Realities of paediatric pharmacotherapy in the developing world

Kalle Hoppu,[1–3] Shalini Sri Ranganathan,[4] Alex N O Dodoo[5,6]

[1]Department of Clinical Pharmacology, University of Helsinki, Helsinki, Finland
[2]Department of Paediatrics, University of Helsinki, Helsinki, Finland
[3]Poison Information Centre, Helsinki University Central Hospital, Helsinki, Finland
[4]Department of Pharmacology, University of Colombo, Colombo, Sri Lanka
[5]Centre for Tropical Clinical Pharmacology and Therapeutics, University of Ghana Medical School, Accra, Ghana
[6]Global Outreach Secretariat, Uppsala Monitoring Centre, Uppsala, Sweden

Correspondence to
Dr Kalle Hoppu, Poison Information Centre, Helsinki University Central Hospital, PO Box 790 (Tukholmankatu 17), Helsinki 00029 HUS, Finland; kaarlo.hoppu@hus.fi

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Abstract
Diseases causing high mortality in children under 5 years of age in resource limited settings (RLS) could be treated if children in these countries had access to existing medicines. It took 30 years before the WHO Essential Medicines List (EML) considered the issue of medicines for children, with the first EML for children being published in 2007. Recent data indicate that less than half of the key paediatric essential medicines are available in countries of sub-Saharan Africa. Problems include substandard medicines, irrational use of medicines, inefficiency and even possible corruption in pharmaceutical management systems. These are global issues which affect RLS most. Clinical trials in developing countries for the benefit of children are needed but challenging in several ways. In this review, the authors will consider the following areas where progress could improve paediatric pharmacotherapy in RLS: registration and regulation of medicines, rational use of medicines, clinical trials in children and restriction of corruption in pharmaceutical management systems.

BACKGROUND

About 8.8 million children die annually before the age of 5 years.[1] The majority of deaths occur in resource limited settings (RLS) from conditions which are treatable with existing medicines. Providing children with appropriate medicines and giving them better access to effective treatments is essential for improving child health and achievement of Millennium Development Goal (MDG) 4 (to reduce child mortality by two-thirds) and MDG 6 (to combat HIV/AIDS, malaria and other major diseases).

In the US and EU paediatric medicines initiatives, in essence regulatory interventions used to stimulate the development of clinical trials data suitable for medicines registration, have successfully increased interest in the study and development of paediatric medicines and have already led to some positive results. However, unless the special needs and requirements of RLS[2] are considered, these largely regional initiatives are unlikely to benefit children living in RLS. The aim of this review is to provide some insights into the realities of paediatric pharmacotherapy in RLS.

LACK OF ACCESS TO PAEDIATRIC MEDICINES

Making medicines available is part of a functioning healthcare system. The first step in making a medicine available in a country is regulatory approval of a pharmaceutical product, granted on the basis of efficacy, safety and quality, to permit the medicine to be imported, distributed, supplied or marketed in the country. A second evaluation process is a comparative cost-effectiveness analysis to limit procurement or reimbursements of drug costs. Developing countries often struggle with these evaluations and rely on international agencies, such as the World Health Organization. Essential for any country are medicines that satisfy the priority healthcare needs of the local and regional populations. The WHO Model List of Essential Medicines (EML) launched in 1977 is a tool which helps countries in the selection process and development of a national EML to guide drug procurement and supply. Many international organisations, including the United Nations Children Fund (Unicef) and the United Nations High Commission for Refugees, as well as non-governmental organisations and international non-profit supply agencies, have adopted the essential medicines concept for their supply systems.

Unfortunately, the WHO EML, a global standard for 30 years, paid little attention to children's needs. Although the list included some paediatric medicines, children's needs were not considered systematically. A recent study on the inclusion of key medicines for children in national EMLs and treatment guidelines, and to assess the availability of these medicines in 14 countries in central Africa, found availability to be poor (table 1).[3] Only three countries had more than 50% of key paediatric medicines available from central medical stores at the time of the survey. Private pharmacies tended to have more medicines in stock than primary healthcare clinics, which generally had the lowest availability. Some examples of causes of lack of access and other problems are presented in box 1.

