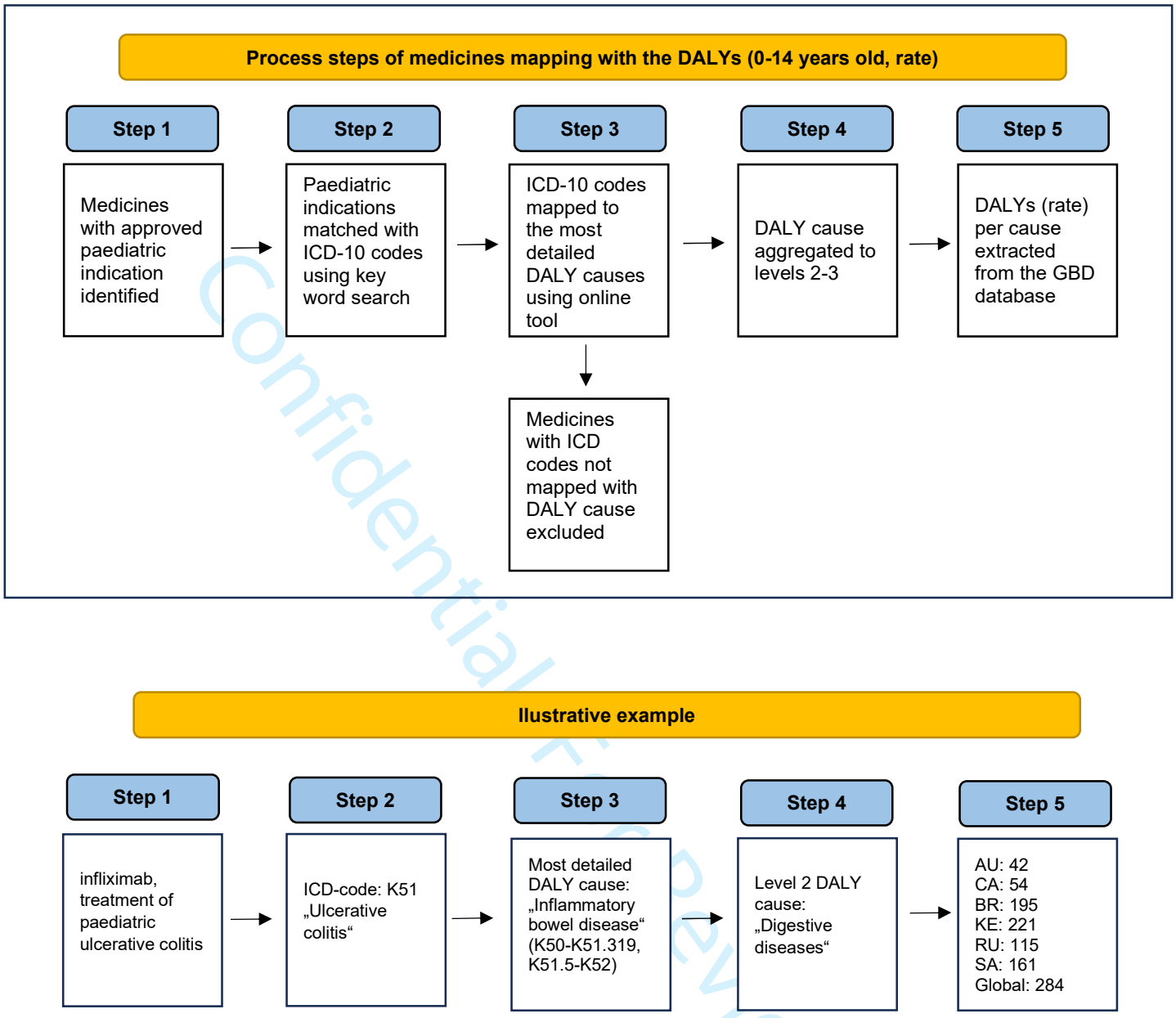
References

1. United Nations. Sustainable Development Goals: Goal 3. Health – United Nations Sustainable Development . Accessed March 5, 2022.
2. United Nations. Sustainable Development Goals: Goal 3. Health , target 3b – United Nations Sustainable Development . Accessed March 5, 2022.
3. Moulis F, Durrieu G, Lapeyre-Mestre M. Off-label and unlicensed drug use in children population. Therapie. 2018;73(2):135-149. Doi:10.1016/j.therap.2018.02.002
4. Vieira I, Sousa JJ, Vitorino C. Paediatric Medicines – Regulatory Drivers, Restraints, Opportunities and Challenges. J Pharm Sci. 2021;110(4):1545-1556. Doi:10.1016/j.xphs.2020.12.036
5. Van der Veken M, Brouwers J, Budts V, et al. Practical and operational considerations related to paediatric oral drug formulation: An industry survey. Int J Pharm. 2022;618:121670. Doi:10.1016/j.ijpharm.2022.121670
6. European Commission. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. 2006. European Commission. EUR-Lex – 32006R1901 – EN – EUR-Lex (12uropa.eu). Accessed January 10, 2022.
7. Food and Drug Administration. Fact Sheet: Pediatric provisions in the Food and Drug Administration Safety and Innovation Act (FDASIA). https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/fact-sheet-pediatric-provisions-food-and-drug-administration-safety-and-innovation-act-fdasia Published March 2018. Accessed April 25, 2022.
8. Rocchi F, Paolucci P, Ceci A, Rossi P. The European paediatric legislation: benefits and perspectives. Ital J Pediatr. 2010;36:56. Published Aug 2010. Doi:10.1186/1824-7288-36-56
9. European Medicines Agency. 10-year Report to the European Commission. General report on the experience acquired as a result of the application of the Paediatric Regulation 10-year

Report to the European Commission (Core report) (13uropa.eu). Published August 2017. Accessed December 5, 2021.
10. Thaul S. FDA's Authority to Ensure That Drugs Prescribed to Children Are Safe and Effective. https://sgp.fas.org/crs/misc/RL33986.pdf Published June 25, 2012. Accessed December 18, 2020.
11. World Health Organization. Disability-adjusted life years (DALYs). https://www.who.int/data/gho/indicator-metadata-registry/imr-details/158. Accessed January 17, 2023.
12. 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
13. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019). Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2020 https://www.healthdata.org/research-analysis/gbd. Accessed February 2023.
14. Institute for Health Metrics and Evaluation. Global Burden of Disease (GBD) data and tools guide. https://www.healthdata.org/research-analysis/about-gbd Accessed December 17, 2023.
15. World Health Organization. Expert Committee on Selection and Use of Essential Medicines. https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines. Accessed February 17, 2023
16. World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision. https://icd.who.int/browse10/2016/en Accessed February 17, 2023
17. Institute for Health Metrics and Evaluation. Global Burden of Disease Study 2019 (GBD 2019) Cause List Mapped to ICD Codes. https://ghdx.healthdata.org/record/ihme-data/gbd-2019-cause-icd-code-mappings. Accessed March 2023.
18. WHO Collaborating Centre for Drug Statistics and Methodology. ATC/DDD Index 2023. https://www.whocc.no/atc_ddd_index/. Last updated January 23, 2023. Accessed March 2023.
19. European Commission. Commission Staff Working Document. Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. https://health.ec.europa.eu/system/files/2020-08/orphan-regulation_eval_swd_2020-163_part-1_0.pdf. Published August 11, 2020. Accessed February 18, 2023.
20. Netherlands Institute For Health Services Research. Study on off-label use of medicinal products in the European Union. February 2017. https://www.nivel.nl/sites/default/files/bestanden/Report_OFF_LABEL_Nivel-RIVM-EPHA.pdf. Accessed February 17, 2023.
21. Allen HC, Garbe MC, Lees J, et al. Off-Label Medication use in Children, More Common than We Think: A Systematic Review of the Literature. J Okla State Med Assoc. 2018;111(8):776-783.
22. Congressional Budget Office. Research and Development in the Pharmaceutical Industry. https://www.cbo.gov/publication/57025. Published April 8, 2021. Accessed February 20, 2023.
23. Fisher JA, Cottingham MD, Kalbaugh CA. Peering into the pharmaceutical "pipeline": investigational drugs, clinical trials, and industry priorities. Soc Sci Med. 2015;131:322-330. Doi:10.1016/j.socscimed.2014.08.023

