Chapter 20
Rational Use of Medicines (RUM) for Children in the Developing World: Current Status, Key Challenges and Potential Solutions

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Introduction

Case 20.1
A 3-year-old boy presented to a private clinic near his village with wheezing for 1 day. He has a past history of infrequent episodic asthma since 2 years of age, with acute exacerbations responding well to inhaled salbutamol given at a nearby public hospital. Due to concerns about long waiting times there and worry about more severe wheezing with the current episode, his mother took him to a closer private clinic on this occasion. The child was seen by a doctor for only a few minutes and given a prescription for medicines that his mother was instructed to purchase from the pharmacy located within the clinic. While in the waiting room, she noticed many advertisements for various medicines (e.g. posters, stationery, desk accessories, water cooler) and a number of well dressed adults with briefcases and no accompanying children also waiting to see the doctor.

The child was not given any inhaled bronchodilator treatment, although his mother enquired about this. The prescribed medicines were very expensive, necessitating a loan from a neighbour in order to be able to purchase them. Despite taking the prescribed medicines, the child's wheezing continued and he also developed diarrhoea; he was afebrile and had no vomiting or other

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symptoms. He was seen again at the clinic by the same doctor and prescribed additional expensive medicines.

On the 3rd day of illness, the child was admitted to the nearby public hospital with continuing wheezing, diarrhoea and some dehydration. He was treated with nebulised salbutamol and oral rehydration solution, with full recovery within 3 days. It was later established that the expensive medicines he had been prescribed at the clinic were: brand cefuroxime axetil, brand azithromycin, salbutamol, theophylline, montelukast and loratadine.

Case 20.2

A 2-year-old girl was diagnosed with epilepsy by a paediatric neurologist at a tertiary care public hospital. She is the fifth child in a family with very low income. The paediatric neurologist prescribed carbamazepine liquid, 50 mg per dose. Liquid carbamazepine was not available in the hospital pharmacy so the pharmacist dispensed carbamazepine 200 mg tablets instead, instructing the child's mother to give a quarter of a tablet for each dose. The child refused to take this medicine, despite her mother's various attempts at crushing or dissolving the tablet and hiding the medicine in honey, milk, water or various foods. It was also very difficult to break the tablets into four equal pieces. In desperation, the child's father went to a nearby community pharmacy to look for carbamazepine syrup. While this pharmacy did have syrup available, the cost was too high and completely unaffordable for the family. They persisted with the tablets, despite the challenges of inaccurate and variable dosing due to problems with this formulation for such a young child. As a result, her epilepsy was uncontrolled and she was admitted to hospital with status epilepticus within 6 months of initial diagnosis.

Rational Use of Medicines (RUM) means that patients receive medicines appropriate to their needs in doses that meet their individual requirements, for an adequate period of time and at the lowest cost to them and their community [1]. Irrational (inappropriate, improper, incorrect) use of medicines occurs when one or more of these conditions is not met, and is a widespread phenomenon worldwide [2].

Another term used to describe a similar concept is Quality Use of Medicines (QUM), which means judicious selection of treatment options (including choice between medicine, non-medicine and no treatment); appropriate choice of suitable medicines if a medicine is considered necessary; and safe and effective use of medicines [3].

In Australia, QUM forms one of the four key objectives of the country's National Medicines Policy (NMP), which acknowledges its interdependence with the other

three objectives, namely: (1) timely access to needed medicines, at a cost individuals and the community can afford; (2) medicines meeting appropriate standards of quality, safety and efficacy; and (3) responsible and viable medicines industry. The NMP recognises that providing access to medicines without having strategies in place to ensure they are used appropriately is not sensible. It also acknowledges that it is not possible to achieve QUM if effective and safe medicines are not available, or not accessible to those who need them because they are unaffordable [4]. These principles are particularly pertinent also to low- and middle-income country (LMIC) settings where there's an even stronger imperative to ensure that scarce financial resources are used wisely to deliver optimal value in improving health outcomes of LMIC populations.

Recently, the term Responsible Use of Medicines has been proposed to widen the concept of RUM. It implies that the activities, capabilities and existing resources of health system stakeholders are aligned to ensure patients receive the right medicines at the right time, use them appropriately and benefit from them [5].

