Stuart MacLeod · Suzanne Hill
Gideon Koren · Anders Rane *Editors*

Optimizing Treatment for Children in the Developing World

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Preface

In September 2014, an important report from John McArthur of the Brookings Institution has provided grounds for optimism recognizing significant progress in improving child mortality worldwide [1]. In an era of increasingly evidence-based practice, there is also a growing awareness of the need for improved randomized trials of paediatric therapies [2, 3], with particular priority assigned to the needs of developing countries [4, 5].

All researchers, clinicians and other caregivers who work in child health are acutely aware of the skewed demographics characterizing the world's population of children and youth. Although most focus on their own practices, hospitals, regions or countries, it is impossible to ignore the overwhelming burden of child illness so prominent in the most heavily populated parts of the world and especially in those countries with limited fiscal resources, referred to in our title as 'developing'. For the most part, in this volume, authors have followed the terminology used by the World Bank, with a division of countries into low, middle and high income. At times, the language used has reverted to discussion of developed and developing countries, and a distinction is also sometimes drawn between upper- and lower-middle-income nations.

This book has been created in recognition of a global responsibility to optimize treatment of children. It is perhaps surprising that such a moral imperative has heretofore gone largely ignored. We think that publication is timely, given the current interest in evaluation of progress made in this century towards achievement of the United Nations Millennium Development Goals focused on maternal and child health.

As noted in Chap. 2, in 2013 the world's total child population (0–14 years) was 1.85 billion, and of that number, 0.33 billion resided in low-income countries (LIC) and 1.342 billion in middle-income countries (MIC). Understandably, the distribution of births is correspondingly skewed, with birth rates of 32 per 1000 in LIC and 19 per 1000 in MIC. The burden of under-5 mortality and of ill health among children is generally found to be in inverse proportion to economic development, and that is the rationale for assembling the medical and research opinions presented in this volume.

The challenges described are real and continuing despite progress made through assiduous pursuit of the United Nations Millennium Development Goals. By 2013, the under-5 mortality rate had declined to 6.3 million, down from 9.7 million in 2000 and 12.7 million in 1990. If measures described in this book are pursued, there are grounds for optimism that child and youth morbidity and mortality will continue to fall. The essential ingredients for success are a blend of public health literacy extending comprehensively to patients and families, researchers with appropriate skills, intense clinical engagement and commitment on the part of political decision-makers.

The picture presented in the following chapters is incomplete but describes at least some of the critical hurdles still to be surmounted if progress is to continue. As described in Chaps. 3 and 11, there will be equal challenges to be met in the distribution of scarce resources to permit equitable access to therapy critical for reduced morbidity or heightened survival for the most vulnerable of children. It is not acceptable, for example, that only 25 % of HIV-infected children in Africa currently have access to proven effective therapies.

It is our hope that this volume will prove valuable to students and practitioners in health sciences and health professions committed to improved global child health. Ideally, it will prove equally useful to teachers, administrators and health policy decision-makers, who bear a major responsibility for improving child health outcomes in often vulnerable LMIC populations.

For the editors, the bringing together of the content has been an interesting journey. It will be clear to readers that we have not yet, in spite of encouraging progress, arrived at our destination. The selection of commentaries presented is a snapshot provided by highly committed clinicians and researchers offering a current overview of where we stand on a critically important global health priority. Of course, the opinions expressed in this volume are those of the authors and may in some cases be controversial. There is, however, no contention about the need for continued worldwide effort to secure the best possible age-appropriate treatments for children everywhere.

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Part I
Introduction and Context

Chapter 1
Children Everywhere Deserve Evidence-Based and Accessible Treatment

Clive Ondari, Lisa Hedman, and Jane Robertson

The availability and affordability of medicines are crucial for the delivery of health services in any community. In many countries, the public sector plays a significant role in providing health services. When public health facilities lack medicines they risk losing the confidence of the populations they serve; people will go elsewhere for the services they need or be forced into the private sector where care and medicines are often more expensive or unaffordable.

The Millenium Development Goals heightened global awareness of the large numbers of women and children dying from preventable diseases, the poor access to cost-effective treatments for common diseases and the particular risks for mothers at the time of delivery and infants in the neonatal period. However this is only part of the story; there are many issues specific to children that complicate the processes of delivering age-appropriate, effective interventions to treat both acute and chronic diseases. The child-specific issues complicate the already challenging issues of the adequate financing, procurement and distribution of quality-assured medicines in many low- and middle-income countries. Some of the special concerns of children are relevant in all income settings.

Poor access to paediatric formulations of medicines often leaves health care providers and caregivers few choices but to adapt adult dosage forms for use in children. In practice, this often means breaking tablets into smaller pieces. This may be acceptable for some medicines, however where tablets are not scored or are friable, it can be difficult to deliver accurate doses. Emptying capsules and estimating fractions of powders is not desirable, and syringes or droppers to accurately measure small volumes of liquids may not be accessible.

For many medicines, small inaccuracies in dosing will not cause adverse events. Where medicines have a narrow therapeutic index, errors in dosing may cause sig-

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nificant problems, risking side effects or toxicity. Breaking or crushing tablets that are designed to be slow or sustained release may lead to overdoses as absorption of the medicines can be much faster than intended. In the case of enteric-coated tablets, crushing will destroy the protective layer that prevents the breakdown of the coating by stomach acids, risking erosive damage to the gastrointestinal tract.

Apart from dosing inaccuracies, crushing tablets may release bitter tasting compounds that children refuse to take. Masking the bitterness in food, juices or even mixing with milk may also affect the absorption of the active ingredient. While it may be possible to administer a bitter medicine once or twice, administering a course of treatment will challenge most caregivers!

So How Much Do I Give?

Just as the practical administration of medicines to children has been based on adaptation of adult dosage forms, much of the information on appropriate dosing in children has been derived from clinical experience or extrapolations of dosing determined in trials conducted in adults. With relatively limited testing in children, there may be no regulatory agency-approved uses and doses of many medicines for children – giving rise to the term 'off-label' use. While prescribing 'off-label' is not illegal in many jurisdictions, it means there is often limited guidance to physicians on the safe and appropriate use of the medicine in children and little recognition that there may be special considerations that apply for use in populations that span from newborns weighing 1,000 g to children of 12–15 years weighing 50–60 kg.

Doses for children are often estimated with consideration to weight (mg/kg doses) assuming a linear relationship between weight and dose, to body surface area (mg/m^2 doses) or to age with different recommendations for newborns, infants and children. Given differences in the pharmacodynamics, pharmacokinetics, growth, maturation and metabolism across the paediatric spectrum, methodologies such as pharmacokinetic–pharmacodynamic modelling and physiologically based pharmacokinetic approaches can assist in determining appropriate paediatric doses for some medicines (e.g. morphine doses in neonates and young children, caffeine in neonates) [1–3].

The importance of dosing issues is illustrated with paediatric medicines for the treatment of HIV/AIDS. The World Health Organization (WHO) has developed a dosing tool to calculate doses for HIV medicines that incorporates weight-based tables and dosing informed by manufacturers' information, available antiretroviral formulations, data from clinical trials and expert paediatric pharmacology advice [4]. The resulting guidance is intended as a balance between optimal doses, available formulations and the advantages of simplified dosing regimens.

The issues in relation to paediatric TB medicines are slightly different – WHO has a role working with global partners to identify the products that are needed and to work with manufacturers to produce medicines that may not be commercially viable and might not otherwise come to market (see Box 1.1).

Box 1.1: Case Study – Paediatric Medicines for Tuberculosis

As with adults, appropriate doses of anti-TB drugs are needed to achieve cure of the infection; suboptimal treatment may lead to drug resistance. While the principles of treatment of TB in children are similar to those for adults, there are some important considerations in establishing effective medicine regimens for children.

Doses for isoniazid, rifampicin and ethambutol extrapolated from adult pharmacokinetic studies will produce suboptimal serum concentrations in children. Children eliminate isoniazid faster than adults, requiring a doubling of weight-based (mg/kg) dosing to achieve comparable serum levels; doses of rifampicin and ethambutol also require a higher body weight dose (mg/kg) to achieve effective doses [5]. Weight-based dosing has further implications in children – as malnourished children respond to treatment and gain weight, doses need to be adjusted upward to ensure adequate serum levels are maintained. These differences in dosing mean that standard adult formulations, particularly combination formulations cannot be easily adapted to meet the needs of children. Further, while liquids are easier to administer to children, there are issues of supply and cost of bulky liquids and some liquid formulations have unacceptable side effects in children, for example, sorbitol-based solutions of isoniazid can cause diarrhoea [5].

In 2010, WHO issued Rapid Advice for the treatment of TB in children [6] including instructions on how to safely adapt and combine existing adult and paediatric products until appropriate new formulations could be developed and marketed. The Expert Committee recommended a fixed-dose combination (FDC) of rifampicin, isoniazid and pyrazinamide with ethambutol as an option when this was needed. The FDC approach was considered important in order to reduce pill burden (up to 24 pills per day), simplify the regimen for caregivers and improve treatment adherence. In addition to the advice on how to manage paediatric TB, the Expert Group drafting the rapid advice identified a substantial research agenda to address a number of outstanding questions.

Many countries with high TB burden initially were not able to implement the new recommendations on paediatric treatment, in part due to concerns that the new dosing guidelines were temporary and the new clinical studies had not been performed. Response from the pharmaceutical industry to the need was limited as well. Paediatric TB represented a small market (perhaps one million paediatric patients worldwide); the regulatory and market entry costs for reaching the 22 highest TB-burden countries were considered significant without any clear financing for the these new products [7].

Progress in the development of paediatric anti-TB medicines has been slow. The Speeding Treatments to End Paediatric Tuberculosis (STEP-TB) programme is working to promote the development, market authorization, availability and uptake of new paediatric treatment options, including the FDC drugs as well as second-line treatment options [8].

Some work has been done to advance the agenda of responsible and appropriate research in medicines for children. The Better Medicines for Children project funded by the Bill and Melinda Gates Foundation and the WHO campaign to Make Medicines Child Size [9] represent efforts to stimulate the research and development of child appropriate medicines. Medicine regulators have also responded to these gaps in knowledge about the use of important medicines in children giving special attention to the conduct of clinical trials in paediatric populations [10, 11].

Investing in Clinical Trials in Children

Traditionally, children have been largely excluded from clinical trials with the ethical issue of informed consent a major barrier to such studies. The result is a smaller number of medicines with approved indications for use in children. To address this, the development of specific guidance on the ethical considerations for clinical trials on medicinal products conducted in paediatric populations highlights the special concerns and protections required [12]. This guidance balances the potential risks and harms to children from participating in trials to the benefits from the information gained from properly conducted research. A particular challenge is that 'child' is not a homogeneous category, but rather represents children of numerous ages and developmental levels, from neonates to adolescents, who may respond differently to a disease and a medicine and may be at differing risk of adverse events.

Study protocols for children must be adapted to avoid unnecessary discomfort and risk, such as swallowing large pills or repeated blood draws. Pain, fear, distress and parental separation need to be considered and minimized in trials involving younger children. In adolescent populations, there are issues of disclosures to parents versus the need to respect and protect patient confidentiality, especially where there are socially sensitive issues involved. Aspects of trial conducting may also need to be altered to avoid psychological distress or humiliation, such as repeated undressing. The combined effects of these constraints are a limited number of clinical trials, limited evidence to support regulatory applications and relatively few products reaching market with approved indications for use in children.

In response to the low numbers of submissions for paediatric formulations, a number of stringent regulatory authorities have created incentives to stimulate development of appropriate dosage forms for children (see Chap. 10). Since 2007, the European Medicines Agency has required paediatric investigation plans as a requirement in applications for new medicines [13]. Other incentives in both Europe and the United States include extensions of patents with market exclusivity for products that include the results of paediatric studies as well as assistance with scientific advice and protocol development for such studies. Waiving of application fees is also granted for 'orphan' paediatric products and in some cases special funding is available to support studies of priority medicines that are off-patent.

Regulatory Issues and Market Authorization of Paediatric Formulations

While these regulatory initiatives may promote development of paediatric medicines in higher income settings, there are criticisms that the medicines studied in these trials more often closely match the distribution of medicines in adult markets rather than reflecting the medication needs of children [14]. This situation can leave behind the needs of children in low-income countries where pneumonia and diarrhoea remain major killers and where flexible dose forms of anti-infective agents are needed that, unlike some syrup formulations, do not require refrigeration.

Even when new products are developed, there may be regulatory delays in achieving market authorization in some countries. Some of this relates to deficiencies and limited capacities in national regulatory systems in low- and middle-income countries. A procedural advancement that has shown promise is joint reviews and assessments conducted together by multiple regulatory authorities reducing duplication of efforts in product evaluation. In addition, the Paediatric Medicines Regulatory Network, hosted by WHO [15], works to reinforce training and to provide access to paediatric specialists in regulatory agencies of low- and middle-income countries. However the relatively small markets and the cost of entry into each of these may diminish manufacturers' enthusiasm for launching child-friendly products in some areas of greatest need. The UN Commission on Life Saving Commodities for Women and Children has also highlighted the need for efficiency in regulatory processes to ensure access to important paediatric and maternal health medicines [16].

Availability and Affordability of Medicines for Children

Beyond the marketing authorization of appropriate medicines for children, it is important that such products are included in national Essential Medicines Lists and medicine reimbursement lists for health insurance programmes to ensure that children in need can access effective medicines. If products are not included in these lists, they are much less likely to be included in public sector medicines procurement. The first WHO Model List of Essential Medicines for Children was produced in 2007 and has been updated every 2 years since then in parallel with the adult list. The intent of the separate list for children was to recognize special paediatric needs and to promote the inclusion of essential paediatric formulations as priority medicines, and for these formulations to be included in national procurement programmes.

Once appropriate products are procured, there need to be efficient distribution and supply systems in place to ensure that children in all communities can equally access the medicines they need. WHO in conjunction with other international agencies and partners is working to support countries to strengthen their pharma-

ceutical supply systems. While there has been progress in some low- and middle-income countries, it is sometimes uneven; rural and remote communities remain disadvantaged with poor access to public sector services and few or no private sector services as alternatives available to them.

Positive results have been achieved by supporting capacity development in logistics and supply management, notably in supply initiatives that have integrated paediatric medicines, such as HIV programmes. Scaling these innovations to meet the demands anticipated by population growth may be challenging, and they will face the persistent problems of the lack of dedicated and qualified staff to run, monitor and maintain these systems and limited financial resources for the public procurement of essential medicines for children.

Cost remains a significant barrier impeding reliable access to medicines for children. Paediatric formulations often have higher costs for reasons including relatively lower volumes of product required. Wastage and transportation are cost drivers for some paediatric formulations, for example, syrups that expire more rapidly and are bulky. Import duties, taxes and supply chain mark ups have not been specifically assessed for paediatric products, and further work may be needed to understand their possible impact on initiatives to ensure availability of treatment for children. In many low- and middle-income countries, medicines in the public sector are provided free for children less than 5 years of age; however, this is only meaningful if the products are available in the local public sector facilities attended by these children. The low availability of important medicines sometimes forces parents to purchase medicines in the private sector where high prices can place medicines out of reach. In the absence of affordable medicines, families may rely on informal medicine vendors, heightening the risks of inadequate courses of treatment and exposure to substandard, falsified and counterfeit medicines. In addition, high costs may result in prescribing of cheaper, less preferred medicine choices. The 2011 Global Asthma Report highlighted the poor availability and high costs of inhaled bronchodilators and corticosteroids that are the mainstays for management of asthma in children in high-income settings [17].

Access to Reliable Information to Guide Medicines Use

Patients and their families need to rely on health care professionals to guide them in appropriate treatment choices; early education in schools and e-health options provide some promise for the future to improve knowledge and medicines. Supported by the US Agency for International Development optimal use of (USAID)-funded Systems for Improved Access to Pharmaceutical Services (SIAPS) Program implemented by Management Sciences for Health (MSH), the WHO Essential Medicines and Health Products Information Portal aims to provide medicines and health products-related full-text articles available online [18]. Innovative methods need to be considered for translating the wealth of information currently available into messages that are understood by caregivers and in formats that are accessible to those in

low- and middle-income countries. Low literacy compounds the problems in many cases, along with beliefs in unsubstantiated claims about medicines and treatment of diseases, reliance on ineffective or harmful medicines and use of ineffective traditional remedies [19]. Mass media resources for the general public and teaching resources for school children that are tailored to context are being examined as means to improve health literacy and enable people to make informed choices about health care.

Monitoring and Evaluation of Use of Medicines in Children

Monitoring and evaluation are also critical to sustainable systems of supply of essential medicines for children. Monitoring is not only about availability and costs of medicines in public and private health facilities, but also about understanding how medicines are used in practice. Prescription-based audits can shed some light on medicine choices for particular clinical conditions and concordance with accepted treatment guidelines. However, household and other consumer surveys are required to help elucidate community preferences for care, beliefs about medicines and satisfaction with services available to them. Traditional beliefs about the causes of illness, suspicions and myths around vaccination and the stigma in some societies of particular diagnoses must be acknowledged if health care interventions are to be successfully introduced.

Policy and decision-makers also have an important role to play. Regular review and evaluation of important data on medicines availability, affordability and use are needed and a culture of using information for decision-making and policy development encouraged. For example, the WHO Service Availability and Readiness Assessments (SARA) are extensive, statistically representative surveys that provide information on medicines availability in public and private health facilities [20]. These surveys have been conducted (and repeated) in a number of African countries and are carried out in advance of planned country health policy reviews in order to inform Ministry of Health decision-making. Such information is critical if the problems of access to appropriate medicines for children are to be addressed.

The Future

Over the last few years, there have been renewed efforts at the global, regional and national level to improve access to medicines for children. The focus has been on an effort to reduce ‘stock-outs’ and to ensure availability of appropriate dosage forms. Emphasis has also been placed on increasing demand for evidence-based prescribing, supporting quality use by health providers and caregivers, sustaining research in many critical facets including preclinical and clinical studies and incentivization of manufacturing. Many players have been at the forefront of these efforts including

national governments, international organizations, public–private partnerships, philanthropic, professional associations and many others, including a dedicated community of child health researchers. If these efforts are sustained, then the future looks promising for children.

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Chapter 2
Shifting Demographics and Clinical Pharmacy/Pharmacology Priorities

Stuart MacLeod, Zhiping Li, and Atieno Ojoo

Children have a right to health and well-being and children who are ill need treatment that is appropriate for the age and stage of developing bodies and mind. Council of Canadian Academies, September 2014 [1].

While this quotation seems axiomatic, the actions of health policy makers in both developed and developing countries have consistently undermined the basic right described and have left far too many children as therapeutic orphans [2, 3].

In choosing to address the issues that appear in the volume that follows, a decision has been made to underscore the duty of care that is owed to children worldwide. Multidisciplinary alliances are required that will include the entire spectrum of caregivers interested in child health with a commitment to see that drug therapy for children is based, wherever possible in future, on sound evidence from exemplary clinical trials [4, 5]. It hardly seems earthshaking to suggest that children deserve treatment that would at least meet the standards of scientific validity that have long been required for drug treatment of adults. Although this is glaringly obvious, the needs of children have, until recently, mostly been ignored and this is especially true, for understandable reasons, in LMIC.

While there are many alarming observations in the chapters that follow concerning deficiencies in the knowledge base supporting therapeutic choices for children, the situation has, nonetheless, considerably improved over the past 25 years [1]. During that time, child caregivers have argued passionately that products used in the

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treatment of children should be adequately labelled and enormous progress has been made through legislative efforts, particularly in the United States and Europe, to address the needs of children through regulatory and policy reform [6–9].

Perhaps the greatest advance in defining the therapeutic rights of children has been made in Europe where legislation was introduced in 2007 requiring companies filing for licensure of new drug products to submit a pediatric investigation plan, unless there was no potential for use in children [10]. The details of this regulatory process are discussed in Chap. 10.

This volume is particularly concerned with ways in which the progress made in developed countries can now be extended for the benefit of the much greater number of children residing in LMIC. According to the world development indicators of the World Bank in 2013 [11], out of a total world child population (0–14 years) of 1.85 billion, approximately 331 million are in low-income countries, with a further 1.342 million residing in middle-income countries. In sub-Saharan Africa, 43 % of a total population of 936 million people are under the age of 14 and most of these children are living in circumstances where the performance of the health care system and delivery of essential care are compromised by low availability of required fiscal resources. Perhaps most alarmingly, the number of children living in low-income countries continues to escalate rapidly. Although total fertility rates and birth rates are declining in many countries, there is no expectation that overall trends will suddenly change.