24. Milne CP, Kaitin KI. Are Regulation and Innovation Priorities Serving Public Health Needs?. Front Pharmacol. 2019;10:144. Published 2019 Mar 8. doi:10.3389/fphar.2019.00144
25. European Commission. Reform of the EU Pharmaceutical Legislation. https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en. Published April 26, 2023. Accessed April 30, 2023.
26. Volodina A, Jahn RH, Jahn A. Suitability of paediatric legislation beyond the United States and Europe: a qualitative study on access to paediatric medicines. 2023. Unpublished manuscript in review at BMJ Public Health.
27. World Health Organization. Priority medicines for Europe and the world / Warren Kaplan, Richard Laing. World Health Organization. November 2004. https://iris.who.int/handle/10665/68769. Accessed April 30, 2023
28. United Nations Commission On Life-Saving Commodities For Women And Children. https://www.unfpa.org/sites/default/files/pub-pdf/Final%20UN%20Commission%20Report_14sept2012.pdf. August 31, 2012. Accessed April 30, 2023
29. Ozawa S, Shankar R, Leopold C, Orubu S. Access to medicines through health systems in low- and middle-income countries. Health Policy Plan. 2019;34(Supplement_3):iii1-iii3. Doi:10.1093/heapol/czz119
30. European Commission. Regulation (EC) No 141/2000 Of The European Parliament And Of The Council of 16 December 1999 on orphan medicinal products. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32000R0141&from=EN. Accessed February 23, 2023.
31. Herder M. What Is the Purpose of the Orphan Drug Act?. PLoS Med. 2017;14(1):e1002191. Published 2017 Jan 3. Doi:10.1371/journal.pmed.1002191
32. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019 [published correction appears in Lancet. 2020 Nov 14;396(10262):1562]. Lancet. 2020;396(10258):1204-1222. doi:10.1016/S0140-6736(20)30925-9

Figure 1 Process steps of medicines mapping to the Disability Adjusted Life Years with an illustrative example



AU- Australia; CA- Canada; BR – Brazil; KE – Kenya; RU – Russia; SA – South Africa

Supplement 1: All Disability Adjusted Life Years causes with mapped sampled medicines

	DALYs (0-14 years old, both sexes, rate), 2019							Sampled medicines, N
	Australia	Brazil	Canada	Kenya	Russia	South Africa	Global	
Acne vulgaris	67	51	53	78	38	73	65	2
Acute glomerulonephritis	0	2	0	2	1	2	3	0
Acute hepatitis A	2	6	2	26	5	8	59	0
Acute hepatitis B	0	3	0	5	4	1	22	6
Acute hepatitis C	0	1	0	2	0	0	4	1
Acute hepatitis E	0	1	0	1	0	1	3	0
Acute lymphoid leukemia	29	92	26	41	57	16	66	3
Acute myeloid leukemia	20	46	20	20	18	6	30	0
Adverse effects of medical treatment	21	40	17	51	25	46	61	8
African trypanosomiasis	0	0	0	0	0	0	2	0
Age-related and other hearing loss	38	71	28	161	78	161	106	0
Age-related macular degeneration	0	0	0	0	0	0	0	0
Alcohol use disorders	4	3	6	2	3	2	2	0
Alcoholic cardiomyopathy	0	0	0	0	0	0	0	0
Alopecia areata	3	3	4	2	3	2	3	0
Alzheimer's disease and other dementias	0	0	0	0	0	0	0	0
Amphetamine use disorders	0	0	0	0	0	0	0	0
Anorexia nervosa	13	6	8	3	4	4	4	0
Anxiety disorders	249	231	131	115	128	149	157	0
Aortic aneurysm	0	0	0	0	0	0	0	0
Appendicitis	3	15	2	15	5	11	16	2

Asbestosis	0	0	0	0	0	0	0	0
Ascariasis	0	4	0	8	0	1	22	0
Asthma	455	416	301	212	148	274	210	5
Atopic dermatitis	250	208	183	80	396	96	160	1
Atrial fibrillation and flutter	0	0	0	0	0	0	0	0
Attention-deficit/hyperactivity disorder	65	37	42	12	21	11	21	1
Autism spectrum disorders	80	66	112	71	75	70	66	0
Benign and in situ cervical and uterine neoplasms	0	0	0	0	0	0	0	0
Benign and in situ intestinal neoplasms	0	0	0	0	0	0	0	0
Benign prostatic hyperplasia	0	0	0	0	0	0	0	0
Bipolar disorder	37	34	31	13	10	12	12	3
Bladder cancer	0	0	0	0	0	0	0	0
Brain and central nervous system cancer	70	139	75	54	93	35	85	0
Breast cancer	0	0	0	0	0	0	0	0
Bulimia nervosa	18	4	10	3	4	4	4	0
Cannabis use disorders	3	1	6	0	1	0	1	0
Caries of deciduous teeth	9	11	9	11	12	10	10	0
Caries of permanent teeth	10	12	11	10	14	11	13	0
Cataract	0	0	0	0	0	0	0	0
Cellulitis	3	9	4	3	3	3	3	0
Cervical cancer	0	0	0	0	0	0	0	0
Chagas disease	0	1	0	0	0	0	0	0
Chlamydial infection	0	0	0	0	0	0	0	0
Chronic kidney disease due to diabetes mellitus type 1	0	1	0	1	1	2	2	0
Chronic kidney disease due to diabetes mellitus type 2	0	0	0	0	0	0	0	0
Chronic kidney disease due to glomerulonephritis	4	24	8	25	19	25	32	0
Chronic kidney disease due to hypertension	0	0	0	0	0	0	0	0
Chronic kidney disease due to other and unspecified causes	8	41	16	31	30	46	59	0

Chronic lymphoid leukemia	0	0	0	0	0	0	0	0
Chronic myeloid leukemia	1	1	1	7	1	1	8	3
Chronic obstructive pulmonary disease	9	12	8	26	11	25	22	0
Cirrhosis and other chronic liver diseases due to alcohol use	0	0	0	0	0	0	0	0
Cirrhosis and other chronic liver diseases due to hepatitis B	0	0	0	1	0	0	1	0
Cirrhosis and other chronic liver diseases due to hepatitis C	0	1	0	1	0	0	2	0
Cirrhosis and other chronic liver diseases due to NAFLD	0	0	0	0	0	0	0	0
Cirrhosis and other chronic liver diseases due to other causes	2	22	4	47	11	22	71	0
Coal workers pneumoconiosis	0	0	0	0	0	0	0	0
Cocaine use disorders	1	1	1	0	0	0	0	0
Colon and rectum cancer	1	2	1	1	1	2	2	0
Conduct disorder	193	181	157	194	187	193	172	0
Congenital heart anomalies	172	1185	197	546	369	415	866	0
Congenital musculoskeletal and limb anomalies	90	103	75	106	83	144	107	0
Contact dermatitis	2	4	16	4	16	4	5	0
Cutaneous and mucocutaneous leishmaniasis	0	1	0	0	0	0	2	0
Cystic echinococcosis	0	0	0	2	1	0	1	0
Cysticercosis	0	1	0	1	0	1	0	0
Decubitus ulcer	0	1	0	0	0	0	0	0
Dengue	2	20	0	4	0	0	54	0
Diabetes mellitus type 1	12	24	15	20	11	19	26	5
Diabetes mellitus type 2	0	0	0	0	0	0	0	5
Diarrheal diseases	76	561	138	4147	226	2431	2636	2
Dietary iron deficiency	104	368	39	395	91	323	695	0
Digestive congenital anomalies	59	372	63	155	118	115	215	0
Diphtheria	0	0	0	4	0	4	18	4
Down syndrome	45	164	46	44	35	102	72	0
Drug-susceptible tuberculosis	1	25	1	213	9	587	285	0

Dysthymia	11	7	12	11	7	9	9	0
Ebola	0	0	0	0	0	0	2	0
Edentulism	0	0	0	0	0	0	0	0
Encephalitis	9	28	9	19	60	15	121	1
Endocarditis	1	15	1	5	3	5	10	0
Endocrine, metabolic, blood, and immune disorders	167	161	134	79	154	186	159	29
Endometriosis	0	0	0	0	0	0	0	0
Esophageal cancer	0	0	0	0	0	0	0	0
Extensively drug-resistant tuberculosis	0	0	0	0	2	0	1	0
Female infertility	0	0	0	0	0	0	0	0
Food-borne trematodiases	0	0	0	0	1	0	1	0
Fungal skin diseases	20	26	7	64	15	36	45	2
G6PD deficiency	0	12	2	1	1	7	5	0
G6PD trait	0	0	0	0	0	0	0	0
Gallbladder and biliary diseases	3	9	4	5	7	5	9	0
Gallbladder and biliary tract cancer	0	0	0	0	0	0	0	0
Gastritis and duodenitis	3	5	2	6	6	10	10	0
Gastroesophageal reflux disease	1	2	1	1	1	1	1	3
Genital herpes	0	0	0	0	0	0	0	0
Genital prolapse	0	0	0	0	0	0	0	0
Glaucoma	0	0	0	0	0	0	0	0
Gonococcal infection	0	0	0	0	0	0	0	0
Gout	0	0	0	0	0	0	0	0
Guinea worm disease	0	0	0	0	0	0	0	0
Hemolytic disease and other neonatal jaundice	3	52	3	113	33	113	252	0
HIV/AIDS	2	79	4	1875	150	3072	338	15
Hodgkin lymphoma	1	3	1	6	3	2	7	0
Hookworm disease	0	4	0	19	0	16	19	0

