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Evidence Update

Medicines for children: Rationale and recent advances

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The World Health Organization (WHO) recently published the 20th essential medicine list (EML) and the 6th essential medicine list for children (EMLc) [1]. The WHO Model List of Essential Medicines was first published in 1977 and has been updated regularly every 2 years. However, for about 30 long years, until 2007 when the first EMLc was published, the needs of children were neglected in the WHO model EML. Until recently, the same laxity towards paediatric medicines prevailed among pharmaceutical industries and regulatory bodies as well. In fact, around 80% of the medicines approved by the Food and Drug Administration (FDA), USA, between 1965 and 1995 did not have paediatric labelling as pharmaceutical industries conveniently excluded children from clinical trials and did not seek paediatric license even for medicines which had potential use in children [2,3,4,5]. This prompted Dr Harry Shirkey, in 1968, to refer or name children as "therapeutic orphans" [6]. This neglect occurred despite the realization, almost 100 years ago, that children are not small adults. Dr. Abraham Jacobi (1830-1919), the father of American paediatrics, argued that "Pediatrics does not deal with miniature men and women with reduced doses and the same class of disease in smaller bodies but . . . has its own independent range and horizon" [7].

In this backdrop, pioneers in paediatric clinical pharmacology started to demand that children have the right to medicines fulfilling the same criteria for quality, safety and efficacy as required by adult medicines and to enjoy the benefits of modern drug development [8,9,10] In addition, it was highlighted that children have the right to get their medicines in age appropriate doses and formulations [11,12,13]. However, one would always wonder whether children are not half adults and could not they be managed with medicines meant for adults? Children are not half adults [12,14]: They respond to (pharmacodynamics) and handle (pharmacokinetics) medicines differently. In addition, dose, dosage form and administration of medicines should be tailored to their age, body weight, structure and function [11,12,15] It is beyond the scope of this update to discuss in detail the differences in pharmacokinetic profiles between children and adults.

Table 1 presents some key differences and Table 2 shows the age at which key physiological parameters related to pharmacokinetics reach adult values.

Table 1. A few examples of differences in pharmacokinetic profiles between children and adults [12,16,17,18]

Difference	Affected medicines	Mechanism
Gastric pH is relatively high during neonatal period	Acid labile medicines (e.g. erythromycin, ampicillin amoxicillin)	Increased bioavailability
	Weak bases	Increased bioavailability
	Weak acids (e.g. phenytoin)	Reduced bioavailability
Increased gastric emptying and shorter intestinal transit time in neonates and young infants	All medicines given by mouth Poorly soluble and sustained release products are more affected (e.g. theophylline)	Slow rate of absorption and time required to achieve maximal plasma levels is prolonged
Decreased plasma protein in newborns and early infancy	Highly protein bound drugs (95% or more) (e.g. phenytoin, salicylates, ampicillin)	Increased free fraction. Increased effect and interferes with drug level monitoring
1. Increased hepatic blood flow due to larger liver relative to body mass 2. Ontogeny of cytochrome enzymes (mainly CYP3A4 and CYP1A2)	Highly metabolized drugs (e.g. carbamazepine, valproate, theophylline, caffeine)	Increased hepatic clearance and higher weight adjusted doses
Ontogeny of liver enzymes (delayed maturation of the enzymes)	Drugs metabolism by specific pathways e.g. UDP glucuronoyltransferase – chloramphenicol, morphine	Decreased metabolism of chloramphenicol in neonates, especially premature ones (reduced mg/kg dose)
Ontogeny of renal tubular transport mechanisms.	Loading dose decreases with age. e.g. relative digoxin resistance in infants and pre-school children	Digoxin is extensively secreted via P-gp within the tubular cell in infants and pre-school children
Larger relative size of kidneys	Drugs which are excreted unchanged in urine (levetiracetam, certirizine)	Increased renal clearance
Delayed maturation of glomerualr filtration rate	Drugs which are excreted primarily by the glomeruli (famotidine, aminoglycosides, ceftazidime)	Reduced renal clearance

Table 2. Age at which key physiological parameters related to pharmacokinetics reach adult levels [12,16,61,62]

Physiological parameter	Age at which it reaches adult levels *
Gastric pH	2 – 3 years
Gastric emptying	6-8 months
Intestinal colonization	1- 4 years
Passive and active transport in the gastrointestinal tract.	4 months
Hepatic blood flow	1 year
Expressing CYP3A in the duodenum	6 -18 months
Plasma protein levels	1 year
Hepatic Phase 1 metabolism	6 months – 3 years 1. Some reach adult levels at 10-12 years 2. Some fluctuate during childhood **
Hepatic Phase II metabolism	3 years (some reach adult values at 10 years)
Glomerular filtration rate	1-2 year