The first WHO Essential Medicines List for children (EMLc) was developed in 2007, and updated in 2009.[4] This and other recent developments such as long-term funding for procurement of paediatric medicines for poor countries by organisations like UNITAID, which collects most of its funds from a levy or 'tax' on airline tickets and concentrates on specific niches such as paediatric treatments, will help to improve children's access to essential medicines.

PROBLEMS OF PAEDIATRIC FORMULATIONS

Many essential medicines, when available, do not exist in formulations suitable for children, and, of those that do a number are not optimal when it comes to dosing, dispensing and administering. These problems are accentuated in RLS.

Most resource poor countries are in the tropics and the climatic issues coupled with problems of

Table 1 Availability of 20 key essential medicines for children in 14 countries in central Africa[3]

Survey medicines available in	Proportion of medicines available, range
National essential medicines lists	50–90%
Standard treatment guidelines	15–100%
Central medical stores	15–75%
Non-governmental organisation stores	10–65%
Teaching hospitals	15–70%
District hospitals	10–80%
Primary healthcare	18–48%
Retail pharmacies	38–62%

transport make logistics and storage of medicines a real challenge. High humidity, particularly in combination with high temperature, is detrimental to the quality of medicines and may render them rapidly inactive. In such areas access to electricity is often unreliable making facilities for cold storage of medicines – a common requirement for liquid formulations once reconstituted – variable. While it is possible to formulate stable oral liquid dosage forms for paediatric administration, these tend to be more expensive than oral solid dosage forms, such as dispersible tablets.[5] A suggested change of paradigm from liquid medicines to flexible solid dosage forms as the standard paediatric formulation is needed to overcome the problems of cold storage and bulk transportation.[6]

Paediatric formulations often have to be dissolved in water at the time of dispensing or before administration. Unfortunately, clean water is not always available. Another issue is injectable medicines. These are usually provided in strengths and vials for adults, and remain stable only for a short time after reconstitution and extensive wastage occurs if only one child can use them. The use of multidose phials also poses safety problems, but single dose phials are more expensive. The need to handle the waste compounds exacerbates these problems.

PRESCRIBING AND ADMINISTERING THE RIGHT DOSE

Medicines for children are typically prescribed on the basis of body weight, but functioning scales are often unavailable. As an example of a response to this problem, for programmatic treatment of uncomplicated falciparum malaria, regional age-based dose regimens have been developed based on 'epidemiological' modelling, carried out to translate weight-based recommendations to age-based dosing regimens in the target population.[7] For malaria and other diseases where medicines are bought over-the-counter, age-based dosing is appropriate. However, for treatment and management of a disease like HIV, weight information is imperative, since antiretroviral drugs have a narrow therapeutic index, and weight change is used to monitor response to treatment.

In RLS several medicines may be prescribed and dispensed by health professionals with limited training, for example, community health workers. If drug administration is not possible by the parents at home, for example injections for severe neonatal infections, and treatment as an inpatient is not an option, administration of every dose will require a visit by the healthcare worker to the patient or vice versa. Only a simple, short course of a minimal number of administrations is feasible under such circumstances. Simplicity in dosing and administration is critically important if a parent or a care giver administers treatment at home. Written instructions are useless in areas where illiteracy is common and verbal instructions of limited use when the parents are not the ones that administer the medicines, requiring them to communicate instructions to another care giver.

Fixed dose combinations (FDCs) are used to reduce the pill burden of combination therapies necessary for successful treatment of acute infections, for preventing emergence of resistance in many of the priority diseases and to improve adherence to treatment. Difficulties in administration of even a single dose of medicine to a child, and the increased physical mass to be carried and stored when liquid formulations are used for long-term

Box 1 Examples of problems in resource limited settings leading to challenges for paediatric pharmacotherapy