Hypertensive heart disease	0	0	0	0	0	0	0	7
Idiopathic developmental intellectual disability	16	20	27	41	25	20	81	0
Idiopathic epilepsy	89	167	64	207	84	183	180	10
Inflammatory bowel disease	3	3	7	4	2	5	4	4
Inguinal, femoral, and abdominal hernia	9	31	9	33	46	53	36	0
Interstitial lung disease and pulmonary sarcoidosis	2	4	4	2	2	3	3	0
Intracerebral hemorrhage	3	12	4	22	6	14	46	0
Invasive Non-typhoidal Salmonella (iNTS)	0	3	0	712	1	113	276	0
Iodine deficiency	1	0	1	3	2	2	12	0
Ischemic heart disease	0	0	0	0	0	0	0	0
Ischemic stroke	8	9	12	25	14	23	22	0
Kidney cancer	8	22	7	4	13	10	12	0
Klinefelter syndrome	0	0	0	0	0	0	0	0
Larynx cancer	0	0	0	0	0	0	0	0
Latent tuberculosis infection	0	0	0	0	0	0	0	0
Leprosy	0	0	0	0	0	0	0	0
Lip and oral cavity cancer	1	1	1	1	1	1	1	0
Liver cancer due to alcohol use	0	0	0	0	0	0	0	0
Liver cancer due to hepatitis B	0	0	0	1	1	0	1	0
Liver cancer due to hepatitis C	0	0	0	0	0	0	0	0
Liver cancer due to NASH	0	0	0	0	0	0	0	0
Liver cancer due to other causes	6	7	7	5	13	4	13	0
Low back pain	109	137	133	71	148	65	100	0
Lower respiratory infections	62	997	57	3119	397	2527	3196	14
Lymphatic filariasis	0	3	0	24	0	0	14	0
Major depressive disorder	135	178	91	47	28	42	57	1
Malaria	0	7	0	2450	0	40	1820	2
Male infertility	0	0	0	0	0	0	0	0

Malignant skin melanoma	5	2	2	1	2	1	1	1
Maternal disorders	0	3	0	5	0	0	4	0
Measles	0	0	0	196	0	281	349	0
Meningitis	24	146	24	600	59	261	604	7
Mesothelioma	0	0	0	0	0	0	0	0
Migraine	132	417	176	89	133	127	165	3
Motor neuron disease	25	7	13	1	4	1	4	0
Multidrug-resistant tuberculosis without extensive drug resistance	0	1	0	7	4	33	25	0
Multiple myeloma	0	0	0	0	0	0	0	0
Multiple sclerosis	0	0	1	0	0	0	0	1
Myelodysplastic, myeloproliferative, and other hematopoietic neoplasms	1	5	4	1	2	1	2	0
Myocarditis	8	17	8	5	7	4	12	0
Nasopharynx cancer	1	1	1	2	1	1	2	0
Near vision loss	0	0	0	0	0	1	0	0
Neck pain	10	8	18	7	8	7	13	0
Neonatal encephalopathy due to birth asphyxia and trauma	346	1313	327	3220	355	2341	2625	0
Neonatal preterm birth	513	2240	791	2250	482	4103	3182	0
Neonatal sepsis and other neonatal infections	33	1077	68	1621	288	1157	1093	2
Neural tube defects	79	324	60	258	76	146	383	0
Non-Hodgkin lymphoma	9	26	11	27	17	15	25	0
Non-melanoma skin cancer (basal-cell carcinoma)	0	0	0	0	0	0	0	0
Non-melanoma skin cancer (squamous-cell carcinoma)	0	0	0	0	0	0	0	0
Non-rheumatic calcific aortic valve disease	0	0	0	0	0	0	0	0
Non-rheumatic degenerative mitral valve disease	0	0	0	0	0	0	0	0
Onchocerciasis	0	0	0	0	0	0	11	0
Opioid use disorders	0	0	0	0	0	0	0	0
Orofacial clefts	3	9	1	14	3	17	17	0

Osteoarthritis hand	0	0	0	0	0	0	0	0
Osteoarthritis hip	0	0	0	0	0	0	0	0
Osteoarthritis knee	0	0	0	0	0	0	0	0
Osteoarthritis other	0	0	0	0	0	0	0	0
Other benign and in situ neoplasms	0	0	0	0	0	0	0	2
Other cardiomyopathy	8	74	14	47	25	49	32	0
Other cardiovascular and circulatory diseases	13	45	14	41	13	29	58	0
Other chromosomal abnormalities	112	178	166	59	78	127	95	0
Other chronic respiratory diseases	13	30	14	34	13	38	32	8
Other congenital birth defects	132	659	170	519	320	561	589	2
Other digestive diseases	3	11	4	16	9	11	16	1
Other drug use disorders	0	0	1	0	0	0	0	0
Other gynecological diseases	0	1	0	1	0	1	1	1
Other hemoglobinopathies and hemolytic anemias	4	17	2	15	4	13	26	3
Other intestinal infectious diseases	0	2	0	4	1	3	5	4
Other leukemia	3	20	11	38	5	25	43	0
Other malignant neoplasms	56	108	76	82	73	48	120	1
Other mental disorders	3	1	3	1	1	1	2	1
Other musculoskeletal disorders	7	15	65	2	3	2	10	1
Other neglected tropical diseases	10	53	4	42	14	33	101	0
Other neonatal disorders	245	1226	354	1797	299	2955	1731	0
Other neurological disorders	57	76	59	75	75	68	71	1
Other non-rheumatic valve diseases	0	0	0	0	0	0	0	0
Other nutritional deficiencies	2	10	3	9	6	6	31	0
Other oral disorders	31	32	31	32	32	32	31	1
Other pharynx cancer	0	0	0	0	0	0	0	0
Other pneumoconiosis	0	0	0	0	0	0	0	0
Other sense organ diseases	15	15	13	15	13	15	14	10

Other sexually transmitted infections	0	0	0	0	0	0	0	2
Other skin and subcutaneous diseases	23	24	23	20	22	22	23	1
Other unspecified infectious diseases	37	70	26	104	93	290	138	6
Other urinary diseases	3	4	3	17	4	7	11	1
Other vision loss	5	8	4	4	4	3	5	2
Otitis media	26	49	26	57	46	55	51	2
Ovarian cancer	1	2	1	1	2	2	2	0
Pancreatic cancer	0	0	0	0	0	0	0	0
Pancreatitis	1	2	1	1	2	0	2	0
Paralytic ileus and intestinal obstruction	13	91	16	84	21	39	103	0
Paratyphoid fever	0	0	0	16	0	0	50	0
Parkinson's disease	0	0	0	0	0	0	0	0
Peptic ulcer disease	0	2	1	5	2	2	10	0
Periodontal diseases	0	0	0	0	0	0	0	0
Peripheral artery disease	0	0	0	0	0	0	0	0
Polycystic ovarian syndrome	2	0	1	0	0	0	1	0
Premenstrual syndrome	20	23	22	24	21	21	21	0
Prostate cancer	0	0	0	0	0	0	0	0
Protein-energy malnutrition	10	194	10	1188	36	802	555	1
Pruritus	4	5	5	8	5	7	5	0
Psoriasis	52	32	41	6	13	9	15	2
Pyoderma	6	24	2	23	5	15	21	4
Rabies	0	0	0	15	0	3	21	0
Refraction disorders	46	54	27	17	39	18	31	0
Rheumatic heart disease	2	28	1	38	2	32	36	0
Rheumatoid arthritis	1	2	2	1	1	1	1	7
Scabies	6	162	5	54	13	31	76	0
Schistosomiasis	0	10	0	68	0	37	14	0