These definitions and concepts are applicable to decision-making about medicines use at an individual and a population level, in both developed and developing world settings. The wider concepts also acknowledge the importance and interdependence of different elements of the health system and the need for their appropriate alignment in order to achieve RUM/QUM. Although there are no paediatric-specific definitions, the key components of an overarching framework to support RUM/QUM specifically in the paediatric population have previously been described [4]. The appropriate application of these general and paediatric-specific principles and frameworks to improve the health of children worldwide also requires specialised paediatric clinical and therapeutics knowledge, understanding and skills to help inform sound decisions, at all levels of the health system, and in all settings.

The cases above illustrate some commonly encountered examples of suboptimal or irrational medication use in children living in the developing world, with multiple contributing factors. This chapter will elaborate further examples to help delineate the current status of RUM for the paediatric population in developing world settings more generally, outline the key challenges for delivering RUM to these children and propose some potential solutions.

Current Status of RUM in Children in the Developing World

Any assessment of the status of RUM in children living in the developing world should optimally be informed by relevant data, specifically from the paediatric population in these settings. However, such data from LMICs are often either lacking or methodologically dissimilar, which means that an evidence-based analysis of the overall status of RUM in the paediatric populations in these settings is currently not possible. Although the World Health Organization (WHO) has published indicators to facilitate uniform assessments of medicines use [6], very few studies from LMIC

settings have focused on children [7–10]. It is also important to note that the WHO indicators are not child focused and lack specificity and sensitivity to ascertain the unique challenges associated with achieving RUM in the paediatric population. In addition, factors specific to LMIC settings (e.g. lack of appropriate financial and human resources, including insufficient paediatric clinical and therapeutics expertise in health care and regulatory settings) contribute to the lack of data preventing an accurate assessment of RUM in children in these settings.

Despite this gap in the current evidence base, anecdotal information from various sources points to some common themes and issues in irrational or suboptimal use of medicines in children in LMIC settings, as outlined in the following section:

Irrational Use of Antibiotics

This includes first and foremost "non-judicious" uses, such as prescribing antibiotics when not indicated, for example, for viral infections, such as acute gastroenteritis or upper respiratory tract infections (as outlined in Case 20.1). A study from Gambia has reported high antibiotic prescription in children with cough and coryzal symptoms and simple diarrhoea without dehydration [7]. This is likely to be a prevalent problem, in view of the high incidence of such infections in the paediatric age group. In situations where an antibiotic may be required for certain bacterial infections, "inappropriate" uses include choosing broad-spectrum instead of narrow-spectrum antibiotics; choosing new (usually more expensive) antibiotics when older (usually cheaper) antibiotics would be appropriate, using the wrong antibiotic or using irrational combinations (as outlined in Case 20.1); and use in ways that are not "safe and effective", such as inappropriate dosage or duration of antibiotics. The wide availability of antibiotics without prescription in many LMIC settings further exacerbates these problems, leading to overuse, inappropriate self-medication and non-adherence to dosing regimens [11].

Not Prescribing Effective Therapy (or Prescribing Ineffective or Suboptimal Therapy)

Less than 60 % of children with acute diarrhoea in developing world settings receive necessary oral rehydration therapy, yet more than 40 % receive unnecessary antibiotics [2]. This issue is also illustrated well by Case 20.1, where simple oral rehydration solution was not prescribed by the clinic doctor, yet several unnecessary, broad- spectrum, expensive antibiotics were prescribed. This child also did not receive appropriate effective therapy (inhaled bronchodilator) for his acute asthma exacerbation at initial presentation. Instead he was given suboptimal therapy with medicines (salbutamol syrup, theophylline syrup) that have an unfavourable benefit:

risk profile compared to available alternatives, resulting in unnecessary morbidity and subsequent hospitalisation which may have been preventable.

Irrational Formulations

Case 20.2 highlights this issue well. Due to the absence of suitable (and affordable) age appropriate formulations, young children who cannot swallow tablets receive some fraction of adult tablets which have been crushed and dissolved in various vehicles. These "home-made recipes" are commonly of inaccurate dose [12], unproven bioavailability and questionable palatability. Alternatively, forcing very small children to swallow large tablets may cause choking and asphyxiation. Four small children died from choking on albendazole tablets during a deworming campaign in Ethiopia in 2007 [13].

