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Measuring Access to Essential Medicines for Children with Sustainable Development Goal Indicator 3.b.3 - A Proof-of-Concept Study

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ABSTRACT

Objectives

To aid countries in assessing accessibility to pediatric medicines in a validated manner and on a longitudinal basis, a conceptual methodology for measuring access to medicines for children was developed based on the principles embedded in Sustainable Development Goal (SDG) Indicator 3.b.3 which measures access as a combination of availability and affordability. We aimed to provide proof-of concept of this adapted methodology by applying the method to historical datasets.

Method

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

Results

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

Conclusion

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

KEY MESSAGES

What is already known on this topic

Although considerable progress in child health has been achieved in recent decades, high child morbidity and mortality rates remain a major challenge for developing health systems. Access to child-appropriate medicines is a key element towards improvement. The Sustainable Development Goal (SDG) indicator that was developed to measure and express access to medicines seems to exclude children and their specific health needs.

What this study adds

A targeted methodology for measuring access to pediatric medicines was developed based on SDG indicator 3.b.3 and proof-of-concept was provided. This standardized yet flexible tool will enable international comparison of research findings on access to medicines for children.

How this study might affect research, practice or policy

This adapted methodology could be an important tool for policy-makers and program managers to help identify drivers of suboptimal access to pediatric medicines and develop appropriate policies to improve it. This standardized methodology may also guide others researching access to medicines for children.

INTRODUCTION

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

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

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

No specific methodology for assessing accessibility of essential medicines for children has been developed yet, although a number of studies have measured the availability or price of medicines, or both [7-35]. The methodologies for measuring these two important dimensions of access to pediatric medicines and the medicines surveyed varied greatly between studies, covering different age groups of children (e.g. children under five, children under twelve, or all children and adolescents), priority diseases (anticancer medicines, cardiovascular medicines or a range of diseases) and numbers of surveyed medicines. Results are therefore difficult to compare and may not reflect overall access to medicines for children in a country. This emphasizes the need for a standardized and validated methodology for measuring access to medicines for children that will allow for global comparisons, and eventually benchmark indicators.

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

METHODOLOGY

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

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

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

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

As both availability and affordability are important dimensions of access, the combination of these core concepts into a single measure allows evaluation of overall access to medicines. As the same holds true for pediatric medicines, we propose to use the current SDG indicator 3.b.3 framework as a starting point for a methodology for estimating access to medicines for children. In this section, we discuss the critical steps of the original framework and describe how the core concepts have been adapted to allow calculation of access to pediatric medicines.

A core set of globally relevant essential medicines

The core set of medicines consists of tracer essential medicines, together indicative of the overall access to medicines for primary health care. Over the years, several baskets of pediatric medicines have already been proposed. The list of medicines defined for the 2007 'Better medicines for children' project, although intended for a similar purpose, is not only dated but also purposely excluded antiretroviral therapies (ART) for HIV [3]. As ART are still needed to treat a large part of the pediatric population in low- and middle-income countries, this selection of medicines is not suitable for the current purpose. In 2012, the World Health Organization (WHO) published a list of thirteen 'Priority life-saving medicines' for children under the age of five, intended to help countries in prioritizing those medicines that will have the biggest impact on reducing child morbidity and mortality [36]. Yet, an access indicator should serve a broader age group of children, especially since those between 5 and 12 years may have different treatment requirements. Additionally, the priority list only targets seven prevalent diseases, and is thus limited in its scope. With that, no existing basket of pediatric medicines was deemed suitable for the current purpose.

A new core set of medicines for children with ages 1 month to 12 years for treating acute and chronic, communicable and non-communicable diseases in the primary health care setting, including child-appropriate formulations, was thus established. To cater to the unique needs of children with different ages, separate baskets for two age groups were created: young children (infants, toddlers and pre-school children) aged 1 month to 59 months, and school-aged children 5 to 12 years of age. These groups will allow stakeholders to differentiate between different health needs in terms of disease prevalence, required dosage strengths and preferred formulations. Children above the age

of 12 often do not require specific pediatric formulations [37] thus their health needs may already be adequately covered in the original SDG indicator 3.b.3 methodology.

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

Priority conditions were linked to specific first-choice medicines used in primary health care using international treatment guidelines [40-44]. Multiple medicines from the same therapeutic class of medicines were selected in some cases (including antiepileptics, anthelminthics, antimalarials) and can be considered interchangeable. Medicines requiring cold-chain management and vaccines were excluded, as these may not be widely available in primary health facilities. The primary selection of medicines for children aged 1 month to 5 years that is used in the current case study, was validated through expert consultation and can be found in Table 1. Child-appropriate medicines were selected pragmatically, based on formulations present on the WHO EMLC and required dosage strengths.

Availability of medicines

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

Affordability of medicines

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

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

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

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

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

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

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

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

Cap/tab = capsule/tablet; GHE = Global Health Estimate.

Number of units needed per treatment

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

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

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

[figure 1]

Weighing for burden of disease

In the original framework, accessible medicines are weighted according to the regional burden of disease to address differences in demand for specific medicines[1] [4]. This concept was applied to pediatric medicines as well, based on the GHEs [38]. Each medicine in the baskets was assigned a GHE code for one or several disease(s) that are treated/cured/controlled by that medicine. Indications of the medicines were determined according to their uses as described in the WHO EMLc (see table 1) [39]. Antibacterial medicines were given a GHE code specific for the primary indication described on the WHO EMLc, and in some cases an additional code (370) as a proxy for the broad use of these medicines in a variety of bacterial diseases.

The weight that each medicine is given in the calculation was computed as the proportion of the medicine's specific disability-adjusted life years (DALYs) compared to the total sum of DALYs in the basket. Of note, the GHEs include data for children 1-59 months and children 5-14 years. Weighting school-aged children up to 12 years based on data for children up to 14 years old does not have a significant impact on the results as assigned weights are relative weights.

Calculating SDG indicator 3.b.3

The age-specific SDG indicator 3.b.3 can be calculated with formula 1. Assessing availability and affordability of medicines, and subsequent weighing for regional disease burden, was done at the

[1] Weighing for regional burden of disease is a different process than selecting medicines for the core set based on global burden of disease.

facility level, meaning that a separate score is calculated for each facility surveyed. Facilities with at least 80% of medicines in the basket available and affordable were considered to have accessible medicines. This threshold was adopted by the WHO Global Action Plan on Non-Communicable Diseases and used as a reference [49]. Table 2 presents a full summary of the adaptations to the original SDG 3.b.3 methodology needed for a child-specific methodology.

Case studies

As proof-of-concept, the methodology described above was applied to three historical datasets for the young children age group (1 month-5 years).

Medicines' availability and price data for Burundi (2013), China (2012) and Haiti (2011) was obtained from Health Action International (HAI). These datasets were selected because the highest absolute number of age-appropriate medicines in the proposed basket was included in these surveys (11, 10 and 12 out of 22 medicines, respectively). Additionally, this selection represents countries with different income levels (e.g. Burundi and Haiti low-income countries, China an upper-middle income country) and from different geographical regions.

Data on NPLs were obtained from World Bank reports on poverty [50-52]. NPLs were adjusted for inflation and deflation between the year data was reported and the survey year using the Consumer Price Index (CPI) [53]. Monthly poverty lines were converted to daily time periods. LPGW wages were directly obtained from the datasets provided by HAI and thus required no corrections for the year of survey.

Because regional data on burden of disease in DALYs is published only every five years, the year closest in time to the year of survey was used (e.g. 2010 publication for China and Haiti and 2015 publication for Burundi) to weigh for burden of disease [38].

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

Patient and public involvement

There was no patient or public involvement in the design or conduct of this study.

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

Input	Original $SDG_{3.b.3}$ methodology [4]	Child-specific $SDG_{3.b.3}$ methodology
SDG indicator 3.b.3		
Calculation	- Based on individual facility scores. - Facilities considered as having accessible medicines when reaching an 80% threshold.	- Based on individual facility scores. - Facilities considered as having accessible medicines when reaching an 80% threshold.
Core set of globally relevant essential medicines		
Selection of medicines	- Defined on a global level. - Selected from 2017 WHO EML. - Selection process not described.	- Defined on a global level. - Selected from 2019 WHO EMLc. - Selection based on global burden of disease (top 10 conditions causing disability/mortality that can be treated with medicines), international treatment guidelines and expert consultation.
The basket	- One basket for all. - 32 tracer essential medicines for acute and chronic, communicable and non-communicable diseases.	- Baskets defined for two age groups (young children; school-aged children). - 22 tracer essential medicines for acute and chronic, communicable and non-communicable diseases for both young and school-aged children. - Age-appropriate formulations selected per age group.
Burden of disease	- Weighting according to regional burden of disease (in DALYs). - Based on WHO GHEs. - Pre-defined GHE codes, with overarching GHE code for 'infectious and parasitic diseases' for antibacterials. - Equal weights assigned to medicines that are used to treat the same disease.	- Weighting according to regional burden of disease (in DALYs). - Based on WHO GHEs, from period closest to year of survey. - Affiliated GHE codes determined according to the uses as described in EMLc. GHE codes for antibacterials determined according to uses as described in EMLc plus code for 'other infectious diseases'. - Equal weights assigned to medicines that are used to treat the same disease.
Availability of medicines		
Availability	- Captured as binary variable. - As surveyed.	- Captured as binary variable. - As surveyed.
Affordability of medicines		
Required inputs	- Captured as binary variable. - Calculated from the price of a medicine, the number of units needed for treatment, the NPL and the wage of the LPGW.	- Captured as binary variable. - Calculated from the price of a medicine, the NUNT, the NPL and the wage of the LPGW.
Number of units needed for treatment	- Total number of units needed per month or treatment course based on DDDs. - Process for defining duration of treatment not described.	- NUNT based on duration of treatment and recommended daily dosages per age or weight group. Weight-based dosing transformed to age-based dosing. - Recommended daily dosages and duration of treatment derived from international treatment guidelines.

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

RESULTS

Access to medicines for children aged 1 month to 5 years was calculated for each of the three countries across its different health sectors. Analysis of Burundi data showed a stark contrast between lowest-price generic medicines (LPM) and the originator brand (OB), with a mean facility score of about 40% for LPMs versus 0% for the OB. The public and mission sector provided more accessible medicines than the private sector. The difference between LPMs and the OB was not as pronounced in China having mean facilities scores of 22.3% and 16.5% respectively, with LPMs more accessible in the public sector and the OB in the private sector. In Haiti, access was calculated for the public sector, the private sector, the non-profit sector, and the mixed sector (health facilities managed by the government and non-profit organization together). Mean facility scores for LPMs were similar across the sectors, with an overall average of approximately 22%. For OB medicines, scores varied between 0.6% in the private sector and 15.1% in the public sector. Results on SDG indicator 3.b.3 and mean facility scores across health facilities from different sectors are summarized in table 3.

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

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

None of the facilities in either of the three countries were categorized as providing sufficient access to medicines, as all facilities failed to reach the 80% threshold. This resulted in SDG indicator 3.b.3 outcomes of 0% in all three countries. The main driver for the low scores was the low availability of medicines, as illustrated in figure 2. Notably, those medicines that were available on the day of survey were generally also affordable, with a few exceptions (four cefotaxime injections, six ceftriaxone injections, two ibuprofen tablets, one phenobarbital tablet). Age-appropriate dosage forms such as oral suspension or liquids were not associated with unaffordable prices in this case study.

[figure 2]

DISCUSSION

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

With no reliable method for measuring access to pediatric medicines having been established yet, the child-specific methodology presented in this paper can provide guidance to others aiming to study access to medicines for children. When a single method to express access to medicines is applied across countries, this will allow for international comparison. Another important advantage of such a standardized tool is its ease of use. By predetermining which medicines and formulations should be surveyed, providing the typical NUNT and demonstrating how accessibility should be calculated, this method only requires countries to collect the facility data and some additional inputs. Yet, standardization can also be viewed as rigidity and be a limitation, as the methodology allows for few differences between countries. Local guidelines that recommend use of other medicines than those in the core set or used in different dosages could lead to skewed outcomes. Therefore, this standardized method incorporates some flexibilities, allowing for several formulations or active ingredients from within the same therapeutic class to be interchanged (i.e. antiepileptics, antimalarials, etc.). This allows countries to apply this method to their national situation.

Several outcomes of the case studies of Burundi, China and Haiti are worth mentioning in more detail. First of all, since no facilities met the benchmark, the overall SDG indicator 3.b.3 was 0% in all countries. If the SDG indicator is reported as a single outcome, the detail required for identifying the major obstacles in accessibility is missing. This highlights that underlying and disaggregated data on facility and medicine level is vital in understanding the drivers of inaccessibility to medicines, particularly when the indicator value reflects a sub-optimal level of access. Secondly, the widespread inaccessibility seen in the case studies seemed to stem from unavailable rather than unaffordable medicines, for both LPMs and OBs. A recent systematic review on children's medicines identified fourteen studies that reported on the availability of children's medicines and found a median availability of 38.1% and 24.2% for LPMs and OBs in the public sectors and of 35.9% and 21.1% in the private sectors, respectively [54]. With that, the unavailability of child medicines detected in the present case studies is in line with the results of the systematic review. The same systematic review identified eleven studies that reported on the affordability of medicines, based on the number of days' wages of the LPGW. In the public sector, affordability was 83.6% and 48.5% for LPMs and OBs, with 72.2% and 68.8% in the private sector. The results of this systematic review emphasize the need for a method that combines the two dimensions into a single indicator, as separate evaluation of these elements overestimates actual access to medicines for the patient. Beyond that, some of the studies included in the systematic review included unrepresentative samples of medicines (e.g. studies focused on a single disease area or studies simply failing to consider child-appropriate

formulations such as oral liquids or appropriate medicine strengths), again confirming the need for a standardized methodology to measure access to child medicines.

Before this methodology can, however, be applied on a widespread scale, several steps must be undertaken to further validate the methodology. For one, although the primary basket of medicines for young children was validated through expert consultation, this validation step should be repeated for school-aged children. Simultaneously, the robustness of the adapted methodology with regard to the NUNT will need to be tested through sensitivity analyses as it is an important variable when calculating affordability. The NUNT was determined based on recommended dosages and duration of treatment prescribed in international guidelines, which were often expressed as ranges. This generates some uncertainty when converting to a single NUNT. Also, in many cases determining a NUNT involved transformation of weight-based to age-based dosing through weight-to-age charts, introducing further uncertainties. The WHO provides international weight-for-age charts for boys and girls until the age of five [45] and ages 5-10 years [46], but no international charts are available for children above the age of 10. Therefore Dutch growth diagrams were used to approximate median weights of children 10-12 years [47]. Initial comparison of international and Dutch growth charts shows that differences, if any, are small and will likely have had no significant impact on determining the NUNT. Furthermore, the NUNT is a single number used to represent an entire age group. How big the uncertainties with regard to the NUNT are and whether a single NUNT is indeed sufficiently representative for an entire age group should become clear in sensitivity analyses. Additionally, the case studies now performed were on a subset of the complete basket for young children, limited by the small number of age-appropriate medicines that had been surveyed in the three countries. Sensitivity analyses should also be performed to determine the minimum number of medicines required for a reliable measure of accessibility. To perform meaningful sensitivity analyses, more data on child medicines is needed than was available in the present case studies.

Besides the uncertainties introduced through our adaptation of the methodology, this child-specific methodology inherits some of the limitations of the original 3.b.3 indicator methodology. Particularly, weighing for regional burden of disease when calculating access at the facility level as done in the original methodology raises several concerns. For one thing, the methodology assigns equal weights to medicines that are used to treat the same disease and counts the burden of this disease multiple times. To illustrate, the basket of medicines includes both oral rehydration salts and zinc sulphate for diarrheal diseases, whereas only retinol was selected for measles/vitamin A deficiency. This leads to disproportionate weighing for actual burden of disease when calculating access at the facility level. Disproportionality is also a concern for antibacterial medicines, which use may be overrepresented by using GHE code 20, a code that is linked to all infectious and parasitic diseases. Although a proxy for this GHE code was used in the present study (GHE code 370 for 'other infectious diseases'), additional analyses should demonstrate how different weighing approaches affect the results. Additionally, the quality of the underlying GHEs data is unclear, especially because these data may be more difficult to obtain for children than for adults. Lastly, arguments can be made that the current approach of weighing for burden of disease is undesirable because it implies that some medicines are more important than others, even though all medicines in the basket are essential medicines and should always be accessible.

On a similar note, expressing affordability as a function of a poverty line instead of the LPGW wage has been used previously [55], but a measure combining the NPL and LPGW wage as is used in the

original 3.b.3 indicator has yet to prove itself. This is particularly relevant because it seems that somewhat less medicines were unaffordable in the present case studies than what was observed using the LPGW wage alone [54]. Further testing of the proposed child-specific methodology should include several scenarios for weighing for burden of disease and calculating affordability, which could lead to further adaptations of the methodology.

In selecting appropriate countries for the case studies, it was observed that a limited number of children's medicines are being surveyed in low- and middle-income countries alike. Needless to say, such a small number of medicines and disease areas covered fails to provide a comprehensive account of the overall situation. Moving forward, this lack of data on child-appropriate medicines should be addressed to allow stakeholders to identify potential barriers to accessible medicines and enact directed and effective interventions to improve access. New technologies such as the WHO Essential Medicines and Health Products Price and Availability Monitoring Mobile Application (WHO EMP MedMon app) may provide particular opportunities in collecting this data [56].

CONCLUSION

This paper is the first to propose a standardized methodology for measuring access to medicines for children. Such a standardized method will aid countries in assessing national accessibility to pediatric medicines in a validated manner and on a regular basis and is an important addition to SDG indicator 3.b.3 on access to medicines for adults. The proposed validation steps of this method will help identify critical steps in the calculation and will determine its robustness, which could lead to further improvements of the method.

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COMPETING INTERESTS

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AUTHOR STATEMENT

All authors were involved in conception and study design. IRJ drafted the article, HAvdH, AKM-T and FS were involved in critical revision of the article. All authors approved the final article.