Schizophrenia	2	2	1	2	2	2	2	5
Seborrhoeic dermatitis	2	2	2	3	1	3	3	0
Self-harm and interpersonal violence	70	279	90	133	171	321	240	1
Sickle cell disorders	0	31	1	82	0	3	122	0
Sickle cell trait	1	6	0	86	0	2	43	0
Silicosis	0	0	0	0	0	0	0	0
Stomach cancer	0	0	0	0	0	0	0	0
Subarachnoid hemorrhage	3	21	5	4	6	3	18	0
Sudden infant death syndrome	102	45	68	87	102	135	125	0
Syphilis	0	37	0	419	2	1321	371	0
Tension-type headache	13	18	17	11	17	12	13	0
Testicular cancer	4	3	4	1	3	3	3	0
Tetanus	0	2	0	384	0	3	89	4
Thalassemias	4	6	2	0	9	5	28	0
Thalassemias trait	3	7	0	5	8	5	56	0
Thyroid cancer	1	1	1	1	1	1	1	1
Tracheal, bronchus, and lung cancer	1	1	1	0	0	0	1	0
Trachoma	0	0	0	0	0	0	0	0
Transport and other unintentional injuries	683	1168	435	825	1085	1432	1482	0
Trichomoniasis	0	0	0	0	0	0	0	0
Trichuriasis	0	4	0	3	0	4	4	0
Turner syndrome	0	0	0	0	0	0	0	0
Typhoid fever	0	0	0	359	0	3	275	0
Upper respiratory infections	132	154	144	154	100	106	114	0
Urinary tract infections and interstitial nephritis	5	48	5	7	10	4	23	0
Urogenital congenital anomalies	28	84	29	33	25	26	50	0
Urolithiasis	0	0	0	0	1	0	0	0
Urticaria	71	80	88	80	133	81	80	2

Uterine cancer	0	0	0	0	0	0	0	0
Uterine fibroids	0	0	0	0	1	0	0	0
Varicella and herpes zoster	4	27	3	36	8	19	30	1
Vascular intestinal disorders	1	2	1	1	2	1	2	0
Viral skin diseases	204	105	326	175	104	121	122	0
Visceral leishmaniasis	0	70	0	49	0	0	14	0
Vitamin A deficiency	0	29	1	110	0	22	51	0
Whooping cough	4	17	7	478	1	593	515	4
Yellow fever	0	0	0	6	0	0	8	0
Zika virus	0	0	0	0	0	0	0	0

Volodina et al., Public health relevance of medicines developed under paediatric legislation in Europe and the United States: a systematic mapping study

Supplement 2. Paediatric indications not mapped with Disability Adjusted Life Year cause

N	Approved indication in EU/US	Assigned ICD 10 classification
1	Maintenance of anesthesia in non-intubated patients	Z00-Z13 Persons encountering health services for examination and investigation
2	Adjunct to general anesthesia	
3	Contrast agent for intravenous use with magnetic resonance imaging	
4	Diagnostic evaluation of tissue pathologies with contrast-enhanced magnetic resonance imaging	
5	Emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure	Z30 Contraceptive management
6	Oral contraception	
7	Management of mild to moderate pain and the management of moderate to severe pain as an adjunct to opioid analgesics, and for the reduction of fever in pediatric patients 6 months and older	R52 Pain, not elsewhere classified
8	Management of pain severe enough to require daily, around the-clock, long-term opioid treatment in pediatric patients 11 years and older	

BMJ Paediatrics Open

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

Journal:	*BMJ Paediatrics Open*
Manuscript ID	bmjpo-2023-002455.R1
Article Type:	Original research
Date Submitted by the Author:	13-Mar-2024
Complete List of Authors:	Volodina, Anna; Heidelberg University, Heidelberg Institute of Global Health Jahn, Albrecht; Heidelberg University, Heidelberg Institute of Global Health Jahn, Rosa; University Hospital Heidelberg, Section for Health Equity Studies & Migration
Keywords:	Therapeutics, Child Health, Health Policy

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Anna Volodina[1], Albrecht Jahn[1], Rosa Jahn[2]

Corresponding author details: Anna Volodina, Heidelberg Institute of Global Health, Heidelberg University, Im Neuenheimer Feld 130.3, 69120 Heidelberg, Germany. Email: anna.volodina@uni-heidelberg.de

[1] *Heidelberg Institute of Global Health, Heidelberg University, Heidelberg, Germany.*
[2]*Section for Health Equity Studies & Migration, University Hospital Heidelberg, Heidelberg, Germany*

Anna.Volodina@uni-heidelberg.de
Albrecht.Jahn@uni-heidelberg.de
RosaHelene.Jahn@med.uni-heidelberg.de

Word count:3184 out of max 2500

Table count: 6

Abstract–296 out of max 300 words

Background

Legislation in the European Union (EU) and the United States (US) promoting the development of paediatric medicines has contributed to new treatments for children. This study explore show 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 World Health Organisation 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 2 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 US 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 United States 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.

Keywords: access to medicines, paediatric legislation, unmet needs, burden of disease

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 United States (US) 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 US 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 measures 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 World Health Organisation (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 (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 to 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 between1 January 2007 and 31 December 2018. Paediatric development was indicated by completed Paediatric Investigations 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 was 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 (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 (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 US.

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 4 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 and 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 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 supplement 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).

Table 1: Overview of compound level 2 DALYS causes and corresponding Level 3 DALYS causes utilised for mapping

Compound Level 2 DALY causes	Level 3 DALY causes utilised 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 ("EMBI"); hemoglobinopathies & 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

Results were calculated as percentages (proportions) according to the rounding rules and organised according to the level 1DALY 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 INN 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 3 ICD-10 codes no DALY cause could be found in the online DALY tool, and 8 medicines were excluded from the analysis (supplement 2). In total, 61 (21%) of the293 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, 9 medicines (5%) were mapped to 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 2 medicines, tuberculosis with 311 (1%) global CMNN DALYs and neglected tropical diseases with 290 (1%) global CMNN DALYs was 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, 7 were multicomponent childhood vaccines.

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

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.

	DALYs per 100 000, 0-14 years, 2019 [% of total burden of DALYS attributed to CMNN diseases]							Mapped Medicines, n [% of CMNN mapped medicines]
DALY cause	AU	BR	CA	KE	RU	SA	Global	
Neonatal disorders*	1139 [69]	5907 [66]	1543 [76]	9000 [34]	1456 [52]	10669 [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	8 897	2041	26340	2777	23685	21915	

Lower DALYs **Higher DALYs** **Fewer medicines** **More medicines**

All DALY causes aggregated at the second level unless marked with *
* - DALY causes aggregated to the third level

DALY Source: Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.

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%) NCD DALYs globally. It was mapped to 2 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 "EMBI", which accounted for 3% NCD DALYs globally. The most targeted "EMBI" indications were anaemia, rare coagulation and metabolic disorders.

For several NCD DALY causes at level 2 and 3, medicines were indicated for a few conditions. For example, in "musculoskeletal disorders" 7 out of 8 medicines were for juvenile arthritis. In "chronic respiratory diseases" 8 medicines were for allergic rhinitis and the remaining 5 for asthma. "Diabetes and kidney diseases" was mapped exclusively to insulins.

Table 3. Medicines for children mapped to non-communicable diseases (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 & 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]
Hemoglobinopathies & hemolytic anemias*	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]
Gynecological 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	3 985	7 446	3 847	5 018	4 082	4 704	6 333	

Lower DALYs **Higher DALYs** **Fewer medicines** **More medicines**

All DALY causes aggregated at the second level unless marked with *
* - DALY causes aggregated to the third level

DALY Source: Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.

Table 4 shows the mapping results for the level 1 DALY group “Injuries”, which was mapped with 9 (5%) of all mapped medicines. 8 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.

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

	DALYs per 100 000, 0-14 years, 2019 [% of total burden of DALYS attributed to Injuries]							Mapped Medicines, n [% of injury mapped medicines]
DALY cause	**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.

In total, 28 medicines were mapped to DALY causes at the most detailed level that had a negligible burden of disease (< 0.05DALYs) (see Table 5). 18 of these medicines targeted conditions uncommon in children in all studied countries and globally. These were either generally rare diseases (e.g., rare tumour), diseases that primarily affect the adult population but are uncommon in children (e.g., hypertension), and human papilloma virus 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	Poliomyelitis	4

measurable burden in some studied countries	Diphteria	4
	Tetanus	4
	Treatment or prevention of hepatitis B	6
	Malaria	2
	Chronic hepatitis C	1

WHO EMLs review results

Of all 195sampled 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 mental disorders, emergency contraception or HIV/AIDS pre-exposure prophylaxis.