Given the demography described, it is not surprising that there is continuing worldwide concern about stubbornly high levels of child mortality. In 2013 a report on the trends in child mortality 1990–2012 was released and showed substantial progress [12]. Nonetheless, in 2012 an estimated 6.6 million children died before their fifth birthday, mostly from preventable causes and treatable diseases. The average under-5 mortality rate (U5MR) in low-income countries was 82, more than 13 times the average rate in high-income countries. Nearly half of the under-5 mortality reported was seen in sub-Saharan Africa. The Child Health Epidemiology Reference Group (CHERG) of WHO and UNICEF has reported that 64 % of deaths in children younger than 5 years were attributable to infectious causes, while 40 % of such deaths occurred in neonates. Among neonates, sepsis and meningitis account for an estimated 400 million deaths annually. In children, following the neonatal period, most of the major causes of mortality, including diarrhea, pneumonia, malaria, HIV-AIDS, pertussis, meningitis, measles, and a host of other infections are treatable by drugs or preventable in large measure by vaccines.

A recent report by John W. McArthur of the Brookings Institution entitled “Seven Million Lives Saved” [13] has provided a very encouraging view of progress made in child mortality since the launch of the Millenium Development Goals (MDG). Since 2000, we have entered, for the first time in four decades, into an era during which rates of U5MR decline are no longer negatively correlated with the underlying U5MR. McArthur estimates that at least 7.5 million additional children’s lives have been saved between 2002 and 2013, the majority of them in sub-Saharan Africa. He further points out that significant structural progress has been made even in many countries that will fail to achieve their formal MDG targets.

In recent years two Copenhagen Consensus Conferences have been held challenging Nobel prizewinners in economics to identify the probable most cost-effective initiatives worldwide for health, wellness, and survival [14]. It is not surprising that both times when this challenge has been put forward, experts agreed on essential initiatives with a disproportionate focus on measures to improve child health. A number of the recommended interventions are preventive, including provision of micronutrients, particularly zinc and iron, and improvement in worldwide availability of vitamin A. Other identified priorities include better treatment of malaria, helminthic diseases, and HIV-AIDS, all important opportunities in the developing world that exemplify the critical importance of efforts to achieve optimal evidence-based drug treatment.

It is notable that many international organizations concerned with the welfare of children have recently placed heavy emphasis on their nutritional and therapeutic needs. This prioritization explicitly recognizes the amazingly cost-effective gains that can be made through provision of improved nutritional supports, preventive therapies, or active treatments for common childhood conditions that are causing intolerably high levels of child mortality in many parts of the world [12].

As greater emphasis is placed on evidence based treatment of children in all jurisdictions it may be anticipated that there will be a growing call for agreement on principles to guide clinical investigations in low-income countries. Positive lessons can already be drawn from a number of successful initiatives, such as the African Vaccine Regulatory Forum, the Pan-African Clinical Trials Registry, and the European and Developing Countries Clinical Trials Partnership [15–17].

There has been a parallel growth worldwide in recognition of the essential role to be played by pediatric clinical pharmacology, clinical pharmacy, and clinical toxicology in developing the information base on which efforts to improve drug therapy for children will rest. Contributions to this critically important effort have been made from a number of organizational and institutional sources, including the International Union of Basic and Clinical Pharmacology [2] and the International Pediatric Association [18]. A number of recent articles have examined the relevant issues from regional perspectives [19–24].

It is timely to examine the priorities that should be addressed by pediatric clinical pharmacologists, clinical pharmacists, and clinical toxicologists from high income and, more particularly, from LMIC. Many of the details concerning these priorities are presented in the chapters that follow; however, an outline is presented here proceeding from the sociocultural–political environment through drug development to eventual measures that will determine medication access and use in clinical practice.

1. The social, political, and cultural environment in which drugs are studied is of critical importance. There is a high priority to develop public support for essential medicines for children for treatment of diseases that disproportionately affect resource-limited settings, with specific emphasis on age-appropriate formulations. Collaborating to encourage adequate financing to ensure availability of medicines for children has been successfully achieved through the Medicines

for Malaria Venture [25] and the Drugs for Neglected Diseases Initiative (DNDi) [26, 27].

2. The policy environment is of equal importance. Medicines for children must be budgeted for and procured by national and local governments. Those interested in securing a consistent supply of better medicines for children in poor resource settings must be prepared to add their voices to appropriate advocacy efforts.
3. Policy initiatives: Consideration should be given to adaptation in resource-limited settings, of the drug regulatory pathways already applied by the United States and Europe to accelerate access to child-approved and appropriate medications. Development of an appropriate regulatory framework for low-income countries should also address all relevant issues of formulations, manufacturing, quality assurance, availability, and pricing.
4. Formulations: Participation in the prioritization and development of age-appropriate product formulations is of high importance (see Chap. 6). Progress in this area will require close cooperation of pharmaceutical scientists in high-income countries and in international agencies such as the World Health Organization, working closely with their counterparts in LMIC settings. Progress will also include robust and cost-effective assessment of product quality. Further research is also required to be directed to identification of active substances and drug delivery mechanisms that can withstand extreme climates, yet remain affordable across all patient populations globally. Scientific possibilities that balance cost-effectiveness with the need for dosage forms that a child can take and the caregiver can administer are optimal. Manufacturers should also take into account the health system and in-country logistics when designing final finished products.
5. Pediatric clinical trial standards: Engaged clinician scientists should contribute to the achievement of agreements on pediatric clinical trial standards suitable for application following some local adaptation in a majority of low resource settings (see Chap. 14). Consensus must also be sought on practical and appropriate ethical principles to be applied to the review of pediatric trials in developing countries. The difficulty of this challenge cannot be underestimated, given that ethical decisions are invariably based on legal norms heavily influenced by local, social, and cultural values [28, 29]. In this sensitive area attention should be paid to the development of effective collaborative partnerships between individuals and organizations in high-income countries and those in LMIC. Strategies to incentivize clinical research including therapeutic trials in pediatrics in resource-limited settings should be explored. Of particular value would be targeted grants made to young scientists.
6. Guidelines: The policy development and adoption process at national and subnational levels must account for the pharmacotherapy needs of children by including age-appropriate dosage forms of essential medicines in national standard treatment guidelines and national essential medicines lists, accompanied by adequate prescribing, dispensing and availability information. Regulatory pathways that enable quick access to medicines for children are a prerequisite for success (see Chaps. 6 and 10).

7. Pharmacoepidemiology: The disciplines of clinical pharmacology, clinical pharmacy and clinical toxicology cannot stand alone without a foundation in epidemiology that will support educational and research prioritization. A strong pharmacoepidemiology capacity that is well integrated with clinical investigation will allow for better prioritization of trial selection for the pediatric evaluation of drug safety and efficacy (see Chap. 17).
8. Knowledge transfer and exchange: The return on an investment made in a more solid foundation in clinical child health investigation will only be realized if there is an equivalent development in knowledge transfer. Leaders in clinical pharmacology and pharmacy must be committed to the consolidation of a worldwide knowledge transfer system that will support the development and dissemination of standardized treatment guidelines appropriate to regional needs (see Chap. 20).
9. Research gaps: In LMIC settings the safety and efficacy of pharmacotherapeutic agents cannot easily be separated from the nutritional state of children requiring treatment (see Chap. 16). There are numerous research gaps in this area that must be addressed if optimal pharmacotherapy for children is eventually to be achieved. In line with the above comments concerning pharmacoepidemiology, it should be recognized that progress will not be made unless systems for collection and sharing of data are greatly improved in poor resource settings.
10. Education and training: Progress in clinical investigation of new therapies for children will be stalled without the development of modern shared programs for education, training and, skills development. Involved clinician scientists must be enlisted to support state of the art training targeting prospective clinician investigators in low-income countries. Efforts should include distance education and online learning opportunities in clinical pharmacology, pharmacy, toxicology, and other relevant disciplines. As described in Chap. 13, progress will also be abetted by development of efficient, effective clinical research networks that will facilitate sharing of infrastructure and human resources between high-income countries and low/middle-income countries [30, 31]. An efficient system for education and training will also be facilitated by the creation of international hubs or regional centers for methods development, diagnostic validation, and promotion of skills relevant to clinical investigation.

Conclusion

All of the above observations relate to the general environment at a national level of child health to which the disciplines of clinical pharmacology, pharmacy, and toxicology may contribute. The final integration of efforts in this field must be achieved through a mechanism for reaching consensus on priority areas for action. It is of paramount importance that clinical studies focus on therapies likely to benefit child health in developing countries in the areas of greatest concern, such as, neonatal

sepsis, meningitis, pneumonia, malaria, diarrhea, anemias, helminthic infestations, HIV-AIDS, mental health disorders, and pain and palliation. Several of these topics are addressed in the following chapters.

During the past decade at least one watershed has been passed. It has now become uncommon to hear objections to research in children expressed on the grounds that they must be protected from experimental treatments. On the contrary, there is now general acceptance of the view that children need to be protected from non-evidence-based interventions and from substandard treatments. Remaining questions relate to how best to stimulate research activity that will serve the needs of infants, children, and youth in developing countries and assign high priority to ethically sound research that will meet their clinical requirements.

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Chapter 3
Access to Medicines – More Than Just Affordability

Andy Gray, Prakash Jeena, and Atieno Ojoo

Introduction

The importance of medicines in any health system, be that in a developing or developed country, has been succinctly summarized in the basic text relied upon by many pharmaceutical managers – *MDS-3: Managing Access to Medicines and Other Health Technologies* (Management Sciences for Health, 2011) [1]: medicines are costly, but they "can save lives and improve health, and they promote trust and participation in the health system". This text has also popularized a technical approach to understanding access to medicines, as a consequence of the efforts in relation to selection, procurement, distribution and use, underpinned by a management support function, and operating within an environment described by policy, law and regulation. In the same vein, access to health care has been defined in terms of availability and adequacy of supply [2]. However, it has also been acknowledged that other factors may impact on access, such as social or cultural barriers. Accordingly, it has been stated that access is "dependent on the affordability, physical accessibility and acceptability of services and not merely adequacy of supply" [2]. The lack of a simple and widely applied definition of "access to medicine" was cited as a barrier to measuring the extent to which "obtaining the needed medicine" was achieved in different settings [3].

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More recently, two comprehensive conceptual models for access have been advanced, one specifically aimed at access to medicines. A patient-centred conceptualization has emphasized five dimensions of accessibility (approachability, acceptability, availability and accommodation, affordability and appropriateness) [4]. However, this conceptualization has also placed emphasis on the abilities of populations to interact with the health system, in terms of their ability to perceive, to seek, to reach, to pay and to engage. Building on the World Health Organization's 2004 access framework (which emphasized the interaction of rational selection, affordable prices, sustainable financing and reliable health systems), a comprehensive conceptual framework has been advanced that views access to medicines from a health systems perspective [5]. This chapter draws on the following elements of this framework to examine access to medicines for children in developing countries:

- Issues relevant to individuals, households and communities
- Issues relevant to the resources building-block of the health system (focused on availability, accessibility, affordability, acceptability and quality of medicines for children, but also on health financing, health information and human resources)
- Issues related to governance (including consideration of the impact of market forces, innovation, transparency and donors' agenda and funding)

Recognizing that improved access to medicines is a prerequisite to improved health outcomes in children, the World Health Assembly in May 2007 passed a resolution (WHA60.20) identifying key steps to improve the medicines situation for children [6]. The Resolution urged the 193 member states "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". While monitoring prices may appear at first glance to be a rather limited intervention, it needs to be placed in the context of wider efforts at the international level to develop accessible methods for comparing medicine prices and to identify the policy options that governments and health systems might employ to address the cost of all medicines, including those for children [7].

Individuals, Households and Communities

A patient-centred approach to the question of access starts from the realization that the demand-side factors are as important as the supply-side. In well-resourced countries where the population is aware of its human rights and is able to exercise such rights through mature systems of governance, demand for equitable access to quality health care, including access to appropriate medicines for all, is likely to be met by the health system. However, in countries where health systems are competing with other pressing needs, and where populations are unaware of their basic health rights, or unable to exercise those rights freely, access to health services, including medicines for children, may be severely restricted. The plight of children is often forgotten because they are voiceless and voteless. It is left to local and international

organizations who have the best interest of the poor and the young at heart to fight for the rights of children to access quality essential medicines.

A major issue that limits access of children to health services is the inflexibility of the system, and its inability to accommodate the lifestyle of children. Schooling forms a major part of a child's life and the frequency of administration of the majority of medicines for childhood illnesses may mean that a child has to miss school or miss some doses of the medicines. Such trade-offs are challenging for the caregiver to weigh.

A key determinant of health-and medicines-seeking behaviour is the extent to which individuals, households and communities have access to the financial resources necessary to access care. The provision of inappropriate medicines may place an added burden on families. Where appropriate policies guide the quality use of medicines, such costs may be minimized [8]. Access to medicines for children is also hampered by the fact that they often depend on a caregiver to take them to the health care facility, obtain the medicines and then administer them. In resource limited settings, the caregiver who brings the child to the health facility is often not the one who administers the medicines to the child, yet this is the person who receives instructions on how to administer the medicines. Over time, different caregivers may attend health facilities with the same child, with potentially serious consequences for those requiring consistent longer term care. Often, medicines for children, particularly antibiotics, require storage in the refrigerator after reconstitution and access to refrigeration facilities (and energy) is very limited in such settings. Medicines for children, where available, are more complex to prepare and administer than those for adults. Often, in resource-limited settings, these processes are delegated to the caregiver, without the necessary information or resources. Challenges such as the ability to accurately measure an oral liquid medicine become barriers to access. Specialized dosing devices for very young children may not be available or affordable.

The Resources Building Block of Health Systems

Health Financing, Selection and Human Resources

The supply-side elements of medicines access are those related to the resources necessary to deliver care, in terms of health financing, human resources, health information and the medicines themselves.

Health financing options can have a marked impact on access, especially where user fees at the point of care represent a significant barrier. However, even where user fees are not a major element, the adequacy of budgetary provisions for medicines for children may be questionable. Medicines in liquid form are often more expensive, difficult to transport, may require specific storage conditions (such as refrigeration) and may not be available in resource-constrained settings. Universal health coverage is receiving increasing attention, particularly in low- and

middle-income countries, as a means to improve access to health care services and products. It has been argued that equitable access can be advanced by prioritizing the needs of women and children first, such as by providing free services at the point of care to these easily identifiable groups [9] (see also Chap. 29).

Safe and effective use of medicines in children requires access to the necessary human resources. Suitably trained personnel also need to have access to the necessary information resources to guide quality care. In terms of paediatric pharmacotherapy, a full complement of medical, nursing and pharmacy personnel are needed. All are in short supply in many developing countries. For instance, based on 2004 data, only 7 of 46 countries in the African region had access to 20 or more pharmacists per 100,000 population [10].

Access to medicines for children, particularly in countries where public sector provision predominates, depends to a large extent on the selection of such medicines for national or subnational essential medicines lists, and their inclusion in standard treatment guidelines. Globally, a World Health Assembly resolution (WHA60.20) [6] informed a concerted effort to address access to medicines for children, starting with the development of the World Health Organization (WHO) Model Essential Medicines List for Children in 2007 [11, 12]. Up to that date, while some medicines for children had been included in the previous editions of the WHO Model List of Essential Medicines, no systematic attempt had been made to ensure that all necessary medicines were listed. However, the preparation of a model list at the global level is insufficient, if the necessary selection decisions are not taken at national and subnational levels. In mid-2007, a survey was conducted of the inclusion of 17 medicines for children (in 20 dosage forms) in the standard treatment guidelines/essential medicines lists of 14 African countries [13]. The proportion of medicines listed varied from 50 to 90 %. However, in only four countries was a match shown between what was included on the list and what was mentioned in local treatment guidelines. Where inclusion on the list is a prerequisite for procurement, inclusion only in the treatment guidelines may not ensure access.

Where there is confusion about the best selection, access may be hampered. This is well illustrated by the proliferation of formulations that have emerged for paediatric antiretrovirals. In 2013, a UNAIDS task team developed a criteria-based formulary review process to arrive at a list of optimal paediatric antiretroviral products (The Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women Mothers and Children, 2013) [14]. The numerous options for paediatric medicines, combined with relatively low paediatric patient numbers, make these medications vulnerable to supply disruptions and stock-outs. By consolidating demand around an optimal subset of products, the fragmentation of procurement orders across multiple, and often duplicative products is eliminated and the reliable delivery of high quality, cost-effective, paediatric-adapted products can be assured.

While it is an important tool, an essential medicines list alone cannot guarantee access, in the absence of a well-functioning logistics system which ensures procurement and effective distribution. The limitations of isolated selection decisions are perfectly illustrated by the challenges of ensuring access to low-osmolarity oral rehydration salts and zinc supplementation for diarrhoea in children [15]. Despite a

clear signal from WHO in 2004, endorsement from UNICEF and support from other donors, as well as inclusion in local guidelines and essential medicines lists, access to both products has been slow. Changes to local manufacturing of oral rehydration salts lagged behind the policy process. More importantly, few commercial suppliers of palatable, dispersible zinc tablets have emerged internationally. Globally, progress has been slow in the last 5 years, with very few suitable zinc products available in African countries [16]. However, where local manufacture, the deliberate removal of regulatory barriers (such as allowing over-the-counter sale) and social marketing have been combined, progress has been possible [17].

The selection of medicines for children is guided by the available evidence, most importantly from well-designed and executed clinical trials in the age groups of interest. Historically, there has been reluctance to conduct clinical trials in children, informed by misplaced concerns about the ethics and feasibility of such trials. A comparison of the numbers of prescription medicines specifically labelled for children and subsidized for government-funded care in the United Kingdom, Australia and New Zealand in 1998, 2002 and 2007 showed interesting trends [18]. There were considerably fewer medicines registered and listed for children than for adults at all three time points in all three countries. Over the period, the number decreased in the United Kingdom (albeit from a higher starting point), but increased in Australia and New Zealand. These are all sophisticated developed countries with well-established national health systems. The situation in developing countries that are only now embarking on efforts to ensure universal health care coverage can be expected to be far worse. Although both US and European regulators have put in place legislative amendments to both require the completion of paediatric investigations where these are warranted and systems to reward holders of marketing authorization that provide such data, these interventions have not been replicated in developing countries. It is unclear whether the sanctions and rewards applied in developed countries would be as effective in the smaller and more dependent markets of developing countries. In addition, there is evidence that even the strong carrot-and-stick measures in Europe and the United States have failed to make sufficient inroads in relation to two key gaps: studies in neonatal patients, and the development of age-appropriate paediatric dosage forms. [19] The most recent version of the US legislation requires the regulator to explain its rationale when requesting studies that do not include neonates. This may go some way to raising the profile of neonatal needs in the development of new medicines. However, for older, off-patent products that may be needed in neonatal populations, the situation is far more dire. There are few incentives, for example, to develop neonate-appropriate dosage forms and strengths of injectable opioid analgesics, such as morphine.

Two disease areas provide examples of the progress that can be made, and both reflect the efforts of government-funded research structures, rather than the market-driven actions of manufacturers or developers of new medicines [19]. These are the Children's Oncology Group and the International Maternal Pediatric Adolescent AIDS Clinical Trials network. Nonetheless, moving from research evidence to rational selection and finally to availability and accessibility remains a long process. In 2013, the Working Group on Essential Medicines of the Pediatric Oncology in

Developing Countries committee of the Societe d'Oncologie Pediatrique (SIOP) produced a list of 51 medicines (including chemotherapeutics, infectious disease agents and supportive care medicines) that it considered essential to improving the survival of children with cancer in low- and middle-income countries [20]. An additional 13 medicines were identified as being of further value in this age group. In justifying the need for the inclusion of such medicines on national selections, the group pointed to the high burden of cancer in children in developing countries, estimated to represent at least 80 % of incident cases globally. Importantly, the Working Group noted that all of the medicines on their list already appeared in the 2011 edition of the WHO Model Essential Medicines List. Two areas of challenge remain: ensuring the inclusion of at least the basic list in all country lists in settings where the minimum level of care can be ensured, and then advocating for the extension to the larger list in those settings where more advanced care is possible. Cancer does not, unfortunately, enjoy the global access to donor funding that has been developed for AIDS, tuberculosis and malaria. The same can probably be said of chronic non-communicable diseases that affect children, such as asthma, diabetes and epilepsy.

The situation with age-appropriate dosage forms is also more complex and resistant to intervention on the basis of the existing carrot-and-stick legislation. A systematic review of the literature has shown that evidence for the effects of the pharmaceutical technology aspects of paediatric oral medicines (such as taste, route and frequency of administration, user instructions) on patient-related outcomes (such as efficacy, tolerability, patient preferences and adherence) is generally lacking [21]. Although 94 publications were retrieved, only 2 were regarded as methodologically sound. The majority of the studies retrieved were conducted in North America (51 %) or Europe (29 %). The specific needs of paediatric patients in resource-constrained settings are therefore unlikely to have shaped this research agenda. Likewise, the guidance on formulations of choice that are issued by major regulators in developed countries are also not expected to take into account the needs of children in developing countries. Where, for example, preference is expressed for oral liquid formulations, this ignores the problems of transport, specific storage conditions and higher costs that are expected with such dosage forms.