ETHICS APPROVAL STATEMENT

This study does not involve human or animal participants.

DATA SHARING STATEMENT

The data that support the findings of this study are available from Health Action International. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors upon reasonable request and with the permission of Health Action International.

REFERENCES

1. Unicef. Goal 3: Good Health And Well-Being [internet]. Date accessed: 9 May 2022. URL: https://data.unicef.org/sdgs/goal-3-good-health-wellbeing/.
2. United Nations. About the Sustainable Development Goals [internet]. Date accessed: 17 Sep 2020. URL: https://www.un.org/sustainabledevelopment/sustainable-development-goals/.
3. World Health Organization (WHO). Better Medicines for Children Project. Geneva: WHO; 2009. Date accessed 1 June 2021. URL : https://www.who.int/childmedicines/progress/ChildMeds_pricing_surveys.pdf.
4. United Nations. SDG Indicators: Metadata repository [internet]. Accessed 17 Sep 2020. URL: https://unstats.un.org/sdgs/metadata?Text=&Goal=3&Target=3.b.
5. Kristensen HG. WHO guideline development of paediatric medicines: points to consider in pharmaceutical development. *Int J Pharm* 2012;435(2):134-5.
6. World Health Organization (WHO). Promoting safety of medicines for children. Geneva: WHO; 2007. URL: https://www.who.int/medicines/publications/essentialmedicines/Promotion_safe_med_childrens.pdf.
7. Martei YM, Iwamoto K, Barr RD, et al. Shortages and price variability of essential cytotoxic medicines for treating children with cancers. *BMJ Glob Health* 2020;5(11):e003282.
8. Simonyan T, Papyan R, Danielyan S, et al. Availability of Essential Medicines for Pediatric Oncology in Armenia. *Asian Pac J Cancer Prev* 2019;20(4):991-994.
9. Droti B, O'Neill KP, Mathai M, et al. Poor availability of essential medicines for women and children threatens progress towards Sustainable Development Goal 3 in Africa. *BMJ Glob Health* 2019;4(Suppl 9):e001306.
10. Orubu ESF, Robert FO, Samuel M, et al. Access to essential cardiovascular medicines for children: a pilot study of availability, price and affordability in Nigeria. *Health Policy Plan* 2019;34 Suppl 3:20-26.
11. Roy V, Singhal S, Tayal H, et al. Availability of Pediatric Formulations in Public Health Care System in India: A Case Study. *Indian J Pediatr* 2021;88(3):227-234.
12. Faruqui N, Martiniuk A, Sharma A, et al. Evaluating access to essential medicines for treating childhood cancers: a medicines availability, price and affordability study in New Delhi, India. *BMJ Glob Health* 2019;4(2):e001379.
13. Cohen P, Friedrich P, Lam C, et al. Global Access to Essential Medicines for Childhood Cancer: A Cross-Sectional Survey. *J Glob Oncol* 2018;4:1-11.
14. Hailu AD, Mohammed SA. Availability, price, and affordability of WHO priority maternal and child health medicine in public health facilities of Dessie, north-East Ethiopia. *BMC Med Inform Decis Mak* 2020;20(1):221.
15. Johansson EW, Lindsjö C, Weiss DJ, et al. Accessibility of basic paediatric emergency care in Malawi: analysis of a national facility census. *BMC Public Health* 2020;20(1):992.
16. Dorj G, Sunderland B, Sanjjav T, et al. Availability, affordability and costs of pediatric medicines in Mongolia. *BMC Pediatr* 2018;18(1):149.
17. Tujo TM, Gurmu TG. Availability and Utilization of WHO Lifesaving Medicines for Children under Five in Public Health Facilities of the Jimma Zone, South West Ethiopia: A Cross-Sectional Survey. *Int J Pediatr* 2020;2020:3505672.
18. Swain TR, Rath B, Dehury S, et al. Pricing and availability of some essential child specific medicines in Odisha. *Indian J Pharmacol* 2015;47(5):496-501
19. Božić B, Stupar S, Stupar D, et al. Availability of pediatric-evaluated formulations in Serbia. *Indian J Pharmacol* 2017;49(2):189-193.

20. Sun X, Wei J, Yao Y, et al. Availability, prices and affordability of essential medicines for children: a cross-sectional survey in Jiangsu Province, China. *BMJ Open* 2018;8(10):e023646.
21. Wang X, Fang Y, Yang S, et al. Access to paediatric essential medicines: a survey of prices, availability, affordability and price components in Shaanxi Province, China. *PLoS One* 2014;9(3):e90365.
22. Sado E, Sufa A. Availability and affordability of essential medicines for children in the Western part of Ethiopia: implication for access. *BMC Pediatr* 2016;16:40.
23. Balasubramaniam R, Benaragama BV, Sri Ranganathan S. A national survey of price and affordability of key essential medicines for children in Sri Lanka. *Indian J Pediatr* 2014;81(4):362-7.
24. Vassal G, Kozhaeva O, Griskjane S, et al. Access to essential anticancer medicines for children and adolescents in Europe. *Ann Oncol* 2021;32(4):560-568.
25. Barr R, Robertson J. Access to Cytotoxic Medicines by Children With Cancer: A Focus on Low and Middle Income Countries. *Pediatr Blood Cancer* 2016;63(2):287-91.
26. Nsabagasani X, Ogwal-Okeng J, Mbonye A, et al. Availability and utilization of the WHO recommended priority lifesaving medicines for under five-year old children in public health facilities in Uganda: a cross-sectional survey. *J Pharm Policy Pract* 2015;8(1):18.
27. Rutebemberwa E, Buregyeya E, Lal S, et al. Assessing the potential of rural and urban private facilities in implementing child health interventions in Mukono district, central Uganda-a cross sectional study. *BMC Health Serv Res* 2016;16:268.
28. Robertson J, Forte G, Trapsida JM, et al. What essential medicines for children are on the shelf? *Bull World Health Organ* 2009;87(3):231-7.
29. Shafiq Y, Shaikh BT, Kumar R. Availability and affordability of essential medicines: exploring the health seeking behaviours and health service utilisation for children under-5 years living in squatter settlement of Karachi, Pakistan. *J Ayub Med Coll Abbottabad* 2011;23(1):132-8.
30. Balasubramaniam R, Beneragama BV, Sri Ranganathan S. A national survey of availability of key essential medicines for children in Sri Lanka. *Ceylon Med J* 2011;56(3):101-7.
31. Gitanjali B, Manikandan S. Availability of five essential medicines for children in public health facilities in India: A snapshot survey. *J Pharmacol Pharmacother* 2011;2(2):95-9.
32. Tadesse T, Abuye H, Tilahun G. Availability and affordability of children essential medicines in health facilities of southern nations, nationalities, and people region, Ethiopia: key determinants for access. *BMC Public Health* 2021;21(1):714.
33. Anson A, Ramay B, de Esparza AR, et al. Availability, prices and affordability of the World Health Organization's essential medicines for children in Guatemala. *Global Health* 2012;8:22.
34. Abu-Arja MH, Rojas Del Río N, Morales La Madrid A, et al. Evaluation of the Pediatric Neuro-Oncology Resources Available in Chile. *JCO Glob Oncol* 2021;7:425-434.
35. Abrha S, Tadesse E, Atey TM, et al. Availability and affordability of priority life-saving medicines for under-five children in health facilities of Tigray region, northern Ethiopia. *BMC Pregnancy Childbirth* 2018;18(1):464.
36. World Health Organization (WHO). Priority life-saving medicines for women and children 2012. Geneva: WHO; 2012. URL: https://www.who.int/reproductivehealth/publications/general/emp_mar2012.1/en/.
37. European Medicines Agency (EMA). Reflection paper: Formulations of choice for the paediatric population. London: EMA; 2006. URL: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-formulations-choice-paediatric-population_en.pdf.
38. Global Health Observatory, World Health Organization (WHO). Global health estimates: Leading causes of DALYs [internet]. Date accessed 18 Oct 2020. URL:

https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/global-health-estimates-leading-causes-of-dalys.

39. World Health Organization (WHO). WHO Model List of Essential Medicines for Children - 7th list, 2019. Geneva: WHO; 2019. URL: https://www.who.int/publications/i/item/WHOMVPEMPIAU201907.
40. World Health Organization (WHO). Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Childhood Illnesses. 2nd edition. Geneva: WHO; 2013. URL: https://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/#:~:text=It%20is%20for%20use%20by,of%20Childhood%20Illness%20(IMCI).
41. National Department of Health. Primary Healthcare Standard Treatment Guideline and Essential Medicine List. 6th ed. Republic of South Africa: National Department of Health; 2018. URL: https://www.knowledgehub.org.za/elibrary/primary-healthcare-standard-treatment-guidelines-and-essential-medicines-list-6th-edition.
42. World Health Organization (WHO). Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: WHO; 2021. URL: https://www.who.int/publications/i/item/9789240031593
43. World Health Organization (WHO). WHO guidelines for Malaria. Geneva: WHO; 2021. URL: https://www.who.int/publications/i/item/guidelines-for-malaria
44. World Health Organization (WHO). Paediatric emergency triage, assessment and treatment: care of critically-ill children. Geneva: WHO; 2016. URL: https://www.who.int/publications/i/item/9789241510219
45. World Health Organization (WHO). Child Growth Standards [internet]. Date accessed 2 Mar 2021. URL: https://www.who.int/tools/child-growth-standards/standards/weight-for-age.
46. World Health Organization (WHO). Growth Reference Data for 5-19 years [internet]. Date accessed 2 Mar 2021. URL: https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/weight-for-age-5to10-years.
47. TNO. Groeidiagrammen in PDF-formaat [internet]. Date accessed 11 Jun 2021. URL: https://www.tno.nl/nl/aandachtsgebieden/gezond-leven/roadmaps/youth/groeidiagrammen-in-pdf-formaat/.
48. Akkawi El Edelbi R, Lindemalm S, et al. Estimation of body surface area in neonates, infants, and children using body weight alone. *Int J Pediatr Adolesc Med* 2021;8(4):221-228.
49. World Health Organization (WHO). Global action plan for the prevention and control of noncommunicable diseases 2013-2020. Geneva: WHO; 2013. URL: https://www.who.int/publications/i/item/9789241506236.
50. World Bank. Burundi Poverty Assessment. Washington, DC: World Bank; 2016. URL: https://openknowledge.worldbank.org/handle/10986/35555.
51. World Bank. Poverty and Equity Brief China. Washington, DC: World Bank; 2021. URL: https://www.worldbank.org/en/topic/poverty/publication/poverty-and-equity-briefs.
52. World Bank and Observatoire National de la Pauvreté et de l'Exclusion Sociale (ONPES). Investing in People to Fight Poverty in Haiti, Reflections for Evidence-based Policy Making. Washington, DC: World Bank; 2014. URL: https://openknowledge.worldbank.org/handle/10986/21519.
53. World Bank. Consumer Price Index (2010 = 100) [internet]. Date accessed 18 Mar 2022. URL: https://data.worldbank.org/indicator/FP.CPI.TOTL.
54. Chen Z, Li S, Zeng L, et al. Accessibility of Medicines for Children: A Systematic Review. *Front Pharmacol* 2021;12:691606.
55. Niëns LM, Van de Poel E, Cameron A, et al. Practical measurement of affordability: an application to medicines. *Bull World Health Organ* 2012 Mar 1;90(3):219-27.

56. World Health Organization (WHO). MedMon - WHO Essential Medicines and Health Products Price and Availability Monitoring Mobile Application [internet]. Date accessed 21 Sep 2021. URL: https://www.who.int/news/item/18-02-2018-medmon-mobile-application.

Figure 1 Two example calculations of the NUNT

Figure 2 Proportion of medicines accessible in Burundi, China and Haiti

Paracetamol 100 mg cap/tab

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

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

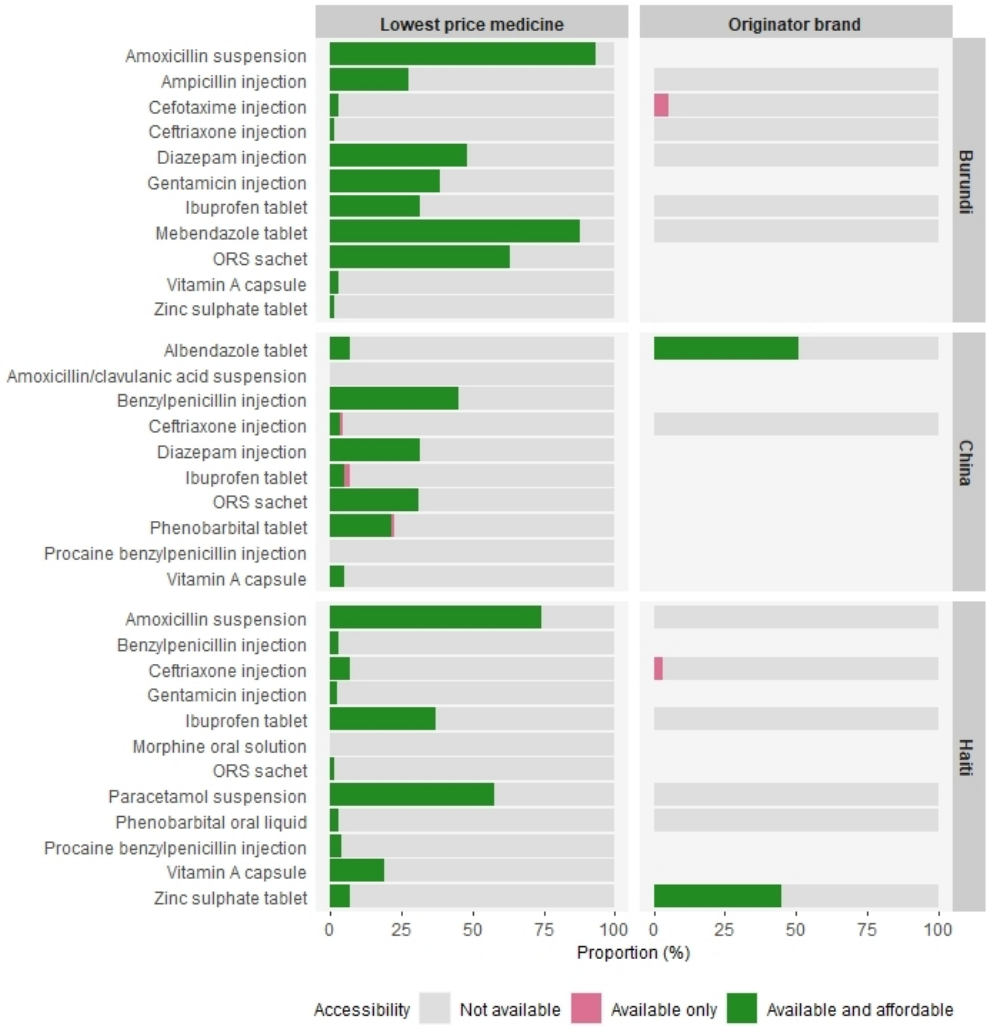
$$NUNT = 1\ unit * \ 5\ daily\ intake\ moments * 30\ days = 150\ units$$

Amoxicillin 50 mg/ml suspension

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

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

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



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Annex 1

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

Medicine name	**Acceptable formulation**	**NUNT**
Oral rehydration salts	Powder sachet 200 ml	2
	Powder sachet 500 ml	2
	Powder sachet 1L	1
Zinc sulphate	Cap/tab 20 mg	14
Carbamazapine	Cap/tab 100 mg	60
	Oral liquid 100 mg/5 ml	180
Phenobarbital	Cap/tab 30 mg	60
	Cap/tab 100 mg	30
	Injection 100 mg/ml	30
	Injection 200 mg/ml	15
	Oral liquid 15 mg/5 ml	600
Phenytoin	Cap/tab 25 mg	90
	Cap/tab 50 mg	60
	Cap/tab 100 mg	60
	Injection 50 mg/ml	60
	Oral liquid 25 mg/5 ml	480
	Oral liquid 30 mg/5 ml	420
Lamotrigine	Cap/tab 25 mg	60
	Cap/tab 50 mg	30
	Cap/tab 100 mg	30
Valproic acid	Cap/tab 100 mg	60
	Cap/tab 150 mg	60
	Cap/tab 200 mg	60
	Cap/tab 500 mg	30
	Oral liquid 200 mg/5 ml	240
Diazepam	Rectal solution 5 mg/ml	1
	Injection 5 mg/ml	1
Lorazepam	Parenteral solution 2 mg/ml	0.5
	Parenteral solution 4 mg/ml	0.5
Midazolam	Oromucosal solution 5 mg/ml	10
	Oromucosal solution 10 mg/ml	6
	Ampoule 10 mg/ml	6
Abacavir/lamivudine	Cap/tab 120/60 mg	60
Dolutegravir	Cap/tab 10 mg	60
Lopinavir/ritonavir	Cap/tab 40/10 mg	120
	Cap/tab 100/25 mg	60
Ferrous salt	Cap/tab 60 mg	28
	Cap/tab 200 mg	14
	Oral liquid 25 mg/ml	56
Albendazole	Cap/tab 200 mg	2
	Cap/tab 400 mg	1
Mebendazole	Cap/tab 100 mg	6
Artemether/lumefantrine	Cap/tab 20/120 mg	6
Artesunate/amodiaquine	Cap/tab 25/67.5 mg	6
	Cap/tab 50/135 mg	3
Artesunate/mefloquine	Cap/tab 25/55 mg	6
Dihydroartemisinin/piperaquine	Cap/tab 20/160 mg	6

	Cap/tab 20/320 mg	3
Artesunate/Sulfadoxine-pyrimethamine	Cap/tab 50/500/25 mg	1
	Cap/tab 500/25 mg (sulfadoxine-pyrimethamine)	1
Chloroquine	Cap/tab 100 mg	5
	Oral liquid 50 mg/5 ml	30
Artesunate	Cap/tab 50 mg	3
	Suppository 50 mg	3
Retinol	Cap/tab 25,000 IU	4
	Cap/tab 100,000 IU	2
	Cap/tab 200,000 IU	2
Paracetamol	Cap/tab 100 mg	150
	Suppository 100 mg	150
	Suspension 120 or 125 mg/5 ml	900
Morphine	Cap/tab (slow release) 10 mg	60
	Injection 10 mg/ampoule	30
	Oral liquid 10 mg/5 ml	300
Ibuprofen	Cap/tab 200 mg	90
	Oral liquid 200 mg/5 ml	180
Ethambutol + isoniazid + pyrazinamide + rifampicin	Cap/tab 100 mg (ethambutol)	60
	Cap/tab 400 mg (ethambutol)	30
	Oral liquid 25 mg/ml (ethambutol)	9
	Cap/tab 50/150/75 mg (isoniazid + pyrazinamide + rifampicin)	60
Amoxicillin	Cap/tab 250 mg	20
	Cap/tab 500 mg	10
	Powder for injection 250 mg/vial	20
	Powder for injection 500 mg/vial	10
	Powder for injection 1 g/vial	5
	Suspension 125 mg/5 ml	100
	Suspension 250 mg/5 ml	90
Amoxicillin + clavulanic acid	Cap/tab 100/125 mg	30
	Cap/tab 250/125 mg	15
	Cap/tab 500/125 mg	15
	Powder for injection 500/100 mg/vial	8
	Oral liquid 125/53.25 mg/5 ml	135
	Oral liquid 250/62.5 mg/5 ml	60
Ampicillin	Cap/tab 250 mg	40
	Cap/tab 500 mg	20
	Injection 500 mg/vial	20
	Injection 1 g/vial	10
Benzylpenicillin	Injection 1 MIU/vial	5
Gentamicin	Injection 10 mg/ml	40
	Injection 40 mg/ml	10
Ceftriaxone	Injection 250 mg/vial	28
	Injection 500 mg/vial	14
	Injection 1 g/vial	7
Cefotaxime	Injection 1 g/vial	18
Procaine benzylpenicillin	Injection 1 MIU/vial	10

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A Sustainable Development Goal indicator for measuring access to medicines for children – a proof-of-concept study

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ABSTRACT

Objectives

To aid countries in assessing accessibility to pediatric medicines in a validated manner and on a longitudinal basis, a conceptual methodology was developed measuring a combination of availability and affordability of medicines based on the principles embedded in Sustainable Development Goal (SDG) Indicator 3.b.3. We aimed to provide proof-of concept of this adapted methodology by applying the method to historical datasets.