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

Discussion

Our study shows that the sampled medicines developed under paediatric legislation in the EU and US area heterogeneous group with a limited responsiveness to children´s health needs. Overall, we found a disproportionate focus on NCDs, many of which have a high burden in adults but not in 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 US 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 show 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 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 US 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 (GAP-f) 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 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, i.e. 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 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 US 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.

Figure 1 Process steps of medicines mapping to the Disability Adjusted Life Years with an illustrative example

Authorship:

AV contributed to conceptualization, carried out data collection, analysis, and interpretation, drafted the initial paper, reviewed, and agreed on the final version.

RJ contributed to the data analysis and interpretation, reviewed, revised the manuscript, and agreed on the final version.

AJ contributed to conceptualization, reviewed, commented, and agreed on the final version of the manuscript.

Funding Information:

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Research Ethics Approval:

No Ethics Approval

Competing Interests

The authors declare no competing interests.

Acknowledgements

Not applicable

Abbreviations

ATC – Anatomic Therapeutic Chemical

CMNN – Communicable, Maternal, Neonatal And Nutritional

DALYs – Disability Adjusted Life Years

EMA – European Medicines Agency

EMBI – Endocrine, metabolic, blood and immune

EML – Essential Medicines List

EMLc – Essential Medicines List for children

EU – European Union

FDA – Food and Drug Administration

HIV/AIDS – Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome

HPV – Human Papilloma Virus

LMICs – Low- and Middle-Income Countries

NCDs – Non-Communicable Diseases

NTDs – Neglected Tropical Diseases

R&D – Research and Development

SDG – Sustainable Development Goals

STDs – Sexually Transmitted Diseases

US – United States

WHO – World Health Organization

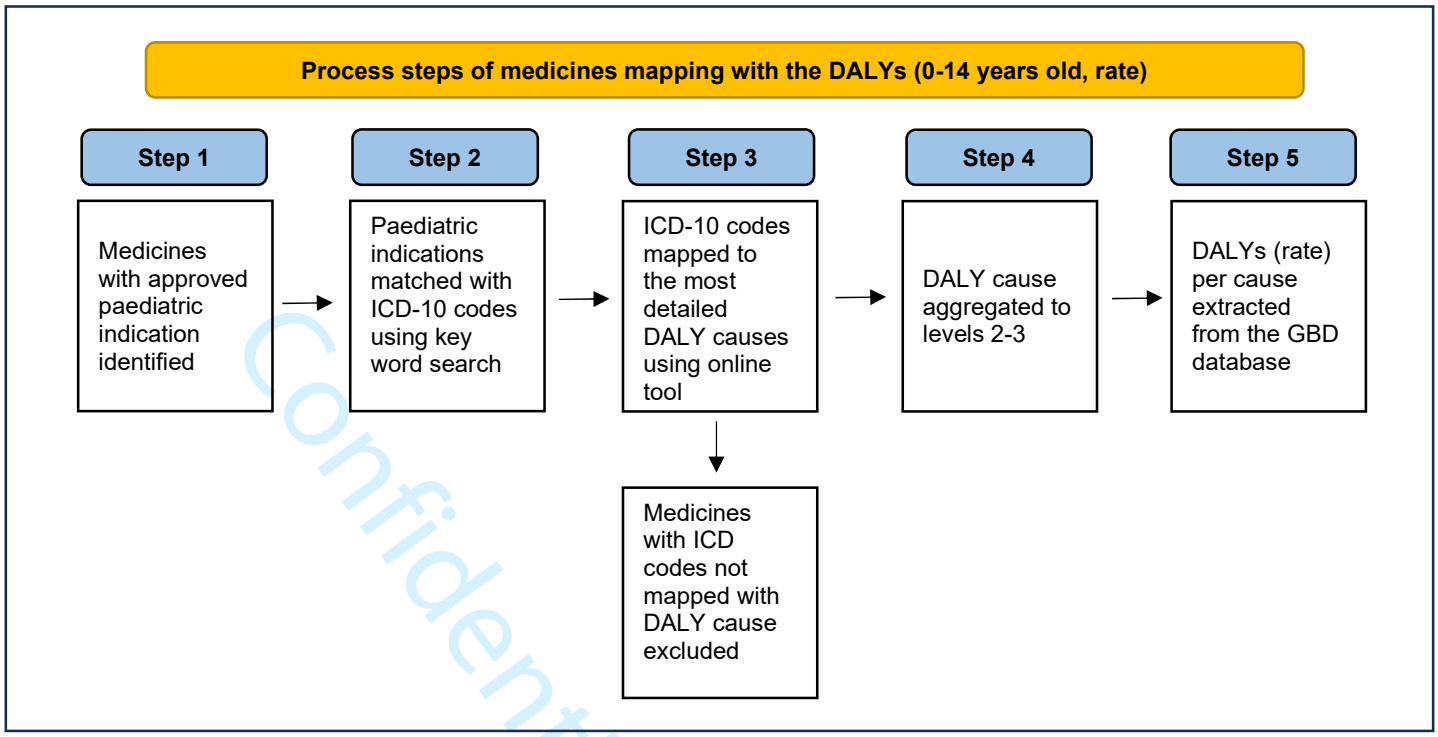
References

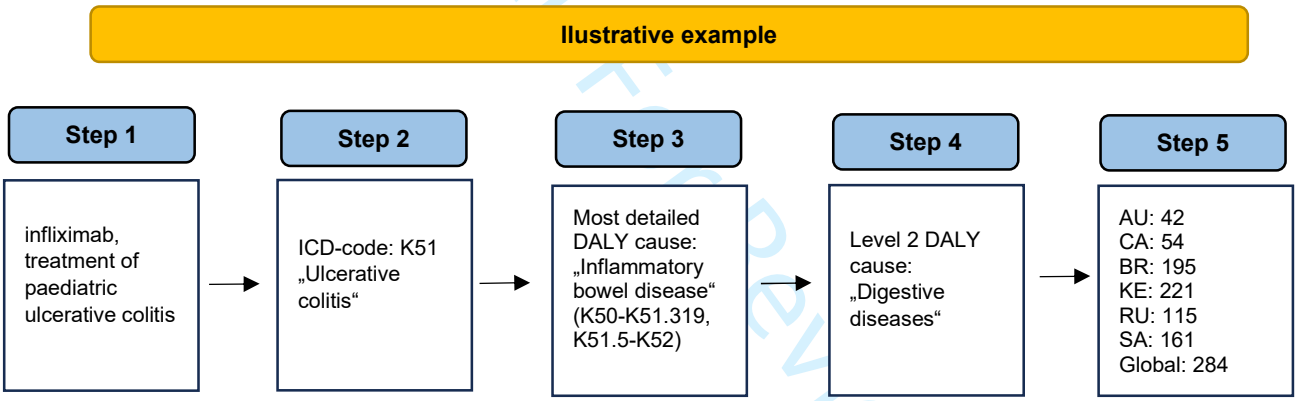
1. United Nations. Sustainable Development Goals: Goal 3. Health – United Nations Sustainable Development . Accessed March 5, 2022.
2. United Nations. Sustainable Development Goals: Goal 3. Health , target 3b– United Nations Sustainable Development . Accessed March 5, 2022.
3. Moulis F, Durrieu G, Lapeyre-Mestre M. Off-label and unlicensed drug use in children population. Therapie. 2018;73(2):135-149. Doi:10.1016/j.therap.2018.02.002
4. Vieira I, Sousa JJ, Vitorino C. Paediatric Medicines – Regulatory Drivers, Restraints, Opportunities and Challenges. J Pharm Sci. 2021;110(4):1545-1556. Doi:10.1016/j.xphs.2020.12.036
5. Van der Veken M, Brouwers J, Budts V, et al. Practical and operational considerations related to paediatric oral drug formulation: An industry survey. Int J Pharm. 2022;618:121670. Doi:10.1016/j.ijpharm.2022.121670
6. European Commission. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. 2006. European Commission. EUR-Lex – 32006R1901 – EN – EUR-Lex (13uropa.eu). Accessed January10, 2022.
7. Food and Drug Administration. Fact Sheet: Pediatric provisions in the Food and Drug Administration Safety and Innovation Act (FDASIA).https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/fact-sheet-pediatric-provisions-food-and-drug-administration-safety-and-innovation-act-fdasia Published March 2018. Accessed April25, 2022.
8. Rocchi F, Paolucci P, Ceci A, Rossi P. The European paediatric legislation: benefits and perspectives. Ital J Pediatr. 2010;36:56. Published Aug 2010. Doi:10.1186/1824-7288-36-56
9. European Medicines Agency. 10-year Report to the European Commission. General report on the experience acquired as a result of the application of the Paediatric Regulation 10-year Report to the European Commission (Core report) (13uropa.eu). Published August 2017. Accessed December 5, 2021.
10. Thaul S. FDA's Authority to Ensure That Drugs Prescribed to Children Are Safe and Effective. https://sgp.fas.org/crs/misc/RL33986.pdfPublished June 25, 2012. Accessed December 18, 2020.
11. Toma M, Felisi M, Bonifazi D, Bonifazi F, Giannuzzi V, Reggiardo G, de Wildt S, Ceci A; TEDDY European Network of Excellence for Paediatric Research. Paediatric Medicines in Europe: The Paediatric Regulation-Is It Time for Reform? Front Med (Lausanne). 2021 Feb 2;8:593281. doi: 10.3389/fmed.2021.593281. PMID: 33604345; PMCID: PMC7884470.
12. World Health Organization. Disability-adjusted life years (DALYs). https://www.who.int/data/gho/indicator-metadata-registry/imr-details/158. Accessed January17, 2023.
13. 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