The evidence submitted for regulatory approval not only informs approved labelling, but is also the basis for the development of medicines information resources, such as formularies. While some progress has been achieved with the development of paediatric-specific formularies, such as the regularly updated British National Formulary for Children (BNF-C) and the WHO Model Formulary for Children (which drew extensively on the BNF-C), this effort has not been replicated in developing countries. Although the WHO Model Formularies are intended as the starting points for national efforts, to be adapted and amended as needed to reflect national selection decisions and needs, the development process remains onerous and is therefore dependent on access to significant local capacity and/or funding.

Using paediatric tuberculosis as the starting point, an extensive review of the sociocultural, pharmacological and structural barriers that impede the delivery of medicines to children was published in 2009 [22]. Beyond the technical aspects of dosage form design, palatability and the physical attributes of medicines can have

profound impact on caregivers' and patients' behaviour. The authors identified a lack of palatability studies in developing country settings. Definitions of what constitutes a "child" are also culturally bound, affecting local pharmacotherapeutic decision-making. There is also a lack of data on how illness classification varies in different settings, and how this impacts on health-seeking behaviour.

Availability, Accessibility and Affordability

The rational selection of medicines is a necessary, but on its own insufficient, element determining access. Medicines may well appear on the national essential medicines list, or be considered as reimbursable by insurance systems, but their physical availability at the point of care may be uncertain. Even when physically present at health facilities, such medicines may not be accessible to patients in need, or affordable.

Although the survey conducted in 14 African countries in mid-2007 showed only minor differences between what appeared in local standard treatment guidelines and essential medicines lists, a far lower proportion were available at central medical stores [13]. In only 3 of 14 countries were more than 50 % of the medicines for children that appeared on the national essential medicines list available in the central medical stores at the time of the survey. The medicines that were least likely to be found included rifampicin oral liquid (essential for the first-line treatment of tuberculosis), vitamin A liquid in a capsule (an important routine supplement in such settings), zinc dispersible tablets (for acute diarrhoea) and beclometasone inhaler (essential for the long-term management of persistent asthma). However, medicines at central stores are also not accessible to patients. This cross-sectional survey showed that physical availability varied between settings, such as teaching hospitals (15–70 %), district hospitals (10–80 %), primary health care clinics (18–48 %) and private pharmacies (38–62 %). Generally, private sector facilities had more medicines available on the day of the survey than public sector facilities. While the highest prices charged were not always in the private sector, prices for the five medicines for which data was sought were generally lower in the public sector.

Other studies have also highlighted less than acceptable levels of availability of medicines for paediatric populations. A cross-sectional survey of 124 birth centres in 41 countries in Africa and Asia showed that facilities in low-income countries were less likely to have access to vitamin K than middle-income or upper-middle income countries [23]. As expected, facilities with a higher volume of births recorded per annum were more likely to have access to necessary technologies, including medicines, than those with lower volumes. Lower volume facilities are likely to be more remote, such as in rural and underserved areas. Although not specifically directed at medicines for children, surveys of the availability and affordability of essential medicines for chronic noncommunicable diseases conducted in six low- and middle-income countries showed poor access to key medicines that are relevant to children [24]. The availability of soluble insulin in representative public

and private sector medicine outlets, expressed as the percentage of facilities in which one innovator or one generic brand was found, varied from just 0.5 % in Pakistan to 40.8 % in Sri Lanka. The availability of beclometasone inhaler varied from 0.2 % in Nepal to 35.0 % in Sri Lanka. A number of studies of availability and affordability of medicines in particular countries have been conducted using the methodology developed by the WHO and Health Action International (HAI). These have included some medicines of relevance to children. For example, a survey in Malaysia also showed low availability of beclometasone inhaler [25, 26].

Availability of medicines at the point of care generally depends on the presence of an effective and efficient pharmaceutical service, also referred to as supply chain management. A review of the literature, focused on a list of potential pharmacy interventions, showed a paucity of evidence [27]. Among the pharmaceutical systems interventions that were expected to improve availability were improvements to procurement and distribution systems (including efforts to increase the involvement of the private sector), efforts to increase resources through user fees (while considering the potential negative impacts on affordability), the use of revolving funds, disease or medicine-specific programmes, structured supervision of frontline staff, training or continuing education, community-directed interventions, nonmonetary staff incentives and the establishment of national pharmacy standards. While some evidence was found for staff training and disease or medicine-specific programmes, none was found for nonmonetary staff incentives or national pharmacy standards. Only staff supervision and community-directed interventions were considered to be supported by good evidence. The evidence for staff supervision came from a single, randomized trial conducted in Zimbabwe, where the supervision programme provided instruction and guidelines on stock management and adherence to treatment guidelines. The evidence in relation to community-directed interventions came predominantly from a multi-country study (Cameroon, Uganda, Nigeria) in which participatory meetings were held between community members and health services to consider possible interventions, including commodity distribution processes, and the selection and use of community "implementers" responsible for oversight and liaison. For the balance, the evidence was weak or mixed. The authors noted the disparate definitions of medicines availability that were used, and that in some cases, no definition was recorded. The same can be said for the broader construct of access.

Another barrier to access is when medicines are not licensed for use in children. This is often the case with neonates, where off-label use of medicines is prevalent. Often, where medicines are licensed for specific indications, neither health workers nor caregivers have the capacity to check what the approved labelling might be. Absence of reliable reference information in low-resource settings is a major barrier.

All of the issues above point to the need to design medicines that are specifically targeted for children and to allocate resources for their procurement, distribution and eventual use. The challenge to the pharmaceutical industry is to make orally administered child-specific medicines that do not require weight-based dosing, complex reconstitution steps, cold storage and accurate measurement. Dispersible tablets offer a potential solution, but other options also exist. The commercial lifespan of medicines is short, because of the rapid pace at which clinical recommenda-

tions evolve. This places added pressure on an industry that is under considerable cost pressure.

Even where medicines are available and perhaps accessible and affordable, questions need to be asked about their quality. A reliable pharmaceutical system will also include effective registration of medicines and the assurance of continued quality through compliance with current Good Manufacturing Practice and Good Distribution Practice. A review of the available quality studies of medicines on the WHO Model List of Essential Medicines for Children identified 70 articles, describing the quality of 75 medicines from 28 developing countries [26]. Only a small proportion of these studies were specifically targeting paediatric medicines. Of the products identified by the WHO as of high priority, it was notable that no quality studies were reported on zinc, morphine and vitamin A. The authors noted that a number of studies which identified sub-standard medicines attributed this to counterfeiting. However, poor manufacturing standards or poor storage were considered to be more important contributors to low quality. Overall, though, the degree to which products are appropriate sampled from the distribution chain and tested for quality needs attention across the developing world. The review also highlighted the potential risks with extemporaneously compounded medicines. Pharmacy compounding was considered to be a "measure of last resort in dispensing paediatric medicines", but is commonly required where health systems fail to procure and make available age-appropriate dosage forms, or where such dosage forms are not commercially available.

Governance Issues

The global gap between the medicines that are needed and those that are accessible has been referred to as "morally uncomfortable" [28]. Cohen-Kohler has pointed to the slow realization that the tools are at hand to address at least some of the barriers, such as the flexibilities that have been identified in the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). The intellectual property regime lies at the very core of the system of innovation that is currently in place, despite the realization that alternatives are needed. Children, in that sense, can also be regarded as "neglected", and hence deserving of specific and close attention. However, it is not only intellectual property provisions, including provisions on data exclusivity, which contribute to high costs of medicines. Locally applied taxes and mark-ups also need careful attention [29]. It has also been argued that recognizing access to essential medicines (not only, but also for children) as a human right has implications for the way in which intellectual property rights can be limited [30].

Given the evident inequality in access to medicines between children presenting to rural or urban health care facilities, governments are also under a moral (and in some cases constitutional) obligation to ensure the progressive realization of the right to access health care services. The inequality in access is often based on poor infrastructure for the procurement and distribution of medications, budgetary constraints and the lack of efficient management systems to identify problems. The

urban–rural dichotomy is sometimes stark and requires deliberate interventions. Any access policy must start and end with a process of surveillance, monitoring and evaluation, from the determination of need to the active monitoring of service levels, including medicine stock-outs. A deliberate intervention requires the continual review of outcomes in order to review progress. The community viewpoint on the successes and failures of any such a programme should always be sought.

Conclusions and Recommendations

Access to essential medicines for children is a complex construct, which requires attention to all elements of the medicines use cycle (selection, procurement, distribution and use), but also to issues related to health-seeking behaviour, beliefs and practices at a community and individual level, as well as to the broader governance of the health system and its component parts. It also requires active engagement with research and development entities and manufacturers as partners. The available data on the degree to which children in developing countries enjoy access to essential medicines is sparse. However, there is every reason to believe that access for children is even worse than it is for the population as a whole. While some progress has been made in relation to specific high-profile diseases (such as AIDS, tuberculosis and malaria), much more needs to be done across the therapeutic spectrum. There is an increasing focus on access to medicines for noncommunicable diseases, including cancer, but specific attention will still be needed to the needs of children. One of the key factors that hampers research into access is the lack of a clear definition of availability of medicine. There is also a lack of evidence to guide interventions aimed at enhancing access to essential medicines for children in developing countries. Health systems strengthening efforts need attention to all of the building blocks, not just the logistics system. This includes access to suitably trained prescribers and dispensers, and attention to the information needs of such staff. Locally relevant formularies are still lacking in most settings, not only in developing countries. Lastly, while progress has been achieved with the legal interventions in the United States and Europe that have promoted the generation of data to support paediatric medicines registrations, the same mechanisms have not been applied across the developing world, and may not be feasible in such settings. Continued attention is therefore needed to the system of innovation and to measures that can advance access to age-appropriate dosage forms.

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Chapter 4
Challenges in Pediatric Oral Dosing

Jennifer L. Goldman, Atieno Ojoo, and Susan M. Abdel-Rahman

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 formulations are missing from the spectrum of available treatment options. [Dr Howard Zucker, Assistant-Director General at World Health Organization, 2006]

The safe administration of medicines to children relies on several critical factors; among these are the provider's ability to correctly determine the drug dose, and the caregiver's ability to accurately administer the desired medication. This chapter discusses a few of the challenges surrounding optimal dosing in children, particularly those in the setting of limited resources.

Determining the Weight of a Child

In pediatric medicine, weight, like other vital signs, should be assessed at each medical visit to assure adequate development and signal potential health issues (e.g. underlying illness, behavioral change). Weight also serves as the foundation for appropriate

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drug dosing. The vast majority of pediatric medicines are administered on a milligram-per-kilogram basis necessitating an accurate patient weight. In developed countries where resources are abundant, obtaining a child's weight is routine; however, in resource-limited settings, determining an accurate weight can be far more challenging. The majority of community workers and health care providers in these settings simply do not have access to functional, calibrated, scales [1–4]. Contributing to the inaccessibility of weighing scales are (1) costs related to their acquisition, maintenance, and calibration, (2) difficulties in transporting them between sites, and (3) facility requirements needed for their proper use (e.g. a level surface for balance beam scales, electricity for bench scales, a suitable supporting rod for hanging scales) [5]. Further, the demands placed on health care facilities in resource-restrained settings can be overwhelming and many health providers do not have the necessary time or ancillary staff to obtain patients' weights, even when a scale is available.

As an alternative to the universal gold standard, there have been numerous attempts to identify a surrogate method for weight estimation. These strategies incorporate one or more patient specific variables, each of which correlate with total body weight to varying degrees. Importantly, the majority of these strategies were conceived of for emergency and trauma settings where speed is generally favored over accuracy and only a limited repertoire of medications are employed. Consequently, there has been mixed success when trying to extend these methods to primary care settings where the balance of acuity and accuracy shifts. The sections below provide a general overview of the categories of weight estimation methods.

Age-Based Weight Estimation

Weight estimation methods that are based on age account for the majority of clinically applied estimation approaches (Table 4.1) [6–27]. Most methods were developed in a single ethnic population and all possess upper and lower age limits within which they can be applied. Each method relies on anywhere from one to three relatively simple mathematical calculations which incorporate age in months or years.

Age-based methods tend to decrease in accuracy at the extremes of age. They also tend to overestimate weight in underweight or malnourished children and underestimate weight in children that are overweight or obese [28]. When we examine the performance of selected age-based methods in children under 5 years of age whose weight sits at either the 3rd or 97th percentile as defined by the World Health Organization (WHO) [29], we observe that estimated weights can be as much as 80 % higher and 40 % lower than actual weights in children that are underweight and overweight, respectively (Fig. 4.1). These inaccuracies would result in significant dosing errors with potentially untoward effects for many medications.

Apart from their issues of accuracy, age-based weight estimation methods have pragmatic limitations which include (1) the potential for calculation errors, the rates of which differ depending on the mathematical order of operations nested into the equations, and (2) the reality that in developing settings, the age of a child may simply be unknown as dates and times are a less integral part of daily life.

Table 4.1 Published, peer-reviewed weight estimation methods

Basis	Method	Source population	Restrictions
Age	Ali [6]	Trinidad ($n=1,723$)	1–5 years
	APLS (original and revised) [7, 8]	Not available	1–12 years
	ARC [9]	Not available	>1 year
	Argall [10]	UK ($n=300$)	1–10 years
	Best Guess [11]	Australia ($n=70,181$)	<14 years
	Leffler [12]	Not available	<10 years
	Luscombe-Owens [13]	UK ($n=13,998$)	1–10 years
	Nelson [14]	Not available	3 months – 12 years
	Park [15]	Korea ($n=124,095$)	<14 years
	Shann [16]	Not available	>1 year
	Theron [16]	Pacific Islands ($n=909$)	1–10 years
Length	Broselow [17]	US ($n>20,000$)	46–143 cm and <12 years
	Malawi [18]	Malawi ($n=729$)	45–130 cm
	Oakley [19]	Not available	50–160 cm and <14 years
	Traub-Johnson [20]	US ($n=122$)	1–18 years
	Traub-Kitchen [21]	US ($n>20,000$)	1–17 years and >74 cm
Habitus	Cattermole [22]	Hong Kong ($n=1,370$)	6–11 years
	Dhar [23]	Bangladesh ($n=316$)	Newborns
	Taufiq [24]	Indonesia ($n=892$)	Newborns
Length and habitus	DWEM [25]	US ($n=258$)	50–175 cm
	Mercy (method and TAPE) [26, 27]	US ($n=19,625$)	2 months – 16 years

Length-Based Weight Estimation

Length serves as the second most commonly used surrogate in pediatric weight estimation methods (Table 4.1) [6–27]. All of these methods require total body length and are capped at a predefined minimum and maximum length. Some require mathematical manipulation of length as derived from a standard tape measure; however, these also require more complex equations which could not be reasonably solved without a scientific calculator [20, 21]. Others are integrated into a proprietary measuring device which provides a weight without the need for added calculations [17]. Importantly, the most commonly used length-based method (i.e. the Broselow tape) was designed to predict ideal body weight for US children. This severely limits its applicability in children who are either malnourished or overweight and has prompted some investigators to explore adjustments to the device that account for regional differences in body habitus [18].

Similar to age-based methods, the use of a single patient-specific variable results in increased bias at the extremes of age and weight. A similar exercise evaluating

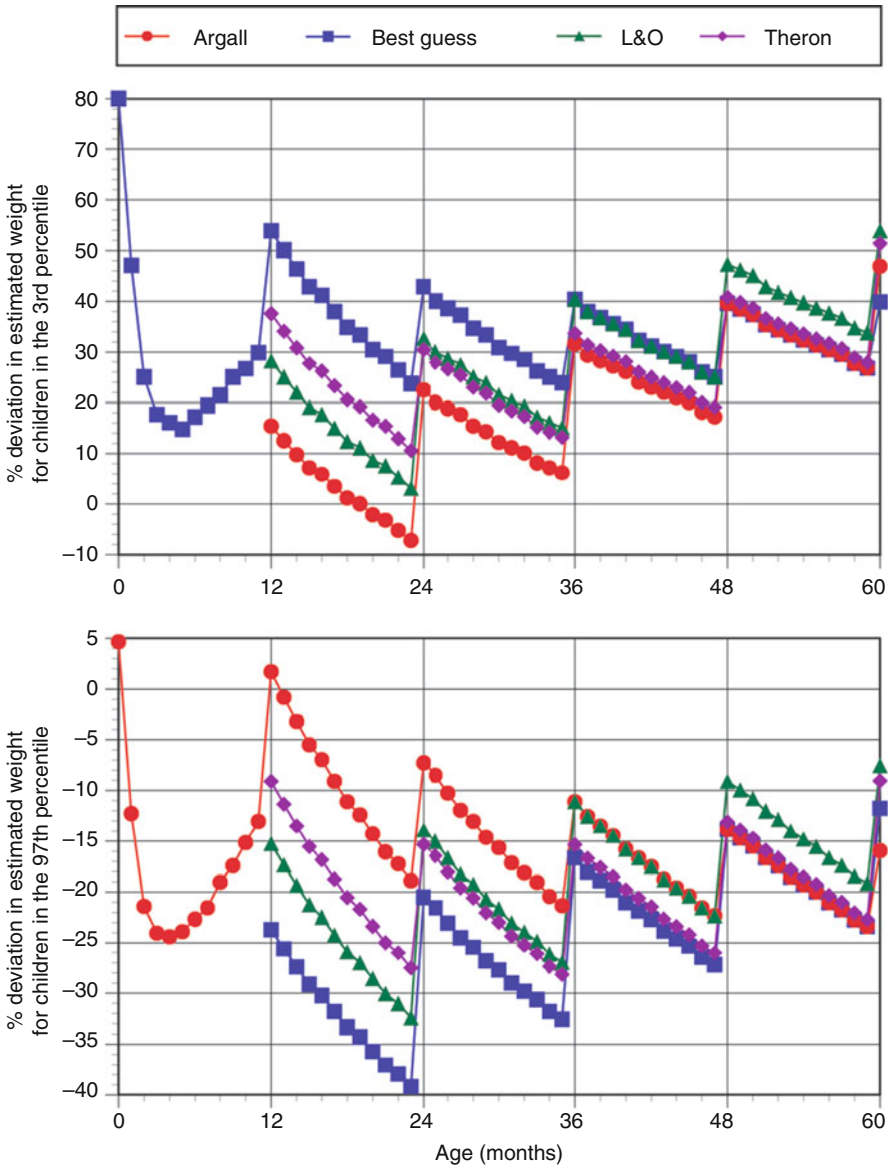

Fig. 4.1 Deviations between estimated weight and actual weight determined by four age-based weight estimation methods

the performance of selected length-based methods in children under 5 years of age whose height is at either the 3rd or the 97th percentile as defined by WHO [29], reveals estimates of bias that can exceed 30 % with some of these methods (Fig. 4.2). The more pragmatic limitations of these methods include the fact that (1) all require an external measuring device, which may be costly, and (2) obtaining an accurate total body length can be challenging in an uncooperative child.

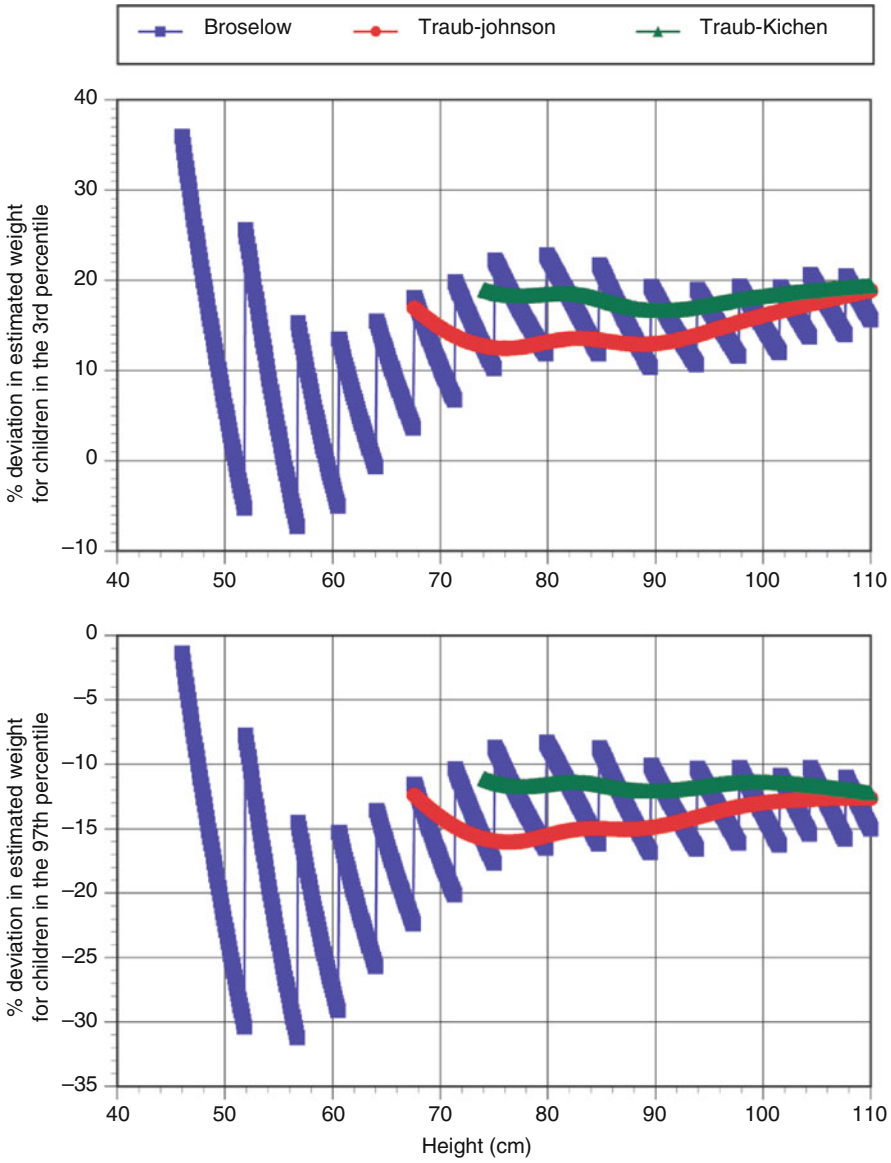

Fig. 4.2 Deviations between estimated weight and actual weight determined by three length-based weight estimation methods

Habitus-Based Weight Estimation

The central principle of habitus-based methods is that selected anatomic locations offer a reasonable approximation of the bone:muscle:fat ratio in the entire body [30]. Historically, these methods have been used to provide a qualitative assessment

of nutritional status assessment; however, attempts to apply them to weight estimation have recently emerged (Table 4.1) [6–27]. Essentially all of these methods are restricted to very narrow age ranges (e.g. infants or young children) and none have been validated outside of the ethnic population in which they were derived. As with length-based methods, these strategies require a measuring device and a reference table or equations to convert circumference to an estimated weight.