**: These ages are not uniform in the literature. This Table gives the approximate range*
***: CYP1A2 (theophylline and caffeine are principally metabolized by this enzyme) activity is 50% of adult values in neonates, 50% greater than adult values by 5 years of age and decreases to adult values by 15 years* (63)

Globally, many initiatives continue to take place to improve the status of paediatric medicines. These initiatives are strong, sustainable, integrated and multidisciplinary, covering major dimensions in paediatric medicines such as legislation, regulation, expertise development, information resources, research, education and training, prescribing and dispensing standards, formulations, access and rational use. This update summarizes recent developments related to a few key areas in paediatric medicines namely (i) obtaining paediatric data for medicines, (ii) issues related to dose determination for children, (iii) recent paradigm shifts in paediatric oral formulations and (iv) administering medicines to children.

Obtaining paediatric data for medicines

Marketing authorization for a new medicine is given only after the regulatory authorities evaluate clinical trial data on safety, efficacy and quality. For many years, only adults enjoyed this privilege whilst children remained therapeutic orphans as many marketed medicines that are commonly used, or could potentially be used, in children did not have paediatric data [9,19]. Regulatory authorities avoided giving a license for paediatric use and consequently, clinicians were compelled to use the adult-tested medicines in children as "off-label" [9,19]. This differential attitude towards children led the United States in 1997 to bring in strong legislation to address paediatric needs and to generate paediatric data for medicines [20,21,22] This was followed in 2007, by the European Union's Paediatric Regulation [20,23,24] and the World Health Assembly's adoption of resolution WHA 60.20 which called for better medicines for children in the same year [20,25].

Both US and EU regulations target pharmaceutical industries which have been evading the responsibility of providing paediatric data for many years. For on-patent medicines there is a requirement part with a reward whereas for off-patent medicines there is a voluntary part and incentive for paediatric medicine development. Pharmaceutical industries should submit data from paediatric studies (paediatric data) to regulatory

authorities for appraisal of market authorization or label change to be eligible for the reward or incentive. The reward/incentive in this case where the medicine is still under intellectual property protection is chiefly a 6-month patent protection which is of great benefit to industry in terms of profit and reputation. For off-patent medicines which are not under intellectual property protection providing paediatric data is voluntary: data protection and some form of public funding for studies are offered as incentives [20,21,22,23,24,25,26,27].

Ten years after adopting paediatric regulations, the European Medicines Agency (EMA) has reported many successes, including (i) more medicines for children (new medicines for paediatric use=238, new paediatric pharmaceutical forms=39), (ii) better information on use of medicines in children (e.g. 89 additions of dosing information in the first 5 year period with a total of 248 changes related to paediatric use in the 10 year period) and (iii) ethical and high quality paediatric research (e.g. number of trials involving neonates increased from 9.3% to 11.5%, with no delays in adult medicines or unnecessary studies in children [28,29].

The FDA implemented similar paediatric regulations about 10 years prior to the European Union and produced promising results in terms of paediatric data for medicines. During the period between September 2007 and September 2010, 305 studies recruiting over 111,000 paediatric patients were concluded. In addition, paediatric studies resulted in over 350 labelling changes by early 2010 [20,30]. These labelling changes included dosing changes, new pharmacokinetic data, new safety data, data about lack of efficacy in some conditions, expansion of age-range of on-label use and new formulations. Interestingly, of the 16 pharmacokinetic studies in children, 9 studies on medicines that were in use for several years, showed that the 'expected' clearance, based on body weight was inaccurate [31]. Similar regulatory changes are taking place in other developed countries as well. However, the fruits of these paediatric regulations will take long time to reach the children of resource limited settings (RLS). In addition, evidence has emerged that results from clinical trials done in RLSs to satisfy the regulatory framework of developed counties (especially the FDA) often do not benefit the children in the RLS in which the trials were largely conducted. In the absence of financial incentives, the pharmaceutical industry generally ignores the children from RLS, who carried the burden to provide the much needed paediatric data, to get marketing approval in developed countries [20,32].

The 2007 World Health Assembly resolution on "Better Medicines for Children" addresses some key issues related to paediatric medicines in RLSs. The resolution urged WHO Member States and the WHO "*to undertake many activities, such as improving paediatric medicines research, regulation, access and rational use*" and *"to promote access to essential medicines for children through inclusion, as appropriate, of those medicines in national medicine lists, procurement and reimbursement schemes and to devise measures to monitor prices".* This prompted the WHO to publish the first Model EMLc in 2007. This list is updated every two years and the 6th revision was published in 2017. Every revision incorporates some important new paediatric medicines or introduction of new dosage forms or dose revisions.