14. European Medicines Agency. Paediatric Investigation Plans - download table. Download medicine data. https://www.ema.europa.eu/en/medicines/download-medicine-data. Accessed May 17, 2021
15. Food and Drug Administration. Web BPCA PREA Pediatric Labelling and Studies report. https://www.fda.gov/media/151598/download. Accessed September 21, 2021.
16. European Medicines Agency. Medicines. Medicines | European Medicines Agency (europa.eu). Accessed May 20, 2022
17. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019). Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2020 https://www.healthdata.org/research-analysis/gbd. Accessed February 2023.
18. Institute for Health Metrics and Evaluation. Global Burden of Disease (GBD) data and tools guide.https://www.healthdata.org/research-analysis/about-gbdAccessed December 17, 2023.
19. World Health Organization. Expert Committee on Selection and Use of Essential Medicines. https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines. Accessed February 17, 2023
20. World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision. https://icd.who.int/browse10/2016/enAccessed February 17, 2023
21. Institute for Health Metrics and Evaluation. Global Burden of Disease Study 2019 (GBD 2019) Cause List Mapped to ICD Codes. https://ghdx.healthdata.org/record/ihme-data/gbd-2019-cause-icd-code-mappings. Accessed March 2023.
22. WHO Collaborating Centre for Drug Statistics and Methodology. ATC/DDD Index 2023. https://www.whocc.no/atc_ddd_index/. Last updated January 23, 2023. Accessed March 2023.
23. European Commission. Commission Staff Working Document. Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 onorphan medicinal products.https://health.ec.europa.eu/system/files/2020-08/orphan-regulation_eval_swd_2020-163_part-1_0.pdf. Published August 11, 2020. Accessed February 18, 2023.
24. Netherlands Institute For Health Services Research. Study on off-label use of medicinal products in the European Union. February 2017. https://www.nivel.nl/sites/default/files/bestanden/Report_OFF_LABEL_Nivel-RIVM-EPHA.pdf. Accessed February 17, 2023.
25. Allen HC, Garbe MC, Lees J, et al. Off-Label Medication use in Children, More Common than We Think: A Systematic Review of the Literature. J Okla State Med Assoc. 2018;111(8):776-783.
26. Congressional Budget Office. Research and Development in the Pharmaceutical Industry. https://www.cbo.gov/publication/57025. Published April 8, 2021. Accessed February 20, 2023.
27. Fisher JA, Cottingham MD, Kalbaugh CA. Peering into the pharmaceutical "pipeline": investigational drugs, clinical trials, and industry priorities. Soc Sci Med. 2015;131:322-330. Doi:10.1016/j.socscimed.2014.08.023
28. Milne CP, Kaitin KI. Are Regulation and Innovation Priorities Serving Public Health Needs?. Front Pharmacol. 2019;10:144. Published 2019 Mar 8. doi:10.3389/fphar.2019.00144

29. European Commission. Reform of the EU Pharmaceutical Legislation. https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en. Published April 26, 2023. Accessed April 30, 2023.
30. Volodina A, Jahn RH, Jahn A. Suitability of paediatric legislation beyond the United States and Europe: a qualitative study on access to paediatric medicines. 2023. Unpublished manuscript in review at BMJ Public Health.
31. World Health Organization. Priority medicines for Europe and the world / Warren Kaplan, Richard Laing. World Health Organization. November 2004. https://iris.who.int/handle/10665/68769.Accessed April 30, 2023
32. United NationsCommission On Life-Saving Commodities For Women And Children. https://www.unfpa.org/sites/default/files/pub-pdf/Final%20UN%20Commission%20Report_14sept2012.pdf. August 31, 2012. Accessed April 30, 2023
33. Lewis T, Wade KC, Davis JM. Challenges and opportunities for improving access to approved neonatal drugs and devices. J Perinatol. 2022 Jun;42(6):825-828. doi: 10.1038/s41372-021-01304-2. Epub 2022 Feb 7. PMID: 35132149; PMCID: PMC8819193.
34. Penazzato M, Watkins M, Morin S, Lewis L, Pascual F, Vicari M, Lee J, Hargreaves S, Doherty M, Siberry GK. Catalysing the development and introduction of paediatric drug formulations for children living with HIV: a new global collaborative framework for action. Lancet HIV. 2018 May;5(5):e259-e264. doi: 10.1016/S2352-3018(18)30005-5. Epub 2018 May 1. PMID: 29739700.
35. Ozawa S, Shankar R, Leopold C, Orubu S. Access to medicines through health systems in low- and middle-income countries. Health Policy Plan. 2019;34(Supplement_3):iii1-iii3. Doi:10.1093/heapol/czz119
36. Stevenson M, Yu J, Hendrie D, et al. Reducing the burden of road traffic injury: translating high-income country interventions to middle-income and low-income countries. Inj Prev. 2008;14(5):284-289. Doi:10.1136/ip.2008.018820
37. Gallegos D, Eivers A, Sondergeld P, Pattinson C. Food Insecurity and Child Development: A State-of-the-Art Review. Int J Environ Res Public Health. 2021;18(17):8990. Published 2021 Aug 26. Doi:10.3390/ijerph18178990
38. European Commission. Regulation (EC) No 141/2000 Of The European Parliament And Of The Council of 16 December 1999 on orphan medicinal products. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32000R0141&from=EN. Accessed February 23, 2023.
39. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019 [published correction appears in Lancet. 2020 Nov 14;396(10262):1562]. Lancet. 2020;396(10258):1204-1222. doi:10.1016/S0140-6736(20)30925-9

Figure 1 Process steps of medicines mapping to the Disability Adjusted Life Years with an illustrative example





AU- Australia; CA- Canada; BR – Brazil; KE – Kenya; RU – Russia; SA – South Africa

Volodina et al., Public health relevance of medicines developed under paediatric legislation in Europe and the United States: a systematic mapping study

Supplement 1: All Disability Adjusted Life Years causes with mapped sampled medicines

	DALYs (0-14 years old, both sexes, rate), 2019							Sampled medicines, N
	Australia	Brazil	Canada	Kenya	Russia	South Africa	Global	
Acne vulgaris	67	51	53	78	38	73	65	2
Acute glomerulonephritis	0	2	0	2	1	2	3	0
Acute hepatitis A	2	6	2	26	5	8	59	0
Acute hepatitis B	0	3	0	5	4	1	22	6
Acute hepatitis C	0	1	0	2	0	0	4	1
Acute hepatitis E	0	1	0	1	0	1	3	0
Acute lymphoid leukemia	29	92	26	41	57	16	66	3
Acute myeloid leukemia	20	46	20	20	18	6	30	0
Adverse effects of medical treatment	21	40	17	51	25	46	61	8
African trypanosomiasis	0	0	0	0	0	0	2	0
Age-related and other hearing loss	38	71	28	161	78	161	106	0
Age-related macular degeneration	0	0	0	0	0	0	0	0
Alcohol use disorders	4	3	6	2	3	2	2	0
Alcoholic cardiomyopathy	0	0	0	0	0	0	0	0
Alopecia areata	3	3	4	2	3	2	3	0
Alzheimer's disease and other dementias	0	0	0	0	0	0	0	0
Amphetamine use disorders	0	0	0	0	0	0	0	0
Anorexia nervosa	13	6	8	3	4	4	4	0
Anxiety disorders	249	231	131	115	128	149	157	0
Aortic aneurysm	0	0	0	0	0	0	0	0
Appendicitis	3	15	2	15	5	11	16	2