- Lack of efficient medicines policy
  - National essential medicines list does not adequately cover children's medicines
  - Medicines purchases for the country are governed by the list, leading to non-availability of some paediatric medicines or paediatric formulations in the country
- Lack of regulatory capacity
  - National competent authorities, even in countries with a functioning regulatory system for adult medicines, do not have competence to asses paediatric medicines, authorise paediatric clinical trials, evaluate the pharmaceutical quality of medicines or carry out pharmacovigilance
- Difficulties in determining the dose to be prescribed
  - Guidelines, a paediatric formulary or other drug information resources are not available or out of date
  - In day-to-day practice, it may not be possible to calculate the dose because weight is not available and even age may be uncertain
- Poor adherence to guidelines
  - When new paediatric medicines become available and are included in updated guidelines, changes in clinical practices at the point of care take longer than expected[42]
- Poor prescribing practice
  - Use of puyers, irrational cocktails of several medicines ground and compounded into a powder in Indonesia[27]
- Poor dispensing practice
  - Inadequate labelling of drugs, pharmacies mushrooming, untrained drug sellers, lack of professional pharmacists[24]
  - Untrained drug sellers, shop owners selling medicines like other commodities and making medicines like antimicrobials available without proper diagnosis or prescription[23 25]
- Lack of drug information resources, medication errors
  - Lack of access to drug information resources,[43] passive attitude of physicians towards drug information centres,[44] underutilisation of drug information centres,[44] overuse of medicines with therapeutic intent,[45] inadequate labelling of drugs[24] and parental mistaken beliefs and undesirable attitudes towards medication use,[25] all possibly leading to medication errors in children
- High prices of medicines
  - Paediatric formulations are more expensive than adult medicines. In Sri Lanka, the price of 200 mg carbamazepine as a liquid formulation was about 40 times more expensive than the adult equivalent.[46] Neither the country nor most families can afford it, leading to inappropriate use of adult dosage forms.

combination therapy, are further arguments in favour of FDCs. However, scoring of adult FDCs into infinitely small fragments to adjust dosing for children cannot be safely done, unless the pharmaceutical specifications of the product guarantee that dose accuracy is maintained. In practice, dosing children with ¼ or ½ of adult FDC tablets is only feasible for as long as the tablet is suitable for scoring, although tablet splitters have been developed when smaller fragments are needed.

QUALITY OF MEDICINES: A MAJOR CHALLENGE

The quality problems of medicines available in some RLS are concerning.[8 9] Malaria is one of the leading causes of mortality in children under 5 years of age in countries in RLS, but medicines available are often of unknown quality.[10] In a recent study of 25 shops selling medicines in Lao PDR, oral artesunate was undetectable by standard techniques in samples from 88% of the shops.[11] In Pakistan substandard antimalarials have caused documented clinical treatment failures in epidemics.[12] In another study in Pakistan, 15.6% of ceftriaxone injections were found to be out of specification.[13] To help make quality medicines available in RLS for HIV/AIDS, tuberculosis (TB) and malaria, the WHO is running a Medicines Prequalification Programme to enable countries procure medicines of assured quality.[14]

IRRATIONAL USE OF MEDICINES

Examples of irrational use include use of too many medicines per patient ('polypharmacy'), inappropriate use of antimicrobials (often with inadequate dosage) for non-bacterial infections, overuse of injections when oral formulations would be more appropriate, failure to prescribe in accordance with clinical guidelines, inappropriate self-medication (often of prescription-only medicines) and non-adherence to dosing regimes.[15] Overuse, underuse or misuse of medicines results in wastage of scarce resources and serious health hazards.

The extent of irrational use of medicines seems to be high in children worldwide. Rational use is not necessarily directly related to available resources as the example of cough and cold medications illustrates.[16] In RLS with high infant mortality, empirical therapy for pneumonia on the basis of a defined clinical case management strategy without radiography can lead to more rational use of antimicrobials than in settings where radiography is performed on all children suspected of having pneumonia.[17] Children in RLS and with priority diseases, like respiratory tract infections, diarrhoea and malaria, are sometimes unfortunately susceptible to such prescribing.[18–20]

Inappropriate prescription and use of antidiarrhoeals and other forms of therapeutic agents for acute gastroenteritis is a substantial problem. Overprescription of antibiotics or the use of incorrect doses nurtures resistance.[4 19 20] Additional problems include overuse of injections or use of injections for mild symptoms, use of drugs which have little or no value, self-medication with medicines purchased from the 'informal private sector' or using left-over drugs.[21–26]