Inappropriate Dosing

Paediatric doses should not be extrapolated from adult doses but calculated based on paediatric-specific dosing recommendations (e.g. mg/kg/dose or mg/m^2/dose) and the child's weight, body surface area or age. Accurate weighing scales, calculators and up-to-date paediatric formularies are therefore crucial in prescribing and administering correct doses to children, but may not necessarily be available widely in health care facilities. In addition, the need to perform dose calculations for each child increases the likelihood of dosing errors, particularly where health care staff (doctors, clinical officers, nurses, paramedics and pharmacists) may not have adequate paediatric training. This is an issue in both developed and developing country settings, but may be more pronounced in the latter with overall lower level of fiscal and human resources for health. Dosing errors of tenfold or greater in neonates because of miscalculation or misplacement of the decimal point has been reported [14]. Under-dosing is also a problem [15]. Further, many medicines are only available in large adult strengths leading to inaccurate dosing when they are split or crushed for paediatric use [12].

Misuse or Overuse of Nonprescription Medicines and Micronutrients

Overuse or misuse of cough and cold medicines, unsafe antipyretics and multivitamins is very common, with documented cases of significant morbidity and some deaths associated with such uses [16, 17]. The irrational prescription of

micronutrients is also a well recognised problem in many LMICs, with high rates of such prescriptions (for vitamin C and multivitamins) being reported from Gambia and Nigeria [7, 18].

Additional Problems

Additional problems that have been identified in LMIC settings include: over-use of injections, "self-medication" (of children by their parents or carers) with medicines purchased from the "informal private sector", using "left over" medicines and using "paediatric packets" (puyer) which are parcelled, ground-up and compounded mixtures of on average four different medicines per puyer, as reported from Indonesia [19]. Most of these problems are undocumented. Parents and carers, as well as many health care workers, consider a wide range of suboptimal practices as the norm. These include prescribing antibiotics for any type of fever on the first day; syrups dispensed in polythene bags; dissolving tablets in co-prescribed syrups; giving intravenous preparations via alternative routes (e.g. diazepam, given rectally for convulsions); giving powders where no-one other than the prescriber knows the content; administration of "injections" for "weak" children; over-prescription of oral drops for older children; and non-provision of appropriate advice, leading to parents administering medicines via the wrong route (e.g. nasal drops given orally) or storing incorrectly (e.g. reconstituted suspensions kept at room temperature despite having refrigerators at home); these are problems which are commonly observed, but remain poorly documented and reported due to a multitude of reasons.

Unethical Pharmaceutical Industry Promotional Activities

Although this is a general issue which is globally prevalent, its extent and consequences are amplified in LMIC settings due to relatively weak drug regulatory policies and regulations, corruption, doctors engaging in private practice, shortage of sponsors for medical conferences, poor payment of health professionals working in the public sector, poorly trained health workers in general and non-regulated pharmacies. The paucity of independent medicines information (especially for the paediatric population) is a major problem, which is compounded by health workers' exposure to biased information and industry promotional activities. For example, the main source of "drug information" for doctors in LMIC settings is "medical representatives" from pharmaceutical companies [2, 20]. A combined report from the WHO and Health Action International has provided research evidence that doctors who tend to rely more on promotional materials appear to prescribe less appropriately, prescribe more often and embrace new drugs more quickly [21].

Consequences of Irrational Use of Medicines

The general consequences of irrational use of medicines are multiple, ranging from the emergence of drug resistant microbes, to sacrifice of therapeutic efficacy generally or exposure to harmful effects of medicines (e.g. adverse drug reactions, medication errors, drug interactions) and wastage of limited financial resources (public and private) [11], which is of particular concern for LMICs. In addition, irrational use of medicines in the paediatric population could have further child-specific consequences, which include: (1) impairment of growth and development (e.g. due to suboptimal treatment of epilepsy or other chronic childhood illnesses); (2) preventable deaths (e.g. due to young infants choking on adult tablets); (3) poor quality of life (e.g. due to suboptimal treatment of asthma or other chronic childhood illnesses); (4) general suffering and unhappiness (e.g. due to need to swallow bitter manipulated adult tablets, unnecessary injections, side effects of unnecessary medicines); and (5) learning difficulties (e.g. due to side effects of prescribed medicines or suboptimal treatment of conditions like hypothyroidism or epilepsy).