Dual Length- and Habitus-Based Weight Estimation

There are a few strategies that attempt to address the limitations of the methods described above by combining more than one patient-specific variable to estimate weight (Table 4.1) [6–27]. Both integrate length and girth surrogates, though one relies on a subjective assessment of habitus while the other uses a quantitative measure. This latter approach offered by the Mercy method and Mercy TAPE demonstrates markedly improved accuracy, irrespective of age and body mass index, across a broad range of ages (Fig. 4.3). These findings are supported by validation studies in children of ethnic and racial groups that differ from the population in which it was developed (e.g. West Africa and India) [31, 32]. As denoted for the length-based methods, these dual methods also require a reference measuring device with or without a reference table for implementation.

When scales are not readily available, the critical metric of weight cannot be integrated into pediatric health assessment and management. In much of the developing world, surrogates to estimate weight must be incorporated into medical care. This persistent need has served to challenge the scientific community for improved weight estimation methods and the result has been the recent development of some highly accurate tools. However, the ultimate success of any of these weight-estimation technologies requires that they be readily accessible, easy to use, and accurate across a broad range of children. Recognizing the strengths and limitations of the various strategies should enable the health care provider to identify the tool that is most closely suited to the needs of their population.

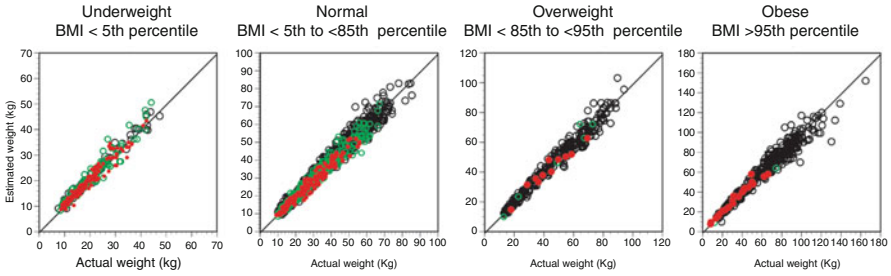

Fig. 4.3 Predictive performance of the Mercy method by BMI percentile group in children from North America (*black circles*), Africa (*green circles*), and South Asia (*red circles*)

Measuring and Delivering the Right Oral Dose to a Child

Even when an accurate weight can be estimated, and the correct drug dose determined, administration of medications to children can be fraught with challenges. Not only must the child be willing to accept the medication but a caregiver must be willing to participate in a process that assures the correct dose is administered, at the appropriate time, every time. Even the most dedicated of caregivers can be tested when the necessary medications are unpalatable, unavailable, or unsuited for children. This section examines some of the challenges in pediatric drug administration and touches on some of the innovative strategies being evaluated to improve drug delivery in children.

Oral Liquid Formulations

Oral liquids are frequently the preferred formulation for drug administration in young children. For these formulations safety and efficacy depend, in large part, on the accuracy with which the prescribed volume can be measured and administered. Droppers, oral syringes, dosing cups, and dosing spoons are commonly used for medication administration but it is very common to see administration extended to household spoons and other uncalibrated measuring devices. Oral dosing syringes offer the most accurate delivery; however, cost and availability may restrict their use in resource-limited areas [33].

Accuracy of delivery is also influenced by the final concentration of the preparation. Drugs that are manufactured at high concentrations result in overall volume requirements that may be quite small in the newborn or young infant. Though medication droppers are expressly designed for this purpose, the residual volumes they retain can result in smaller than intended doses being administered with an undesirable impact on drug exposure [34]. By contrast, formulations that are excessively dilute can result in dose volumes that exceed the functional gastric volume of a young infant and may not be tolerated by an older child. For the latter population there exists the option to transition to solid dosage forms; however, reliable data on the differences in bioequivalence between formulations is critical to assure therapeutically equivalent dosing [35].

Powders and tablets for oral suspension/solution are partial alternatives to ready-to-use oral liquids. They retain the stability of solid oral dosage forms and are only reconstituted when dispensed making them easy to transport and store. However, some reconstituted powders require refrigeration which may serve as the limiting factor for their use in resource-limited settings that lack access to electricity or refrigeration. In contrast to powders, tablets for oral suspension/solution (i.e. dispersible tablets) have the advantage of single dose reconstitution at the time of administration relieving requirements for refrigeration. At present, these formulations offer the most optimal solution for children across a spectrum of ages.

Oral Solid Formulations

Though liquid formulations are preferred for administering medications to infants and toddlers, they are often unavailable or prohibitively expensive in resource restricted settings [36]. Consequently, practitioners frequently modify solid oral dosage forms that are intended for adults. The principal challenge in doing so is delivering a dose with the desired level of precision. Some products are not intended to be crushed or split and those that are may require being split in fourths, eights, or tenths to accommodate the dosing needs of the child. The challenges of pill splitting are compounded by uneven breaking, crumbling, and crush resistant coatings that result in doses of varying strength [37]. While this variance will not be clinically significant in all cases, for drugs that have a narrow therapeutic index and/or a significant toxicity profile there may be significant clinical consequences.

Additional manipulation of solid oral dosage forms is accomplished with extemporaneous compounding; however, crushing medications and dispersing the contents in water can be fraught with risks. Drugs that are insoluble in water may not disperse uniformly without the addition of suspending agents. If not completely administered, the delivered doses may not be uniform. Further, the stability of the active ingredient can be compromised depending on the nature of the vehicle being used for dissolution. There is also evidence for unanticipated physicochemical interactions with the delivery container in which the formulation is dispensed that can severely influence bioavailability [38]. Perhaps most relevant to children in developing countries is access to uncontaminated (e.g. chemical, microbial) drinking water, without which safe medication administration can be an insurmountable task.

Extemporaneous admixtures of crushed solid dosage forms with food stuffs present their own challenges. Some oral powders or granules can be safely sprinkled on food to increase palatability and easy administration. However the phytochemicals contained in selected foods and juices can interfere with intestinal transporters and drug metabolizing enzymes that act on these medications [39–42]. For other drugs, compromising the integrity of the formulation can interfere with absorption in ways that are unexpected and unexplained [43].

Novel Pediatric Formulations and Dosing Devices

Several new and innovative attempts have been made to improve dosing in children (Table 4.2). Though the strategies are varied, the goal of enhancing the accuracy of medication dosing in children is the unifying objective. Multiparticulate formulations (e.g. sprinkles, granules, minitablets) are products intended to ease swallowing. These formulations retain the advantages of an adult solid oral dosage form (e.g. stability, taste masking, ease of shipping),

and require no manipulation in the field, resulting in enhanced dosing accuracy [44, 45]. Orodispersible formulations (e.g. tablets, film strips, buccal wafers) which are designed to rapidly disintegrate in the mouth offer similar advantages and provide an alternative for those unable to swallow larger tablets or capsules [44, 45].

Several dosing devices have also been developed to optimize medication administration in children (Table 4.2). A few deliver medications in harmony with sucking or sipping when initiated by the infant/child; however, the child must be well enough to feed [46]. Others deliver single-dose servings of selected medications. These approaches address specific pediatric dosing challenges and have the potential to enhance adherence and accuracy; however, each is accompanied by unique limitations [47].

Table 4.2 Examples of novel dosing devices and formulation strategies

Method	Advantages	Limitations
Dosing devices		
Medibottle®	Avoids dilution of medication in larger volume	Expensive
	Masks bitter tasting medication	Requires administration with safe fluid
	User satisfaction	Potentially interferes with breastfeeding
Dose sipping straw	Improved palatability	Compatibility with different liquids is unknown
	No dose manipulation	
Single-use spoon	Avoids measuring error	Limited to prepackaged doses
Formulations		
Minitablets	No dose manipulation required	Theoretical risk of choking in younger children
	Enhanced drug stability	Multiple tablets per dose
	Sustained-release option	
Orodispersible formulations (disintegrating tablets, oral strips, buccal wafers, medicated lollipops)	No external liquid needed for ingestion	Single strength
	Not taste adverse	Unable to split or cut
	Alternative for pill swallowing	Rapid absorption with potential of toxic levels
		Require a moist palate
Dispersible tablets	Not taste adverse	Requires administration with safe fluid
	Easy to formulate to liquid	Unable to split or cut
	Prolonged stability	
	Alternative for pill swallowing	

Conclusions

Caregivers, health care providers, policy makers and drug developers must recognize the barriers faced when dosing medication for children. Having the tools to determine the correct dose for each child and having the ability to administer the correct dose are just some of the many challenges that must be overcome. Novel strategies are desperately needed to address the commonly encountered diseases such as malaria, HIV, and tuberculosis that plague resource-limited countries. The pediatric population is highly heterogenous and a single dosing strategy would be ill suited to all children. However, continuing on the current path wherein many of the strategies employed in the field are accompanied by little to no evidence of safety and efficacy is untenable. The need to develop safe, effective, readily available, easy to dose and well-tolerated medications remains clear. Although novel approaches to drug dosing in children continue to evolve, the transition from concept to actual clinical application, particularly in resource-limited regions of the world, remains stagnant, representing a public health challenge of the highest priority.

Key Messages

- Nearly all medicines for children should be dosed according to the weight of the child.
- Weight should be measured accurately at every health care visit.
- If weighing scales are not available, alternative methods to estimate weight might be used; however, not all are equally valid and reliable.
- Formulations of medicines for children need to be suitable to administer without requiring complex and expensive storage and delivery devices. At present oral dispersible dosage forms seem to be the best option.
- Giving medicines mixed with food is not always a reliable way to give the right dose to a child, even though it may be palatable.

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Chapter 5
Therapeutic Research in Low-Income Countries: Studying Trial Communities

Susan Reynolds Whyte

Introduction

Since the landmark introduction of randomized controlled trials (RCTs) in the 1940s, stringent statistical methods have become standard in medical research. As RCTs and other quantitative methods were further refined and more widely used, concern grew about the need to protect patients, especially the most vulnerable. The Helsinki Declaration of 1964 promoted the establishment of Research Ethics Committees, a trend strengthened by influential US agencies. Nonmaleficence, human rights and protection of individuals began to take precedence over beneficence as the objective of medical research ethics [1]. The 1990s saw the growth of Evidence-Based Medicine as a principle for policy and practice. Experimental, statistical, and epidemiological methods and models were extended to the evaluation of interventions in order to ensure that outcome assessments were scientifically sound. Increasing standardization included demonstration of adherence to ethical guidelines [2].

Ethical challenges are pronounced in research in developing countries. Concerns focus on the danger of exploiting poor individuals, subject to high levels of morbidity and low levels of health care, unfamiliar with scientific research and incapable of asserting their rights due to weak democratic structures. Children in developing countries are at a particular disadvantage since they are frequently ill, underresearched, and in need of safe 'child-size' medicines [3]. The issue of vulnerability takes on even greater urgency for small children who are dependent on adults. Bioethicists have played a leading role in moving considerations beyond a narrow

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focus on informed consent to guidelines of greater breadth and complexity. The ethical framework for research in developing countries proposed by Emanuel and colleagues, for example, sets out eight principles relevant for research on children as well as adults (Box 5.1) [4].

These efforts to ensure protection are commendable, but in codifying and institutionalizing ethical requirements, subtle matters of context, and community concern may be lost. Relationships and conditions of great importance to health in different social worlds can be ignored if they do not easily fit into the universal statistical frameworks of Evidence-Based Medicine and the institutional requirements of bioethics [2, 5]. In reports of research involving children, there is a lack of information on implementation processes, which would help in applying findings to different settings [6, 7]. Using qualitative methods, social scientists take up these matters with a commitment to widen the focus beyond ethics to ethos, that is, the study of values and perceptions as reflected in practice. To this end a conference on 'Studying Trial Communities' was held at the Kenyan Medical Research Institute (KEMRI) in Kilifi, Kenya in 2005. The participants, mainly anthropologists and historians, presented studies on the ethnography and history of medical research in Africa. The conference and subsequent related research have generated three special issues of journals [8–10] and an edited volume [11] that show how qualitative research can open a field to new insights (Box 5.2).

Box 5.1: Ethical Principles for Multinational Clinical Research [4]

- Collaborative partnership
- Social value
- Scientific validity
- Fair selection of study population
- Favourable risk–benefit ratio
- Independent review
- Informed consent
- Respect for recruited participants and study communities

Box 5.2: Research Findings on Trial Communities

- Object of study: relations between medical researchers, research staff, community members, families of research subjects
- Mediation: frontline research staff are the bridge between the protocol and community members
- 'Undue inducement': poor families are drawn by hope of better health care
- Ethics: overall inequalities are greater concerns to poor families than risks of participating in a specific trial
- Duration: enduring local institutions are more trusted as research implementers than short-lived projects

Trial Communities

Anthropologists have previously been called upon to contribute to therapeutic research by analysing illness perceptions, treatment seeking practices, and understanding of informed consent in local communities. One might call this 'ethnography in research'. What is new is the ambition to undertake 'ethnography of research'. The object of study is not just 'local communities' but 'trial communities': the networks and interactions that link local research subjects, other members of their society, different levels of research staff, health care providers, government officials, national and international academics, and funders [12]. In investigating trial communities, social scientists have focused on values (what is at stake for the diverse actors brought together in these networks), the qualities of social relations (trust, access to resources), and the political economy that ties seemingly disparate worlds together [13].

Researching trial communities allows recognition of the crucial role of local clinical staff and fieldworkers, who mediate the requirements of the research protocol and local realities. Although it is a hallmark of research that the investigator is responsible, the social science approach recognizes that in practice different positions within the trial community involve different roles and perspectives. As intermediaries, fieldworkers must explain inclusion and exclusion in the study, give information that is meaningful for local participants, and deal with the concrete tasks of taking blood, weighing children, administering medicines, and writing out records. Ethnographic research suggests that their representations of the research may be at odds with those of the senior research managers, in that they emphasize certain aspects, and try to describe procedures in ways that make sense to local people. Fairhead and colleagues describe the efforts of fieldworkers to explain a childhood pneumococcal vaccine trial in the Gambia. The fieldworkers asserted that they explained procedures to parents just as they had been trained to do, and the research managers confirmed this. However, fieldworkers added that they had to reformulate some aspects of trial procedures considered too difficult for villagers to grasp: '…fieldworkers' own narratives suggest a certain pride in finding creative ways to bridge the conceptual worlds of the trial, and of villagers'[14, p. 109].

Given that research staff are the daily practitioners of data acquisition, it is essential to examine their interactions with others in the trial community, their motivations, and their understandings of their jobs. In situations of high unemployment, they obviously appreciate the salaries and allowances provided by international research projects. (Large medical research organizations like Centers for Disease Control (CDC) and Medical Research Council (MRC) are among the biggest employers in the Kenyan towns of Kisumu and Kilifi; in Gambia the MRC is the third largest employer in the entire country [6].) But local staff enjoy more than their salaries. They acquire prestige through association with resourceful organizations. They value training, new knowledge, wider networks, and the broader social horizons of an international endeavour. Even the opportunity to interact with local residents in novel ways is appreciated. In eastern Uganda, staff told of more personal relations to mothers, who

continued to bring 'research' babies to show how well they were growing, even after the project closed. Those who work temporarily for a research project while simultaneously holding a position in a government health unit, gain new competences but are disappointed when the research project ends [15].

Trial communities have varying duration. Organizations like the CDC, the MRC, and the Wellcome Trust-KEMRI Unit are well established in certain locations, with impressive buildings and a history of relations with local residents and health care institutions. Often they are host to a series of research projects, sometimes employing the same local staff on one study after another. They can develop a long-term community engagement strategy [16]. Families gain experience with the organization and may develop a broad trust in it, not so much as a research centre as a provider of high quality medical care [17]. Demographic Surveillance Sites into which research projects are inserted have a similar persistence and familiarity. Research projects anchored in existing health care units, whether public or private, can have extended effects through the enduring host institution. The clinical trials of new drugs for the pharmaceutical industry that are carried out by contract research organizations create only transitory trial communities as testing sites shift and companies change [18]. However, no trial community provides the uninterrupted continuity of good health care that parents want for their children. Even long-standing organizations like MRC are characterized by successions of research projects. Thus health care is 'projectified' rather than being continuously available over the years.

Keeping Children Healthy

The combination of poverty, high infant morbidity and mortality, and poor health services means that keeping children alive and healthy is the highest priority for parents. Whether or not the research protocol spells out the provision of care for participants, parents perceive medical research projects as providing examinations, medicines, and (often) clinical care when a child falls sick [19–21]. Moreover, they provide contacts to fieldworkers, clinical staff, and ultimately international medical professionals.[15, 19] These benefits are far more important to parents than the research aims of the project. Molyneux and colleagues follow others in using the term 'therapeutic misconception' to denote the belief that the research project is primarily for the benefit of the study participant, and that it has a reasonable chance of success. They argue, however, that the term may not be appropriate where research projects provide quality health care in situations of poverty and insufficient public health services. In such trial communities, it may not be a misconception to conflate research and health care, and to perceive research projects as providing health benefits [17].

Keeping children healthy needs money as well as health care, a requirement that clinical research does not directly confront. The example in Box 5.3 shows that the study protocol and the public discourse of international scientific collaboration required one position, while another was based in the local reality of scarcity. HIV positive mothers appreciated transport reimbursement and medical care, and expensive

Box 5.3: Undue Inducement and Unspoken Realities of Poverty
At the regular weekly staff meeting of an HIV trial in Kenya, a clinician questioned the entitlement of a pregnant participant who needed a taxi to come to the clinic, but expected the standard cash 'travel reimbursement' in addition to provision of the taxi. For a moment, unspoken assumptions came out in the open. The fieldworkers present affirmed the necessity of travel reimbursement as a standard payment to all. But the more senior staff toed the bioethical line that study participants were not paid, only compensated for their actual expenses. Cash payment to poor people would constitute 'undue inducement' and would undermine the voluntary nature of participation in the study. Ethnographic research revealed that the senior staff, including the Principal Investigator, were aware that trial participants perceived transport reimbursement as payment (they walked and saved the money). The field staff, who lived in the same neighbourhoods as the trial subjects, encouraged mothers to use the transport money to buy food for their children.

brand name pharmaceuticals, in terms of money. What was never discussed openly as an ethical problem was the poverty of the research subjects. That would put the issue of undue inducement in another light. Acknowledging social injustices suggests the need to consider 'responsibility' and 'care' as frames for ethical concern [13].

Some of the most detailed ethnographies of medical research on children come from well-established research institutions in Africa. They show that relying on trusted research organizations is a strategy for keeping children healthy. In the Gambia, parents who consented for their children to be in the pneumococcal vaccine trial spoke of 'joining the MRC' rather than consenting to a trial. Given the hazards of raising an infant in an uncertain world, 'being with MRC' was a kind of insurance. In the MRC Birth Cohort Study, it was the routine examinations, health care, and plentiful supply of medicines that outweighed the dangers of taking blood and made 'belonging to MRC' the best option in the therapeutic landscape [20]. Similar findings are reported from Kenya. In Kisumu, HIV positive mothers in the CDC/KEMRI research also talked of 'being with' the study, implying a broad sense of attachment [13]. On the Kenyan coast, people spoke of those participating in a malaria vaccine trial and enjoying associated medical care as 'KEMRI's children'. They and their parents formed a community of 'trial participants' and to some extent saw themselves in opposition to nonparticipants [21].