Method

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

Results

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

Conclusion

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

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A strength of this study is the adaptation of an existing tool that was made appropriate for children.
- In using an existing tool as starting point, the adapted methodology also inherits some of the limitations of this tool, such as the burden of disease weighting and the national poverty line in the calculation of affordability.
- In providing proof-of-concept of this tool, we were limited to historical data that were already available which are of little relevance to the current situation.
- The historical datasets used are quality-assured through standardized data collection and through data validation and verification steps.
- Only a modest sample of age-appropriate medicines were surveyed in the historical datasets, demanding further analyses on larger datasets.

INTRODUCTION

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

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

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

No specific methodology for assessing accessibility of essential medicines for children has been developed yet, although a number of studies have measured the availability or price of medicines, or both [7-35]. The methodologies for measuring these two important dimensions of access to pediatric medicines and the medicines surveyed varied greatly between studies, covering different age groups of children (e.g. children under five, children under twelve, or all children and adolescents), priority diseases (anticancer medicines, cardiovascular medicines or a range of diseases) and numbers of surveyed medicines. Results are therefore difficult to compare and may not reflect overall access to medicines for children in a country. This emphasizes the need for a standardized and validated methodology for measuring access to medicines for children that will allow for global comparison and eventually benchmark indicators.

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

METHODOLOGY

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

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

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

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

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

A core set of globally relevant essential medicines

The core set of medicines consists of tracer essential medicines, together indicative of the overall access to medicines for primary health care. Over the years, several baskets of pediatric medicines have already been proposed. The list of medicines defined for the 2007 'Better medicines for children' project, although intended for a similar purpose, is not only dated but also purposely excluded antiretroviral therapies (ART) for HIV [3]. As ART are still needed to treat a large part of the pediatric population in low- and middle-income countries, this selection of medicines is not suitable for the current purpose. In 2012, the World Health Organization (WHO) published a list of thirteen 'Priority life-saving medicines' for children under the age of five, intended to help countries in prioritizing those medicines that will have the biggest impact on reducing child morbidity and mortality [36]. Yet, an access indicator should serve a broader age group of children, especially since those between 5 and 12 years may have different treatment requirements. Additionally, the priority list only targets seven prevalent diseases, and is thus limited in its scope. With that, no existing basket of pediatric medicines was deemed suitable for the current purpose.

A new core set of medicines for children with ages 1 month to 12 years for treating acute and chronic, communicable and non-communicable diseases in the primary health care setting, including child-appropriate formulations, was thus established. To cater to the unique needs of children with different ages, separate baskets for two age groups were created: young children (infants, toddlers and pre-school children) aged 1 month to 59 months, and school-aged children 5 to 12 years of age. These groups will allow stakeholders to differentiate between different health needs in terms of disease prevalence, required dosage strengths and preferred formulations. Children above the age

of 12 often do not require specific pediatric formulations [37] thus their health needs may already be adequately covered in the original SDG indicator 3.b.3 methodology.

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

Priority conditions were linked to specific first-choice medicines used in primary health care using WHO and South African treatment guidelines [40-44]. Multiple medicines from the same therapeutic class of medicines were selected in some cases (including antiepileptics, anthelminthics, antimalarials) and can be considered interchangeable. Medicines requiring cold-chain management were excluded, as these may not be widely available in primary health facilities. Additionally, although vaccines are a key component in health care, vaccination coverage is already included within indicator 3.b.1 of the SDGs and will therefore not be covered in indicator 3.b.3 as well. The proposed selection of medicines for children aged 1 month to 5 can be found in Table 1. Child-appropriate medicine formulations were selected pragmatically, based on formulations present on the WHO EMLc and the required dosage strengths.

Availability of medicines

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

Affordability of medicines

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

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

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

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

(4)

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

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

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

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

Cap/tab = capsule/tablet; GHE = Global Health Estimate.

Number of units needed per treatment

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

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

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

[figure 1]

Weighing for burden of disease

In the original framework, accessible medicines are weighted according to the regional burden of disease to address differences in demand for specific medicines[1] [4]. This concept was applied to pediatric medicines as well, based on the GHEs [38]. Each medicine in the baskets was assigned a GHE code for one or several disease(s) that are treated/cured/controlled by that medicine. Indications of the medicines were determined according to their uses as described in the WHO EMLc (see table 1) [39]. Antibacterial medicines were given a GHE code specific for the primary indication described on the WHO EMLc, and in some cases an additional code (370) as a proxy for the broad use of these medicines in a variety of bacterial diseases.

The weight that each medicine is given in the calculation was computed as the proportion of the medicine's specific disability-adjusted life years (DALYs) compared to the total sum of DALYs in the basket. Of note, the GHEs include data for children 1-59 months and children 5-14 years. Weighting school-aged children up to 12 years based on data for children up to 14 years old does not have a significant impact on the results as assigned weights are relative weights.

Calculating SDG indicator 3.b.3

The age-specific SDG indicator 3.b.3 can be calculated with formula 1. Assessing availability and affordability of medicines, and subsequent weighing for regional disease burden, was done at the

[1] Weighing for regional burden of disease is a different process than selecting medicines for the core set based on global burden of disease.

facility level, meaning that a separate score is calculated for each facility surveyed. Facilities with at least 80% of medicines in the basket available and affordable were considered to have accessible medicines. This threshold was adopted by the WHO Global Action Plan on Non-Communicable Diseases and used as a reference [49]. Table 2 presents a full summary of the adaptations to the original SDG 3.b.3 methodology needed for a child-specific methodology. A hypothetical working example is provided in Annex 2.

Case studies

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

[figure 2]

Medicines' availability and price data for Burundi (2013), China (2012) and Haiti (2011) was obtained from HAI. These datasets were selected because the highest absolute number of age-appropriate medicines in the proposed basket was included in these surveys (11, 10 and 12 out of 22 medicines, respectively) [51]. Additionally, this selection represents countries with different income levels (e.g. Burundi and Haiti low-income countries, China an upper-middle income country) and from different geographical regions. To make the datasets appropriate for analysis, only the age-appropriate medicines as listed in table 1 were selected. No further selection in health facilities was done.

Data on NPLs were obtained from World Bank reports on poverty [52-54]. NPLs were adjusted for inflation and deflation between the year data was reported and the survey year using the Consumer Price Index (CPI) [55]. Monthly poverty lines were converted to daily time periods. LPGW wages were directly obtained from the datasets provided by HAI and thus required no corrections for the year of survey.

Because regional data on burden of disease in DALYs is published only every five years, the year closest in time to the year of survey was used (e.g. 2010 publication for China and Haiti and 2015 publication for Burundi) to weigh for burden of disease [38].

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

Patient and public involvement

There was no patient or public involvement in the design or conduct of this study.

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

Input	Original $SDG_{3.b.3}$ methodology [4]	Child-specific $SDG_{3.b.3}$ methodology
SDG indicator 3.b.3		
Calculation	- Based on individual facility scores. - Facilities considered as having accessible medicines when reaching an 80% threshold.	- Based on individual facility scores. - Facilities considered as having accessible medicines when reaching an 80% threshold.
Core set of globally relevant essential medicines		
Selection of medicines	- Defined on a global level. - Selected from 2017 WHO EML. - Selection process not described.	- Defined on a global level. - Selected from 2019 WHO EMLc. - Selection based on global burden of disease (top 10 conditions causing disability/mortality that can be treated with medicines), international treatment guidelines and expert consultation.
The basket	- One basket for all. - 32 tracer essential medicines for acute and chronic, communicable and non-communicable diseases.	- Baskets defined for two age groups (young children; school-aged children). - 22 tracer essential medicines for acute and chronic, communicable and non-communicable diseases for both young and school-aged children. - Age-appropriate formulations selected per age group.
Burden of disease	- Weighting according to regional burden of disease (in DALYs). - Based on WHO GHEs. - Pre-defined GHE codes, with overarching GHE code for 'infectious and parasitic diseases' for antibacterials. - Equal weights assigned to medicines that are used to treat the same disease.	- Weighting according to regional burden of disease (in DALYs). - Based on WHO GHEs, from period closest to year of survey. - Affiliated GHE codes determined according to the uses as described in EMLc. GHE codes for antibacterials determined according to uses as described in EMLc plus code for 'other infectious diseases'. - Equal weights assigned to medicines that are used to treat the same disease.
Availability of medicines		
Availability	- Captured as binary variable. - As surveyed.	- Captured as binary variable. - As surveyed.
Affordability of medicines		
Required inputs	- Captured as binary variable. - Calculated from the price of a medicine, the number of units needed for treatment, the NPL and the wage of the LPGW.	- Captured as binary variable. - Calculated from the price of a medicine, the NUNT, the NPL and the wage of the LPGW.
Number of units needed for treatment	- Total number of units needed per month or treatment course based on DDDs. - Process for defining duration of treatment not described.	- NUNT based on duration of treatment and recommended daily dosages per age or weight group. Weight-based dosing transformed to age-based dosing. - Recommended daily dosages and duration of treatment derived from international treatment guidelines.

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

RESULTS

Access to medicines for children aged 1 month to 5 years was calculated for each of the three countries across its different health sectors. Analysis of Burundi data showed a stark contrast between lowest-price generic medicines (LPM) and the originator brand (OB), with a mean facility score of about 40% for LPMs versus 0% for the OB. The public and mission sector provided more accessible medicines than the private sector. The difference between LPMs and the OB was not as pronounced in China having mean facilities scores of 22.3% and 16.5% respectively, with LPMs more accessible in the public sector and the OB in the private sector. In Haiti, access was calculated for the public sector, the private sector, the non-profit sector, and the mixed sector (health facilities managed by the government and non-profit organization together). Mean facility scores for LPMs were similar across the sectors, with an overall average of approximately 22%. For OB medicines, scores varied between 0.6% in the private sector and 15.1% in the public sector. Results on SDG indicator 3.b.3 and mean facility scores across health facilities from different sectors are summarized in table 3.

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

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

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

[figure 3]

DISCUSSION

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

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

Upon closer examination of the case studies of Burundi, China and Haiti, the widespread inaccessibility seen in the case studies seemed to stem from unavailable rather than unaffordable medicines, for both LPMs and OBs. A recent systematic review on children's medicines identified fourteen studies that reported on the availability of children's medicines and found a median availability of 38.1% and 24.2% for LPMs and OBs in the public sectors and of 35.9% and 21.1% in the private sectors, respectively [56]. With that, the unavailability of child medicines detected in the present case studies is in line with the results of the systematic review. The same systematic review identified eleven studies that reported on the affordability of medicines, based on the number of days' wages of the LPGW. In the public sector, affordability was 83.6% and 48.5% for LPMs and OBs, with 72.2% and 68.8% in the private sector. The results of this systematic review emphasize the need for a method that combines the two dimensions into a single indicator, as separate evaluation of these elements overestimates actual access to medicines for the patient. Beyond that, some of the studies included in the systematic review included unrepresentative samples of medicines (e.g. studies focused on a single disease area or studies simply failing to consider child-appropriate formulations such as oral liquids or appropriate medicine strengths), again confirming the need for a standardized methodology to measure access to child medicines.

Before this methodology can, however, be applied on a widespread scale, several steps must be undertaken to further validate the methodology and examine the uncertainties introduced through

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

An important strength of this child-specific methodology is the use of an existing, formally approved tool as starting point which was adapted to suit the needs of children. Core concepts used in the adapted methodology and its data requirements are therefore in line with conventional methods and data collection tools. However, through this approach our methodology also inherits some of the limitations of the original 3.b.3 indicator methodology. Particularly, weighting for regional burden of disease when calculating access at the facility level as done in the original methodology raises several concerns. For one thing, the methodology assigns equal weights to medicines that are used to treat the same disease and counts the burden of this disease multiple times. To illustrate, the basket of medicines includes both oral rehydration salts and zinc sulphate for diarrheal diseases, whereas only retinol was selected for measles/vitamin A deficiency. This leads to disproportionate weighing for actual burden of disease when calculating access at the facility level. Disproportionality is also a concern for antibacterial medicines, which use may be overrepresented by using GHE code 20, a code that is linked to all infectious and parasitic diseases. Although a proxy for this GHE code was used in the present study (GHE code 370 for 'other infectious diseases'), additional analyses should demonstrate how different weighing approaches affect the results. Additionally, the quality of the underlying GHEs data is unclear, especially because these data may be more difficult to obtain for children than for adults. Lastly, arguments can be made that the current approach of weighting for burden of disease is undesirable because it implies that some medicines are more important than others, even though all medicines in the basket are essential medicines and should always be accessible.

On a similar note, expressing affordability as a function of a poverty line instead of the LPGW wage has been used previously [57], but a measure combining the NPL and LPGW wage as is used in the original 3.b.3 indicator has yet to prove itself. This is particularly relevant because it seems that

somewhat less medicines were unaffordable in the present case studies than what was observed using the LPGW wage alone [56]. Further testing of the proposed child-specific methodology should include several scenarios for weighing for burden of disease and calculating affordability, which could lead to further adaptations of the methodology.

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

To provide first evidence of the child-specific tool that we developed, we were limited to the use of historical datasets. In selecting suitable datasets for the case studies it was observed that only a small number of age-appropriate medicines are being surveyed in low- and middle-income countries alike [58]. The WHO/HAI datasets used for the present case studies were selected for their quality of data and relatively high inclusivity of age-appropriate medicines, yet they still included a modest sample of child-appropriate medicines. Further analyses on a dataset with a higher number of age-appropriate medicines are thus required, which may need to be collected prospectively. Although the relevance of the findings to the current situation of Burundi, China and Haiti is limited because of the older data, the aim of providing proof-of-concept of the adapted methodology was achieved nonetheless. Finally, the individual facility data that support the findings of this study are not publicly available, but aggregated data per medicine and country can be obtained from the Health Action International website [51]. The aggregated data are sufficient to allow initial comparison of our methodology to previously existing tools.

CONCLUSION

This paper is the first to propose a standardized methodology for measuring access to medicines for children. Such a standardized method will aid countries in assessing national accessibility to pediatric medicines in a validated manner and on a regular basis and is an important addition to SDG indicator 3.b.3 on access to medicines for adults. The proposed validation steps of this method will help identify critical steps in the calculation and will determine its robustness, which could lead to further improvements of the method.

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COMPETING INTERESTS

The authors have no competing financial and/or non-financial interests in relation to this work to declare.

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CONTRIBUTORSHIP STATEMENT

All authors were involved in conception and study design. IRJ drafted the article, HAvdH, AKM-T and FS were involved in critical revision of the article. All authors approved the final article.

ETHICS APPROVAL STATEMENT

This study does not involve human or animal participants.

DATA SHARING STATEMENT

The individual facility data that support the findings of this study were obtained from Health Action International after submission and approval of the research protocol. Restrictions apply to the availability of these data, which were used under agreement for this study. Aggregated data on medicine and country level can be obtained from the Health Action International website.