Details of the selection of these essential medicines and all six versions of EMLccan be accessed at http://www.who.int/medicines/publications/essentialmedicines/en/.

Paediatric dose determination

Safe and effective use of medicines in children is not restricted to availability of paediatric data but also expands to include safe administration of medicines. Accurate dose determination and correct administration are two essential prerequisites for safe administration of medicines to children, for which we need data on age-specific dose, dosage form/formulation and measuring device. For many years, most of these data had been either extrapolated from adult studies or derived from experience. However, evidence emerging from recent paediatric studies challenges these practices [12,33,34]. For example, a paediatric dose is traditionally based on body weight. This paradigm is challenged now [33,34,35] Adjusting paediatric doses based on any demographic covariate is questioned as there is lack of evidence on how these factors affect drug exposure in children [36]. Continuing this practice with lack of evidence always runs the risk of administering unsafe or ineffective paediatric doses.

The rationale for dose adjustment in the paediatric population is based on factors which differentiate drug exposure in children from that of adults, namely pharmacokinetics, pharmacodynamics and disease spectrum. However, none of these parameters change proportionally with age, weight or even body surface area [34,36]. Thus, the relationship between these demographic covariates and dose cannot always be linear. Hence scaling paediatric dose based on these factors would lead to either underdose or overdose. This is critical for medicines with a narrow therapeutic index and medicines which exhibit steep dose-response curves. Potential sources of pharmacokinetic differences in the paediatric population include age, gender, body-composition, concentration of plasma proteins, liver blood flow, liver function, glomerular filtration rate and, most importantly, ontogeny (development and maturation of metabolic pathways) [34,36]. The latter four factors have a significant influence on drug elimination which is the important pharmacokinetic component which determines drug exposure*. Ontogeny is unrelated to body weight or even age. Each enzyme system follows its unique phenotype with varying times of onset and maturation.

Paediatric pharmacokinetic experts currently maintain that “size itself may not be a surrogate for developmental growth”. Hence, when calculating paediatric doses, scaling had to be for function, not for size [35]. So, it is highly recommended that (i) for medicines already on the market, pharmacokinetic studies/ reviews be encouraged and paediatric doses re-visited and (ii) for new medicines, paediatric doses should be scaled for function during the early drug development phase itself. For example, in 2010, the WHO revised and increased the recommended dosages for rifampicin, isoniazid and pyrazinamide following a review of toxicity and pharmacokinetics data. Previously recommended doses gave rise to relatively lower peak serum levels which was more apparent in infants, young children and HIV infected children [37,38]. Table 3 gives some examples where there is no linear relationship between paediatric dose and body weight.

Table 3. Some examples where there is no linear relationship between paediatric dose and body weight [36]

Drug	Indication	Adult dose	Paediatric dose
Chloramphenicol	Bacterial infection	50 mg/kg/day	50 mg/kg/day neonates: 25 mg/ kg/day
Carbamazepine	Epilepsy	5–8 mg/kg Every 12 h	>12 years: 5–8 mg/ kg every 12 h Children: 3–10 mg/ kg every 8 h Infants: 3–10 mg /kg every 8 h
Phenytoin	Epilepsy	2 mg/ kg Every 12 h	Children: 2.3–2.6 mg/kg every 8 h Infants: 2.3 mg/ kg every 8 h Neonates: 2.5–4.0 mg/ kg every 12 h
Oseltamivir	Influenza	150 mg/day	<15 kg: 60 mg/day 15–23 kg: 90 mg/day 23–40 kg: 120 mg/ day
Digoxin	Heart failure	1.4–4.0 µg/kg/day	Children: 3–8 µg/kg/day Infants: 7.5–12 µg/kg/day Neonates: 4-8 µg/kg/day

*"*Drug exposure is a function of the concentration of drug in the body, and usually levels in the blood/plasma/serum with respect to time, serve as surrogates" [39]. "Response is a measure of effect and can relate to both advantageous (efficacy) and untoward (toxic) reactions*" [39].