Key Challenges for Delivering RUM to Children in the Developing World

There are many challenges to achieving RUM in the developing world, generally and with specific challenges for the paediatric population. First, a fundamental problem is the lack of a well coordinated (and appropriately resourced) NMP in many countries. The WHO estimates that less than half of all countries have implemented basic policies to ensure appropriate use of medicines [2]. Furthermore, in countries where general medicines policies exist, explicit policies or programmes are often lacking to systematically identify and address issues specific to the paediatric population. These same countries often fail to systematically engage with relevant paediatric expertise where available. This has many consequences, including a failure of appropriate prioritisation and relevant resourcing to meet important paediatric RUM needs. Paediatric issues often go unconsidered when national RUM programmes are being developed, implemented or evaluated. For example, a recent WHO report provides interesting data on medicines use worldwide in various conditions of high relevance to paediatric RUM (e.g. treatment of acute respiratory infection and acute diarrhoea) but the report does not present any analysis of trends specifically in the paediatric population [2]. Usage patterns (and outcomes) in the paediatric population may be different to those in the general population and may require specific and specially tailored interventions. However, these issues are not being routinely captured by currently available monitoring systems, leaving a critical knowledge gap.

Second, additional special challenges for the paediatric population are that some of the key underpinnings of RUM, such as availability of, and timely/affordable access to medicines meeting appropriate standards of quality, safety and efficacy and addressing priority child health needs are missing. While these issues are relevant worldwide, the effects are magnified for children in the developing world, primarily due to significant limitations in resources (human and financial) and lack of relevant infrastructure and systems. Major global initiatives have been under way in recent years to address the need for better paediatric medicines research, regulation and access to needed medicines [4, 22]. These exciting developments will hopefully lead to future improvements in such key underpinnings for RUM in children worldwide. However, there are additional challenges for achieving RUM in the developing world even when these important underlying gaps have been addressed. These relate broadly to lack of appropriate paediatric-specific medicines information, lack of appropriate skills and knowledge relevant to RUM at a number of levels (e.g. health care workers, parents and carers and policy makers), lack of practical tools and presence of perverse financial incentives, as outlined in the following Box 20.1.

Box 20.1 Key Challenges for Achieving RUM in Paediatric LMIC Populations

1. Lack of paediatric-specific information	Independent, balanced, evidence-based and regularly updated information about the efficacy and safety (including safe/effective doses); comparative effectiveness/safety; and cost effectiveness of medicines for use in the paediatric population is not widely available.
To inform decisions about medicines use	More ready access (by health care workers, parents/carers, health administrators and policy makers) to biased information and exposure to unethical promotional activities by the pharmaceutical industry compounds this problem.
	Most prescribers in LMICs get medicines information from pharmaceutical industry sources rather than through independent sources, often leading to over-use [11]. Some LMICs also allow direct-to-consumer advertising of prescription medicines, which may lead to patients pressuring doctors for inappropriate prescriptions [11].
	Lack of differentiation of paediatric-specific information needs in these types of sources is likely to have additional important, though currently unknown or undocumented consequences.
To evaluate and monitor medicines use and outcomes	Relevant information to adequately identify, define and describe paediatric-specific RUM issues and inform RUM activities in LMIC settings is lacking.
	Contributing factors include: lack of appropriately validated tools (particularly those with applicability to the paediatric population); limited political and financial commitment and lack of awareness of the value of monitoring medicines use and outcomes; lack of appropriate incentives; limited workforce capacity and skills to appropriately design, conduct, analyse, interpret and communicate relevant information.