In some instances, irrational uses go unrecognised because they are considered inevitable daily occurrences, and are acknowledged as customary practice. A prime example is the Indonesian practice of puyers, prescribing 'paediatric packets' which are parcelled, ground-up and compounded drug mixtures of, on average, four different medicines per puyer.[27]

CLINICAL TRIALS IN CHILDREN IN RLS

A WHO and Council for International Organizations of Medical Sciences (CIOMS) document exploring the challenges of clinical trials and drug development in RLS offers suggestions on how ICH guidelines could be implemented in even the most resource constrained setting.[28] Research in RLS is increasing and is to be encouraged in view of the huge burden of especially priority (chiefly infectious) diseases in those settings, the different health systems in place and the need to obtain local data for decision making. The importance of clinical trials aimed specifically at addressing the safety and efficacy of medicines and formulations in children is important and critical in all settings, including RLS. Few trials are undertaken in RLS, thus the experience of investigators and regulators regarding the ethical and scientific requirements for patient and data protection are limited. The challenges of undertaking trials in RLS include shortage of health professionals with training or experience in clinical trials, weak or absent national drug regulatory agencies, little or no drug development activity in endemic diseases and little or no incentive to develop medicines for neglected diseases in populations who would be unable to purchase these medicines after approval.

For clinical trials the ethical framework for recruitment and protection of study subjects, including children, is provided by international agreements. However, the real situation in an RLS is often significantly different from that in high-income countries and children in RLS may be extremely vulnerable to exploitation either deliberately or accidentally. Almost any form of reimbursement of expenses may run the risk of being an undue inducement for the family to provide consent for the participation of their children in trials in a bid to obtain financial benefits. In some cases, participation in a clinical trial may be the only real chance to get a treatment that may be life saving – a maximum benefit on an individual level. In relation to this, the immediate risk:benefit ratio may appear positive even when the unknown risks could be long term adverse effects not treatable in the local healthcare system, or risk of relapse when the child no longer has access to the study medicine after the trial ends.

In Africa, only the higher profile diseases with major paediatric morbidity such as malaria are afforded research attention. For example, 90% of participants in the clinical trial of chlorphroguanil–dapdsone (LAPDAP) were children.[29] While such a trial population is appropriate in view of the high number of children who die from malaria, the issue of safeguards for trial participants, appropriate ethics approval and proper informed consent remain extremely important in view of the vulnerability of the participants.

Evidence suggests that reporting of recruitment procedures is often poor and post-trial access to medicines limited.[30] However, rigorous and ethical trials could make a major contribution in diseases like schistosomiasis, onchocerciasis, trypanosomiasis, malaria, TB, HIV/AIDS, Chagas disease and visceral leishmaniasis often unique to RLS. Examples of valuable trials include moxidectin in west Africa,[31] the CHER study (Children with HIV Early Antiretroviral Therapy) and the intermittent preventive treatment of malaria in infants (IPTi) study which demonstrated the safety and efficacy of sulfadoxine–pyrimethamine as IPTi.[32 33]

In addition to the lack of necessary clinical trials in RLS, a growing number of those that are performed there are a result of global redistribution of clinical trials from high-income to low- to middle-income countries.[34] These trials involve non-priority diseases and medicines that are not intended or unlikely to become available for children in RLS. Such trials are primarily intended to provide data for

regulatory approval of a medicine in the competitive markets of the developed countries, especially in the areas providing lucrative incentives for the development of medicines for children (USA and EU). Less developed countries have some characteristics which make them attractive for such clinical trials, including high prevalence of diseases, commonly in treatment-naïve form, and lower trial costs. Such trials are not necessarily inherently unethical, but run the risk of leading to exploitation, particularly if the population from which the trial subjects come do not have access to the medicine once it is approved.

The need to protect vulnerable research subjects on one hand and the importance of enticing and encouraging the pharmaceutical industry to undertake clinical trials in RLS on the other hand is a delicate and complex issue, associated with ethical and legal challenges and governmental/pharmaceutical industry tensions. The (as yet unresolved) court case involving trovafloxacin (Trovan) an antibiotic produced by Pfizer and tested in Nigeria is an example (box 2).