REFERENCES

1. Unicef. Goal 3: Good Health And Well-Being [internet]. Date accessed: 9 May 2022. URL: https://data.unicef.org/sdgs/goal-3-good-health-wellbeing/.
2. United Nations. About the Sustainable Development Goals [internet]. Date accessed: 17 Sep 2020. URL: https://www.un.org/sustainabledevelopment/sustainable-development-goals/.
3. World Health Organization (WHO). Better Medicines for Children Project. Geneva: WHO; 2009. Date accessed 1 June 2021. URL : https://www.who.int/childmedicines/progress/ChildMeds_pricing_surveys.pdf.
4. United Nations. SDG Indicators: Metadata repository [internet]. Accessed 17 Sep 2020. URL: https://unstats.un.org/sdgs/metadata?Text=&Goal=3&Target=3.b.
5. Kristensen HG. WHO guideline development of paediatric medicines: points to consider in pharmaceutical development. *Int J Pharm* 2012;435(2):134-5.
6. World Health Organization (WHO). Promoting safety of medicines for children. Geneva: WHO; 2007. URL: https://www.who.int/medicines/publications/essentialmedicines/Promotion_safe_med_childrens.pdf.
7. Martei YM, Iwamoto K, Barr RD, et al. Shortages and price variability of essential cytotoxic medicines for treating children with cancers. *BMJ Glob Health* 2020;5(11):e003282.
8. Simonyan T, Papyan R, Danielyan S, et al. Availability of Essential Medicines for Pediatric Oncology in Armenia. *Asian Pac J Cancer Prev* 2019;20(4):991-994.
9. Droti B, O'Neill KP, Mathai M, et al. Poor availability of essential medicines for women and children threatens progress towards Sustainable Development Goal 3 in Africa. *BMJ Glob Health* 2019;4(Suppl 9):e001306.
10. Orubu ESF, Robert FO, Samuel M, et al. Access to essential cardiovascular medicines for children: a pilot study of availability, price and affordability in Nigeria. *Health Policy Plan* 2019;34 Suppl 3:20-26.
11. Roy V, Singhal S, Tayal H, et al. Availability of Pediatric Formulations in Public Health Care System in India: A Case Study. *Indian J Pediatr* 2021;88(3):227-234.
12. Faruqui N, Martiniuk A, Sharma A, et al. Evaluating access to essential medicines for treating childhood cancers: a medicines availability, price and affordability study in New Delhi, India. *BMJ Glob Health* 2019;4(2):e001379.
13. Cohen P, Friedrich P, Lam C, et al. Global Access to Essential Medicines for Childhood Cancer: A Cross-Sectional Survey. *J Glob Oncol* 2018;4:1-11.
14. Hailu AD, Mohammed SA. Availability, price, and affordability of WHO priority maternal and child health medicine in public health facilities of Dessie, north-East Ethiopia. *BMC Med Inform Decis Mak* 2020;20(1):221.
15. Johansson EW, Lindsjö C, Weiss DJ, et al. Accessibility of basic paediatric emergency care in Malawi: analysis of a national facility census. *BMC Public Health* 2020;20(1):992.
16. Dorj G, Sunderland B, Sanjjav T, et al. Availability, affordability and costs of pediatric medicines in Mongolia. *BMC Pediatr* 2018;18(1):149.
17. Tujo TM, Gurmu TG. Availability and Utilization of WHO Lifesaving Medicines for Children under Five in Public Health Facilities of the Jimma Zone, South West Ethiopia: A Cross-Sectional Survey. *Int J Pediatr* 2020;2020:3505672.
18. Swain TR, Rath B, Dehury S, et al. Pricing and availability of some essential child specific medicines in Odisha. *Indian J Pharmacol* 2015;47(5):496-501
19. Božić B, Stupar S, Stupar D, et al. Availability of pediatric-evaluated formulations in Serbia. *Indian J Pharmacol* 2017;49(2):189-193.

20. Sun X, Wei J, Yao Y, et al. Availability, prices and affordability of essential medicines for children: a cross-sectional survey in Jiangsu Province, China. *BMJ Open* 2018;8(10):e023646.
21. Wang X, Fang Y, Yang S, et al. Access to paediatric essential medicines: a survey of prices, availability, affordability and price components in Shaanxi Province, China. *PLoS One* 2014;9(3):e90365.
22. Sado E, Sufa A. Availability and affordability of essential medicines for children in the Western part of Ethiopia: implication for access. *BMC Pediatr* 2016;16:40.
23. Balasubramaniam R, Benaragama BV, Sri Ranganathan S. A national survey of price and affordability of key essential medicines for children in Sri Lanka. *Indian J Pediatr* 2014;81(4):362-7.
24. Vassal G, Kozhaeva O, Griskjane S, et al. Access to essential anticancer medicines for children and adolescents in Europe. *Ann Oncol* 2021;32(4):560-568.
25. Barr R, Robertson J. Access to Cytotoxic Medicines by Children With Cancer: A Focus on Low and Middle Income Countries. *Pediatr Blood Cancer* 2016;63(2):287-91.
26. Nsabagasani X, Ogwal-Okeng J, Mbonye A, et al. Availability and utilization of the WHO recommended priority lifesaving medicines for under five-year old children in public health facilities in Uganda: a cross-sectional survey. *J Pharm Policy Pract* 2015;8(1):18.
27. Rutebemberwa E, Buregyeya E, Lal S, et al. Assessing the potential of rural and urban private facilities in implementing child health interventions in Mukono district, central Uganda-a cross sectional study. *BMC Health Serv Res* 2016;16:268.
28. Robertson J, Forte G, Trapsida JM, et al. What essential medicines for children are on the shelf? *Bull World Health Organ* 2009;87(3):231-7.
29. Shafiq Y, Shaikh BT, Kumar R. Availability and affordability of essential medicines: exploring the health seeking behaviours and health service utilisation for children under-5 years living in squatter settlement of Karachi, Pakistan. *J Ayub Med Coll Abbottabad* 2011;23(1):132-8.
30. Balasubramaniam R, Beneragama BV, Sri Ranganathan S. A national survey of availability of key essential medicines for children in Sri Lanka. *Ceylon Med J* 2011;56(3):101-7.
31. Gitanjali B, Manikandan S. Availability of five essential medicines for children in public health facilities in India: A snapshot survey. *J Pharmacol Pharmacother* 2011;2(2):95-9.
32. Tadesse T, Abuye H, Tilahun G. Availability and affordability of children essential medicines in health facilities of southern nations, nationalities, and people region, Ethiopia: key determinants for access. *BMC Public Health* 2021;21(1):714.
33. Anson A, Ramay B, de Esparza AR, et al. Availability, prices and affordability of the World Health Organization's essential medicines for children in Guatemala. *Global Health* 2012;8:22.
34. Abu-Arja MH, Rojas Del Río N, Morales La Madrid A, et al. Evaluation of the Pediatric Neuro-Oncology Resources Available in Chile. *JCO Glob Oncol* 2021;7:425-434.
35. Abrha S, Tadesse E, Atey TM, et al. Availability and affordability of priority life-saving medicines for under-five children in health facilities of Tigray region, northern Ethiopia. *BMC Pregnancy Childbirth* 2018;18(1):464.
36. World Health Organization (WHO). Priority life-saving medicines for women and children 2012. Geneva: WHO; 2012. URL: https://www.who.int/publications/i/item/WHO-EMP-MAR-2012-1.
37. European Medicines Agency (EMA). Reflection paper: Formulations of choice for the paediatric population. London: EMA; 2006. URL: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-formulations-choice-paediatric-population_en.pdf.
38. Global Health Observatory, World Health Organization (WHO). Global health estimates: Leading causes of DALYs [internet]. Date accessed 18 Oct 2020. URL: https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/global-health-estimates-leading-causes-of-dalys.

39. World Health Organization (WHO). WHO Model List of Essential Medicines for Children - 7th list, 2019. Geneva: WHO; 2019. URL: https://www.who.int/publications/i/item/WHOMVPEMPIAU201907.
40. World Health Organization (WHO). Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Childhood Illnesses. 2nd edition. Geneva: WHO; 2013. URL: https://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/#:~:text=It%20is%20for%20use%20by,of%20Childhood%20Illness%20(IMCI).
41. National Department of Health. Primary Healthcare Standard Treatment Guideline and Essential Medicine List. 6th ed. Republic of South Africa: National Department of Health; 2018. URL: https://www.knowledgehub.org.za/elibrary/primary-healthcare-standard-treatment-guidelines-and-essential-medicines-list-6th-edition.
42. World Health Organization (WHO). Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: WHO; 2021. URL: https://www.who.int/publications/i/item/9789240031593
43. World Health Organization (WHO). WHO guidelines for Malaria. Geneva: WHO; 2021. URL: https://www.who.int/publications/i/item/guidelines-for-malaria
44. World Health Organization (WHO). Paediatric emergency triage, assessment and treatment: care of critically-ill children. Geneva: WHO; 2016. URL: https://www.who.int/publications/i/item/9789241510219
45. World Health Organization (WHO). Child Growth Standards [internet]. Date accessed 2 Mar 2021. URL: https://www.who.int/tools/child-growth-standards/standards/weight-for-age.
46. World Health Organization (WHO). Growth Reference Data for 5-19 years [internet]. Date accessed 2 Mar 2021. URL: https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/weight-for-age-5to10-years.
47. TNO. Groeidiagrammen in PDF-formaat [internet]. Date accessed 11 Jun 2021. URL: https://www.tno.nl/nl/aandachtsgebieden/gezond-leven/roadmaps/youth/groeidiagrammen-in-pdf-formaat/.
48. Akkawi El Edelbi R, Lindemalm S, et al. Estimation of body surface area in neonates, infants, and children using body weight alone. *Int J Pediatr Adolesc Med* 2021;8(4):221-228.
49. World Health Organization (WHO). Global action plan for the prevention and control of noncommunicable diseases 2013-2020. Geneva: WHO; 2013. URL: https://www.who.int/publications/i/item/9789241506236.
50. World Health Organization (WHO) & Health Action International (HAI). Measuring medicine prices, availability, affordability and price components, 2nd edition. Geneva: WHO; 2008. URL: https://apps.who.int/iris/handle/10665/70013.
51. Health Action International (HAI). Medicine Prices, Availability, Affordability & Price Components Database [internet]. Date accessed 3 Feb 2021. URL: https://haiweb.org/what-we-do/price-availability-affordability/price-availability-data/.
52. World Bank. Burundi Poverty Assessment. Washington, DC: World Bank; 2016. URL: https://openknowledge.worldbank.org/handle/10986/35555.
53. World Bank. Poverty and Equity Brief China. Washington, DC: World Bank; 2021. URL: https://www.worldbank.org/en/topic/poverty/publication/poverty-and-equity-briefs.
54. World Bank and Observatoire National de la Pauvreté et de l'Exclusion Sociale (ONPES). Investing in People to Fight Poverty in Haiti, Reflections for Evidence-based Policy Making. Washington, DC: World Bank; 2014. URL: https://openknowledge.worldbank.org/handle/10986/21519.
55. World Bank. Consumer Price Index (2010 = 100) [internet]. Date accessed 18 Mar 2022. URL: https://data.worldbank.org/indicator/FP.CPI.TOTL.

56. Chen Z, Li S, Zeng L, et al. Accessibility of Medicines for Children: A Systematic Review. *Front Pharmacol* 2021;12:691606.
57. Niëns LM, Van de Poel E, Cameron A, et al. Practical measurement of affordability: an application to medicines. *Bull World Health Organ* 2012 Mar 1;90(3):219-27.
58. Joosse IR, Mantel-Teeuwisse AK, Wirtz VJ, Suleman F, van den Ham HA. Missing data on accessibility of children's medicines. Bull World Health Organ. 2022 Oct 1;100(10):636-642.

Figure 1 Two example calculations of the NUNT

Figure 2 Core elements of the World Health Organization/Health Action International methodology (adapted from [50])

Figure 3 Proportion of medicines accessible in Burundi, China and Haiti.
Since the originator brand was not surveyed for all active ingredients, findings in the private sectors of all three countries are based on a very small number of medicines only.
ORS = Oral Rehydration Salts.

Paracetamol 100 mg cap/tab

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

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

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

Amoxicillin 50 mg/ml suspension

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

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

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

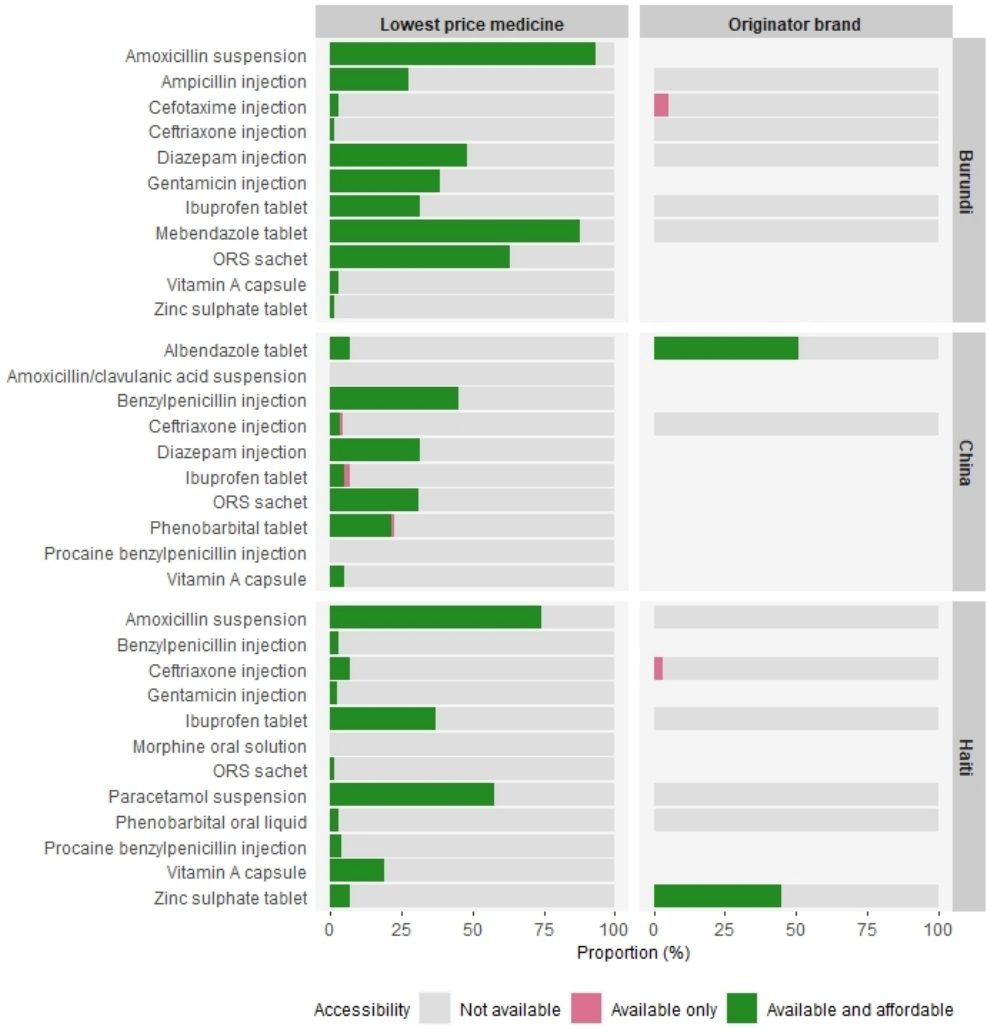
The World Health Organization/Health Action International methodology

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

Key elements of the methodology include:

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

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



Proportion of medicines accessible in Burundi, China and Haiti.
Since the originator brand was not surveyed for all active ingredients, findings in the private sectors of all three countries are based on a very small number of medicines only.
ORS = Oral Rehydration Salts.

185x194mm (96 x 96 DPI)

Annex 1

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

Medicine name	Acceptable formulation	NUNT
Oral rehydration salts	Powder sachet 200 ml	2
	Powder sachet 500 ml	2
	Powder sachet 1L	1
Zinc sulphate	Cap/tab 20 mg	14
Carbamazapine	Cap/tab 100 mg	60
	Oral liquid 100 mg/5 ml	180
Phenobarbital	Cap/tab 30 mg	60
	Cap/tab 100 mg	30
	Injection 100 mg/ml	30
	Injection 200 mg/ml	15
	Oral liquid 15 mg/5 ml	600
Phenytoin	Cap/tab 25 mg	90
	Cap/tab 50 mg	60
	Cap/tab 100 mg	60
	Injection 50 mg/ml	60
	Oral liquid 25 mg/5 ml	480
	Oral liquid 30 mg/5 ml	420
Lamotrigine	Cap/tab 25 mg	60
	Cap/tab 50 mg	30
	Cap/tab 100 mg	30
Valproic acid	Cap/tab 100 mg	60
	Cap/tab 150 mg	60
	Cap/tab 200 mg	60
	Cap/tab 500 mg	30
	Oral liquid 200 mg/5 ml	240
Diazepam	Rectal solution 5 mg/ml	1
	Injection 5 mg/ml	1
Lorazepam	Parenteral solution 2 mg/ml	0.5
	Parenteral solution 4 mg/ml	0.5
Midazolam	Oromucosal solution 5 mg/ml	10
	Oromucosal solution 10 mg/ml	6
	Ampoule 10 mg/ml	6
Abacavir/lamivudine	Cap/tab 120/60 mg	60
Dolutegravir	Cap/tab 10 mg	60
Lopinavir/ritonavir	Cap/tab 40/10 mg	120
	Cap/tab 100/25 mg	60
Ferrous salt	Cap/tab 60 mg	28
	Cap/tab 200 mg	14
	Oral liquid 25 mg/ml	56
Albendazole	Cap/tab 200 mg	2
	Cap/tab 400 mg	1
Mebendazole	Cap/tab 100 mg	6
Artemether/lumefantrine	Cap/tab 20/120 mg	6
Artesunate/amodiaquine	Cap/tab 25/67.5 mg	6
	Cap/tab 50/135 mg	3
Artesunate/mefloquine	Cap/tab 25/55 mg	6
Dihydroartemisinin/piperaquine	Cap/tab 20/160 mg	6

	Cap/tab 20/320 mg	3
Artesunate/Sulfadoxine-pyrimethamine	Cap/tab 50/500/25 mg	1
	Cap/tab 500/25 mg (sulfadoxine-pyrimethamine)	1
Chloroquine	Cap/tab 100 mg	5
	Oral liquid 50 mg/5 ml	30
Artesunate	Cap/tab 50 mg	3
	Suppository 50 mg	3
Retinol	Cap/tab 25,000 IU	4
	Cap/tab 100,000 IU	2
	Cap/tab 200,000 IU	2
Paracetamol	Cap/tab 100 mg	150
	Suppository 100 mg	150
	Suspension 120 or 125 mg/5 ml	900
Morphine	Cap/tab (slow release) 10 mg	60
	Injection 10 mg/ampoule	30
	Oral liquid 10 mg/5 ml	300
Ibuprofen	Cap/tab 200 mg	90
	Oral liquid 200 mg/5 ml	180
Ethambutol + isoniazid + pyrazinamide + rifampicin	Cap/tab 100 mg (ethambutol)	60
	Cap/tab 400 mg (ethambutol)	30
	Oral liquid 25 mg/ml (ethambutol)	9
	Cap/tab 50/150/75 mg (isoniazid + pyrazinamide + rifampicin)	60
Amoxicillin	Cap/tab 250 mg	20
	Cap/tab 500 mg	10
	Powder for injection 250 mg/vial	20
	Powder for injection 500 mg/vial	10
	Powder for injection 1 g/vial	5
	Suspension 125 mg/5 ml	100
	Suspension 250 mg/5 ml	90
Amoxicillin + clavulanic acid	Cap/tab 100/125 mg	30
	Cap/tab 250/125 mg	15
	Cap/tab 500/125 mg	15
	Powder for injection 500/100 mg/vial	8
	Oral liquid 125/53.25 mg/5 ml	135
	Oral liquid 250/62.5 mg/5 ml	60
Ampicillin	Cap/tab 250 mg	40
	Cap/tab 500 mg	20
	Injection 500 mg/vial	20
	Injection 1 g/vial	10
Benzylpenicillin	Injection 1 MIU/vial	5
Gentamicin	Injection 10 mg/ml	40
	Injection 40 mg/ml	10
Ceftriaxone	Injection 250 mg/vial	28
	Injection 500 mg/vial	14
	Injection 1 g/vial	7
Cefotaxime	Injection 1 g/vial	18
Procaine benzylpenicillin	Injection 1 MIU/vial	10

Annex 2

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

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

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

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

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

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

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

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

In which 1 = available and 0 = not available.