2. Lack of paediatric-specific skills and knowledge	Using medicines judiciously, appropriately, safely and effectively in the paediatric population requires awareness of special issues and considerations relevant to this group both as a whole and for specific age groups within it.
	Many health care workers in LMICs involved in prescribing, dispensing and administering medicines to children lack basic awareness of these issues and core competencies (knowledge, skills and behaviour) relevant to paediatric RUM. This is a major gap and is also shared by other key groups such as parents/carers and policy makers.
	These issues are also common to the developed world setting, but their impacts may be greater in the developing world due to the overall lower level of resourcing and absence of appropriate systems and processes to support RUM.
	The virtual nonexistence of expertise in paediatric clinical pharmacology/therapeutics and paediatric pharmacy in most LMICs presents major challenges, with direct and indirect consequences, including lack of capacity to appropriately educate and inform health care workers, policy makers and parents/carers at country level.
3. Lack of practical tools	Absence of weighing scales in many settings prevents the calculation of an appropriate dose using an accurate weight (see Chap. 4).
	Lack of electronic calculators impedes consistently accurate dose calculation.
	Absence of suitable measuring devices for oral liquid medicines or tablet splitters in many settings prevents accurate administration of the prescribed dose.
4. Presence of perverse financial incentives	In many LMICs drug retailers prescribe and sell medicines over-the-counter.
	Health insurance is virtually nonexistent in many LMICs and health care providers derive part of their income from selling medicines from their own pharmacies (as illustrated by Case 20.1). Over-use of medicines, especially more expensive ones, is therefore often driven by the objectives of income generation rather than RUM [11].
	While these are important general challenges for RUM in LMIC settings, any potentially differential impact unique to the paediatric population is difficult to estimate.

Potential Solutions

The WHO has proposed 12 core interventions to improve RUM worldwide [23]. In addition, the World Health Assembly's (WHA's) historic resolution 60.20 on "Better Medicines for Children" urges member states to facilitate "rational use" of medicines in the paediatric population, amongst a range of recommendations to promote appropriate paediatric medicines research, regulation and access to essential medicines in child-friendly formulations, to optimally support RUM. While there has been much-needed attention paid to the latter needs globally, with significant

Box 20.2 Recommendations for national policies to encourage or ensure more appropriate use of medicines in the paediatric population

General WHO recommendations [23]	Proposed paediatric-specific recommendations
"Establishing a mandated multidisciplinary national body to coordinate policies on medicines use and monitor impact"	The mandated multidisciplinary national body should have (or engage with) specialised expertise in paediatric medicines and therapeutics to appropriately inform policies with respect to issues relevant to the paediatric population
	Any paediatric-specific priority medicines use issues that are identified for coordinated national action should be appropriately resourced (with dedicated human and financial resources) and evaluated
"Formulating and using evidence-based clinical guidelines or standard treatment guidelines (STGs) for training, supervision and supporting critical decision-making about medicines"	Paediatric expertise (in clinical medicine and therapeutics) should be involved when developing clinical guidelines or STGs for conditions common to adult and paediatric populations.
	Priority health conditions (or medicines issues) that are specific to the paediatric population should have paediatric-specific STGs developed
	Strategies promoting use of STGs (e.g. for training, supervision and supporting critical decision-making) should be tailored to address paediatric-specific needs
"Selecting, on the basis of treatments of choice, lists of essential medicines (EMLs) that are used in medicine procurement and insurance reimbursement"	The WHO Essential Medicines List for children (EMLc) should be used to inform medicine procurement and insurance reimbursement decisions routinely
"Setting up drug (medicine) and therapeutics committees (DTCs) in districts and hospitals to improve the use of medicines"	Paediatric expertise (in clinical medicine and therapeutics) should inform key decisions of district or hospital DTCs in issues relevant to the paediatric population
	Paediatric-focused national or regional DTCs would enable optimal use of the limited specialised paediatric expertise and resources available
	International collaboration (with sharing of paediatric-specific information and expertise) could support these national or regional DTCs