Box 2 The case of the clinical trial of Pfizer's antibiotic trovafloxacin (Trovan) in Nigeria as described in scientific journals[47–49]

- In 1996 Pfizer's performed a clinical trial of its antimicrobial trovafloxacin (Trovan) in children during an outbreak of meningococcal meningitis in Kano, Nigeria.
- Some years after the trial was finished, charges were filed in Nigeria and USA against Pfizer.
- The Nigeria government contended that the trial was undertaken without proper parental consent or federal approval.
- Reportedly, Pfizer paid a local investigator US$20 000 (a huge sum for the country) to undertake the study.
- The investigator appointed himself chairman of the ethics review committee, and backdated its approval for the trial.
- In the trial, 99 children received a dose of the then experimental Trovan, while a control group of 101 children was given ceftriaxone already used to treat meningitis.
- The lawsuits allege that ceftriaxone was given in a dangerously low dose.
- Lawsuits charged that 11 children died and scores more suffered debilitating injuries.
- Pfizer is accused of hiding or destroying data on the trial.
- The patients/parents have claimed that they did not know whether or not they were participating in research, they just knew the children were sick.
- Trovafloxacin side-effects, that include severe liver damage, have caused the European Medicines Agency to ban it and the Food and Drug Administration to severely restrict its use.
- Pfizer has denied any wrongdoing and is fighting the lawsuits. It maintains that it has followed all the protocols and international standards.
- The results of the lawsuits are still pending 14 years after the clinical trial.

CORRUPTION

The World Bank has identified corruption as the single greatest obstacle to social and economic development.[35] Pharmaceutical systems are particularly vulnerable to corruption worldwide. In RLS the system tends to be more vulnerable, because corruption can be detrimental to a country's ability to improve the health of its population.[36 37] The Medicines Transparency Alliance (http://www.medicinestransparency.org), a collaboration between governments, business and civil society in seven countries, aims to tackle the weak links of the medicine supply chain and reduce corruption by attention to the following: mandatory regulatory approval of clinical trials, registration of medicines to include all requisite information, tackling counterfeit and substandard medicines, preventing re-sale of stolen medicines and fighting unethical promotion. A special tool has been developed for assessment of the problems.[38] Some examples of how children are affected by corruption in the paediatric medicines supply chain have been described above, but it is not in the scope of this review to discuss corruption in detail.

CHANGE FOR BETTER IS BECOMING A REALITY

Although this review has focused on the negative aspects of paediatric pharmacotherapy in RLS, there are also reasons for optimism due to the many important paediatric initiatives launched in recent years.[39] One of the most important developments was the adoption by the World Health Assembly of resolution WHA 60.20 'Better medicines for children' in May 2007.[40] Concrete results already include the EMLc, which in its second edition now includes a list of essential medicines that can be used in neonates.[4] WHO has launched an initiative called 'Make medicines child size' (http://www.who.int/childmedicines/en/) aiming to accelerate the research and development of the missing essential child-specific medicines. Some early signs indicate that children's access to medicines is improving. For example, while in 2005 only 7% of children in low- and middle-income countries needing antiretrovirals received them, the proportion at the end of 2009 had increased to 29%.[41] We are entering a new era of paediatric pharmacotherapy where appropriate medicines should be available for all children including children in RLS.

Competing interests KH has been a member of the WHO Expert Panel on the Selection and Use of Essential Medicines since 2007. He has served on two Expert Committees (2007, 2009) and two Paediatric Subcommittees of the Expert Committee on the Selection and Use of Essential Medicines (2007, 2008) and has been a temporary adviser to WHO programmes. SSR has served on WHO's Paediatric Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines (2007) and also as temporary adviser to two (Essential Medicine and Pharmacovigilance) WHO–South East Asian Region programmes (WHO-SEARO). ANOD has been a member of the WHO Expert Panel on Drug Evaluation since 2007 and the WHO Advisory Committee on the Safety of Medicinal Products since 2008. He is also the Director of the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance. He has served on one Expert Committee on the Selection and Use of Essential Medicines (2009) and been a temporary adviser to several WHO programmes.

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