Asbestosis	0	0	0	0	0	0	0	0
Ascariasis	0	4	0	8	0	1	22	0
Asthma	455	416	301	212	148	274	210	5
Atopic dermatitis	250	208	183	80	396	96	160	1
Atrial fibrillation and flutter	0	0	0	0	0	0	0	0
Attention-deficit/hyperactivity disorder	65	37	42	12	21	11	21	1
Autism spectrum disorders	80	66	112	71	75	70	66	0
Benign and in situ cervical and uterine neoplasms	0	0	0	0	0	0	0	0
Benign and in situ intestinal neoplasms	0	0	0	0	0	0	0	0
Benign prostatic hyperplasia	0	0	0	0	0	0	0	0
Bipolar disorder	37	34	31	13	10	12	12	3
Bladder cancer	0	0	0	0	0	0	0	0
Brain and central nervous system cancer	70	139	75	54	93	35	85	0
Breast cancer	0	0	0	0	0	0	0	0
Bulimia nervosa	18	4	10	3	4	4	4	0
Cannabis use disorders	3	1	6	0	1	0	1	0
Caries of deciduous teeth	9	11	9	11	12	10	10	0
Caries of permanent teeth	10	12	11	10	14	11	13	0
Cataract	0	0	0	0	0	0	0	0
Cellulitis	3	9	4	3	3	3	3	0
Cervical cancer	0	0	0	0	0	0	0	0
Chagas disease	0	1	0	0	0	0	0	0
Chlamydial infection	0	0	0	0	0	0	0	0
Chronic kidney disease due to diabetes mellitus type 1	0	1	0	1	1	2	2	0
Chronic kidney disease due to diabetes mellitus type 2	0	0	0	0	0	0	0	0
Chronic kidney disease due to glomerulonephritis	4	24	8	25	19	25	32	0
Chronic kidney disease due to hypertension	0	0	0	0	0	0	0	0
Chronic kidney disease due to other and unspecified causes	8	41	16	31	30	46	59	0

Chronic lymphoid leukemia	0	0	0	0	0	0	0	0
Chronic myeloid leukemia	1	1	1	7	1	1	8	3
Chronic obstructive pulmonary disease	9	12	8	26	11	25	22	0
Cirrhosis and other chronic liver diseases due to alcohol use	0	0	0	0	0	0	0	0
Cirrhosis and other chronic liver diseases due to hepatitis B	0	0	0	1	0	0	1	0
Cirrhosis and other chronic liver diseases due to hepatitis C	0	1	0	1	0	0	2	0
Cirrhosis and other chronic liver diseases due to NAFLD	0	0	0	0	0	0	0	0
Cirrhosis and other chronic liver diseases due to other causes	2	22	4	47	11	22	71	0
Coal workers pneumoconiosis	0	0	0	0	0	0	0	0
Cocaine use disorders	1	1	1	0	0	0	0	0
Colon and rectum cancer	1	2	1	1	1	2	2	0
Conduct disorder	193	181	157	194	187	193	172	0
Congenital heart anomalies	172	1185	197	546	369	415	866	0
Congenital musculoskeletal and limb anomalies	90	103	75	106	83	144	107	0
Contact dermatitis	2	4	16	4	16	4	5	0
Cutaneous and mucocutaneous leishmaniasis	0	1	0	0	0	0	2	0
Cystic echinococcosis	0	0	0	2	1	0	1	0
Cysticercosis	0	1	0	1	0	1	0	0
Decubitus ulcer	0	1	0	0	0	0	0	0
Dengue	2	20	0	4	0	0	54	0
Diabetes mellitus type 1	12	24	15	20	11	19	26	5
Diabetes mellitus type 2	0	0	0	0	0	0	0	5
Diarrheal diseases	76	561	138	4147	226	2431	2636	2
Dietary iron deficiency	104	368	39	395	91	323	695	0
Digestive congenital anomalies	59	372	63	155	118	115	215	0
Diphtheria	0	0	0	4	0	4	18	4
Down syndrome	45	164	46	44	35	102	72	0
Drug-susceptible tuberculosis	1	25	1	213	9	587	285	0

Dysthymia	11	7	12	11	7	9	9	0
Ebola	0	0	0	0	0	0	2	0
Edentulism	0	0	0	0	0	0	0	0
Encephalitis	9	28	9	19	60	15	121	1
Endocarditis	1	15	1	5	3	5	10	0
Endocrine, metabolic, blood, and immune disorders	167	161	134	79	154	186	159	29
Endometriosis	0	0	0	0	0	0	0	0
Esophageal cancer	0	0	0	0	0	0	0	0
Extensively drug-resistant tuberculosis	0	0	0	0	2	0	1	0
Female infertility	0	0	0	0	0	0	0	0
Food-borne trematodiases	0	0	0	0	1	0	1	0
Fungal skin diseases	20	26	7	64	15	36	45	2
G6PD deficiency	0	12	2	1	1	7	5	0
G6PD trait	0	0	0	0	0	0	0	0
Gallbladder and biliary diseases	3	9	4	5	7	5	9	0
Gallbladder and biliary tract cancer	0	0	0	0	0	0	0	0
Gastritis and duodenitis	3	5	2	6	6	10	10	0
Gastroesophageal reflux disease	1	2	1	1	1	1	1	3
Genital herpes	0	0	0	0	0	0	0	0
Genital prolapse	0	0	0	0	0	0	0	0
Glaucoma	0	0	0	0	0	0	0	0
Gonococcal infection	0	0	0	0	0	0	0	0
Gout	0	0	0	0	0	0	0	0
Guinea worm disease	0	0	0	0	0	0	0	0
Hemolytic disease and other neonatal jaundice	3	52	3	113	33	113	252	0
HIV/AIDS	2	79	4	1875	150	3072	338	15
Hodgkin lymphoma	1	3	1	6	3	2	7	0
Hookworm disease	0	4	0	19	0	16	19	0

Hypertensive heart disease	0	0	0	0	0	0	0	7
Idiopathic developmental intellectual disability	16	20	27	41	25	20	81	0
Idiopathic epilepsy	89	167	64	207	84	183	180	10
Inflammatory bowel disease	3	3	7	4	2	5	4	4
Inguinal, femoral, and abdominal hernia	9	31	9	33	46	53	36	0
Interstitial lung disease and pulmonary sarcoidosis	2	4	4	2	2	3	3	0
Intracerebral hemorrhage	3	12	4	22	6	14	46	0
Invasive Non-typhoidal Salmonella (iNTS)	0	3	0	712	1	113	276	0
Iodine deficiency	1	0	1	3	2	2	12	0
Ischemic heart disease	0	0	0	0	0	0	0	0
Ischemic stroke	8	9	12	25	14	23	22	0
Kidney cancer	8	22	7	4	13	10	12	0
Klinefelter syndrome	0	0	0	0	0	0	0	0
Larynx cancer	0	0	0	0	0	0	0	0
Latent tuberculosis infection	0	0	0	0	0	0	0	0
Leprosy	0	0	0	0	0	0	0	0
Lip and oral cavity cancer	1	1	1	1	1	1	1	0
Liver cancer due to alcohol use	0	0	0	0	0	0	0	0
Liver cancer due to hepatitis B	0	0	0	1	1	0	1	0
Liver cancer due to hepatitis C	0	0	0	0	0	0	0	0
Liver cancer due to NASH	0	0	0	0	0	0	0	0
Liver cancer due to other causes	6	7	7	5	13	4	13	0
Low back pain	109	137	133	71	148	65	100	0
Lower respiratory infections	62	997	57	3119	397	2527	3196	14
Lymphatic filariasis	0	3	0	24	0	0	14	0
Major depressive disorder	135	178	91	47	28	42	57	1
Malaria	0	7	0	2450	0	40	1820	2
Male infertility	0	0	0	0	0	0	0	0