Risk, Power Disparities, and Gender

Appreciation of the benefits of joining a medical research project was tempered with worries about risks. A major concern, which sometimes caused parents to withdraw their children from a trial, was the removal of blood from children [22].

Both in The Gambia and on the Kenya coast, parents were apprehensive that taking blood could weaken the child. Moreover, it might be surreptitiously tested for HIV; it might be sold, or used for nefarious purposes. In both locations, there was an implicit political critique in that white people were thought to desire African blood for their own secret ends [14], a suspicion that has surfaced at various points in African colonial and post-colonial history [23]. It is striking that these dangers were of a different order than those about which researchers informed potential study subjects: '…levels of perceived risk as illustrated in rumours and concerns were often far greater and more dramatic than the biomedical risks outlined in consent forms'[21, p. 716].

While mothers, who had the daily responsibility for care and seeking medical treatment, were positive about trials, they sometimes had to contend with objections from their husbands [14, 20]. In two malaria vaccine trials on healthy children in Kenya, both parents were invited to feedback meetings at the end of the projects, but very few fathers attended. It appeared that some mothers evaded their husbands' potential antipathy to the trials by emphasizing the benefits and not mentioning details that might be seen as negative [24].

Men were more suspicious of the motives of the researchers, perhaps because they were more politically conscious. The MRC in The Gambia and the KEMRI Unit in Kilifi addressed these concerns by directing communication to fathers, local chiefs, and other leaders. They thus recognized and confirmed local patterns of authority, even though they ultimately sought permission from individual parents and interacted mostly with mothers.

Ethics and Benefits

Social science studies of therapeutic research in Africa encompass the relations between all members of the trial community and place these in the context of political economy. Where levels of morbidity and poverty are high and public health services are weak, well-funded research programmes take on significance as providers of care, and even jobs. Locally employed research staff act as mediators between international researchers with their scientific protocols, and study subjects. While standard ethical guidelines require informed consent and avoidance of undue inducement, ethnographic research shows that everyday reality gives these considerations a different twist. There is a strong inducement, though perhaps not 'undue', to join a programme that provides medical care and other benefits [25]. Study participants are much more focused on the benefits for themselves and their children than on the research issues. Their willingness to participate and their concerns about risks have less to do with the details of a specific research project (outlined in an informed consent procedure), and more to do with the overall context of health care and past experience with the institutions and people conducting the intervention.

The social science research affirms the necessity of individual informed consent but also the need for a wider view of ethics. The primacy of medical care as a

motivation for parents should be reflected in more systematic information about clinical investigations and results and more effective communication about key elements of health care for children [26]. The relation of medical research projects to established research and clinical care institutions is crucial since these durable institutions form the nexus for broad-based trust or mistrust. Scepticism or refusal to participate is not just a problem to overcome. Under conditions like those investigated, there is need for healthy scepticism and open discussion of the broader concerns not addressed in the information given to prospective trial participants.

Research on trial communities has involved collaboration between medical and social science researchers. There is need for further dialogue and cooperation to extend this useful research and apply its results so that therapeutic trials contribute even more fully to improving health of children in developing countries.

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Chapter 6
MicroResearch: Finding Sustainable Local Health Solutions in East Africa Through Small Local Research Studies

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Background

In 2013, the United Nations proposed the *Action Agenda for Sustainable Development Goals (Action Agenda)* [1] as a means of building on the achievements of the *Millennium Development Goal*s (MDG), including those in health [2]. In limited resource countries, developing local capacity to improve on health gains as proposed in the *Action Agenda* will continue to be a major challenge since these countries bear 25 % of the global disease burden but have less than 1 % of its health care professionals [3]. Local research could help by finding local solutions for community health problems. However, capacity and resources for research within these

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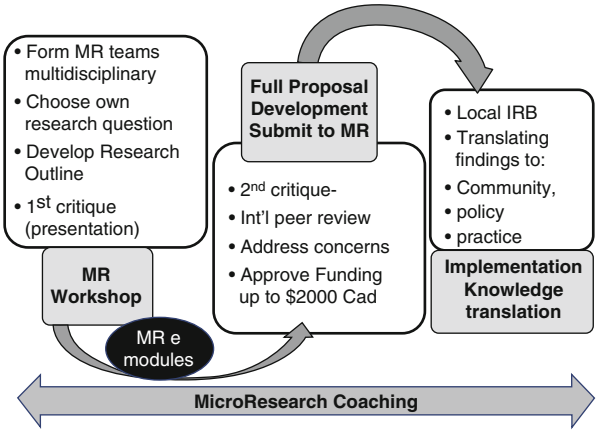

Fig. 6.1 MicroResearch program overview

countries are often limited. The 2008 Bamako "Call to Action" from the *Global Ministerial Forum on Research for Health* highlighted three critical objectives to enhance the capacity of the world's poorer nations to improve health for their citizens through research: (1) achieve greater equity in research; (2) make knowledge translation linking evidence to policy-making a priority; and (3) create stronger institutions for research [4]. The research gap for limited resource countries remains a major problem as they receive only 2 % of global research funding. In addition, much of the research undertaken in these countries is driven by the needs of industrialized countries for access to patient populations and data collection at modest cost [5]. This research model fails to expand local research capacity and to find the evidence needed to drive local policy.

Both the MDG and the *Action Agenda* encourage national and/or regional strategies and collaborations to address complex health problems. However, local health problems need sustainable, culturally appropriate community solutions to improve local health outcomes if the objectives of the *Action Agenda* are to be achieved.

MicroResearch (http://microresearch.ca/) is an innovative program developed in 2008 in East Africa aimed at enhancing the capacity of local health care professionals to find local solutions for community health problems that can then influence health programs and/or government policy [6]. MicroResearch has borrowed the principles of microfinance (train, coach and provide capital) while trying to avoid microfinance program problems, such as the negative impact of repayment of high interest loans and the focus on poorest of poor rather than on poor local entrepreneurs [7]. In place of small loans, MicroResearch provides small non-repayable research grants to teams of health care professionals keen to address community health problems through development of their own scientifically credible research proposals. The MicroResearch program has three integrated components: (1) 2-week long training workshops; (2) small grant proposal development with international peer review followed by project funding, implementation and knowledge translation; and (3) coaching throughout from experienced researchers (Fig. 6.1). As MicroResearch in East Africa is now 5 years old, the following study reports on its early outcomes and lessons learned.

Methods

Initially in 2008, then annually since 2010, 2-week long training workshops were carried out at each participating MicroResearch site in East Africa. Based upon initial local advice, these 10-day workshops were limited to half days to allow participating health care professionals to attend to clinical responsibilities in the off time. Participants were recruited through local posters, word of mouth and direct invitations developed by the local MicroResearch site leaders. Participation from any one discipline, such as nursing or medicine, was limited to no more than 50 % of participants in a workshop. Professionals from non-health disciplines (e.g., engineering, information technology, library sciences, etc.) were encouraged to participate in the training if their interests complemented health care needs.

At each workshop, participants were divided into interdisciplinary teams of 6–8 to learn the principles of health research, community engagement and knowledge translation through "hands on" development of a research proposal outline (Table 6.1).

Table 6.1 MicroResearch workshop outline

	Week 1		Week 2
Day 1	Welcome and introduction of faculty and participants Introduction to the workshop and objectives Introduction to the web program Defining the research question *Team activity: each course participant challenged to identify a community directed research question from their own experience.*	Day 6	Writing an abstract exercise Oral and poster exercise *Team activity: refine outline, consider budget*
Day 2	Principles of clinical research Pitfalls in research Getting started on writing a proposal *Team activity: the team selects one of the questions to develop into a research outline.*	Day 7	Principles of knowledge translation Moving research into policy exercise *Team activity: further refine outline.*
Day 3	What editors are looking for Team Reports – question selected and why *Team activity: refine research question; introduction team to their local coach*	Day 8	Principles of knowledge translation Moving research into policy *Team activity: refine outline, develop oral presentation*
Day 4	How a manuscript is reviewed Basics and local research ethics *Team activity: develop proposal background outline*	Day 9	Career documentation *Team activity: "Polish" outline for presentation.*
Day 5	Grant proposal review Writing a report *Team activity: refine background, looks at methodology, consider ethics for outline*	Day 10	Each MicroResearch team presents research outline to judges *Team activity: constructive critique each presentation, Awards and graduation ceremony*

As homework from Day 1, each participant was invited to formulate a community-directed research question to propose to their team on Day 2. Each team then reviewed the proposed questions and selected the best one, based on criteria learned on Day 1. Over the remainder of the workshop, each team refined their chosen question, developed a draft research outline and prepared a 10 min oral presentation of their outline. Each team was supported by a team workshop coach and the daily lectures focused on knowledge and skills needed to develop a research proposal. On Day 10, the first formal critique and feedback on the research outlines occurred after each team presented their 10 min summary and answered questions. A panel of senior faculty from the host site offered constructive criticisms of each research outline and judged whether the research outline should be developed into a full MicroResearch application and, if so, how it might be enhanced. The workshop curriculum was supplemented with online MicroResearch modules covering different research aspects to support the development of research knowledge and skills.

After the workshop, a local East African and an online Canadian or American MicroResearch coach helped each team judged worthy of moving on to develop a full research application to one of the twice yearly MicroResearch grant opportunities (grants up to $2,000 CAD). All submissions underwent an international (Canadian, American and East African) peer review. If ranked in the fundable range, the team, with the help of their coaches, then had the opportunity to further improve their proposal by addressing reviewers' comments and concerns. When the proposal was refined sufficiently to merit grant support, funding was approved pending local institutional ethics board approval at their site. The team then carried out the project with coach support. If a proposal was not deemed to be in the fundable range at peer review, the team was encouraged to work with their coach to revise the proposal for submission to the next MicroResearch grant opportunity. Each participating East Africa MicroResearch grant administering site was provided with overhead support ($400 per grant) to cover local ethics board review and grant administration costs. Initially funds were also given to cover the material costs of each workshop, but in 2013, based upon local site advice, each site began charging a workshop fee of $25–50 CAD per participant. Of note, participants were never paid to attend the workshops and local site teachers and coaches received only small honorariums.

As knowledge translation is a key component in MicroResearch to ensure that the local community benefits from the research findings, each application required a knowledge translation plan. Once the study was completed, their coaches helped the team implement their plan. Plans might have included feedback to communities, reports to government departments, curriculum changes, health care program changes, etc. The MicroResearch program also provided coaching and extensive internal peer review support upon project completion for the team to write an extended project abstract for submission for publication to one of four Pub Med journals that have abstract publication agreements with MicroResearch.

Feedback from the East African MicroResearch participants and site leaders was solicited in several ways. To assess workshops, participants were invited to complete an anonymous standardized evaluation questionnaire after each workshop. The questionnaire included both closed- and open-ended questions and findings

Table 6.2 Summary of 15 workshops and outcomes for the years 2008–2013: MicroResearch team projects attributed to year team formed

Number	2008	2010	2011	2012	2013	Total
Health care professionals and others trained	22	48	64	152	105	391
Training sites	1	2	3	5	4	NA
MicroResearch team proposal outlines developed in workshops	3	7	10	20	16	56
Full MicroResearch proposals submitted for international peer review	1	6+2[a]	10+1[a]	13+2[a] (3[b])	2 N/A (2[b])	37
Proposals approved for funding in principle	1	8[c]	9[c]	11	N/A	29
Projects completed as of Sept 2013	1	6	N/A	N/A	N/A	7

N/A not applicable as insufficient time since workshop to submit a full proposal or complete the funded project

[a]Additional proposals from previously successful MicroResearch workshop graduates who formed new teams with proposals not originating from a MicroResearch workshop; attributed to year proposal was submitted

[b]Proposals submitted to November 2013 competition

[c]Includes three projects funded in part or in full outside of MicroResearch

were used to modify the next workshop's content, lectures, participant exercises and to evaluate impact. To assess perceived local health problems, research needs and obstacles in East Africa, recent (2012) workshop participants and the local MicroResearch site and other leaders at the five East African sites were invited to complete an online survey in February 2013.

In order to enhance the sharing of MicroResearch project ideas and results locally within East Africa and to develop a local sustainability plan, two East African MicroResearch Forums were held with invitees from the five sites, one organized with Makerere University in March 2013 [8] and one with the University of Nairobi in November 2013 [9]. These were followed by standardized evaluation questionnaires.

Results

Between 2008 and 2013, 15 MicroResearch workshops were conducted at five East African locations: in Uganda at Mbarara University of Science and Technology (MUST) (five workshops) and at Makerere University (MU) (four workshops), in Kenya at the University of Nairobi (three workshops) and Aga Khan University (one workshop) and in Tanzania at the Tanzanian Training Centre for International Health (TTCIH) (two workshops) (Table 6.2). By the end of 2013, a total of 391 participants from a wide range of disciplines had been trained (Fig. 6.2). Physicians, nurses and midwives made up about 45–50 % of the participants of each workshop. The addition of the small workshop fee charged in 2013 did not appear to change workshop diversity nor hamper participant recruitment. Daily workshop attendance

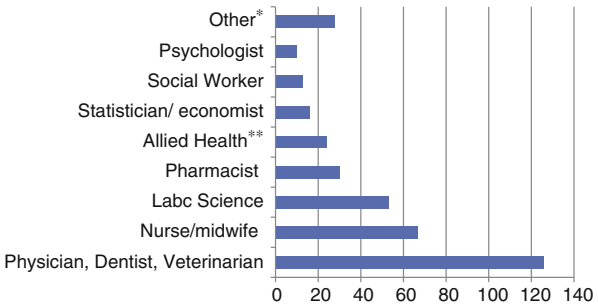

Fig. 6.2 Disciplines of 368 of 391 MicroResearch workshop participants (excludes 23 disciplines that were not stated). *Other = information technologists, computer science, ethno-botanists, librarians, accountants, engineers, etc. **Allied Health: occupational therapy, physiotherapy, nutritionist, dental technician, etc.

ranged from 80 to 100 %. With the workshop fee charge, daily attendance rates were over 90 %.

Table 6.2 summarizes the workshops and the outcomes of the research outlines developed in the workshops. In the first 4 years, i.e., including the 2012 workshop teams, 40 research outlines were started in workshops with 30 (75 %) further refined and submitted to a MicroResearch grants competition. Of note, all but three teams required at least a year to expand their outline into a full MicroResearch application. Although teams formed in the 2013 workshops had little time to develop an application for the November 2013 competition, two managed to do this. For these 32 proposals, the principal investigator for each was a woman in 18 (56 %). In addition to these 32 applications, a further 5 previously successful MicroResearchers formed new teams to address other community directed research questions through a new application. Thus altogether, 37 applications had been submitted for funding by the end of 2013 with the five from November 2013 newly under review. Of 32 with peer review and refinement processes completed, 29 (91 %) were approved for MicroResearch grants based upon scientific merit. Three were sent back with recommendations to reapply after deficiencies were addressed. Two of the 29 did not need MicroResearch grants as funds were obtained externally and a third obtained additional support to supplement their MicroResearch grant. In addition to the two fully out-funded projects coached by MicroResearch, at least eight other projects developed by MicroResearch training graduates had been undertaken and were completed external to MicroResearch by 2013.

Of the 29 MicroResearch grant-supported projects, 14 (48 %) were from Mbarara University of Science and Technology in Uganda, the longest running MicroResearch program. Of these 29, 10 (35 %) focused on child health, 12 (41 %) on maternal health and 7 (24 %) on both mothers and children. Table 6.3 presents 12 examples of MicroResearch projects: 5 completed, 5 funded and underway and 2 reviewed in the fundable range undergoing minor refinement.

With respect to the impact of completed MicroResearch projects, 6 of 7 (83 %) have had observable outcomes. The first funded project (2008), on immunization

Table 6.3 Twelve examples of MicroResearch projects

Year team started	Title	Site and principal investigator	Project status
2008	Assessment of activities and impact of community owned resource persons (CORPS) on families and communities in Healthy Child Uganda Bwizibwera Project Area.	Mbarara University of Science and Technology, Uganda *Basil Tibanyendera*	Completed Reported [10] and used to change policy
2010	No benefit of glutamine supplementation on persistent diarrhea in Ugandan children	Makerere University, Uganda *Justine Kamuchaki*	Completed Published [11] Supported no changed in health practice
	Knowledge and practices of women regarding prevention of mother-to-child transmission of HIV (PMTCT) in rural south-west Uganda.	Mbarara University of Science and Technology, Uganda *Barnabas Atwiine*	Completed Extended Abstract Published [12] Knowledge translation in progress
	Healthy Child Uganda survey on Village Health Team Knowledge, Attitudes and Behaviour of VHTs towards their responsibilities in Mbarara District	Mbarara University of Science and Technology, Uganda *Ashaba Scholastic*	Completed Extended Abstract Published [13] Lead to changes in training, support programs
	The practice of traditional rituals and customs in newborns by mothers in selected villages in Southwest Uganda.	Mbarara University of Science and Technology, Uganda *Florence Beinempaka*	Completed Extended Abstract published [14] Lead to newborn cord care program changes
	The impact of the VHT newborn strategy in reducing perinatal deaths in a rural district of Uganda	Makerere University, Uganda *Isha Grant*	Funded, data collection complete Extended Abstract published [15] Lead to newborn cord care program changes
2011	Knowledge, Attitudes and Practices about blood donation in rural communities of Kiruhura District, South Western Uganda	Mbarara University of Science and Technology, Uganda *Natukunda Peace*	Funded, data collection underway
	Pilot Project: Impact of In-Service training of midwives on partogram use	University of Nairobi *Jennifer Oyieke*	Funded, intervention study underway
2012	Use of mobile phones to improve the antenatal care attendance of pregnant women in semi-urban south eastern Tanzania	Tanzanian Training Centre for International Health, Tanzania *Zabron Abel*	Funded, project started

(continued)

Table 6.3 (continued)

Year team started	Title	Site and principal investigator	Project status
	Determinants of maternal health utilization by adolescents in informal settlements in Nairobi	University of Nairobi *Fred Mochache*	Funded, project started.
	Assessing tools, knowledge and practices of the health providers at the antenatal clinic in optimizing maternal health services in Kilombero District	Tanzanian Training Centre for International Health, Tanzania *Boniphace Jullu*	Fundable – in revision phase
	Reasons for and determinants of non-adherence to the UNEPI vaccination schedule among children in Kyabugimbi sub-country in Uganda	Mbarara University of Science and Technology, Uganda *Barnabas Atwiine*	Fundable – in revision phase

gaps, lead to changes in village health team training in South West Uganda [10]. A study on glutamine supplementation for persistent diarrhea showed that this was ineffective in the East African setting [11] and should not be promoted as a local intervention. A study of women 15–45 years old in rural Uganda revealed gaps in knowledge about prevention of mother to child transmission of HIV and highlighted the need for different education strategies [12]. Following publication of the extended abstract, the questionnaire was requested by an American team for adaptation for use in another African country. Findings from a study of knowledge gaps and retention factors for volunteer village health teams in South West Uganda [13] stimulated further local discussions and changes in support of village health team retention. Two Ugandan teams from different sites discovered congruence in their research findings at the 2nd MicroResearch Forum. One had assessed negative aspects of traditional birthing customs in the South West region [14] while the other had found cord related sepsis as a major cause of neonatal deaths in villages in a central rural district [15]. Following the 2nd Forum, together the two MicroResearch team leaders presented their findings to the Ministry of Health in Uganda. The Ministry then proposed a new neonatal chlorhexadine cord care program to be delivered in villages. Beyond policy and practice outcomes, completion and/or publication of the MicroResearch study findings, at least five successful MicroResearchers went on to career development or advancement based upon their work.

From the onset, local site East African faculty members were involved in teaching two modules in the workshops – ethics of research and community engagement. Over time, local faculty took on larger roles. At Mbarara University of Science and Technology the 2012 and 2013 workshops were delivered entirely by local faculty with support from a Canadian trainer/observer.

Feedback from workshop participants over the 5 years was positive with over 90 % rating their MicroResearch workshop experience as a 5 out of 5 and over 90 % stating they would strongly recommend it to colleagues. In spontaneous comments,

about 1 in 5 participants in any given year noted that MicroResearch would change their usual activity, for example, their teaching, clinical work, goals etc. (www.microresearch.ca/workshops). Participants commented that they were now capable of being more than just a supplier of patients and/or a research data collector for studies designed and executed by external researchers from overseas. As one 2012 participant noted "*We* now have the courage to develop our own proposals and submit them elsewhere". Another noted that "…. MicroResearch provides the forum for ordinary individuals to work to nurture relevant novel ideas with big [potential] impact on population health".