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

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

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

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

The price of a daily dose is then calculated as:

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

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

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

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

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

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

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

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

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

In which 1 = affordable and 0 = not affordable. Affordability cannot be computed for medicines without price data.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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A Sustainable Development Goal indicator for measuring access to medicines for children – a proof-of-concept study

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ABSTRACT

Objectives

To aid countries in assessing accessibility to pediatric medicines in a validated manner and on a longitudinal basis, a conceptual methodology was developed measuring a combination of availability and affordability of medicines based on the principles embedded in Sustainable Development Goal (SDG) Indicator 3.b.3. We aimed to provide proof-of concept of this adapted methodology by applying the method to historical datasets.

Method

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

Results

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

Conclusion

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

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A strength of this study is the adaptation of an existing tool that was made appropriate for children.
- In using an existing tool as starting point, the adapted methodology also inherits some of the limitations of this tool, such as the burden of disease weighting and the national poverty line in the calculation of affordability.
- In providing proof-of-concept of this tool, we were limited to historical data that were already available which are of little relevance to the current situation.
- The historical datasets used are quality-assured through standardized data collection and through data validation and verification steps.
- Only a modest sample of age-appropriate medicines were surveyed in the historical datasets, demanding further analyses on larger datasets.

INTRODUCTION

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

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

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

No specific methodology for assessing accessibility of essential medicines for children has been developed yet, although a number of studies have measured the availability or price of medicines, or both [7-35]. The methodologies for measuring these two important dimensions of access to pediatric medicines and the medicines surveyed varied greatly between studies, covering different age groups of children (e.g. children under five, children under twelve, or all children and adolescents), priority diseases (anticancer medicines, cardiovascular medicines or a range of diseases) and numbers of surveyed medicines. Results are therefore difficult to compare and may not reflect overall access to medicines for children in a country. This emphasizes the need for a standardized and validated methodology for measuring access to medicines for children that will allow for global comparison and eventually benchmark indicators.

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

METHODOLOGY

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

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

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

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

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

A core set of globally relevant essential medicines

The core set of medicines consists of tracer essential medicines, together indicative of the overall access to medicines for primary health care. Over the years, several baskets of pediatric medicines have already been proposed. The list of medicines defined for the 2007 'Better medicines for children' project, although intended for a similar purpose, is not only dated but also purposely excluded antiretroviral therapies (ART) for HIV [3]. As ART are still needed to treat a large part of the pediatric population in low- and middle-income countries, this selection of medicines is not suitable for the current purpose. In 2012, the World Health Organization (WHO) published a list of thirteen 'Priority life-saving medicines' for children under the age of five, intended to help countries in prioritizing those medicines that will have the biggest impact on reducing child morbidity and mortality [36]. Yet, an access indicator should serve a broader age group of children, especially since those between 5 and 12 years may have different treatment requirements. Additionally, the priority list only targets seven prevalent diseases, and is thus limited in its scope. With that, no existing basket of pediatric medicines was deemed suitable for the current purpose.

A new core set of medicines for children with ages 1 month to 12 years for treating acute and chronic, communicable and non-communicable diseases in the primary health care setting, including child-appropriate formulations, was thus established. To cater to the unique needs of children with different ages, separate baskets for two age groups were created: young children (infants, toddlers and pre-school children) aged 1 month to 59 months, and school-aged children 5 to 12 years of age. These groups will allow stakeholders to differentiate between different health needs in terms of disease prevalence, required dosage strengths and preferred formulations. Children above the age

of 12 often do not require specific pediatric formulations [37] thus their health needs may already be adequately covered in the original SDG indicator 3.b.3 methodology.

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

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

Availability of medicines

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

Affordability of medicines

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

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

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

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

(4)

(formula 4).

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

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

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

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

Cap/tab = capsule/tablet; GHE = Global Health Estimate.

Number of units needed per treatment

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

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

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

[figure 1]

Weighing for burden of disease

In the original framework, accessible medicines are weighted according to the regional burden of disease to address differences in demand for specific medicines[1] [4]. This concept was applied to pediatric medicines as well, based on the GHEs [38]. Each medicine in the baskets was assigned a GHE code for one or several disease(s) that are treated/cured/controlled by that medicine. Indications of the medicines were determined according to their uses as described in the WHO EMLc (see table 1) [39]. Antibacterial medicines were given a GHE code specific for the primary indication described on the WHO EMLc, and in some cases an additional code (370) as a proxy for the broad use of these medicines in a variety of bacterial diseases.

The weight that each medicine is given in the calculation was computed as the proportion of the medicine's specific disability-adjusted life years (DALYs) compared to the total sum of DALYs in the basket. Of note, the GHEs include data for children 1-59 months and children 5-14 years. Weighting school-aged children up to 12 years based on data for children up to 14 years old does not have a significant impact on the results as assigned weights are relative weights.

Calculating SDG indicator 3.b.3

The age-specific SDG indicator 3.b.3 can be calculated with formula 1. Assessing availability and affordability of medicines, and subsequent weighing for regional disease burden, was done at the

[1] Weighing for regional burden of disease is a different process than selecting medicines for the core set based on global burden of disease.

facility level, meaning that a separate score is calculated for each facility surveyed. Facilities with at least 80% of medicines in the basket available and affordable were considered to have accessible medicines. This threshold was adopted by the WHO Global Action Plan on Non-Communicable Diseases and used as a reference [49]. Table 2 presents a full summary of the adaptations to the original SDG 3.b.3 methodology needed for a child-specific methodology. A hypothetical working example is provided in Annex 3.

Case studies

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

[figure 2]

Medicines' availability and price data for Burundi (2013), China (2012) and Haiti (2011) was obtained from HAI. These datasets were selected because the highest absolute number of age-appropriate medicines in the proposed basket was included in these surveys (11, 10 and 12 out of 22 medicines, respectively) [51]. Additionally, this selection represents countries with different income levels (e.g. Burundi and Haiti low-income countries, China an upper-middle income country) and from different geographical regions. To make the datasets appropriate for analysis, only the age-appropriate medicines as listed in table 1 were selected. No further selection in health facilities was done.

Data on NPLs were obtained from World Bank reports on poverty [52-54]. NPLs were adjusted for inflation and deflation between the year data was reported and the survey year using the Consumer Price Index (CPI) [55]. Monthly poverty lines were converted to daily time periods. LPGW wages were directly obtained from the datasets provided by HAI and thus required no corrections for the year of survey.

Because regional data on burden of disease in DALYs is published only every five years, the year closest in time to the year of survey was used (e.g. 2010 publication for China and Haiti and 2015 publication for Burundi) to weigh for burden of disease [38].

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

Patient and public involvement

There was no patient or public involvement in the design or conduct of this study.

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

Input	Original $SDG_{3.b.3}$ methodology [4]	Child-specific $SDG_{3.b.3}$ methodology
SDG indicator 3.b.3		
Calculation	- Based on individual facility scores. - Facilities considered as having accessible medicines when reaching an 80% threshold.	- Based on individual facility scores. - Facilities considered as having accessible medicines when reaching an 80% threshold.
Core set of globally relevant essential medicines		
Selection of medicines	- Defined on a global level. - Selected from 2017 WHO EML. - Selection process not described.	- Defined on a global level. - Selected from 2019 WHO EMLc. - Selection based on global burden of disease (top 10 conditions causing disability/mortality that can be treated with medicines), international treatment guidelines and expert consultation.
The basket	- One basket for all. - 32 tracer essential medicines for acute and chronic, communicable and non-communicable diseases.	- Baskets defined for two age groups (young children; school-aged children). - 22 tracer essential medicines for acute and chronic, communicable and non-communicable diseases for both young and school-aged children. - Age-appropriate formulations selected per age group.
Burden of disease	- Weighting according to regional burden of disease (in DALYs). - Based on WHO GHEs. - Pre-defined GHE codes, with overarching GHE code for 'infectious and parasitic diseases' for antibacterials. - Equal weights assigned to medicines that are used to treat the same disease.	- Weighting according to regional burden of disease (in DALYs). - Based on WHO GHEs, from period closest to year of survey. - Affiliated GHE codes determined according to the uses as described in EMLc. GHE codes for antibacterials determined according to uses as described in EMLc plus code for 'other infectious diseases'. - Equal weights assigned to medicines that are used to treat the same disease.
Availability of medicines		
Availability	- Captured as binary variable. - As surveyed.	- Captured as binary variable. - As surveyed.
Affordability of medicines		
Required inputs	- Captured as binary variable. - Calculated from the price of a medicine, the number of units needed for treatment, the NPL and the wage of the LPGW.	- Captured as binary variable. - Calculated from the price of a medicine, the NUNT, the NPL and the wage of the LPGW.
Number of units needed for treatment	- Total number of units needed per month or treatment course based on DDDs. - Process for defining duration of treatment not described.	- NUNT based on duration of treatment and recommended daily dosages per age or weight group. Weight-based dosing transformed to age-based dosing. - Recommended daily dosages and duration of treatment derived from international treatment guidelines.

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

RESULTS

Access to medicines for children aged 1 month to 5 years was calculated for each of the three countries across its different health sectors. Analysis of Burundi data showed a stark contrast between lowest-price generic medicines (LPM) and the originator brand (OB), with a mean facility score of about 40% for LPMs versus 0% for the OB. The public and mission sector provided more accessible medicines than the private sector. The difference between LPMs and the OB was not as pronounced in China having mean facilities scores of 22.3% and 16.5% respectively, with LPMs more accessible in the public sector and the OB in the private sector. In Haiti, access was calculated for the public sector, the private sector, the non-profit sector, and the mixed sector (health facilities managed by the government and non-profit organization together). Mean facility scores for LPMs were similar across the sectors, with an overall average of approximately 22%. For OB medicines, scores varied between 0.6% in the private sector and 15.1% in the public sector. Results on SDG indicator 3.b.3 and mean facility scores across health facilities from different sectors are summarized in table 3.

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

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

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

[figure 3]

DISCUSSION

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

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

Upon closer examination of the case studies of Burundi, China and Haiti, the widespread inaccessibility seen in the case studies seemed to stem from unavailable rather than unaffordable medicines, for both LPMs and OBs. A recent systematic review on children's medicines identified fourteen studies that reported on the availability of children's medicines and found a median availability of 38.1% and 24.2% for LPMs and OBs in the public sectors and of 35.9% and 21.1% in the private sectors, respectively [56]. With that, the unavailability of child medicines detected in the present case studies is in line with the results of the systematic review. The same systematic review identified eleven studies that reported on the affordability of medicines, based on the number of days' wages of the LPGW. In the public sector, affordability was 83.6% and 48.5% for LPMs and OBs, with 72.2% and 68.8% in the private sector. The results of this systematic review emphasize the need for a method that combines the two dimensions into a single indicator, as separate evaluation of these elements overestimates actual access to medicines for the patient. Beyond that, some of the studies included in the systematic review included unrepresentative samples of medicines (e.g. studies focused on a single disease area or studies simply failing to consider child-appropriate formulations such as oral liquids or appropriate medicine strengths), again confirming the need for a standardized methodology to measure access to child medicines.

Before this methodology can, however, be applied on a widespread scale, several steps must be undertaken to further validate the methodology and examine the uncertainties introduced through

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

An important strength of this child-specific methodology is the use of an existing, formally approved tool as starting point which was adapted to suit the needs of children. Core concepts used in the adapted methodology and its data requirements are therefore in line with conventional methods and data collection tools. However, through this approach our methodology also inherits some of the limitations of the original 3.b.3 indicator methodology. Particularly, weighting for regional burden of disease when calculating access at the facility level as done in the original methodology raises several concerns. For one thing, the methodology assigns equal weights to medicines that are used to treat the same disease and counts the burden of this disease multiple times. To illustrate, the basket of medicines includes both oral rehydration salts and zinc sulphate for diarrheal diseases, whereas only retinol was selected for measles/vitamin A deficiency. This leads to disproportionate weighing for actual burden of disease when calculating access at the facility level. Disproportionality is also a concern for antibacterial medicines, which use may be overrepresented by using GHE code 20, a code that is linked to all infectious and parasitic diseases. Although a proxy for this GHE code was used in the present study (GHE code 370 for 'other infectious diseases'), additional analyses should demonstrate how different weighing approaches affect the results. Additionally, the quality of the underlying GHEs data is unclear, especially because these data may be more difficult to obtain for children than for adults. Lastly, arguments can be made that the current approach of weighting for burden of disease is undesirable because it implies that some medicines are more important than others, even though all medicines in the basket are essential medicines and should always be accessible.

On a similar note, expressing affordability as a function of a poverty line instead of the LPGW wage has been used previously [57], but a measure combining the NPL and LPGW wage as is used in the original 3.b.3 indicator has yet to prove itself. This is particularly relevant because it seems that

somewhat less medicines were unaffordable in the present case studies than what was observed using the LPGW wage alone [56]. Further testing of the proposed child-specific methodology should include several scenarios for weighing for burden of disease and calculating affordability, which could lead to further adaptations of the methodology.

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

To provide first evidence of the child-specific tool that we developed, we were limited to the use of historical datasets. In selecting suitable datasets for the case studies it was observed that only a small number of age-appropriate medicines are being surveyed in low- and middle-income countries alike [58]. The WHO/HAI datasets used for the present case studies were selected for their quality of data and relatively high inclusivity of age-appropriate medicines, yet they still included a modest sample of child-appropriate medicines. Further analyses on a dataset with a higher number of age-appropriate medicines are thus required, which may need to be collected prospectively. Although the relevance of the findings to the current situation of Burundi, China and Haiti is limited because of the older data, the aim of providing proof-of-concept of the adapted methodology was achieved nonetheless. Finally, the individual facility data that support the findings of this study are not publicly available, but aggregated data per medicine and country can be obtained from the Health Action International website [51]. The aggregated data are sufficient to allow initial comparison of our methodology to previously existing tools.

CONCLUSION

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

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COMPETING INTERESTS

The authors have no competing financial and/or non-financial interests in relation to this work to declare.

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CONTRIBUTORSHIP STATEMENT

All authors were involved in conception and study design. IRJ drafted the article, HAvdH, AKM-T and FS were involved in critical revision of the article. All authors approved the final article.

ETHICS APPROVAL STATEMENT

This study does not involve human or animal participants.

DATA SHARING STATEMENT

The individual facility data that support the findings of this study were obtained from Health Action International after submission and approval of the research protocol. Restrictions apply to the availability of these data, which were used under agreement for this study. Aggregated data on medicine and country level can be obtained from the Health Action International website.