Recent paradigm shift in paediatric oral formulations

Even if we manage to get the dose correct, delivering the accurate dose to children depends on having a suitable formulation / dosage form and dosing device. Hence, evidence is emerging on suitable formulations and dosing devices (for liquid formulations) as well. In September 2016, the Ceylon Medical Journal published a leading article on paediatric oral formulations, authored by Professor Kalle Hoppe, one of the pioneers in paediatric clinical pharmacology (40). It was an excellent, timely article which should be instrumental in improving availability of child friendly formulations in Sri Lanka. Key issues highlighted in that article are summarized in this update. Though, developmental changes in children are known to affect the absorption of drugs from other routes of administration as well [12,16]. this update is limited only to oral dosage forms. Traditionally, liquid formulations, namely syrups and suspensions, are favored for paediatric oral use. However, many problems are recognized with these formulations, some of which are particularly relevant to RLSs [32,40]. Such problems include (i) expensive manufacturing processes (ii) difficulty in taste masking (iii) logistics of transport and storage (iv) requirement of refrigerator to store the reconstituted suspension (v) requirement of clean water to reconstitute dry powders (vi) the necessity to have more excipients, some of which may be not suitable for children and (vii) poor stability in a tropical climate. Moving to solid oral paediatric formulations (flexible solid oral dosage forms) appears to be the most sensible solution to address the above problems. Such alternative flexible solid oral dosage forms include multiparticulate formulations (minitablets, sprinkles and granules), orodispersible formulations (orodispersible minitablets, disintegrating tablets, oral strips, buccal wafers, medicated lollipops) and dispersible tablets [40,41,42,43].

These solid platform technology-based formulations can be manufactured in slow release forms as well, which allows less frequent dosing. Studies have documented the acceptability, swallowability, palatability and accuracy of the dose delivery and bioavailability of these flexible solid oral dosage forms for children [40,45]. Most of them retain the advantages of traditional solid oral dosage forms (tablets and capsules), like stability, taste masking and ease of transport and require no manipulation in the field. At present, oral dispersible dosage forms {mini-tablets (diameter = 2-5 mm) and tablets} appear to be the best option. Table 4 lists some of these dosage forms and their advantages and limitations.

Table 4. Different oral dosage forms with their advantages and limitations [40,41,42,43]

Dosage form	Advantages	Limitations
Liquids (Syrups, suspensions)	1. Traditionally used 2. Relatively cheap 3. Available for many medicines 4. Preferred	1. Stability issues 2. Dose delivery could be inaccurate 3. Need safe water 4. Suspension: boiled cool water, refrigerators 5. Large volume 6. Logistics 7. Need many excipients
Fixed Solids (Tablets, capsules)	1. Traditionally used 2. Preferred 3. Taste masking possible 4. Less expensive 5. Stability satisfactory 6. Easy transport and store	1. Rigid dose content 2. Requires pill swallowing ability 3. Safe water (adult= 250 ml) 4. Manipulating to suit the children has many issues
Tablets for oral suspension/solution (Dispersible tablets)	1. Retain the stability of solid oral dosage forms 2. Single dose reconstitution at the time of administration 3. Easy to transport, store 4. Not taste adverse 5. Alternative for pill swallowing	1. Large volume of fluid required for reconstitution (up to 20 ml < 4 yrs, up to 40 ml for children > 4 yrs) 2. Safe water required 3. Clear instructions required 4. If not dissolved in adequate volume of water, local tissue injury and delay in onset of action 5. Fixed dose, unable to split or cut
Mini tablets	1. Enhanced stability 2. User satisfaction documented 3. Even for 6 -12 months infant 4. No dose manipulation required 5. Sustained release option	1. Risk of choking 2. Multiple tablets per dose 3. Accidental overdose 4. May be expensive
Orodispersible formulations (disintegrating tablets, oral strips, medicated lollipops)	1. No external liquid needed 2. Not taste adverse 3. Easy to administer 4. Alternative for pill swallowing 5. Stability satisfactory	1. Single strength 2. Unable to split or cut 3. Require a moist palate 4. Risk of rapid absorption with potential toxic levels 5. Bioavailability should not be affected even if swallowed whole 6. Suited to highly soluble drugs (but taste masking is difficult)
Powders or multi-particulate systems (powders, granules, pellets or sprinkles for reconstitution)	1. Stability satisfactory 2. Easy transport and store 3. Can be used in neonates and seriously ill child	1. Water / food required 2. Safe water required 3. Mixing with food may affect bioavailability 4. Taste masking required 5. Relatively expensive
Chewing tablets	1. Stability satisfactory 2. Easy transport and store 3. Not taste adverse 4. Alternative for pill swallowing	1. Older than 2 years 2. Single strength 3. Dose rigidity 4. Unable to split or cut

Kalle has concluded that, "It is time we adults start to listen to children and accept that flexible solid oral dosage forms are the new paradigm of first choice for developing, procuring, prescribing and demanding medicines for children". Despite this evidence based recommendations, most medicines are given to children in Sri Lanka either as liquid formulations or by manipulating adult dosage forms [32,55]. Both are far from ideal. In addition to the problems listed above inaccurate dose delivery via these formulations could be a problem, mainly for medicines with a narrow therapeutic index and medicines which need constant steady state concentrations. Doctors caring for children and professional bodies should demand the Medical Supplies Division and the regulatory authority to register, procure and supply these child friendly dosage forms. Studies must be done in Sri Lanka to generate local data for these dosage forms. Prescribers, parents, pharmacists, nurses and other healthcare professionals should be sensitized about this paradigm shift.