Malignant skin melanoma	5	2	2	1	2	1	1	1
Maternal disorders	0	3	0	5	0	0	4	0
Measles	0	0	0	196	0	281	349	0
Meningitis	24	146	24	600	59	261	604	7
Mesothelioma	0	0	0	0	0	0	0	0
Migraine	132	417	176	89	133	127	165	3
Motor neuron disease	25	7	13	1	4	1	4	0
Multidrug-resistant tuberculosis without extensive drug resistance	0	1	0	7	4	33	25	0
Multiple myeloma	0	0	0	0	0	0	0	0
Multiple sclerosis	0	0	1	0	0	0	0	1
Myelodysplastic, myeloproliferative, and other hematopoietic neoplasms	1	5	4	1	2	1	2	0
Myocarditis	8	17	8	5	7	4	12	0
Nasopharynx cancer	1	1	1	2	1	1	2	0
Near vision loss	0	0	0	0	0	1	0	0
Neck pain	10	8	18	7	8	7	13	0
Neonatal encephalopathy due to birth asphyxia and trauma	346	1313	327	3220	355	2341	2625	0
Neonatal preterm birth	513	2240	791	2250	482	4103	3182	0
Neonatal sepsis and other neonatal infections	33	1077	68	1621	288	1157	1093	2
Neural tube defects	79	324	60	258	76	146	383	0
Non-Hodgkin lymphoma	9	26	11	27	17	15	25	0
Non-melanoma skin cancer (basal-cell carcinoma)	0	0	0	0	0	0	0	0
Non-melanoma skin cancer (squamous-cell carcinoma)	0	0	0	0	0	0	0	0
Non-rheumatic calcific aortic valve disease	0	0	0	0	0	0	0	0
Non-rheumatic degenerative mitral valve disease	0	0	0	0	0	0	0	0
Onchocerciasis	0	0	0	0	0	0	11	0
Opioid use disorders	0	0	0	0	0	0	0	0
Orofacial clefts	3	9	1	14	3	17	17	0

Osteoarthritis hand	0	0	0	0	0	0	0	0
Osteoarthritis hip	0	0	0	0	0	0	0	0
Osteoarthritis knee	0	0	0	0	0	0	0	0
Osteoarthritis other	0	0	0	0	0	0	0	0
Other benign and in situ neoplasms	0	0	0	0	0	0	0	2
Other cardiomyopathy	8	74	14	47	25	49	32	0
Other cardiovascular and circulatory diseases	13	45	14	41	13	29	58	0
Other chromosomal abnormalities	112	178	166	59	78	127	95	0
Other chronic respiratory diseases	13	30	14	34	13	38	32	8
Other congenital birth defects	132	659	170	519	320	561	589	2
Other digestive diseases	3	11	4	16	9	11	16	1
Other drug use disorders	0	0	1	0	0	0	0	0
Other gynecological diseases	0	1	0	1	0	1	1	1
Other hemoglobinopathies and hemolyticanemias	4	17	2	15	4	13	26	3
Other intestinal infectious diseases	0	2	0	4	1	3	5	4
Other leukemia	3	20	11	38	5	25	43	0
Other malignant neoplasms	56	108	76	82	73	48	120	1
Other mental disorders	3	1	3	1	1	1	2	1
Other musculoskeletal disorders	7	15	65	2	3	2	10	1
Other neglected tropical diseases	10	53	4	42	14	33	101	0
Other neonatal disorders	245	1226	354	1797	299	2955	1731	0
Other neurological disorders	57	76	59	75	75	68	71	1
Other non-rheumatic valve diseases	0	0	0	0	0	0	0	0
Other nutritional deficiencies	2	10	3	9	6	6	31	0
Other oral disorders	31	32	31	32	32	32	31	1
Other pharynx cancer	0	0	0	0	0	0	0	0
Other pneumoconiosis	0	0	0	0	0	0	0	0
Other sense organ diseases	15	15	13	15	13	15	14	10

Other sexually transmitted infections	0	0	0	0	0	0	0	2
Other skin and subcutaneous diseases	23	24	23	20	22	22	23	1
Other unspecified infectious diseases	37	70	26	104	93	290	138	6
Other urinary diseases	3	4	3	17	4	7	11	1
Other vision loss	5	8	4	4	4	3	5	2
Otitis media	26	49	26	57	46	55	51	2
Ovarian cancer	1	2	1	1	2	2	2	0
Pancreatic cancer	0	0	0	0	0	0	0	0
Pancreatitis	1	2	1	1	2	0	2	0
Paralytic ileus and intestinal obstruction	13	91	16	84	21	39	103	0
Paratyphoid fever	0	0	0	16	0	0	50	0
Parkinson's disease	0	0	0	0	0	0	0	0
Peptic ulcer disease	0	2	1	5	2	2	10	0
Periodontal diseases	0	0	0	0	0	0	0	0
Peripheral artery disease	0	0	0	0	0	0	0	0
Polycystic ovarian syndrome	2	0	1	0	0	0	1	0
Premenstrual syndrome	20	23	22	24	21	21	21	0
Prostate cancer	0	0	0	0	0	0	0	0
Protein-energy malnutrition	10	194	10	1188	36	802	555	1
Pruritus	4	5	5	8	5	7	5	0
Psoriasis	52	32	41	6	13	9	15	2
Pyoderma	6	24	2	23	5	15	21	4
Rabies	0	0	0	15	0	3	21	0
Refraction disorders	46	54	27	17	39	18	31	0
Rheumatic heart disease	2	28	1	38	2	32	36	0
Rheumatoid arthritis	1	2	2	1	1	1	1	7
Scabies	6	162	5	54	13	31	76	0
Schistosomiasis	0	10	0	68	0	37	14	0

Schizophrenia	2	2	1	2	2	2	2	5
Seborrhoeic dermatitis	2	2	2	3	1	3	3	0
Self-harm and interpersonal violence	70	279	90	133	171	321	240	1
Sickle cell disorders	0	31	1	82	0	3	122	0
Sickle cell trait	1	6	0	86	0	2	43	0
Silicosis	0	0	0	0	0	0	0	0
Stomach cancer	0	0	0	0	0	0	0	0
Subarachnoid hemorrhage	3	21	5	4	6	3	18	0
Sudden infant death syndrome	102	45	68	87	102	135	125	0
Syphilis	0	37	0	419	2	1321	371	0
Tension-type headache	13	18	17	11	17	12	13	0
Testicular cancer	4	3	4	1	3	3	3	0
Tetanus	0	2	0	384	0	3	89	4
Thalassemias	4	6	2	0	9	5	28	0
Thalassemias trait	3	7	0	5	8	5	56	0
Thyroid cancer	1	1	1	1	1	1	1	1
Tracheal, bronchus, and lung cancer	1	1	1	0	0	0	1	0
Trachoma	0	0	0	0	0	0	0	0
Transport and other unintentional injuries	683	1168	435	825	1085	1432	1482	0
Trichomoniasis	0	0	0	0	0	0	0	0
Trichuriasis	0	4	0	3	0	4	4	0
Turner syndrome	0	0	0	0	0	0	0	0
Typhoid fever	0	0	0	359	0	3	275	0
Upper respiratory infections	132	154	144	154	100	106	114	0
Urinary tract infections and interstitial nephritis	5	48	5	7	10	4	23	0
Urogenital congenital anomalies	28	84	29	33	25	26	50	0
Urolithiasis	0	0	0	0	1	0	0	0
Urticaria	71	80	88	80	133	81	80	2

Volodina et al., Public health relevance of medicines developed under paediatric legislation in Europe and the United States: a systematic mapping study

Uterine cancer	0	0	0	0	0	0	0	0
Uterine fibroids	0	0	0	0	1	0	0	0
Varicella and herpes zoster	4	27	3	36	8	19	30	1
Vascular intestinal disorders	1	2	1	1	2	1	2	0
Viral skin diseases	204	105	326	175	104	121	122	0
Visceral leishmaniasis	0	70	0	49	0	0	14	0
Vitamin A deficiency	0	29	1	110	0	22	51	0
Whooping cough	4	17	7	478	1	593	515	4
Yellow fever	0	0	0	6	0	0	8	0
Zika virus	0	0	0	0	0	0	0	0

Volodina et al., Public health relevance of medicines developed under paediatric legislation in Europe and the United States: a systematic mapping study

Supplement 2. Paediatric indications not mapped with Disability Adjusted Life Year cause

N	Approved indication in EU/US	Assigned ICD 10 classification
1	Maintenance of anesthesia in non-intubated patients	Z00-Z13 Persons encountering health services for examination and investigation
2	Adjunct to general anesthesia	
3	Contrast agent for intravenous use with magnetic resonance imaging	
4	Diagnostic evaluation of tissue pathologies with contrast-enhanced magnetic resonance imaging	
5	Emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure	Z30 Contraceptive management
6	Oral contraception	
7	Management of mild to moderate pain and the management of moderate to severe pain as an adjunct to opioid analgesics, and for the reduction of fever in pediatric patients 6 months and older	R52 Pain, not elsewhere classified
8	Management of pain severe enough to require daily, around the-clock, long-term opioid treatment in pediatric patients 11 years and older	