REFERENCES

1. Unicef. Goal 3: Good Health And Well-Being [internet]. Date accessed: 9 May 2022. URL: https://data.unicef.org/sdgs/goal-3-good-health-wellbeing/.
2. United Nations. About the Sustainable Development Goals [internet]. Date accessed: 17 Sep 2020. URL: https://www.un.org/sustainabledevelopment/sustainable-development-goals/.
3. World Health Organization (WHO). Better Medicines for Children Project. Geneva: WHO; 2009. Date accessed 1 June 2021. URL : https://www.who.int/childmedicines/progress/ChildMeds_pricing_surveys.pdf.
4. United Nations. SDG Indicators: Metadata repository [internet]. Accessed 17 Sep 2020. URL: https://unstats.un.org/sdgs/metadata?Text=&Goal=3&Target=3.b.
5. Kristensen HG. WHO guideline development of paediatric medicines: points to consider in pharmaceutical development. *Int J Pharm* 2012;435(2):134-5.
6. World Health Organization (WHO). Promoting safety of medicines for children. Geneva: WHO; 2007. URL: https://www.who.int/medicines/publications/essentialmedicines/Promotion_safe_med_childrens.pdf.
7. Martei YM, Iwamoto K, Barr RD, et al. Shortages and price variability of essential cytotoxic medicines for treating children with cancers. *BMJ Glob Health* 2020;5(11):e003282.
8. Simonyan T, Papyan R, Danielyan S, et al. Availability of Essential Medicines for Pediatric Oncology in Armenia. *Asian Pac J Cancer Prev* 2019;20(4):991-994.
9. Droti B, O'Neill KP, Mathai M, et al. Poor availability of essential medicines for women and children threatens progress towards Sustainable Development Goal 3 in Africa. *BMJ Glob Health* 2019;4(Suppl 9):e001306.
10. Orubu ESF, Robert FO, Samuel M, et al. Access to essential cardiovascular medicines for children: a pilot study of availability, price and affordability in Nigeria. *Health Policy Plan* 2019;34 Suppl 3:20-26.
11. Roy V, Singhal S, Tayal H, et al. Availability of Pediatric Formulations in Public Health Care System in India: A Case Study. *Indian J Pediatr* 2021;88(3):227-234.
12. Faruqui N, Martiniuk A, Sharma A, et al. Evaluating access to essential medicines for treating childhood cancers: a medicines availability, price and affordability study in New Delhi, India. *BMJ Glob Health* 2019;4(2):e001379.
13. Cohen P, Friedrich P, Lam C, et al. Global Access to Essential Medicines for Childhood Cancer: A Cross-Sectional Survey. *J Glob Oncol* 2018;4:1-11.
14. Hailu AD, Mohammed SA. Availability, price, and affordability of WHO priority maternal and child health medicine in public health facilities of Dessie, north-East Ethiopia. *BMC Med Inform Decis Mak* 2020;20(1):221.
15. Johansson EW, Lindsjö C, Weiss DJ, et al. Accessibility of basic paediatric emergency care in Malawi: analysis of a national facility census. *BMC Public Health* 2020;20(1):992.
16. Dorj G, Sunderland B, Sanjjav T, et al. Availability, affordability and costs of pediatric medicines in Mongolia. *BMC Pediatr* 2018;18(1):149.
17. Tujo TM, Gurmu TG. Availability and Utilization of WHO Lifesaving Medicines for Children under Five in Public Health Facilities of the Jimma Zone, South West Ethiopia: A Cross-Sectional Survey. *Int J Pediatr* 2020;2020:3505672.
18. Swain TR, Rath B, Dehury S, et al. Pricing and availability of some essential child specific medicines in Odisha. *Indian J Pharmacol* 2015;47(5):496-501
19. Božić B, Stupar S, Stupar D, et al. Availability of pediatric-evaluated formulations in Serbia. *Indian J Pharmacol* 2017;49(2):189-193.

20. Sun X, Wei J, Yao Y, et al. Availability, prices and affordability of essential medicines for children: a cross-sectional survey in Jiangsu Province, China. *BMJ Open* 2018;8(10):e023646.
21. Wang X, Fang Y, Yang S, et al. Access to paediatric essential medicines: a survey of prices, availability, affordability and price components in Shaanxi Province, China. *PLoS One* 2014;9(3):e90365.
22. Sado E, Sufa A. Availability and affordability of essential medicines for children in the Western part of Ethiopia: implication for access. *BMC Pediatr* 2016;16:40.
23. Balasubramaniam R, Benaragama BV, Sri Ranganathan S. A national survey of price and affordability of key essential medicines for children in Sri Lanka. *Indian J Pediatr* 2014;81(4):362-7.
24. Vassal G, Kozhaeva O, Griskjane S, et al. Access to essential anticancer medicines for children and adolescents in Europe. *Ann Oncol* 2021;32(4):560-568.
25. Barr R, Robertson J. Access to Cytotoxic Medicines by Children With Cancer: A Focus on Low and Middle Income Countries. *Pediatr Blood Cancer* 2016;63(2):287-91.
26. Nsabagasani X, Ogwal-Okeng J, Mbonye A, et al. Availability and utilization of the WHO recommended priority lifesaving medicines for under five-year old children in public health facilities in Uganda: a cross-sectional survey. *J Pharm Policy Pract* 2015;8(1):18.
27. Rutebemberwa E, Buregyeya E, Lal S, et al. Assessing the potential of rural and urban private facilities in implementing child health interventions in Mukono district, central Uganda-a cross sectional study. *BMC Health Serv Res* 2016;16:268.
28. Robertson J, Forte G, Trapsida JM, et al. What essential medicines for children are on the shelf? *Bull World Health Organ* 2009;87(3):231-7.
29. Shafiq Y, Shaikh BT, Kumar R. Availability and affordability of essential medicines: exploring the health seeking behaviours and health service utilisation for children under-5 years living in squatter settlement of Karachi, Pakistan. *J Ayub Med Coll Abbottabad* 2011;23(1):132-8.
30. Balasubramaniam R, Beneragama BV, Sri Ranganathan S. A national survey of availability of key essential medicines for children in Sri Lanka. *Ceylon Med J* 2011;56(3):101-7.
31. Gitanjali B, Manikandan S. Availability of five essential medicines for children in public health facilities in India: A snapshot survey. *J Pharmacol Pharmacother* 2011;2(2):95-9.
32. Tadesse T, Abuye H, Tilahun G. Availability and affordability of children essential medicines in health facilities of southern nations, nationalities, and people region, Ethiopia: key determinants for access. *BMC Public Health* 2021;21(1):714.
33. Anson A, Ramay B, de Esparza AR, et al. Availability, prices and affordability of the World Health Organization's essential medicines for children in Guatemala. *Global Health* 2012;8:22.
34. Abu-Arja MH, Rojas Del Río N, Morales La Madrid A, et al. Evaluation of the Pediatric Neuro-Oncology Resources Available in Chile. *JCO Glob Oncol* 2021;7:425-434.
35. Abrha S, Tadesse E, Atey TM, et al. Availability and affordability of priority life-saving medicines for under-five children in health facilities of Tigray region, northern Ethiopia. *BMC Pregnancy Childbirth* 2018;18(1):464.
36. World Health Organization (WHO). Priority life-saving medicines for women and children 2012. Geneva: WHO; 2012. URL: https://www.who.int/publications/i/item/WHO-EMP-MAR-2012-1.
37. European Medicines Agency (EMA). Reflection paper: Formulations of choice for the paediatric population. London: EMA; 2006. URL: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-formulations-choice-paediatric-population_en.pdf.
38. Global Health Observatory, World Health Organization (WHO). Global health estimates: Leading causes of DALYs [internet]. Date accessed 18 Oct 2020. URL: https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/global-health-estimates-leading-causes-of-dalys.

39. World Health Organization (WHO). WHO Model List of Essential Medicines for Children - 7th list, 2019. Geneva: WHO; 2019. URL: https://www.who.int/publications/i/item/WHOMVPEMPIAU201907.
40. World Health Organization (WHO). Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Childhood Illnesses. 2nd edition. Geneva: WHO; 2013. URL: https://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/#:~:text=It%20is%20for%20use%20by,of%20Childhood%20Illness%20(IMCI).
41. National Department of Health. Primary Healthcare Standard Treatment Guideline and Essential Medicine List. 6th ed. Republic of South Africa: National Department of Health; 2018. URL: https://www.knowledgehub.org.za/elibrary/primary-healthcare-standard-treatment-guidelines-and-essential-medicines-list-6th-edition.
42. World Health Organization (WHO). Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: WHO; 2021. URL: https://www.who.int/publications/i/item/9789240031593
43. World Health Organization (WHO). WHO guidelines for Malaria. Geneva: WHO; 2021. URL: https://www.who.int/publications/i/item/guidelines-for-malaria
44. World Health Organization (WHO). Paediatric emergency triage, assessment and treatment: care of critically-ill children. Geneva: WHO; 2016. URL: https://www.who.int/publications/i/item/9789241510219
45. World Health Organization (WHO). Child Growth Standards [internet]. Date accessed 2 Mar 2021. URL: https://www.who.int/tools/child-growth-standards/standards/weight-for-age.
46. World Health Organization (WHO). Growth Reference Data for 5-19 years [internet]. Date accessed 2 Mar 2021. URL: https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/weight-for-age-5to10-years.
47. TNO. Groeidiagrammen in PDF-formaat [internet]. Date accessed 11 Jun 2021. URL: https://www.tno.nl/nl/aandachtsgebieden/gezond-leven/roadmaps/youth/groeidiagrammen-in-pdf-formaat/.
48. Akkawi El Edelbi R, Lindemalm S, et al. Estimation of body surface area in neonates, infants, and children using body weight alone. *Int J Pediatr Adolesc Med* 2021;8(4):221-228.
49. World Health Organization (WHO). Global action plan for the prevention and control of noncommunicable diseases 2013-2020. Geneva: WHO; 2013. URL: https://www.who.int/publications/i/item/9789241506236.
50. World Health Organization (WHO) & Health Action International (HAI). Measuring medicine prices, availability, affordability and price components, 2nd edition. Geneva: WHO; 2008. URL: https://apps.who.int/iris/handle/10665/70013.
51. Health Action International (HAI). Medicine Prices, Availability, Affordability & Price Components Database [internet]. Date accessed 3 Feb 2021. URL: https://haiweb.org/what-we-do/price-availability-affordability/price-availability-data/.
52. World Bank. Burundi Poverty Assessment. Washington, DC: World Bank; 2016. URL: https://openknowledge.worldbank.org/handle/10986/35555.
53. World Bank. Poverty and Equity Brief China. Washington, DC: World Bank; 2021. URL: https://www.worldbank.org/en/topic/poverty/publication/poverty-and-equity-briefs.
54. World Bank and Observatoire National de la Pauvreté et de l'Exclusion Sociale (ONPES). Investing in People to Fight Poverty in Haiti, Reflections for Evidence-based Policy Making. Washington, DC: World Bank; 2014. URL: https://openknowledge.worldbank.org/handle/10986/21519.
55. World Bank. Consumer Price Index (2010 = 100) [internet]. Date accessed 18 Mar 2022. URL: https://data.worldbank.org/indicator/FP.CPI.TOTL.

56. Chen Z, Li S, Zeng L, et al. Accessibility of Medicines for Children: A Systematic Review. *Front Pharmacol* 2021;12:691606.
57. Niëns LM, Van de Poel E, Cameron A, et al. Practical measurement of affordability: an application to medicines. *Bull World Health Organ* 2012 Mar 1;90(3):219-27.
58. Joosse IR, Mantel-Teeuwisse AK, Wirtz VJ, Suleman F, van den Ham HA. Missing data on accessibility of children's medicines. Bull World Health Organ. 2022 Oct 1;100(10):636-642.

Figure 1 Two example calculations of the NUNT

Figure 2 Core elements of the World Health Organization/Health Action International methodology (adapted from [50])

Figure 3 Proportion of medicines accessible in Burundi, China and Haiti.
Since the originator brand was not surveyed for all active ingredients, findings in the private sectors of all three countries are based on a very small number of medicines only.
ORS = Oral Rehydration Salts.

Paracetamol 100 mg cap/tab

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

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

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

Amoxicillin 50 mg/ml suspension

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

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

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

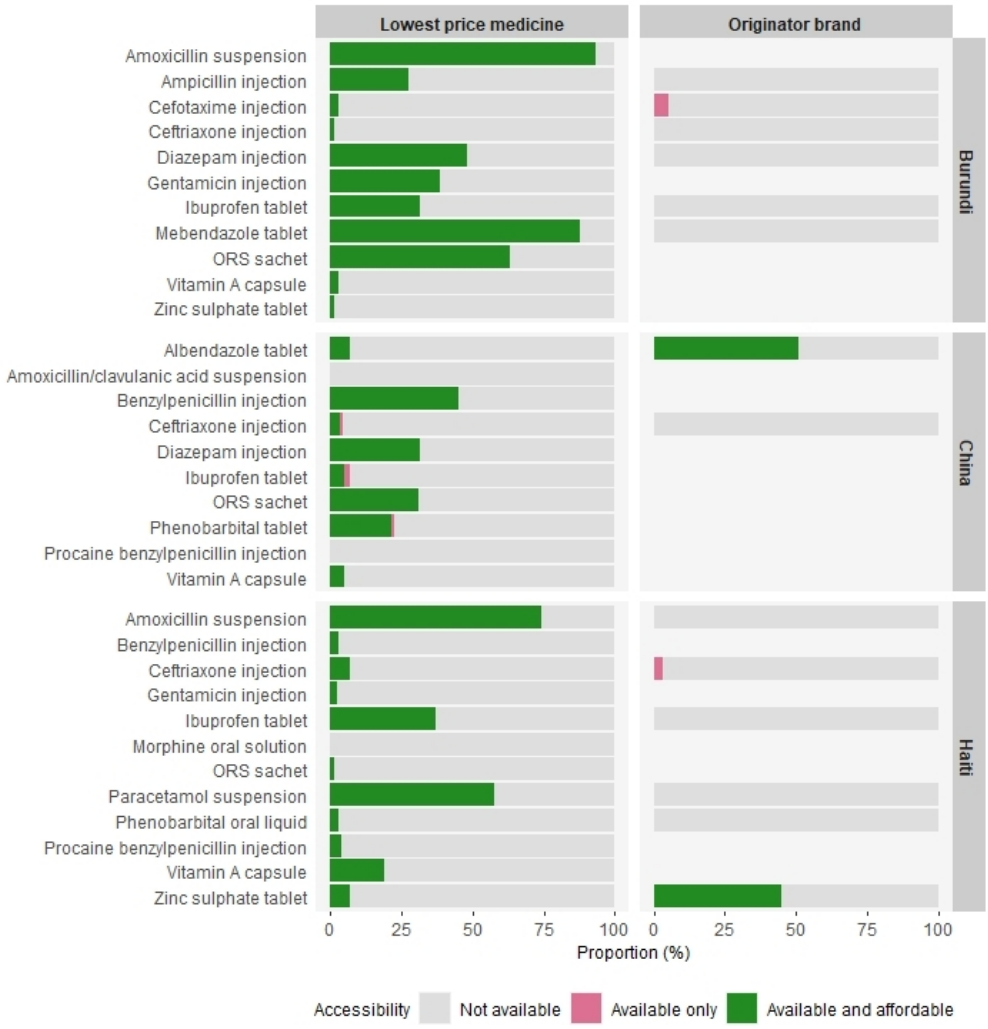
The World Health Organization/Health Action International methodology

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

Key elements of the methodology include:

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

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



Proportion of medicines accessible in Burundi, China and Haiti.
Since the originator brand was not surveyed for all active ingredients, findings in the private sectors of all three countries are based on a very small number of medicines only.
ORS = Oral Rehydration Salts.

185x194mm (96 x 96 DPI)

Annex 1

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

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

Procedures

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

Pilot

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

Participants

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

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

Data analysis

Agreement of experts on which active ingredients to in- or exclude was assessed. Experts were regarded as in agreement if ≥80% of the respondents indicated to agree with inclusion of the active ingredient. Similarly, if ≥80% of the respondents indicated that a specific active ingredient was redundant or missing, it was removed from or added to the selection, respectively. If no consensus was reached (<80% agrees), active ingredients indicated as redundant or missing were compared across respondents. Comments provided by participants were analyzed in-depth and discussed by two authors to reach a decision.

Final basket

The validation process resulted in the addition of four active ingredients to the basket, and the removal of two (see table 1 in main text). No follow-up with participants was required to reach a consensus.

Ethical approval

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

Annex 2

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

Medicine name	Acceptable formulation	NUNT
Oral rehydration salts	Powder sachet 200 ml	2
	Powder sachet 500 ml	2
	Powder sachet 1L	1
Zinc sulphate	Cap/tab 20 mg	14
Carbamazapine	Cap/tab 100 mg	60
	Oral liquid 100 mg/5 ml	180
Phenobarbital	Cap/tab 30 mg	60
	Cap/tab 100 mg	30
	Injection 100 mg/ml	30
	Injection 200 mg/ml	15
	Oral liquid 15 mg/5 ml	600
Phenytoin	Cap/tab 25 mg	90
	Cap/tab 50 mg	60
	Cap/tab 100 mg	60
	Injection 50 mg/ml	60
	Oral liquid 25 mg/5 ml	480
	Oral liquid 30 mg/5 ml	420
Lamotrigine	Cap/tab 25 mg	60
	Cap/tab 50 mg	30
	Cap/tab 100 mg	30
Valproic acid	Cap/tab 100 mg	60
	Cap/tab 150 mg	60
	Cap/tab 200 mg	60
	Cap/tab 500 mg	30
	Oral liquid 200 mg/5 ml	240
Diazepam	Rectal solution 5 mg/ml	1
	Injection 5 mg/ml	1
Lorazepam	Parenteral solution 2 mg/ml	0.5
	Parenteral solution 4 mg/ml	0.5
Midazolam	Oromucosal solution 5 mg/ml	10
	Oromucosal solution 10 mg/ml	6
	Ampoule 10 mg/ml	6
Abacavir/lamivudine	Cap/tab 120/60 mg	60
Dolutegravir	Cap/tab 10 mg	60
Lopinavir/ritonavir	Cap/tab 40/10 mg	120
	Cap/tab 100/25 mg	60
Ferrous salt	Cap/tab 60 mg	28
	Cap/tab 200 mg	14
	Oral liquid 25 mg/ml	56
Albendazole	Cap/tab 200 mg	2
	Cap/tab 400 mg	1
Mebendazole	Cap/tab 100 mg	6
Artemether/lumefantrine	Cap/tab 20/120 mg	6
Artesunate/amodiaquine	Cap/tab 25/67.5 mg	6
	Cap/tab 50/135 mg	3
Artesunate/mefloquine	Cap/tab 25/55 mg	6
Dihydroartemisinin/piperaquine	Cap/tab 20/160 mg	6

	Cap/tab 20/320 mg	3
Artesunate/Sulfadoxine-pyrimethamine	Cap/tab 50/500/25 mg	1
	Cap/tab 500/25 mg (sulfadoxine-pyrimethamine)	1
Chloroquine	Cap/tab 100 mg	5
	Oral liquid 50 mg/5 ml	30
Artesunate	Cap/tab 50 mg	3
	Suppository 50 mg	3
Retinol	Cap/tab 25,000 IU	4
	Cap/tab 100,000 IU	2
	Cap/tab 200,000 IU	2
Paracetamol	Cap/tab 100 mg	150
	Suppository 100 mg	150
	Suspension 120 or 125 mg/5 ml	900
Morphine	Cap/tab (slow release) 10 mg	60
	Injection 10 mg/ampoule	30
	Oral liquid 10 mg/5 ml	300
Ibuprofen	Cap/tab 200 mg	90
	Oral liquid 200 mg/5 ml	180
Ethambutol + isoniazid + pyrazinamide + rifampicin	Cap/tab 100 mg (ethambutol)	60
	Cap/tab 400 mg (ethambutol)	30
	Oral liquid 25 mg/ml (ethambutol)	9
	Cap/tab 50/150/75 mg (isoniazid + pyrazinamide + rifampicin)	60
Amoxicillin	Cap/tab 250 mg	20
	Cap/tab 500 mg	10
	Powder for injection 250 mg/vial	20
	Powder for injection 500 mg/vial	10
	Powder for injection 1 g/vial	5
	Suspension 125 mg/5 ml	100
	Suspension 250 mg/5 ml	90
Amoxicillin + clavulanic acid	Cap/tab 100/125 mg	30
	Cap/tab 250/125 mg	15
	Cap/tab 500/125 mg	15
	Powder for injection 500/100 mg/vial	8
	Oral liquid 125/53.25 mg/5 ml	135
	Oral liquid 250/62.5 mg/5 ml	60
Ampicillin	Cap/tab 250 mg	40
	Cap/tab 500 mg	20
	Injection 500 mg/vial	20
	Injection 1 g/vial	10
Benzylpenicillin	Injection 1 MIU/vial	5
Gentamicin	Injection 10 mg/ml	40
	Injection 40 mg/ml	10
Ceftriaxone	Injection 250 mg/vial	28
	Injection 500 mg/vial	14
	Injection 1 g/vial	7
Cefotaxime	Injection 1 g/vial	18
Procaine benzylpenicillin	Injection 1 MIU/vial	10

Annex 3

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

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

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

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

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

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

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

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

In which 1 = available and 0 = not available.