In total, 26–27 participants came form the 5 sites, were invited to the MicroResearch Forums to discuss research projects either completed, underway or in development. Much interest in new research ideas and in sharing of protocols and potential collaborations was generated. At the 1st Forum, to facilitate further discussions, one participant developed an online closed LinkedIn network for MicroResearchers that has been well subscribed to at all 5 sites. The online survey (response rate 63 % [43/68]) results were also presented at the 1st Forum. The top three East Africa health challenges identified were: (1) access to care; (2) social determinants and poverty; and (3) health service and infrastructure gaps. The top three research challenges reported were: (1) capacity building gaps (lack of mentors, and clear career paths); (2) research skills and knowledge gaps; and (3) lack of access to research funding. In response to the survey and Forum discussions, the MicroResearch site leaders at the 1st Forum formed an East Africa MicroResearch Leaders Consortium aiming to enhance support for MicroResearch as it addresses the top three research gaps; for example, "several small projects are effective and are sustainable"; "small projects are the cornerstone on which research skills are built and a wider spectrum of potential researchers is reached with excellent outcomes" [8]. The 1st Forum learning session on abstract writing was such a success that this became part of subsequent workshops. Following the 2nd Forum, a MicroResearch alumni directory program was developed and knowledge translation collaboration was formed between the two Ugandan teams working on cord sepsis as noted above. Two other teams, each from a different country, working on ways to increase prenatal visits, also discussed joining forces in knowledge translation in the future. The 2nd Forum learning exercise on knowledge translation was recommended to be included in the workshops. The Forum evaluations were positive with participants highly valuing the opportunity to meet with other East Africa MicroResearchers with similar research interests. Many commented that such local opportunities for sharing were rare.

Beyond local site support for MicroResearch workshops and projects, as of 2013, three of the five sites had formally incorporated MicroResearch principles into their undergraduate health care education programs. At Mbarara University of Science and Technology, small interdisciplinary teams of health care students in their senior year address a community-directed health care problem and write up a report that includes recommendations and a poster presentation. At the Tanzanian Training Centre for International Health both senior medical students and senior associate medical officers in training at St Francis University form small teams to address community-directed health care problems with report development and

oral presentation of their findings. At the Kenyan Medical Training College, where a number of faculties have received training through the University of Nairobi MicroResearch workshops, several senior program leaders have incorporated MicroResearch principles into their course programs for training allied health professionals. Additionally, following the 2nd MicroResearch Forum, the College also pledged to help financially support successful MicroResearch teams where the project was led by one of their faculties and the proposal was relevant to the College.

Discussion

The main goal of MicroResearch was to determine if this program would help build the capacity of local health care professionals in East Africa to find sustainable solutions for local community-focused health problems that then influenced government policy and/or local practice. MicroResearch success required strong local uptake; research proposals to be developed, funded and implemented; then research findings to be locally relevant and translated into action.

At 5 years, MicroResearch has been well accepted in the five participating East Africa sites. The MicroResearch experience was that front-line health care workers readily saw problems that needed urgent attention, were keen to address them when given the research skills, coaching and small grant support; and then worked to translate the findings into health policy, program and/or practice changes. Of the research outlines developed by the interdisciplinary MicroResearch teams during the training workshops in the first 4 years, 75 % went on to be submitted and of these 91 % were sufficiently scientifically credible to be accepted and funded by MicroResearch. Gender equity was seen in the leadership of these successful MicroResearch teams. Six of 7 completed projects had observable practice or policy outcomes. Participating in the MicroResearch program also supported career advancement. The joining up of MicroResearch teams from different sites/countries to develop collaborative knowledge translation strategies when their projects were synergistic was unanticipated. The MicroResearch Forums appear to have provided important opportunities to nurture collaborative research relationships.

Similar to the experiences of microfinance participants, MicroResearch graduates demonstrated a sense of independence and empowerment. At least eight went on to develop and garner funding for further research projects independent of MicroResearch. They no longer see themselves simply as suppliers of research patients or as research data collectors, but rather as researchers with important questions to ask and the skills to answer them. Like the wide range of microfinance products, the range of MicroResearch questions tackled has been broad [16]. Given the past history of research in these locales, external donor-initiated projects would be unlikely to ever cover the diversity of maternal child health community-directed initiatives.

A formal external auditing and evaluation program for MicroResearch is needed to document its successes and failures. Potentially this would also provide a better understanding of prerequisites for site and MicroResearch team success. These evaluations were not done due to lack of funding as well over 90 % of all monies in grants and donations have gone to support workshop training and the small MicroResearch grants. However, even with the lack of formal evaluation, the high workshop attendance rates, the positive workshop evaluations, the high rate of proposal outline to full successful grant application, the follow through on knowledge translation and the stimulation of research project development beyond MicroResearch suggest that MicroResearch is valued locally at the five sites in East Africa, and that capacity for community directed health research is growing locally.

To ensure that the local MicroResearch sites continue to thrive in East Africa, more funding support and more highly qualified local and international teachers, reviewers and coaches are needed to ensure program quality. The problems seen with too rapid early expansion of microfinance must be avoided. Like microfinance, MicroResearch requires close interaction and contact with participants. More resources are needed locally. The East African MicroResearch Leaders Consortium will be the key to identifying qualified local expertise to support the MicroResearch training and to finding local funding for projects. Development of partnerships by local MicroResearch with local nongovernmental organizations and government agencies may be a way forward. Links to nongovernmental organizations might also provide more knowledge translation avenues for change in practice. For governments, supporting local MicroResearch programs would fit well with the Bamako "call to action". To further enhance local MicroResearch, further opportunities for more analytic, writing and knowledge translation skills development for graduates are needed. Expansion of the MicroResearch educational online modules or other tools and access to more advanced training opportunities for some would be helpful. The latter might be developed through links to more sophisticated research training programs offered in the region such as the Consortium for Advanced Research Training in Africa (CARTA) [17].

In summary, at 5 years, MicroResearch has successfully started to grow capacity for community-directed research in East Africa. As one East African MicroResearch leader noted "MicroResearch teaches us how to fish, shows us where to fish, then puts fish in the lake so we are sure to catch some…. We can make a difference in the health of our own communities through MicroResearch".

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Chapter 7
Medications in Pregnancy: Can We Treat the Mother While Protecting the Unborn?

Yifat Gadot and Gideon Koren

Pregnancy is of overriding clinical importance in developing countries. As reported elsewhere in the introductory chapters to this volume, birthrates are high in low income countries (32 per 1,000) and in middle income countries (19 per 1,000) and these figures assure the continuing importance of full clinical understanding of the consequences of drug therapy in pregnancy.

With numerous new medications entering the market every year, the formal labeling for most of these drugs does not contain safety or efficacy information related to exposure during pregnancy. Yet, millions of pregnant women have conditions that need to be treated, from chronic conditions such as epilepsy to pregnancy-induced conditions such as nausea and vomiting. The lack of knowledge relevant to maternal effectiveness and fetal safety of medications is a significant challenge for the practitioner, and exposes the mother to risk of insufficient therapy for her condition, and places her unborn baby at potential risk of toxicity.

Since thalidomide was identified to be a major human teratogen [1, 2] medicine is practiced as if any prescribed medication is potentially hazardous to the fetus, leading physicians and pregnant women to avoid use of medications, even for the management of life threatening conditions. Of equally critical importance, drug companies almost never test new molecules in pregnancy, thus orphaning pregnant women from the benefits of therapies. Presently, very few drugs are adequately labeled for use in pregnancy.

The major task for the scientific community and for regulators is to change the climate whereby pregnant women and their unborn babies become therapeutic orphans.

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In contrast with the present state of mind focused on anxiety, in the case of the vast majority of drugs evaluated in pregnancy today, extensive post-marketing data have failed to show fetal risks in humans [3].

When considering potential fetal risks of drugs, it is imperative to remember that all pregnancies have a baseline risk of birth defects in the order of 1–3 %, by chance alone [4]. Hence, any attempt to prove fetal safety/risk must contrast exposure to a given drug with this baseline risk.

Principles of Teratology

In evaluating the fetal safety of drugs in pregnancy it is important to remember that embryogenesis is completed at the end of the first trimester, when all fetal organs are complete. Hence, to cause a malformation, fetal drug exposure must occur in the first 12 weeks of gestation. Examples of drugs causing malformations include thalidomide, isotretinoin and valproic acid; exposure to these medications later in pregnancy does not cause malformations. The only exception to this generalization is brain development, which continues throughout pregnancy, and hence, alcohol, cocaine and methyl mercury have been observed to affect fetal brain development later in gestation.

The "all-or-none" period is the time between fertilization and implantation. At that time the embryo is not yet in contact with the maternal circulation, and any injuries sustained by the conceptus is likely to result in either recovery, repair or death [5]. It is improbable that exposure to teratogens in the "all-or-none" period will result in malformations.

The timing of implantation is approximately 14 days post-ovulation, although recent studies suggest that it may occur several days earlier [6]. Implantation in the uterus lining induces the production of human chorionic gonadotropin (hCG) which enters the maternal circulation, creating a connection between the mother and the conceptus [6].

Estimating the Risk of Drugs in Maternal Milk (See Also Chap. 4)

There are serious concerns among mothers and health professionals regarding neonatal exposure to drugs through breast milk. In order to confirm the safety of use of drugs during breastfeeding one needs to estimate the extent of the infant's exposure to the drug through breast milk, by calculating the infant's weight-adjusted dose (referred to as "relative infant dose"). The calculation of the infant's weight-adjusted dose is based on maternal weight and dose, concentration of the drug in breast milk and a standard estimation of the infant's daily milk consumption of 150 ml/kg. If an infant's received weight-adjusted dose is less than 10 % of the maternal

weight-adjusted dose, it is generally assumed to be unlikely that it will elevate the risk of adverse neonatal effects above baseline [7].

Considering the principles outlined above, we will present three examples of therapeutic classes which have been the subject of confusion and controversies as related to fetal exposure in pregnancy.

Biological Therapies

A rapidly increasing number of biological therapies are IgG monoclonal antibodies that are used for different maternal conditions, such as rheumatoid arthritis, systemic lupus erythematosus and many other immunological conditions. There is limited information currently available on biological therapies, but they do not appear to elevate the risk of congenital malformations above the baseline risk in the general population [8]. The high molecular weight of biologicals prevents them from crossing the placenta in early pregnancy; however they do cross later on (as do other IgGs), when the placenta exhibits higher levels of the Fc transporter, and many of them have been shown to have neonatal concentrations exceeding maternal concentrations. Biologicals which are not IgG, such as certolizumab pegol (Cimzia®) prescribed for rheumatoid arthritis, Crohn's disease and psoriatic arthritis, cross the placenta minimally even in late pregnancy [9].

A case of a neonate who succumbed to vaccinia after maternal use of infliximab highlighted a potential risk of immunological deficiency in exposed babies. Therefore, there is a consensus that live vaccines should be contraindicated in patients treated with biological therapies. Because biologicals have been found in exposed infants up to 6 months after birth, vaccination of infants exposed to biological therapy in utero should be given at standard schedules. An exception is made for live vaccines, which are best not given at all if circulating biological agents are detectable in the infant [9].

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are effective antihypertensive agents that have relatively few maternal adverse effects. The use of ACE inhibitors only in the first trimester does not appear to be related to an elevated risk of major congenital malformation above the average risk in hypertensive pregnant women (untreated or treated with other drugs) [10, 11].

In contrast, exposure to ACE inhibitors in the second and third trimesters appears to be fetotoxic, inducing fetal hypotension and renal failure. Oligohydramnios (reflecting renal failure), reduced urine formation, neonatal anuria and fetal hypotension have been shown as a direct consequence of the effects of these medications on the fetal renin-angiotensin system [12]. The degree of fetal and neonatal

morbidity correlated with ACE inhibitor exposure in the second and third trimesters is estimated to be between 10 and 20 % [13].

The anuria related to oligohydramnios may result in pulmonary hypoplasia, fetal limb contractures and craniofacial deformities. Severe neonatal hypotension, itrauterine growth restriction, persistence of patent ductus arteriosus, prematurity, hypocalvaria, neonatal anuria and neonatal or fetal death have also been shown with exposure to these drugs in the second and third trimesters of pregnancy [14].

Therefore, cessation of ACE inhibitor medication before the second trimester of pregnancy is recommended. In cases where exposure in the second or third trimester takes place patients should be surveyed by ultrasound for toxic signs, including growth restriction, oligohydramnios and fetal distress [14].

Antidepressants (See Also Chap. 25)

The second leading cause of disease burden among women in the United States is major depressive disorders [15]. Up to 20 % of the women in the reproductive age range are afflicted by depression [16] and between 1 and 8 % are treated with antidepressants [17]. The selective serotonin reuptake inhibitors (SSRIs) have been in clinical use for the last two decades and are generally regarded as safe in pregnancy in relationship to dysmorphology and neurodevelopmental measures [17]. Venlafaxine, the selective serotonin and norepinephrine reuptake inhibitor (SNRI), and tricyclic antidepressants (TCA) are also considered safe [18]. Proper control of maternal psychiatric illness during pregnancy is of paramount importance to provide optimal outcome for the infant and mother. Untreated depression in pregnancy has been associated with increased risks of miscarriage, preeclampsia, perinatal complications, bleeding during pregnancy and postpartum [19], increased admissions to NICU and increased risk for post-partum depression [20].

Abrupt discontinuation of these medications can cause both physiological and psychological withdrawal symptoms (general somatic, gastrointestinal, affective and sleep disturbances), including suicidal thoughts and relapse of the psychiatric illness [21].

Several studies have reported an elevated risk for spontaneous abortion with a relative risk/odds ratio of 1.63–2.09 [21, 22]. However, it is not known whether this effect is induced by the antidepressant or the depression itself.

Exposure to an SSRI or an SNRI during pregnancy has been associated with difficulty in feeding and breathing, jitteriness, low blood sugar and neurological symptoms (increased motor activity and sleep disturbances) [23]. In most cases symptoms subside within a week, but may continue for up to 3 weeks [24]. Most studies documented that 10–30 % of infants exposed to SSRIs prenatally exhibit Poor Neonatal Adaptation Syndrome (PNAS), with more than half having mild symptoms [23]. Infants exposed to SSRIs or SNRIs (mainly in the third trimester) should be closely monitored for several days post partum. Symptoms tend to be self-limited with supportive care.

Several studies have associated late pregnancy SSRI exposure with persistent pulmonary hypertension of the newborn (PPHN) [23]. However, other studies have failed to show this [25]. Kielers reported that women who did not use antidepres-

sants in pregnancy but who were hospitalized for psychiatric reasons had an increased likelihood of delivering infants with pulmonary hypertension in the newborn with an Odds Ratio (OR) 1.3 (CI 1.1–1.7) (in comparison to healthy pregnant population) [25]. PPHN may occur in less than 1 % of babies exposed prenatally to SSRIs [23]. Moreover, no mortality has been documented in any infants exposed to SSRIs prenatally that developed PPHN, compared to a mortality rate of 10–15 % reported among infants with other causes of PPHN.

There is a small increase of premature births among babies exposed to antidepressants in late pregnancy. However, it is unknown whether this is the result of the antidepressants or depression itself.

Teratogenicity

Published information from 2004 and onward, based on registries, has suggested that some SSRIs may be associated with increased risk of cardiovascular malformations, mainly ventricular septal defects (VSD). However, for each study postulating such risk there have been two studies refuting an association [26]. It should be taken into account that there is a substantial ascertainment bias: depressed women who use antidepressants undergo significantly more ultrasound and echocardiography. Therefore, they are much more likely to be diagnosed with congenital malformations. Outcomes of more than 20,000 women exposed to all classes of antidepressants documented no overall increased risk for congenital malformations.

The risk:benefit ratio of antidepressant use in pregnancy is strongly tilted toward use of the medication in symptomatic women, due to the high and serious risks of not treating depressed pregnant women, including hospitalization, suicide attempts and increased risk of postpartum depression.

In conclusion, these three examples provide evidence how initial reports, biased toward claiming teratogenic risk, are nullified by larger evidence-based data. It is critical to ensure that expectant women are not orphaned from advances in pharmacotherapy due to misinformation and misperception of teratogenic risk, and that a benefit-risk assessment is performed, that takes into consideration the risks of not treating women during pregnancy.

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Chapter 8
Drugs and Breastfeeding: The Knowledge Gap

Shinya Ito

Introduction

Maternal medication use during pregnancy and breastfeeding poses unique challenges as innocent bystanders are exposed to the drugs. While pregnant mothers taking indispensable medications for chronic conditions do not have many choices to avoid foetal exposure, breastfeeding women in a similar situation have various options to reduce infant drug exposure, which range from temporary cessation to complete termination of breastfeeding. In order to make proper management decisions for these breastfeeding mother–infant pairs, both pharmacokinetic data of drugs in breast milk and infant safety information are crucial. Unfortunately, however, such data remain limited even in developed countries. Moreover, a risk–benefit balance between breastfeeding and maternal medications in the developing world is distinctly different from that in developed countries, because use of replacement foods such as infant formula does not provide a practical solution in resource scarce settings. It should also be noted that the spectrum of prevalent maternal diseases and treatment drugs is dissimilar between the developed and developing world. This chapter will describe clinically important concepts, which can be used in clinical settings to fill the knowledge gap in pharmacokinetics for breastfeeding mother and infant, and will address how the risk–benefit balance is shifted in developing countries, using HIV infection as an example.

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Parameters of Drug Excretion into Breast Milk and Infant Exposure

Milk-to-Maternal Plasma Concentration Ratio

The mammary gland epithelia constitute the functional barrier between milk and maternal interstitial fluid space, playing a key role in transfer of drug/toxin/nutrient into milk. As a result of the physiological function of the barrier, the milk compartment is maintained in a slightly lower pH environment than the maternal plasma/interstitial fluid. The acidic condition favours cationic compounds being ionized and trapped in the milk compartment because charged molecules do not freely diffuse across lipid bilayers. This ion-trapping phenomenon may be captured by an increase in a parameter known as Milk-to-maternal Plasma drug concentration ratio, or MP ratio. Because MP ratio is a time-averaged parameter by definition, the area under the curve (AUC) of drug needs to be compared between milk and plasma. If AUC data is not available, drug concentrations in milk and maternal plasma at a single time point may be used as a surrogate, although cautious interpretation is required due to differences in concentration–time profiles between milk and plasma compartments. MP ratio greater than one indicates that the drug concentration is higher in milk than in maternal plasma. In addition to ionization characteristics of the drug, plasma protein binding and lipophilicity are other important factors which affect MP ratio. For example, reduction in plasma protein binding increases the unbound fraction of drug, which diffuses across the epithelial cell membrane into milk. Lipophilic drugs tend to achieve higher lipid fractions and thus higher concentrations in milk. All these factors influence MP ratio. MP ratio is a straightforward parameter, which is easy to understand, but its value in assessment of drug levels to which infants may be exposed is relatively limited, as described in the following sections.

Relative Infant Dose

There are several parameters which define levels of infant drug exposure through breast milk. Using the ratio between the dose of drug an infant ingests through milk and an infant therapeutic dose (or a predicted therapeutic dose), one may define the relative infant dose (RID) as follows:

$$\mathrm{RID}(\%) = \frac{\text{Infant dose of drug ingested through milk per time}}{\text{Infant therapeutic dose per time}} \times 100$$

The numerator of the above equation is the amount of drug the infant ingests through milk per unit time (e.g., per day), which is obtained by multiplying the mean drug concentration in breast milk with infant milk intake (e.g., 150 ml/kg/day). A RID

value of 100 % indicates that the amount of drug ingested by the infant through milk per day, for example, is the same as the daily therapeutic dose for the infant. Most drugs have RID below 10 %, and therefore short-term exposure for a few days is highly unlikely to result in clinically meaningful consequences, at least insofar as dose-dependent effects are concerned.

Maternal Weight-Adjusted Infant Dose

Given that infant therapeutic doses have not been defined for most drugs, RID may not be readily available. In this case, one may substitute "infant therapeutic dose" with "maternal (therapeutic) dose" to derive a similar parameter known as "Maternal weight-adjusted infant dose (M-ID)". In order to account for weight differences between mother and infant, these parameters need to be adjusted by body weight as follows:

$$\mathrm{M-ID}(\%) = \frac{\text{Infant dose / kg ingested through milk per time}}{\text{Maternal dose / kg per time}} \times 100$$

If "Infant therapeutic dose/kg/time" is equal to "Maternal dose/kg/time", then RID is equivalent to M-ID. If Infant therapeutic dose/kg/time is 50 % of the maternal dose/kg/time, then RID becomes two times as high as M-ID. Literature data usually include M-ID as a substitute for RID. Also, it is important to note that some researchers use RID and M-ID interchangeably, which is often a source of confusion.