Administering the right dose

Getting the accurate dose from oral liquid formulations largely depends on the caregiver's ability to measure and administer the prescribed volume. Droppers, dosing cups, oral syringes and dosing spoons are commonly used but other devices such as domestic spoons, drinking cups, etc. are also often used by parents [46]. Oral dosing syringes have shown to be the most suitable measuring device to deliver an accurate dose [47,48]. Regulatory authorities in developed countries (FDA, EMA, etc.) provide guidance to manufacturers on dosage delivery devices for liquid medicines, initially for over the counter (OTC) products [48] and later for prescription medicines [49]. They recommend that the manufacturer should supply a dosing device suitable to administer the prescribed single dose. If such a dose is other than multiples of 5mL, the dosing device cannot be a routine dosing spoon. Both these documents provide only guidance to the pharmaceutical industry and do not establish legally enforceable responsibilities [48,49]. For the last 15 years or so, there is a call to make this requirement mandatory for all liquid medicines (OTC and prescription) [50,51]. Studies have reported that provision of a suitably calibrated measuring device is now commonly seen with OTC liquid medicines but not for all prescription medicines, even in developed countries [52,53].

In Sri Lanka, oral liquid medicines are mostly provided with 5ml measuring spoons or cups. However, as per emerging evidence, the accuracy of dose delivery via these traditional measuring devices has been queried, even if they have dividing lines for smaller volumes. Pharmacists, themselves, have measured the dose incorrectly when using these dosing spoons [54]. Children in Sri Lanka continue to receive adult strength fixed solid dosage forms (tablets and capsules) which require manipulation before administration [55]. This may happen in the form of tablet splitting, tablet splitting and dissolving in various liquids tablet crushing and dissolving in various liquids or opening the capsules and administering the powder directly or after mixing with food or drink [32,55]. This is an irrational practice and exposes the child to many risks [43,56,57,58,59]. For example, (i) inaccurate splitting of tablets could lead to dose fluctuations. Even commercial tablet cutters have been shown to be unreliable and

inaccurate in segmenting tablets, (ii) increased degradation when broken edges are exposed to air, compromising the stability of the active ingredient, (iii) poor taste, especially when the taste masking coating is removed while splitting/ crushing, (iv) alterations in the dissolution rate of some formulations, (v) physicochemical interaction between the drug, solvent, container and mixing/splitting devices can severely influence the bioavailability of these manipulated mixtures, (vi) some type of tablets should not be split. Examples include un-scored tablets, film coated tablets, enteric coated tablets, thick/odd shaped tablets, and some extended release tablets, (vii) some tablets are difficult to break into two equal halves despite having a score line. Even pharmacists have failed to do so resulting in variability of dose in the two halves and (viii) after splitting, the balance half may not be stable and could melt before the next dose. This happens because the cut surface is exposed to air. This could be a problem especially when pharmacists pre-cut and dispense doses for a week or more in advance.

Despite the efforts taken to manufacture and supply medicines in suitable dosage forms for children, extemporaneously prepared products are still required to ensure accurate and effective doses of some medicines even in developed countries. An extemporaneous preparation is defined as a product which is dispensed immediately after preparation and not kept in stock [60]. It involves modifications to commercially manufactured products such as the preparation of suspension or powders from tablets or the preparation of a product from the individual raw materials. It should be done in a hospital or community pharmacy. Splitting solid forms or dissolving or crushing tablets performed by parents at home or nurses in the ward is not extemporaneous preparation. The extemporaneous preparation of a liquid medicine from a solid dose form in a hospital or community pharmacy should generally be considered as a last resort, in the absence of alternatives which would assure better effectiveness and safely. For successful extemporaneous preparations, pharmacies should have adequate facilities, pharmacists should be specially trained, standard operational procedures(SOP) should be developed for each product, adherence to SOP should be enforced, products should be clearly labeled and parents should be given proper instructions.

"Children are often hailed as the hope and future of humanity, but they don't benefit enough from pharmaceutical research and technology. Too often, the right medicines for children in the right dosages and formulation are missing from the spectrum of available treatment options". Dr. Howard Zucker, Assistant Director General at World Health Organization, 2006 [43].

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