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

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

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

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

The price of a daily dose is then calculated as:

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

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

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

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

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

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

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

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

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

In which 1 = affordable and 0 = not affordable. Affordability cannot be computed for medicines without price data.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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ABSTRACT

Objectives

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

Method

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

Results

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

Conclusion

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

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A strength of this study is the adaptation of an existing tool that was made appropriate for children.
- In using an existing tool as starting point, the adapted methodology also inherits some of the limitations of this tool, such as the burden of disease weighting and the national poverty line in the calculation of affordability.
- In providing proof-of-concept of this tool, we were limited to historical data that were already available which are of little relevance to the current situation.
- The historical datasets used are quality-assured through standardized data collection and through data validation and verification steps.
- Only a modest sample of age-appropriate medicines were surveyed in the historical datasets, demanding further analyses on larger datasets.

INTRODUCTION

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

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

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

At present, there is no methodology for measuring accessibility of essential medicines specifically for children, but a number of studies have reported on the availability or price of medicines, or both [7-35]. The methodologies for measuring these two important dimensions of access varied greatly between studies, as did the medicines surveyed, covering different age groups of children (e.g. children under five, children under twelve, or all children and adolescents), priority diseases (anticancer medicines, cardiovascular medicines or a range of diseases) and number of surveyed medicines. Results are therefore difficult to compare and may not reflect overall access to medicines for children in a country. This emphasizes the need for a standardized and validated methodology for measuring access to medicines for children that will enable global comparison and eventually benchmarking of indicators.

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

METHODOLOGY

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

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

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

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

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

A core set of globally relevant essential medicines

The core set of medicines consists of tracer essential medicines, together indicative of overall access to medicines in primary health care. Over the years, several baskets of pediatric medicines have already been proposed. However, the list of medicines defined for the 2007 'Better medicines for children' project is not only dated, but also purposely excludes antiretroviral therapies (ART) for HIV [3]. Since HIV/AIDS is still prevalent among pediatric populations in low- and middle-income countries, this selection of medicines is not suitable for the current purpose. In 2012, the World Health Organization (WHO) published a list of thirteen 'Priority life-saving medicines' for children under the age of five, intended to help countries in prioritizing those medicines that will have the biggest impact on reducing child morbidity and mortality [36]. We believe that an access indicator should serve a broader age group, especially since children aged 5 to 12 years may have different treatment requirements than the youngest. Additionally, the priority list only targets seven prevalent diseases, and is thus limited in its scope. With that, no existing basket of pediatric medicines was deemed suitable for the current purpose.

A new core set of medicines for children with ages 1 month to 12 years for treating acute and chronic, communicable and non-communicable diseases in the primary health care setting and including child-appropriate formulations was thus established. To cater to the unique needs of children with different ages, separate baskets for two age groups were created: young children (infants, toddlers and pre-school children) aged 1 month to 59 months, and school-aged children 5 to 12 years of age. These groups will allow stakeholders to differentiate between health needs in terms of disease prevalence, required dosage strengths and preferred dosage forms. Children above

the age of 12 often do not require pediatric formulations [37] and their health needs may already be adequately covered in the original SDG indicator 3.b.3 methodology.

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

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

Availability of medicines

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

Affordability of medicines

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

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

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

This measure indicates whether the LPGW wage is enough to cover the costs of daily expenditures for food and non-food items plus the cost of a medicine. The EDW is again transformed into a binary

(4)

variable: a medicine is considered affordable when no EDW are required to purchase it (formula 4).

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

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

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

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

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

Number of units needed for treatment

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

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

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

[figure 1]

Weighting for burden of disease

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

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

Calculating SDG indicator 3.b.3

The age-specific SDG indicator 3.b.3 can be calculated with formula 1. Assessing availability and affordability of medicines, and subsequent weighting for regional disease burden, was done at the facility level, meaning that a separate score is calculated for each health facility surveyed. Facilities

[1] Weighting for regional burden of disease is a different process than selecting medicines for the core set based on global burden of disease.

with at least 80% of medicines in the basket available and affordable were considered to have accessible medicines. This threshold was adopted by the WHO Global Action Plan on Non-Communicable Diseases and used as a reference [49]. Table 2 presents a full summary of the adaptations to the original SDG 3.b.3 methodology to make it child-appropriate. A hypothetical working example is provided in Annex 3.

Proof-of-concept

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

[figure 2]

Data on medicines' availability and price for Burundi (2013), China (2012) and Haiti (2011) was obtained from HAI. These datasets were selected because the highest absolute number of age-appropriate medicines that are listed in the proposed core set of medicines was included in these surveys (11, 10 and 12 out of 22 medicines, respectively) [51]. Additionally, this selection represents countries with different income levels (e.g. Burundi and Haiti low-income countries, China an upper-middle income country) and from different geographical regions. To make the datasets appropriate for analysis, only the age-appropriate medicines as listed in table 1 were selected. A selection in participating health facilities was not made.

Data on NPLs were obtained from World Bank reports on poverty [52-54]. NPLs were adjusted for inflation and deflation between the year data was reported and the survey year using the Consumer Price Index (CPI) [55]. Monthly poverty lines were converted to daily time periods. LPGW wages were directly obtained from the datasets provided by HAI and thus required no corrections for the year of survey.

Because regional data on burden of disease in DALYs is available for every five years only, the year closest in time to the year of survey was used (e.g. 2010 publication for China and Haiti and 2015 publication for Burundi) to weight for burden of disease [38].

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

Patient and public involvement

There was no patient or public involvement in the design or conduct of this study.

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

Input	Original $SDG_{3.b.3}$ methodology [4]	Child-specific $SDG_{3.b.3}$ methodology
SDG indicator 3.b.3		
Calculation	- Based on individual facility scores. - Facilities considered as having accessible medicines when reaching an 80% threshold.	- Based on individual facility scores. - Facilities considered as having accessible medicines when reaching an 80% threshold.
Core set of globally relevant essential medicines		
Selection of medicines	- Defined on a global level. - Selected from 2017 WHO EML. - Selection process not described.	- Defined on a global level. - Selected from 2019 WHO EMLc. - Selection based on global burden of disease (top 10 conditions causing disability/mortality that can be treated with medicines), international treatment guidelines and expert consultation.
The basket	- One basket for all. - 32 tracer essential medicines for acute and chronic, communicable and non-communicable diseases.	- Baskets defined for two age groups (young children; school-aged children). - 22 tracer essential medicines for acute and chronic, communicable and non-communicable diseases for both young and school-aged children. - Age-appropriate formulations selected per age group.
Burden of disease	- Weighting according to regional burden of disease (in DALYs). - Based on WHO GHEs. - Pre-defined GHE codes, with overarching GHE code for 'infectious and parasitic diseases' for antibacterials. - Equal weights assigned to medicines that are used to treat the same disease.	- Weighting according to regional burden of disease (in DALYs). - Based on WHO GHEs, from period closest to year of survey. - Affiliated GHE codes determined according to the uses as described in EMLc. GHE codes for antibacterials determined according to uses as described in EMLc plus code for 'other infectious diseases'. - Equal weights assigned to medicines that are used to treat the same disease.
Availability of medicines		
Availability	- Captured as binary variable. - As surveyed.	- Captured as binary variable. - As surveyed.
Affordability of medicines		
Required inputs	- Captured as binary variable. - Calculated from the price of a medicine, the number of units needed for treatment, the NPL and the wage of the LPGW.	- Captured as binary variable. - Calculated from the price of a medicine, the NUNT, the NPL and the wage of the LPGW.
Number of units needed for treatment	- Total number of units needed per month or treatment course based on DDDs. - Process for defining duration of treatment not described.	- NUNT based on duration of treatment and recommended daily dosages per age or weight group. Weight-based dosing transformed to age-based dosing. - Recommended daily dosages and duration of treatment derived from international treatment guidelines.

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

RESULTS

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

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

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

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

[figure 3]

DISCUSSION

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

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

Upon closer examination of the case studies of Burundi, China and Haiti, the widespread inaccessibility seen in the results seemed to stem from unavailable rather than unaffordable medicines, for both LPMs and OBs. A recent systematic review on children's medicines identified fourteen studies that reported on the availability of children's medicines and found a median availability of 38.1% and 24.2% for LPMs and OBs in the public sectors and of 35.9% and 21.1% in the private sectors, respectively [56]. With that, the unavailability of child medicines detected in the present case studies is in line with the results of the systematic review. The same systematic review identified eleven studies that reported on the affordability of medicines, based on the number of days' wages of the LPGW. In the public sector, affordability was 83.6% and 48.5% for LPMs and OBs, with 72.2% and 68.8% in the private sector. The results of this systematic review emphasize the need for a method that combines the two dimensions into a single indicator, as separate evaluation of these elements overestimates actual access to medicines for the patient. Beyond that, some of the studies included in the systematic review included unrepresentative samples of medicines (e.g. studies focused on a single disease area or studies simply failing to consider child-appropriate formulations such as oral liquids or appropriate medicine strengths), again confirming the need for a standardized methodology to measure access to child medicines.

Before this methodology can, however, be applied on a widespread scale, several steps must be undertaken to further validate the methodology and examine the uncertainties introduced through

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

An important strength of this child-specific methodology is the use of an existing, formally approved tool as starting point which was adapted to suit the needs of children. Core concepts used in the adapted methodology and its data requirements are therefore in line with conventional methods and data collection tools. However, through this approach our methodology also inherits some of the limitations of the original 3.b.3 indicator methodology. Particularly, weighting for regional burden of disease when calculating access at the facility level as done in the original methodology raises several concerns. For one, the methodology assigns equal weights to medicines that are used to treat the same disease and thus counts the burden of this disease multiple times. To illustrate, the basket of medicines includes both oral rehydration salts and zinc sulphate for diarrheal diseases, whereas only retinol was selected for measles/vitamin A deficiency. This leads to disproportionate weighting for actual burden of disease when calculating access at the facility level. Disproportionality is also a concern for antibacterial medicines, which use may be overrepresented by using GHE code 20, a code that is linked to all infectious and parasitic diseases. Although a proxy for this GHE code was used in the present study (GHE code 370 for 'other infectious diseases'), additional analyses should demonstrate how different weighting approaches affect the results. Additionally, the quality of the underlying GHEs data is unclear, especially because these data may be more difficult to obtain for children than for adults. Lastly, arguments can be made that the current approach of weighting for burden of disease is undesirable because it implies that some medicines are more important than others, even though all medicines in the basket are essential medicines and should always be accessible.

On a similar note, expressing affordability as a function of a poverty line instead of the LPGW wage has been used previously [57], but a measure combining the NPL and LPGW wage as is used in the original 3.b.3 indicator has yet to prove itself. This is particularly relevant because it seems that

somewhat less medicines were unaffordable in the present case studies than what was observed using the LPGW wage alone [56]. Further testing of the proposed child-specific methodology should include several scenarios for weighting for burden of disease and calculating affordability, which could lead to further adaptations of the methodology.

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

To provide first evidence of the child-specific tool that we developed, we were limited to the use of historical datasets. In selecting suitable datasets for the case studies it was observed that only a small number of age-appropriate medicines are being surveyed in low- and middle-income countries [58]. The WHO/HAI datasets used for the present case studies were selected for their quality of data and relatively high inclusivity of age-appropriate medicines, yet they still included a modest sample of child-appropriate medicines. Further analyses on a dataset with a higher number of age-appropriate medicines are thus required, which may need to be collected prospectively. Although the relevance of the findings to the current situation of Burundi, China and Haiti is limited because of the older data, the aim of providing proof-of-concept of the adapted methodology was achieved nonetheless. Finally, the individual facility data that support the findings of this study are not publicly available, but aggregated data per medicine and country can be obtained from the HAI website [51]. The aggregated data are sufficient to allow initial comparison of our methodology to previously existing tools.

CONCLUSION

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

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COMPETING INTERESTS

The authors have no competing financial and/or non-financial interests in relation to this work to declare.

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CONTRIBUTORSHIP STATEMENT

All authors were involved in conception and study design. IRJ drafted the article, HAvdH, AKM-T and FS were involved in critical revision of the article. All authors approved the final article.

ETHICS APPROVAL STATEMENT

This study does not involve human or animal participants.

DATA SHARING STATEMENT

The individual facility data that support the findings of this study were obtained from Health Action International after submission and approval of the research protocol. Restrictions apply to the availability of these data, which were used under agreement for this study. Aggregated data on medicine and country level can be obtained from the Health Action International website.

REFERENCES

1. Unicef. Goal 3: Good Health And Well-Being [internet]. Date accessed: 9 May 2022. URL: https://data.unicef.org/sdgs/goal-3-good-health-wellbeing/.
2. United Nations. About the Sustainable Development Goals [internet]. Date accessed: 17 Sep 2020. URL: https://www.un.org/sustainabledevelopment/sustainable-development-goals/.
3. World Health Organization (WHO). Better Medicines for Children Project. Geneva: WHO; 2009. Date accessed 1 June 2021. URL : https://www.who.int/childmedicines/progress/ChildMeds_pricing_surveys.pdf.
4. United Nations. SDG Indicators: Metadata repository [internet]. Accessed 17 Sep 2020. URL: https://unstats.un.org/sdgs/metadata?Text=&Goal=3&Target=3.b.
5. Kristensen HG. WHO guideline development of paediatric medicines: points to consider in pharmaceutical development. *Int J Pharm* 2012;435(2):134-5.
6. World Health Organization (WHO). Promoting safety of medicines for children. Geneva: WHO; 2007. URL: https://www.who.int/medicines/publications/essentialmedicines/Promotion_safe_med_childrens.pdf.
7. Martei YM, Iwamoto K, Barr RD, et al. Shortages and price variability of essential cytotoxic medicines for treating children with cancers. *BMJ Glob Health* 2020;5(11):e003282.
8. Simonyan T, Papyan R, Danielyan S, et al. Availability of Essential Medicines for Pediatric Oncology in Armenia. *Asian Pac J Cancer Prev* 2019;20(4):991-994.
9. Droti B, O'Neill KP, Mathai M, et al. Poor availability of essential medicines for women and children threatens progress towards Sustainable Development Goal 3 in Africa. *BMJ Glob Health* 2019;4(Suppl 9):e001306.
10. Orubu ESF, Robert FO, Samuel M, et al. Access to essential cardiovascular medicines for children: a pilot study of availability, price and affordability in Nigeria. *Health Policy Plan* 2019;34 Suppl 3:20-26.
11. Roy V, Singhal S, Tayal H, et al. Availability of Pediatric Formulations in Public Health Care System in India: A Case Study. *Indian J Pediatr* 2021;88(3):227-234.
12. Faruqui N, Martiniuk A, Sharma A, et al. Evaluating access to essential medicines for treating childhood cancers: a medicines availability, price and affordability study in New Delhi, India. *BMJ Glob Health* 2019;4(2):e001379.
13. Cohen P, Friedrich P, Lam C, et al. Global Access to Essential Medicines for Childhood Cancer: A Cross-Sectional Survey. *J Glob Oncol* 2018;4:1-11.
14. Hailu AD, Mohammed SA. Availability, price, and affordability of WHO priority maternal and child health medicine in public health facilities of Dessie, north-East Ethiopia. *BMC Med Inform Decis Mak* 2020;20(1):221.
15. Johansson EW, Lindsjö C, Weiss DJ, et al. Accessibility of basic paediatric emergency care in Malawi: analysis of a national facility census. *BMC Public Health* 2020;20(1):992.
16. Dorj G, Sunderland B, Sanjjav T, et al. Availability, affordability and costs of pediatric medicines in Mongolia. *BMC Pediatr* 2018;18(1):149.
17. Tujo TM, Gurmu TG. Availability and Utilization of WHO Lifesaving Medicines for Children under Five in Public Health Facilities of the Jimma Zone, South West Ethiopia: A Cross-Sectional Survey. *Int J Pediatr* 2020;2020:3505672.
18. Swain TR, Rath B, Dehury S, et al. Pricing and availability of some essential child specific medicines in Odisha. *Indian J Pharmacol* 2015;47(5):496-501
19. Božić B, Stupar S, Stupar D, et al. Availability of pediatric-evaluated formulations in Serbia. *Indian J Pharmacol* 2017;49(2):189-193.