Most drugs show an M-ID of <10 %, or even <1 %, which indicates that drug exposure through breast milk would be of little clinical consequence unless infant sensitivity to the drug is very high. However, if infant drug clearance is very low due to pathological conditions of the liver and/or the kidney, repeated and prolonged exposure to even a low dose of drug may eventually lead to accumulation and pharmacologically meaningful concentrations in infant serum.

Infant Clearance of Drug

As described above, under most circumstances infant drug exposure through breast milk is considered equivalent to a situation of repeated administration of a relatively small dose of drug. At steady state, average drug concentration in plasma (Css) is defined by bioavailability (F), dose/time (i.e., dose/dosing interval) and clearance as follows:

$$\mathrm{Css} = \mathrm{F} \times (\text{dose / time}) / \text{clearance}$$

In the context of maternal drug use during breastfeeding, F is conservatively assumed to be 1 for risk assessment purposes. Clearly, not only dose but also clearance is an important determinant of Css. If infant drug clearance is low, and if it

remains low for a prolonged period of time, repeated ingestion of even a small dose of drug through milk may cause accumulation, potentially increasing plasma concentrations to a pharmacologically meaningful level. For example, assume that infant drug clearance is 10 % of the mature level (per body weight basis), and that it remains at that level for 2–3 months. Even if the dose of drug the infant would ingest through milk expressed per unit of body weight were 10 % of the dose/time/weight given to a child with mature drug clearance capacity for therapeutic purposes, a plasma concentration would eventually reach the therapeutic level. It is important to recognize that the time to reach such a level may also be prolonged in the case mentioned above, because time to reach a steady state is a function of elimination half-life, which is inversely dependent on clearance. It is also likely that the large volume of distribution in the neonatal period (per weight basis) further contributes to prolonged drug half-life.

However, despite the relatively common occurrence of chronic maternal treatment, such cases of substantial drug accumulation are extremely rare. In most published reports of detectable infant plasma concentrations of drug following exposure through breast milk, the levels are much lower than the therapeutic range. It is likely that the developmental trajectory of drug elimination pathways in the infant counterbalances relatively low clearance during the early neonatal period. In other words, low drug clearance in the early neonatal period does not remain low, but rather increases steadily to a mature level over weeks during the infant period. In addition, milk intake during the early neonatal period is relatively small, resulting as well in reduced drug intake.

As described in the previous section, RID and M-ID (maternal weight-adjusted infant dose), which represent percentages of the infant and maternal therapeutic dose, respectively, are usually lower than 10 %. Importantly, according to the estimated or actual data, RID or MID of none of the medications is known to reach an amount exceeding therapeutic doses on a per weight basis. This indicates that acute toxicity, similar to a single overdose, is very unlikely unless the infant is highly sensitive to such a low level exposure due to altered pharmacodynamics. Rather, accumulation to a clinically recognizable level of plasma concentrations, albeit slowly, is possible, if infant drug clearance remains very low.

Infant Exposure Levels as a Function of MP Ratio and Clearance

As described above, MP ratio defines milk concentrations of drug at maternal therapeutic concentrations in plasma, which reflect infant dose of drug ingested through milk. Because a steady-state concentration in plasma depends on the dose and clearance, one may relate infant drug clearance to achieved plasma levels at steady state with MP ratio as the other variable [1]. Figure 8.1 shows this relationship, expressing the magnitude of infant drug exposure as Exposure Index, which is an estimated percentage of therapeutic concentrations in the infant plasma [2]. For example, if

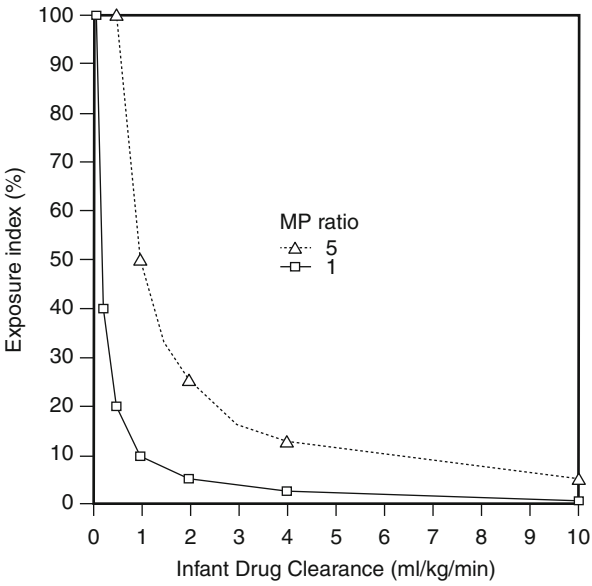

Fig. 8.1 Influence of drug clearance on infant drug exposure through breast milk. The magnitude of infant drug exposure is expressed as Exposure Index (%), which is an estimated percentage of therapeutic concentrations in the infant plasma [2]. Two scenarios of MP ratio are shown (5: *triangle*; 1: *square*). If infant drug clearance is very low, the magnitude of exposure may reach a therapeutic level

the amount of drug the infant ingests through breast milk is the same as a therapeutic dose of drug, the exposure index becomes 100 %. Exposure Index is equivalent to RID, as explained in the previous section. Importantly, drugs with relatively low clearance tend to cause higher exposure levels. Given that most drugs have an MP ratio around 1 or smaller, the impact of low clearance (e.g., <0.5 ml/kg/min) on infant exposure levels is more pronounced than increased MP ratio. Therefore, low clearance drugs such as phenobarbital that are used on a chronic basis, need to be used with caution, and monitoring of adverse effects is warranted. On the other hand, drugs with high clearance are unlikely to cause significant accumulation in the infant. Even if there is little data on drug excretion into human milk, one can use the principle described above to make reasonable estimates of infant drug exposure levels.

Life-Threatening Accumulation of Drug in Infants

Opioids

An important example of accumulation of drug through breastfeeding is opioid toxicity. Opioids are particularly problematic as a result of their life-threatening toxicity profiles. A neonate breastfed by a mother who was taking codeine every day after delivery was found dead at 13 days of age due to possible morphine toxicity [3]. Later, the mother was found to be an ultra-rapid CYP2D6 metabolizer. CYP2D6 is responsible for codeine conversion to morphine. In addition to relatively low

morphine clearance in the infant, genotype-related high morphine concentrations in maternal blood and milk are also likely to have contributed to this unfortunate case. Noteworthy in this case is the fact that at least several days passed before the infant became symptomatic while the mother continued breastfeeding and taking codeine therapy. This temporal profile is consistent with accumulation of morphine over time, highlighting the importance of continuing vigilance for an infant breastfed by a mother on prolonged codeine therapy. Although this case illustrates the significance of maternal CYP2D6 genotype status in a breastfed infant, this specific genotype may not be the only factor. Because CYP2D6 activity is known to overlap with different genotypes, the best approach if the mother requires codeine is to limit the outpatient use to less than 4 days in the early postpartum period. At present, no other opioids are known to have caused fatality through breastfeeding. However, given the high risk toxicity profiles of opioids as a group, close monitoring of infants and limiting the duration of the treatment during breastfeeding are also warranted for maternal use of other opioids.

Influences of Exposure in Utero

When infant drug exposure during breastfeeding becomes a question, it is important to take into account drug exposure *in utero*. As described above, acute exposure to a drug in milk for a short period of time (i.e., 2–3 days) is unlikely to cause a problem, unless in the face of a significant maternal overdose. On the other hand, maternal medication use for chronic conditions could potentially increase the probability of accumulation in the infant, although the risk is remote. Medication use for a chronic condition usually covers both pregnancy and breastfeeding periods. When cord blood levels of drug are similar to those of the maternal blood concentrations, as is the case with most drugs, the infant will have drug concentrations near therapeutic at birth. If the infant receives no drug through breast milk, the plasma concentrations will decline steadily depending on development of the elimination pathways and resultant elimination half-life of the drug during the neonatal period. Because of the development of drug elimination pathways, decrease of the plasma levels will be accelerated as the infant grows. If the mother continues taking the drug during breastfeeding, a small amount of the drug will appear in milk, and the infant will ingest it at a small dose (because of the small intake of milk). As infant milk intake increases to about 150 ml/kg/day, an amount of drug the infant ingests from breast milk will reach levels one can estimate from RID or M-ID (see previous sections). This repeated ingestion of a small amount of drug will define the steady-state concentration. The infant plasma concentration will eventually descend to a level nearly equivalent to maternal plasma concentrations. The differences between the two scenarios (i.e., no breastfeeding vs. breastfeeding during medication use) are reflected in the differences in the slopes of plasma level decline.

Practical Approach

Among medications and diagnostics, radioactive iodine is the only agent absolutely contraindicated for breastfeeding, because iodine is highly concentrated in milk and because it is taken up selectively by the thyroid gland of the infant (and the mother). Other radioactive compounds depend on their disposition characteristics and radioactive/biological half-life. All other drugs can be used with variable degrees of limitation described above in the case opioid prescribing. One of the practical and easy ways to access the most up-to-date information on drug safety in breastfeeding is through the comprehensive database on drugs and breastfeeding, called LactMed.

LactMed

In order to make an informed decision on drug safety during breastfeeding, a comprehensive, up-to-date information resource is crucial. LactMed is an easily accessible database for drug safety in breastfeeding (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT) that has been developed and is used widely. As of April 2014, there are nearly 800 drug entries in the database, and it is considered the most up-to-date information resource for drugs in lactation [4].

Benefits of Breast Milk

All efforts to maintain breastfeeding during maternal drug therapy are based on the fact that breastfeeding has significant benefits for both mother and infant [5]. Breastfeeding is associated with beneficial effects on infant and maternal health. Because of the obvious ethical constraints, an interventional trial to compare breastfeeding and formula feeding head-to-head is impossible to conduct. Therefore, available information is mainly based on observational cohort studies and case-control analyses. Despite the limitation, beneficial effects of breastfeeding have been consistently demonstrated, the best known being anti-infective effects.

A large-scale prospective cohort study showed that exclusive breastfeeding for 4–6 months is associated with a significant reduction in respiratory and gastrointestinal infection in infants, [6] confirming previous findings of beneficial effects. Moreover, a randomized trial of intense breastfeeding promotion (The Promotion of Breastfeeding Intervention Trial: PROBIT) in more than 12,000 mother–infant pairs demonstrated that trial intervention resulted in increased duration and magnitude of breastfeeding, and further decreased gastrointestinal infection in the first year of life [7]. Although the PROBIT findings showed no significant association of the trial intervention with the reduced risk of respiratory infection, it is noteworthy that both the intervention (intense breastfeeding promotion) and the control

(routine care) groups had relatively high breastfeeding rates at 3 months (73 % vs. 60 %) and 6 months of infant age (50 % vs. 36 %). It is possible that protective effects of breastfeeding on respiratory infection in the presence of various environmental factors such as household smoking are difficult to detect. In addition, the above-mentioned PROBIT study further showed that the same trend to benefit occurred in the cognitive function of the intervention group, [8] suggesting that breastfeeding exerts positive influences on cognitive development of the infant. The mean difference in the IQ between the two groups in the PROBIT was about eight points. This is half of the standard deviation of the IQ in the general population, indicating that the effect is not trivial at a population level. Based on these findings, professional organizations in the field of pediatrics invariably recommend exclusive breastfeeding for infants for 6 months, and further continuation of breastfeeding thereafter [5].

HIV, Anti-Retroviral Drugs and Breastfeeding

The risk–benefit assessment of breastfeeding during maternal drug therapy is clearly dependent on the socio-economic environment of the society where the mother and infant live. This is exemplified in the issue of breastfeeding and anti-HIV treatment. In developed countries, maternal HIV infection constitutes a contraindication for breastfeeding, because the risk of HIV transmission to the infant through milk is greater than morbidity and mortality associated with use of infant formula. This risk–benefit balance shows a different picture in limited resource settings due to significantly increased morbidity and mortality as a result of conditions such as diarrhoea and malnutrition if infants are not breastfed [9].

In a non-randomized intervention cohort study of more than 1,000 infants of HIV-infected mothers, exclusive breastfeeding was shown to have lower cumulative mortality at 3 months than was observed in the replacement food group. Furthermore, exclusively breastfed infants showed the lowest incidence of HIV infection compared to infants given replacement foods [10]. The mechanisms of the transmission reduction by breastfeeding have not been clearly established, although bioactive molecules with immune modulating function in breast milk may be responsible.

The 2010 WHO guidelines on feeding in the context of HIV infection [11] are based on these findings and considerations of HIV-relevant health policies in each jurisdiction. In brief, exclusive breastfeeding for at least the first 6 months of life is recommended even in the absence of anti-retroviral treatment. The amount of anti-retroviral drugs excreted into breast milk is invariably small, contributing little to infant drug exposure. Therefore, if indicated, the infant breastfed by a mother taking anti-HIV drugs must be given full doses of anti-retroviral therapy without dose modification.

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Chapter 9
Falsified and Substandard Medicines

Tariq Almuzaini, Helen Sammons, and Imti Choonara

The circulation of poor-quality medicines, whether they are the result of drug falsification or substandard production, is a serious public health problem in low-income countries (LICs) and lower-middle-income countries (LMICs). The prevalence of poor-quality medicines varies considerably among countries and disproportionately affects countries with an unregulated market for medicines. There is a need for more data to determine both the extent of the problem and the types of poor-quality medicines.

Medicines have been used for treating and curing diseases for thousands of years. The production of medicines was once a cottage industry, carried out in a localised environment and helping a limited number of people in a small area. These "apothecary shops" were run by physicians who compounded medicines to be used in their clinics. In the last century, local production of medicines has been replaced by pharmaceutical industries that employ advanced technology. In addition, the discovery of a wide range of therapeutic agents in different pharmacological groups has led to a revolution throughout the pharmaceutical industry as the manufacturing and distribution of medicines have become widely distributed. These developments have raised concerns about the safety and quality of available medications [1, 2].

Globalisation and the large-scale production of medicines carry the potential risk of spreading poor-quality medicines throughout the official supply chain. Moreover, criminal activities involving the production of falsified medicines pose an additional global threat. In response, high-income countries are constantly

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developing regulations and implementing measures to lessen the impact of this problem and to detect substandard medicines before they spread. Low-income countries and LMICs, in contrast, have weak infrastructures and resource shortages. This situation adversely impacts their capacity to regulate and exert quality control over medicines.

Definition of Falsified and Substandard Medicines

There is disagreement on what characterises poor-quality medicines. There is an emerging consensus, however, that the dangerous consequences of these drugs arise from two different types of poor-quality medicines: Falsified (i.e., counterfeit, spurious or fake) and substandard medicines [3–5].

Falsified Medicines

The definition of what is known traditionally as a "counterfeit" medicine is still arguable and in need of clarification. Different terms have been used to describe drug falsification, including counterfeit, falsified, fake, and spurious, and all have been used interchangeably in the literature [6, 7]. WHO's definition, however, has been the one most-often cited during the past two decades. WHO defines a counterfeit medicine as: "a medicine which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products. Counterfeit products may include any of the following: the correct ingredients, the wrong ingredients, no active ingredients, insufficient ingredients or fake packaging" [8]. This definition, however, has been criticised because it combines the issue of public health (wrong, absent, or insufficient active ingredients) and intellectual property (IP) rights (fake packaging) in a single definition and deems them both illegal. The inclusion of IP rights was considered unjustifiable, as regulation in this arena is not a prime responsibility of WHO [3].

The spirit of the definitions for counterfeit medicines is derived from the simple understanding of the terms counterfeit and imitation, as given in the Oxford English Dictionary: "made in exact imitation of something valuable with the intention to deceive or defraud" [9]. From the perspective of IP rights, this can imply for trademark and patent infringements. This is clearly stated in the definition of counterfeit goods provided by the World Trade Organisation, which also refers to trademark violations [10]. This inspired the way the term "counterfeit medicine" is used and defined by some organisations [8, 11, 12].

Drug counterfeiting cannot be compared to the counterfeiting of other goods. Drug manufacturers are subject to stringent quality controls that ensure the safety and efficacy of their products. It is noteworthy that IP rights are private legal rights granted to the trademark owner. They are to be enforced upon the

owner's wish against infringers. Infringements in medicines are private trademark violations as well as crimes against public health [13]. Therefore, such infringements should not be left to the trademark owner but should be initiated by law enforcement bodies to protect the public. IP rights are designed to protect the trademark and the patent, but they do not protect the health and safety of the public. An example would be counterfeit tetracycline tablets that were found in Cambodia. This antibiotic contained nothing but an inert powder filling and was labelled as made by a non-existent manufacturer [14]. A non-existent entity, in this example, cannot be sued under IP rights laws. This meaning of "counterfeit" that considers two distinct problems as one issue, not surprisingly offends and disturbs many [13, 15–18].

Generic and innovator medicines may have similar-sounding brand names or similar-looking packaging. These names are often derived from the scientific names, such as Brufen® and Bonifen®, derived from ibuprofen. As a result, manufacturers of generic drugs may be at risk for civil charges due to trademark infringements. Some researchers and non-governmental organisations, such as Oxfam and Médecins Sans Frontières (MSF), have raised concerns that the involvement of the IP rights issue in the definition of counterfeit medicines may threaten the marketing of generic medicines and lead to their being considered to be counterfeit [13, 15, 17, 18]. Therefore, access to safe medicines in LMICs may be obstructed, undermining generic medicines that are commonly used at a small fraction of the price of innovator products.

The term "falsified medicine" has therefore been suggested instead of "counterfeit" and now is becoming more acceptable [3]. This term was used by the European Parliament in its new Falsified Medicines Directive (Directive2011/62/EU amending Directive 2001/83/EC) [19]. Moreover, the perception of IP was excluded (Box 9.1).

Box 9.1: Definitions of Falsified Medicinal Products by the European Parliament's Falsified Medicines Directive

"Falsified medicinal product is any medicinal product with a false representation of:

(a) Its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients;
(b) Its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or
(c) Its history, including the records and documents relating to the distribution channels used.

The definition does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights."

Source: EC 2011

The competing words used to describe poor-quality medicines were in evidence at the meeting of WHO member states to discuss the problem in 2011. Member states, as an alternative, decided to combine all competing words under a new term: "substandard/spurious/falsely-labeled/falsified/counterfeit medical products" (SSFFC) [20]. This term has also been criticised by those who believe that it does not adequately differentiate between the various categories of poor-quality drugs (i.e., falsified and substandard) that need distinct monitoring and solutions [3].

Substandard Medicines

The debate over the definition of substandard medicines has been less contentious [21–23]. There is a consensus that such products do not meet the regulatory standards. This is due to inadvertent or negligent errors made during the manufacturing or distribution process. WHO defines substandard medicines as follows:

> Substandard medicines (also called out of specification products) are genuine medicines produced by manufacturers authorized by the NMRA (National Medicines Regulatory Authority) which do not meet quality specifications set for them by national standards [21].

In this definition, WHO stressed the national standards rather than official pharmacopoeias, a positive step because there are different pharmacopoeias available with minor deviations in drug requirements and specifications. It is believed that it should be left to national drug regulators to decide upon relevant standards and to test drugs against them [4].

Extent of the Problem

The extent of the problem of falsified and substandard medicines is difficult to gauge accurately [4]. Estimates of its extent, for example, can vary over time or according to the degree of demand for medicines. This is particularly true in tropical regions during rainy seasons, when malaria and other waterborne diseases become more prevalent and the demand for antimicrobials is high [24]. Moreover, the illegal manufacturing of medicines is becoming more sophisticated as criminals gain access to advanced packaging and printing technology. The result is that falsified medicines are becoming more difficult to detect [25].

Another factor that makes the extent of the problem largely impossible to determine is the lack of reliable, accurate, and published data on the quality of drugs [26, 27]. Governmental and non-governmental organisations as well as pharmaceutical companies retain data on falsified and substandard medicines, as they are involved in monitoring drug quality and in investigations involving seizures of illegal drugs

[3, 28]. Access to much of this data, however, is limited to healthcare professionals and researchers interested in public health. The majority of reports are kept confidential to guard against the loss of public confidence in either the healthcare system or the products sold by pharmaceutical companies [4, 28].

The current data suggests that falsified and substandard medicines are a global health problem. However, the problem disproportionately affects LICs and LMICs, where law enforcement systems are inefficient and few regulations for the manufacture of medicines exist [29, 30]. It has been suggested that China is one of the major sources of falsified medicines globally [31–33]. Many shipments of falsified medicines are intercepted by police and customs officials in strongly regulated markets in HICs before they reach consumers. Countermeasures are, however, likely to be less effective in LMICS.

Pharmaceutical Companies and Government Data

WHO received 771 reports of falsified medicines between 1982 and 1999 from its member states, with the majority (77 %) coming from LMICs. Over half of the falsified medicines reported were antimicrobial drugs (Table 9.1).