"Promoting problem-based training in pharmacotherapy in undergraduate curricula"	Paediatric focused educational resources to support appropriate training in paediatric pharmacotherapy should be developed and used
	International collaboration should support the development of new and adaptation of existing high quality educational resources (e.g. from developed world settings)
	Training programmes for integrated teaching of health care students (medical, pharmacy, nursing and other) in paediatric pharmacotherapy should be developed and widely implemented
"Making continuing in-service medical education a requirement of licensure"	CME requirements for all health care workers (medical, pharmacy, nursing and other) should address core competencies (knowledge, skills, behaviour) in paediatric pharmacotherapy
"Promoting systems of supervision, audit and feedback in institutional settings"	Paediatric expertise and tools should be used to support systems of supervision
	Audit and feedback systems should collect and disseminate paediatric-focused data on medicines use and outcomes
	Feedback systems should systematically identify and communicate with relevant health workers involved in paediatric pharmacotherapy
"Providing independent information (including comparative data) about medicines"	Independent, balanced and regularly updated evidence-based medicines information (about prescription and nonprescription medicines) for the paediatric population should be provided for all health care workers and the public
	This information should include data on efficacy, safety, appropriate dose and dosage forms for relevant age groups
	Age-specific information should be provided about the comparative effectiveness/safety and cost-effectiveness of medicines for their intended use in the relevant paediatric population
	Decisions about newly marketed medicines should be optimised with access to this information
	International collaboration to develop a globally relevant paediatric medicines compendium (and therapeutic guidelines) which is regularly reviewed, updated and made available to all health workers caring for children could address these needs
"Promoting public education about medicines"	Educational programs focused specifically on the needs of parents/carers of young children and on the medicines education (and health literacy) needs of older children should be developed and systematically implemented

"Eliminating perverse financial incentives that lead to irrational prescribing"	
"Drawing up and enforcing appropriate regulation, including regulations to ensure that medicinal promotional activities are in keeping with the WHO Ethical Criteria for Medicinal Drug Promotion adopted in resolution WHA 41.17"	
"Reserving sufficient government expenditure to ensure equitable availability of medicines and health personnel"	Expenditure on medicines for use in adult and paediatric populations should be equitably distributed
	Equitable availability of health professionals competent in paediatric pharmacotherapy should be ensured

achievements in recent years [19, 22], it is now also timely to focus attention on the special needs of the paediatric population in the domain of RUM [3].

The core RUM interventions proposed by WHO are general in nature and lack paediatric-specific recommendations, which are also not delineated in the WHA 60.20 resolution. Nevertheless, the WHO core interventions provide a good general framework within which paediatric-specific RUM strategies could be developed, as proposed in Box 20.2. Most of these recommendations might be considered aspirational goals, beyond the reach of most LMICs currently. However, many could be achievable with the right political will and innovative collaborative approaches at regional and global levels, with sharing of information, resources and specialised expertise (including for relevant capacity building) [4, 24].

Examples of successful application of an international collaborative approach to paediatric medicines initiatives include the creation of the WHO Essential Medicines List for Children (EMLc) in 2007 and the more recent establishment of the Global Research in Paediatrics (GRIP) Network of Excellence to address paediatric medicines research needs, including a range of strategies to address specialised capacity building in research [25]. While some resourcing would be required to develop and implement such initiatives for RUM, the potential gains (in health outcomes and costs) for LMICs is likely to far exceed the costs of such investment, and probably less than what might be currently being spent on inappropriate medicines use and associated adverse health consequences.

First and foremost what is needed is commitment by governments to implementing well coordinated national medicines policies, and to explicitly addressing paediatric-specific issues within these, including through allocation of appropriate dedicated resources for paediatric-specific programmes. Engaging with specialised paediatric expertise (in clinical pharmacology/therapeutics and clinical medicine)

to help identify priority paediatric RUM issues and develop, implement and evaluate appropriate strategies to effectively address them is a key element of an optimal overall approach. Box 20.2 provides specific examples of where and how such expertise may be useful. A combination of international collaboration and networking and local commitment could potentially improve access by LMICs to such expertise in the future.

Second, we need much better information on medicines use and outcomes (safety and effectiveness) from the paediatric population in the developing world setting. This is an important component of good RUM but is also crucial for helping to inform medicines policy and practice decisions with meaningful data specific to the paediatric population. This will require the development of paediatric-specific RUM indicators and other methodologies and tools for study of medicines use and outcomes, specifically tailored to the needs of the paediatric population. Some of this work is currently being addressed by the GRIP initiative but more is needed.

Finally, more research is also needed to help identify specific challenges for effective knowledge translation and RUM which may apply to the practice of paediatric pharmacotherapy in the developing world. Identifying and addressing relevant barriers to paediatric RUM in these settings and more systematically applying (or scaling up to national and international levels) multifaceted RUM interventions with demonstrated effectiveness in the paediatric population, will be very important to help maximise the health benefits from the increasing global investment in paediatric medicines research and promotion of access to appropriate essential medicines [4].

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