20. Sun X, Wei J, Yao Y, et al. Availability, prices and affordability of essential medicines for children: a cross-sectional survey in Jiangsu Province, China. *BMJ Open* 2018;8(10):e023646.
21. Wang X, Fang Y, Yang S, et al. Access to paediatric essential medicines: a survey of prices, availability, affordability and price components in Shaanxi Province, China. *PLoS One* 2014;9(3):e90365.
22. Sado E, Sufa A. Availability and affordability of essential medicines for children in the Western part of Ethiopia: implication for access. *BMC Pediatr* 2016;16:40.
23. Balasubramaniam R, Benaragama BV, Sri Ranganathan S. A national survey of price and affordability of key essential medicines for children in Sri Lanka. *Indian J Pediatr* 2014;81(4):362-7.
24. Vassal G, Kozhaeva O, Griskjane S, et al. Access to essential anticancer medicines for children and adolescents in Europe. *Ann Oncol* 2021;32(4):560-568.
25. Barr R, Robertson J. Access to Cytotoxic Medicines by Children With Cancer: A Focus on Low and Middle Income Countries. *Pediatr Blood Cancer* 2016;63(2):287-91.
26. Nsabagasani X, Ogwal-Okeng J, Mbonye A, et al. Availability and utilization of the WHO recommended priority lifesaving medicines for under five-year old children in public health facilities in Uganda: a cross-sectional survey. *J Pharm Policy Pract* 2015;8(1):18.
27. Rutebemberwa E, Buregyeya E, Lal S, et al. Assessing the potential of rural and urban private facilities in implementing child health interventions in Mukono district, central Uganda-a cross sectional study. *BMC Health Serv Res* 2016;16:268.
28. Robertson J, Forte G, Trapsida JM, et al. What essential medicines for children are on the shelf? *Bull World Health Organ* 2009;87(3):231-7.
29. Shafiq Y, Shaikh BT, Kumar R. Availability and affordability of essential medicines: exploring the health seeking behaviours and health service utilisation for children under-5 years living in squatter settlement of Karachi, Pakistan. *J Ayub Med Coll Abbottabad* 2011;23(1):132-8.
30. Balasubramaniam R, Beneragama BV, Sri Ranganathan S. A national survey of availability of key essential medicines for children in Sri Lanka. *Ceylon Med J* 2011;56(3):101-7.
31. Gitanjali B, Manikandan S. Availability of five essential medicines for children in public health facilities in India: A snapshot survey. *J Pharmacol Pharmacother* 2011;2(2):95-9.
32. Tadesse T, Abuye H, Tilahun G. Availability and affordability of children essential medicines in health facilities of southern nations, nationalities, and people region, Ethiopia: key determinants for access. *BMC Public Health* 2021;21(1):714.
33. Anson A, Ramay B, de Esparza AR, et al. Availability, prices and affordability of the World Health Organization's essential medicines for children in Guatemala. *Global Health* 2012;8:22.
34. Abu-Arja MH, Rojas Del Río N, Morales La Madrid A, et al. Evaluation of the Pediatric Neuro-Oncology Resources Available in Chile. *JCO Glob Oncol* 2021;7:425-434.
35. Abrha S, Tadesse E, Atey TM, et al. Availability and affordability of priority life-saving medicines for under-five children in health facilities of Tigray region, northern Ethiopia. *BMC Pregnancy Childbirth* 2018;18(1):464.
36. World Health Organization (WHO). Priority life-saving medicines for women and children 2012. Geneva: WHO; 2012. URL: https://www.who.int/publications/i/item/WHO-EMP-MAR-2012-1.
37. European Medicines Agency (EMA). Reflection paper: Formulations of choice for the paediatric population. London: EMA; 2006. URL: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-formulations-choice-paediatric-population_en.pdf.
38. Global Health Observatory, World Health Organization (WHO). Global health estimates: Leading causes of DALYs [internet]. Date accessed 18 Oct 2020. URL: https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/global-health-estimates-leading-causes-of-dalys.

39. World Health Organization (WHO). WHO Model List of Essential Medicines for Children - 7th list, 2019. Geneva: WHO; 2019. URL: https://www.who.int/publications/i/item/WHOMVPEMPIAU201907.
40. World Health Organization (WHO). Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Childhood Illnesses. 2nd edition. Geneva: WHO; 2013. URL: https://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/#:~:text=It%20is%20for%20use%20by,of%20Childhood%20Illness%20(IMCI).
41. National Department of Health. Primary Healthcare Standard Treatment Guideline and Essential Medicine List. 6th ed. Republic of South Africa: National Department of Health; 2018. URL: https://www.knowledgehub.org.za/elibrary/primary-healthcare-standard-treatment-guidelines-and-essential-medicines-list-6th-edition.
42. World Health Organization (WHO). Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: WHO; 2021. URL: https://www.who.int/publications/i/item/9789240031593
43. World Health Organization (WHO). WHO guidelines for Malaria. Geneva: WHO; 2021. URL: https://www.who.int/publications/i/item/guidelines-for-malaria
44. World Health Organization (WHO). Paediatric emergency triage, assessment and treatment: care of critically-ill children. Geneva: WHO; 2016. URL: https://www.who.int/publications/i/item/9789241510219
45. World Health Organization (WHO). Child Growth Standards [internet]. Date accessed 2 Mar 2021. URL: https://www.who.int/tools/child-growth-standards/standards/weight-for-age.
46. World Health Organization (WHO). Growth Reference Data for 5-19 years [internet]. Date accessed 2 Mar 2021. URL: https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/weight-for-age-5to10-years.
47. TNO. Groeidiagrammen in PDF-formaat [internet]. Date accessed 11 Jun 2021. URL: https://www.tno.nl/nl/aandachtsgebieden/gezond-leven/roadmaps/youth/groeidiagrammen-in-pdf-formaat/.
48. Akkawi El Edelbi R, Lindemalm S, et al. Estimation of body surface area in neonates, infants, and children using body weight alone. *Int J Pediatr Adolesc Med* 2021;8(4):221-228.
49. World Health Organization (WHO). Global action plan for the prevention and control of noncommunicable diseases 2013-2020. Geneva: WHO; 2013. URL: https://www.who.int/publications/i/item/9789241506236.
50. World Health Organization (WHO) & Health Action International (HAI). Measuring medicine prices, availability, affordability and price components, 2nd edition. Geneva: WHO; 2008. URL: https://apps.who.int/iris/handle/10665/70013.
51. Health Action International (HAI). Medicine Prices, Availability, Affordability & Price Components Database [internet]. Date accessed 3 Feb 2021. URL: https://haiweb.org/what-we-do/price-availability-affordability/price-availability-data/.
52. World Bank. Burundi Poverty Assessment. Washington, DC: World Bank; 2016. URL: https://openknowledge.worldbank.org/handle/10986/35555.
53. World Bank. Poverty and Equity Brief China. Washington, DC: World Bank; 2021. URL: https://www.worldbank.org/en/topic/poverty/publication/poverty-and-equity-briefs.
54. World Bank and Observatoire National de la Pauvreté et de l'Exclusion Sociale (ONPES). Investing in People to Fight Poverty in Haiti, Reflections for Evidence-based Policy Making. Washington, DC: World Bank; 2014. URL: https://openknowledge.worldbank.org/handle/10986/21519.
55. World Bank. Consumer Price Index (2010 = 100) [internet]. Date accessed 18 Mar 2022. URL: https://data.worldbank.org/indicator/FP.CPI.TOTL.

56. Chen Z, Li S, Zeng L, et al. Accessibility of Medicines for Children: A Systematic Review. *Front Pharmacol* 2021;12:691606.
57. Niëns LM, Van de Poel E, Cameron A, et al. Practical measurement of affordability: an application to medicines. *Bull World Health Organ* 2012 Mar 1;90(3):219-27.
58. Joosse IR, Mantel-Teeuwisse AK, Wirtz VJ, Suleman F, van den Ham HA. Missing data on accessibility of children's medicines. *Bull World Health Organ*. 2022 Oct 1;100(10):636-642.

Figure 1 Two example calculations of the NUNT

Figure 2 Core elements of the World Health Organization/Health Action International methodology (adapted from [50])

Figure 3 Proportion of medicines accessible in Burundi, China and Haiti.
Since the originator brand (OB) was not surveyed for all active ingredients, findings in the private sectors of all three countries are based on a very small number of medicines only.
ORS = Oral Rehydration Salts.

Paracetamol 100 mg cap/tab

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

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

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

Amoxicillin 50 mg/ml suspension

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

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

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

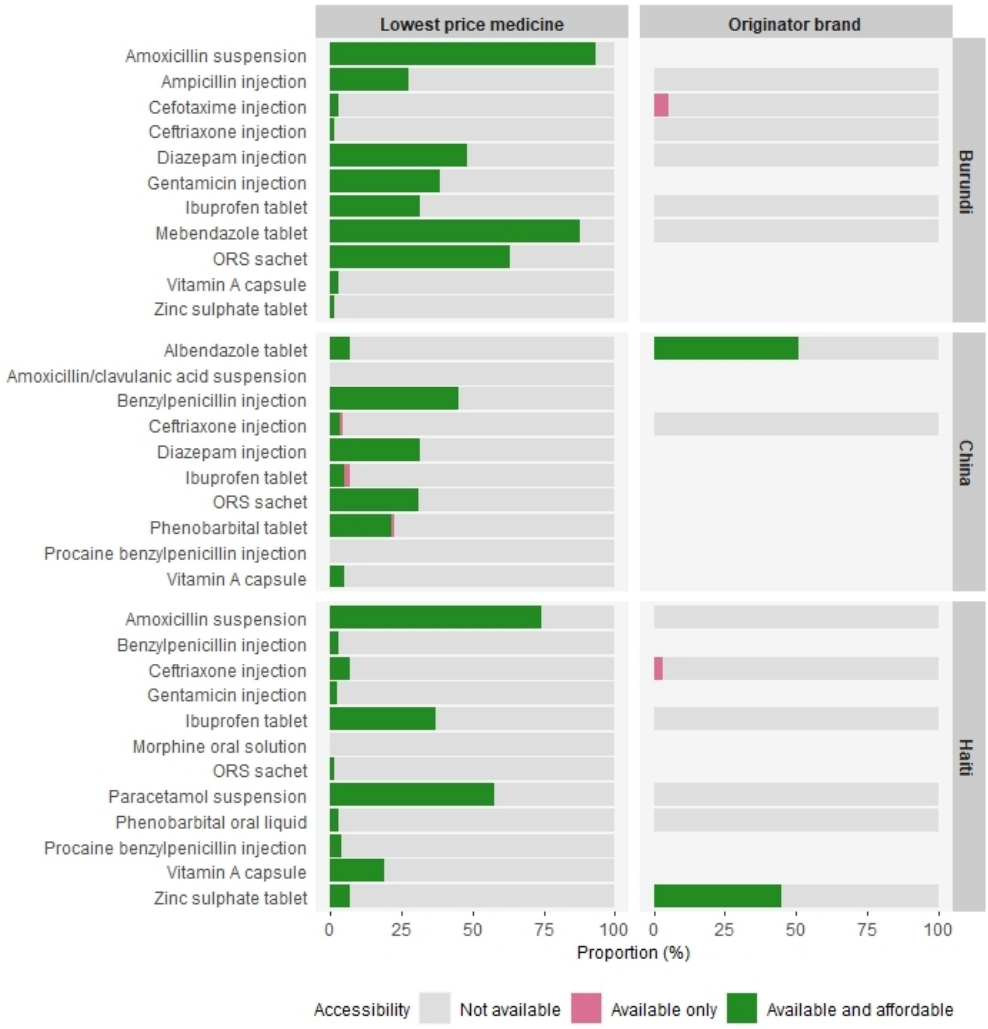
The World Health Organization/Health Action International methodology

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

Key elements of the methodology include:

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

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



Proportion of medicines accessible in Burundi, China and Haiti.
Since the originator brand was not surveyed for all active ingredients, findings in the private sectors of all three countries are based on a very small number of medicines only.
ORS = Oral Rehydration Salts.

185x194mm (96 x 96 DPI)

Annex 1

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

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

Procedures

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

Pilot

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

Participants

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

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

Data analysis

Agreement of experts on which active ingredients to in- or exclude was assessed. Experts were regarded as in agreement if ≥80% of the respondents indicated to agree with inclusion of the active ingredient. Similarly, if ≥80% of the respondents indicated that a specific active ingredient was redundant or missing, it was removed from or added to the selection, respectively. If no consensus was reached (<80% agrees), active ingredients indicated as redundant or missing were compared across respondents. Comments provided by participants were analyzed in-depth and discussed by two authors to reach a decision.

Final basket

The validation process resulted in the addition of four active ingredients to the basket, and the removal of two (see table 1 in main text). No follow-up with participants was required to reach a consensus.

Ethical approval

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

Annex 2

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

Medicine name	Acceptable formulation	NUNT
Oral rehydration salts	Powder sachet 200 ml	2
	Powder sachet 500 ml	2
	Powder sachet 1L	1
Zinc sulphate	Cap/tab 20 mg	14
Carbamazapine	Cap/tab 100 mg	60
	Oral liquid 100 mg/5 ml	180
Phenobarbital	Cap/tab 30 mg	60
	Cap/tab 100 mg	30
	Injection 100 mg/ml	30
	Injection 200 mg/ml	15
	Oral liquid 15 mg/5 ml	600
Phenytoin	Cap/tab 25 mg	90
	Cap/tab 50 mg	60
	Cap/tab 100 mg	60
	Injection 50 mg/ml	60
	Oral liquid 25 mg/5 ml	480
	Oral liquid 30 mg/5 ml	420
Lamotrigine	Cap/tab 25 mg	60
	Cap/tab 50 mg	30
	Cap/tab 100 mg	30
Valproic acid	Cap/tab 100 mg	60
	Cap/tab 150 mg	60
	Cap/tab 200 mg	60
	Cap/tab 500 mg	30
	Oral liquid 200 mg/5 ml	240
Diazepam	Rectal solution 5 mg/ml	1
	Injection 5 mg/ml	1
Lorazepam	Parenteral solution 2 mg/ml	0.5
	Parenteral solution 4 mg/ml	0.5
Midazolam	Oromucosal solution 5 mg/ml	10
	Oromucosal solution 10 mg/ml	6
	Ampoule 10 mg/ml	6
Abacavir/lamivudine	Cap/tab 120/60 mg	60
Dolutegravir	Cap/tab 10 mg	60
Lopinavir/ritonavir	Cap/tab 40/10 mg	120
	Cap/tab 100/25 mg	60
Ferrous salt	Cap/tab 60 mg	28
	Cap/tab 200 mg	14
	Oral liquid 25 mg/ml	56
Albendazole	Cap/tab 200 mg	2
	Cap/tab 400 mg	1
Mebendazole	Cap/tab 100 mg	6
Artemether/lumefantrine	Cap/tab 20/120 mg	6
Artesunate/amodiaquine	Cap/tab 25/67.5 mg	6
	Cap/tab 50/135 mg	3
Artesunate/mefloquine	Cap/tab 25/55 mg	6
Dihydroartemisinin/piperaquine	Cap/tab 20/160 mg	6

	Cap/tab 20/320 mg	3
Artesunate/Sulfadoxine-pyrimethamine	Cap/tab 50/500/25 mg	1
	Cap/tab 500/25 mg (sulfadoxine-pyrimethamine)	1
Chloroquine	Cap/tab 100 mg	5
	Oral liquid 50 mg/5 ml	30
Artesunate	Cap/tab 50 mg	3
	Suppository 50 mg	3
Retinol	Cap/tab 25,000 IU	4
	Cap/tab 100,000 IU	2
	Cap/tab 200,000 IU	2
Paracetamol	Cap/tab 100 mg	150
	Suppository 100 mg	150
	Suspension 120 or 125 mg/5 ml	900
Morphine	Cap/tab (slow release) 10 mg	60
	Injection 10 mg/ampoule	30
	Oral liquid 10 mg/5 ml	300
Ibuprofen	Cap/tab 200 mg	90
	Oral liquid 200 mg/5 ml	180
Ethambutol + isoniazid + pyrazinamide + rifampicin	Cap/tab 100 mg (ethambutol)	60
	Cap/tab 400 mg (ethambutol)	30
	Oral liquid 25 mg/ml (ethambutol)	9
	Cap/tab 50/150/75 mg (isoniazid + pyrazinamide + rifampicin)	60
Amoxicillin	Cap/tab 250 mg	20
	Cap/tab 500 mg	10
	Powder for injection 250 mg/vial	20
	Powder for injection 500 mg/vial	10
	Powder for injection 1 g/vial	5
	Suspension 125 mg/5 ml	100
	Suspension 250 mg/5 ml	90
Amoxicillin + clavulanic acid	Cap/tab 100/125 mg	30
	Cap/tab 250/125 mg	15
	Cap/tab 500/125 mg	15
	Powder for injection 500/100 mg/vial	8
	Oral liquid 125/53.25 mg/5 ml	135
	Oral liquid 250/62.5 mg/5 ml	60
Ampicillin	Cap/tab 250 mg	40
	Cap/tab 500 mg	20
	Injection 500 mg/vial	20
	Injection 1 g/vial	10
Benzylpenicillin	Injection 1 MIU/vial	5
Gentamicin	Injection 10 mg/ml	40
	Injection 40 mg/ml	10
Ceftriaxone	Injection 250 mg/vial	28
	Injection 500 mg/vial	14
	Injection 1 g/vial	7
Cefotaxime	Injection 1 g/vial	18
Procaine benzylpenicillin	Injection 1 MIU/vial	10

Annex 3

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

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

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

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

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

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

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

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

In which 1 = available and 0 = not available.

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

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

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

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

The price of a daily dose is then calculated as:

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

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

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

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

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

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

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

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

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

In which 1 = affordable and 0 = not affordable. Affordability cannot be computed for medicines without price data.

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

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

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

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

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

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

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

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

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

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

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

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

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

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