Data from the Pharmaceutical Security Institute, a non-profit organisation established to share information about the illegal trade of pharmaceutical products, has shown that the reporting rate of falsified medicines is increasing. This data is collected from its 25 member global pharmaceutical companies [34]. The incidence of falsified medicines increased remarkably from 196 incidents in 2002 to 2,018 incidents in 2012 (Fig. 9.1). Each incident represents a seizure by law enforcement officials of illegal medicines. In 2012, approximately 40 % of the medicines seized were commercial shipments of at least 1,000 dosage units of illegal medicines [34]. These falsified medicines were not necessarily found in the official supply chains, as some were intercepted by police or customs officers on their way to target destinations. In addition, the data should be considered with their own limitations, as these incidents reflect the effectiveness of the surveillance and monitoring systems in countries where such seizures have taken place. The figure might be higher if LICs and LMICs had adequate enforcement and surveillance systems in place.

Table 9.1 Pharmaco-therapeutic types of the cases received by WHO (1982–1999)

Pharmaco-therapeutic	%
Antimicrobials	51
Corticosteroids	8
Gastrointestinal agents	7
Analgesics	7
Respiratory agents	6
Androgenics	4
Others	17

Source: Wondemagegnehu [1]

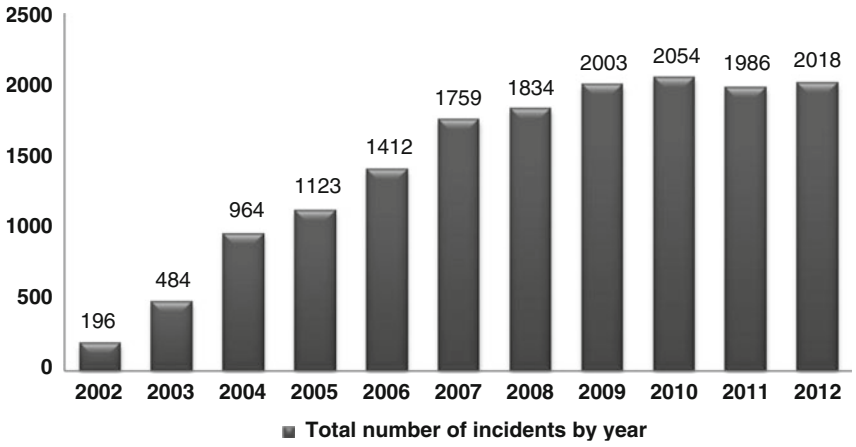

Fig. 9.1 Incidents of falsified medicines reported by the Pharmaceutical Security Institute (*Source*: PSI-Inc [34])

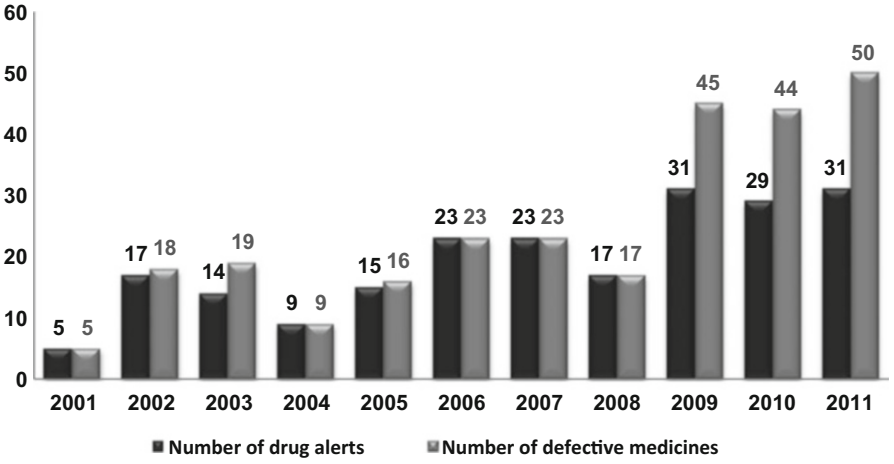

Fig. 9.2 Incidents of defective medicines reported by the MHRA (*Source*: Almuzaini et al. [35])

The surveillance and enforcement systems in HICs, particularly in North America and Europe, are highly advanced compared to those in LMICs. Such systems can be utilised as tools to explore the problem of substandard and falsified medicines, if drug regulators are willing to share this information with the public. For example, the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom (UK) continuously posts on its website recalls and alerts about substandard and falsified medicines (defective medicines) found in the official British supply chain. These reports have been evaluated over a period of 11 years, beginning in 2001 [35]. The incidence of defective medicines reported increased from 5 incidents in 2001 to 50 incidents in 2011 (Fig. 9.2). In total, 291 incidents of defective

medicines were reported over this period; 280 were substandard and 11 were falsified, and each incident represents thousands of dosage units recalled from the official supply chain.

Surveys of Drug Quality

The problem of poor-quality medicines was discussed in a recent systematic review [27]. Quality-assessment criteria for the reviewed studies were applied before inclusion. Only 15 of the 44 studies evaluated were included as studies with good methodological quality. The prevalence of poor-quality medicines reported ranged from 11 to 48 % (Table 9.2). Median prevalence reported across studies was 28.5 %. The review pointed out that poor-quality medicines are more serious problems in LMICs and all studies focused on antimicrobials, as this category of medicines is in high demand. An inadequate amount of the active ingredients was a major problem identified. However, the review, which relied on the literature, was

Table 9.2 Range of the prevalence of falsified and substandard medicines based on the World Bank classification of countries (by income level)

Income level classification		Countries	Number of studies	Prevalence of substandard/ falsified medicines
				Range % (Median %)
Low-income countries		Lao PDR, Tanzania, Cambodia, Uganda	4	12.2–44.5 (24)
Lower-middle-income countries		Indonesia, Nigeria, Cameroon	4	18–48 (38)
Upper-middle-income countries		0	0	----------
High-income countries		0	0	----------
Mixed group	LICs	Myanmar, Cambodia, Lao PDR, Ghana, Kenya, Tanzania, Uganda, Madagascar, Mali, Mozambique, Zimbabwe	7	11–44 (28.5)
	LMICs	Vietnam, Thailand, Cameroon, Nigeria, Senegal, Sudan, Armenia, Ukraine, Uzbekistan		
	UMICs	Gabon, Azerbaijan, Belarus, Kazakhstan		
	HICs	0		

Source: Almuzaini et al. [27]
"Mixed group" represents the studies that have been carried out at more than one income level
LICs low-income countries, *LMICs* lower-middle-income countries, *UMICs* upper-middle-income countries, *HICs* high-income countries

unable to conclude whether poor-quality medicines were a result of quality-control failures by manufacturers (i.e., substandard) or intended falsification by criminals (i.e., falsified).

Types of Substandard Medicines

Substandard medicines can have a variety of quality problems which can result in patient harm. The main types of problems based on the UK data are given below [35].

- Contamination. Formulations for parenteral administration may not have guaranteed sterility and therefore need to be withdrawn. Pharmaceutical products can also be contaminated with other active ingredients including excipients. Outside of the UK diethylene glycol (DEG) contamination has been a major problem.
- Major packaging defects. This may involve the incorrect packaging of alternative medications.
- Minor packaging defects. These usually relate to incorrect information in the patient information leaflet.
- Delivery defects. This often relates to medications that are delivered via inhalers or other devices.
- Defects in active ingredients. The active ingredient can be present in either excessive or inadequate amount

Public Health Consequences

The provision of safe, good-quality medicines is crucial, yet this need is usually ignored in countries with poor regulatory environments for medicines [36]. Substandard and falsified medicines do not meet the prerequisite standards for drug safety and efficacy; therefore, both are considered menaces to public health. At best, these drugs are therapeutically ineffective, and at worst, they can cause death. In most cases, toxicity resulting from such drugs becomes apparent when the impact of the toxicity is high and a large number of patients are affected. In general, adverse health consequences resulting from these drugs can be classified as toxicity or lack of efficacy.

Toxicity

Toxicity can occur when an extraneous contaminant is present in a drug, or when an incorrect or excessive amount of active ingredients are used deliberately or accidently in the drug's formulation. The most catastrophic example of this is DEG

toxicity. DEG is a solvent usually used in consumer products like antifreeze and lubricants. It is considered, however, a potent neurotoxic and nephrotoxic poison; thus, its use in the pharmaceutical industry is banned. The inadvertent contamination or deliberate use of DEG as a solvent in paediatric formulations has been reported. In a period of 4 months (November 2008 to February 2009), 84 children died in Nigeria from acute renal failure after using a teething formula, My Pikin, contaminated with DEG [37, 38]. Investigations revealed that DEG was deliberately and fraudulently provided by a local chemical dealer, resulting in 12 prosecutions [38]. This single cluster report of DEG toxicity was one of many that led to the deaths of more than 300 children around the world [39].

Lack of Efficacy

Treatment failure is the most common serious consequence of substandard and falsified medicines, and it is considered a silent killer. In many cases, these failures go unreported due to other factors complicating treatment. If the planned treatment fails, health care professionals may consider the cause to be patient noncompliance, a too-low dosage, disease severity, or improper diagnosis. Few, if any, would consider the cause to be substandard or falsified medicines. The Partnership for Safe Medicines (PSM), a non-profit organisation, advises healthcare professionals to suspect falsified medicines in treatment failure [40]. This strategy, however, is impractical in resource-constrained settings where required assays for verification are lacking. The easiest and most-practical strategy to assess drug quality, therefore, is to collect samples by investigators from outlets patients usually access [4].

Surveys of medicines' quality have revealed that the quality of life-saving medicines are more likely to be compromised in LICs and LMICs. WHO conducted five studies to evaluate the quality of antimicrobials, especially antimalarials, in 22 countries (14 in Sub-Saharan Africa, 2 in Southeast Asia, and 6 in Eastern Europe). Investigators analysed 1,524 samples collected from different levels of the supply chain. The percentages of samples that failed ranged from 11 to 32 %, indicating a serious problem in antimicrobial quality and efficacy in countries where malaria and other infectious diseases are prevalent [27].

The under-dosing of antimicrobials reduces the blood concentration of these medicines, resulting in opportunities for more-resistant parasites to survive and ultimately leading to drug resistance [41, 42]. The most-common causes for sample failure among antimicrobials tested were found to be inadequate amounts of active ingredients and/or dissolution failure [27]. These effects were considered similar to those of under-dosing. This has the potential not only to increase the mortality rate but also to enhance drug resistance against available anti-infectives. Studies to document the direct effect of poor-quality medicines on drug resistance have yet to be conducted.

Underlying Causes of Falsified and Substandard Medicines

There are many causes responsible for this growing problem, and they are diverse and often overlapping. In general, the root causes are weak regulations or a lack of them, tax law enforcement, financial constraints, and poor control over the manufacturing and distribution of pharmaceuticals.

Falsified Medicines

The high burden of infectious disease in LICs and LMICs continues to increase the demand for essential medicines, especially antimicrobials. Along with high costs or shortages of legitimate drugs, poverty, corruption, and inadequate supply chain controls were considered the main factors [43–46]. Moreover, limited resources in LICs and LMICs, a lack of expertise in drug regulations, and an inadequate number of trained human resources, together with the absence of well-equipped laboratories for drug quality monitoring available to regulatory authorities, exacerbate the problem [43–45].

The unaffordable cost of genuine medicines is one of the main factors that enables criminals to advertise falsified medicines, especially in African and Asian countries where social or health insurance systems are not implemented, and patients with limited income must pay for their treatment. This leads them to seek cheaper medicines from illegal sellers alongside fruit and vegetables markets. Imposing high taxes on pharmaceutical manufacturers is to blame, at least in part, for high drug prices. For example, in Morocco, Congo, and Zimbabwe, taxes levied on medicines are estimated to range from 18.3 to 39.5 %. These taxes are a major source of government revenue, but they have the effect of impeding public access to safe medicines [47].

The production of falsified medicines does not require large manufacturing facilities. Private houses, backyards, or cottage industries are all that is needed for criminals to carry out such businesses. This is exacerbated by light penalties. As an example, the punishment for criminal activities involving falsification of medicines in Indonesia, Tanzania, and Lebanon is imprisonment for between 6 months and 3 years and a fine of between US$30,000 and 57,000 , making this a high-profit, low-risk industry for the criminal element [29, 43, 48, 49].

Substandard Medicines

Compliance with good manufacturing practices (GMP) is a vital and obligatory part of the pharmaceutical industry. Quality control is an important element of these practices [50]. Errors can occur at various points in the manufacturing process, but

applying strict quality-control measures can minimise the risks of errors and facilitate their correction. The process of manufacturing medicines can involve three distinct stages of production: the synthesis of the active pharmaceutical ingredients (APIs) (primary production); formulating the medicines (secondary production); and packaging the final products (tertiary production) [51, 52]. Pharmaceutical production in LICs and LMICs almost always involves the last two production stages, whereas APIs are usually imported from international suppliers whose quality controls are often not verified [53].

In its guidelines on quality assurance of pharmaceuticals, WHO stressed the importance of the presence of an independent quality-control department, with a fully equipped laboratory, for every manufacturing site [50]. This department is responsible for the internal quality inspection of the production lines, which includes raw and intermediate materials, packaging, and final products, confirming that they comply with international standards. Moreover, this department can check the quality control used by the supplier of starting materials [50].

Implementing good quality-control standards in a factory, however, is associated with extra costs for the manufacturer, as it requires staff training and consistent observation as well as verifying the source and quality of all starting materials [4, 51]. International innovator and generic drug manufacturers have a large capital investment, and work on large-scale production, which recovers the cost of operating a high-quality-controlled factory [4]. By contrast, manufacturers in LICs and LMICs often operate on a small production scale with poor infrastructure and insufficient capital available to them, in the absence of any foreign or domestic financial aid [4, 51, 52]. These obstacles adversely affect the quality of medicines in these countries and facilitate the spread of substandard medicines. This problem is worsened by the meagre or even absent role of national drug-regulatory authorities, who are either unaware of the problem or turn a blind eye to it in order to promote domestic drug industries [4]. It was estimated that 30 % of WHO member states have either no or inadequate drug regulations, all from LICs and LMICs [54].

Another problem is the unregulated procurement of medicines. Countries in poor-resource settings procure medicines on a tight budget [55]. Thus, they may find low-priced "deals" attractive. Cheap drugs, however, are sometimes of poor quality and may pose major health risks [56]. Efficient systems to ensure the quality of procured medicines both during and after procurement vary and are often lacking where most needed [55]. Some international manufacturers may use this to their benefit. The MSF pharmacists have noted that the quality controls of some factories are set to different levels based on the destination of their products [30].

The Way Forward

The trade in poor-quality medicines is a multi-sectoral problem; thus, a multi-sectoral approach is required to solve it. Falsified medicines are deliberately and fraudulently manufactured and thus need law enforcement measures, whereas

substandard medicines are the results of inadvertent manufacturing errors by legitimate manufacturers; therefore, regulatory and technical measures are needed [16].

On a national level, governments should support their national drug-regulatory authorities for the development of strategies that strengthen the regulations of medicines and the production of good-quality medicines [8]. The majority of manufacturers in LICs operate with little capital. There are extra costs and technical requirements required to bring the quality of their production facilities up to international standards. These are problems that governments cannot solve on their own [52]. LICs, therefore, can invite the private sector to become involved. Investment institutions such as the International Finance Corporation (IFC), a member of the World Bank Group, and the Overseas Private Investment Corporation (OPIC), an independent development finance institution of the United States government, can provide advice and investment to enhance private-sector growth in LICs and LMICs. These can be utilised to provide initial investments for small pharmaceutical companies. A complementary step can then be made by governments to encourage partnerships with international innovator and generic drug manufacturers [4]. With other regulatory measures that drug-regulatory authorities can implement, such as monitoring and licensing of all processes involving the manufacturing, distribution, and sales of medicines, the problem of substandard medicines can potentially be curbed.

Due to the nature of falsified medicines, different governmental organisations, in addition to drug-regulatory authorities, must be involved in the battle against criminal falsification of medicines. Such organisations include police, customs, the justice system, health ministries, and the media [3]. These organisations should cooperate to disseminate information about falsified medicines. The ultimate aim is to combat the problem through legislation and law enforcement actions, the identification and seizure of falsified medicines, and the prosecution of perpetrators. Moreover, an extensive campaign by the media to increase the awareness of the public and healthcare professionals about the problem is crucial [43].

On an international level, a lack of clarity concerning definitions has challenged previous efforts. All stakeholders should agree, firstly, on definitions of different forms of poor-quality medicines, that is, falsified and substandard medicines, in order to curb the problem [3, 13]. Secondly, a global effort is needed, not only to fight trade in falsified medicines, but also to focus equally on the issue of substandard medicines. An agreement under international law that takes into consideration public health and circumvents the issue of IP rights is required [16]. This agreement will then legally bind all concerned countries and unite national and international efforts against this trade. This will facilitate countries in seizing falsified medicines and strengthen their abilities to investigate and prosecute crimes across borders [3].

Such an agreement can also mandate members to share information on falsified and substandard medicines and send reports on a continuing basis to a central body. An in-depth analysis will be conducted on these reports on a larger scale to provide a precise estimate of the problem [4]. The provision of financial and technical assistance by HICs to resource-poor counties to strengthen their regulation capacities and enhance local production of good quality medicines is also needed [3]. The new

WHO mechanism on the so-called SSFFC medicines that was launched in late 2012 may prove to be a good start, as it addresses many of the aforementioned issues [20].

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Part II
Factors Enabling Improved Therapy

Chapter 10
Regulatory Science for Paediatric Medicines in Low- and Middle-Income Countries

Agnes Saint-Raymond and Emer Cooke

Introduction

Introduced into pharmaceutical parlance by Margaret Hamburg, US FDA Commissioner, the term 'regulatory science' covers "the development and use of new tools, standards and approaches to more efficiently develop products and to more effectively evaluate product safety, efficacy and quality". We looked at what is new in this area concerning paediatric medicines,[1] and in particular how these advances could be useful for children in Low- and Middle-Income Countries (LMIC).

Pharmacological Differences Between Adults and Children

When it comes to paediatrics, regulatory science is progressing fast since the introduction of legislative initiatives in the USA and in Europe. Understanding and predicting pharmacological differences and developing the tools to develop medicines in the various and heterogeneous groups of children between birth and adulthood (16–18 years old) is a challenge, but one that has been taken up by many

[1] 'Medicine' (or drug) as used here includes small molecules, biological products, gene or cell therapy, tissue engineered medicines and vaccines.

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researchers. Moving away from the traditional development in what can be defined as an 'average (young male) adult' has created the need for new methods, new trials and new approaches. Although this is not the focus of this chapter, the issues would be similar for the elderly, who are not the 'average' adults, and for pregnant women.

The complexity of medicine development in children is related mainly to differences in children's growth and maturing physiology, which can affect any aspect of pharmacokinetics, pharmacogenomics, pharmacodynamics [1], as well as the need for specific pharmaceutical forms and formulations [2].

Paediatric regulatory science also includes specific aspects of trial methodology and pharmacovigilance. It is driven by ethical constraints because pharmacological differences and the vulnerability of children dictate specific approaches for research. Children in LMIC have additional vulnerability related to the difficulties of access to care, limited education, poverty and poverty-related conflicts of interests [3].

Paediatric Drug Development as a Regulatory Science Driver

While excluded from the mainstream in the past, paediatric drug development is now stimulating research on and use of innovative approaches to avoid unnecessarily exposing children to the risks of research, and to maximize the use of existing data. Paediatric research has encouraged and driven the reflection on small trials methodology, the use of modelling and simulation for pharmacokinetics and pharmacodynamics, and a reasoned approach to the extrapolation of data across populations [4].

Paediatrics has boosted research and routine manufacturing of forms like dispersible tablets ('a liquid in a solid') or minitablets. It has triggered reflections on the formulations of medicines administered to children, in particular on excipients tested on and acceptable for them and those which are actually toxic for children (e.g., benzyl alcohol). Paediatrics has changed the paradigm of avoiding medicines during pregnancy. Medicines can be given to pregnant women to prevent or treat diseases in the newborn infant, for example, to prevent Rhesus incompatibility or neonatal streptococcus B infection [5,6]. It is possible to immunize the pregnant woman to ensure protection of both the mother and the infant before the latter can generate antibodies in the first weeks of life (e.g., with flu vaccines) [7]. There is also growing interest in long-term effects of childhood use of immunomodulators [8] and neuro-pharmacologic agents [9].

It is important to remember that we learned many lessons on both adult and paediatric medicines from the use of medicines in children: past catastrophes such as the thalidomide teratogenesis, successes with the first gene therapy ever, in the paediatric disease of adenosine-desaminase deficiency, and important knowledge from gene therapy for X-linked severe combined immune deficiency with insertional oncogenesis. This may seem far from the priorities of LMIC, but progress is cascading from high-income countries (HIC) to LMIC, and one can only hope that the pace will accelerate.

Pharmacovigilance Challenges

In the area of paediatric pharmacovigilance, work is only starting. The science and activities of detection, assessment, understanding and prevention of adverse effects to medicines are changing for adults, evolving from a main activity of adverse effect reporting, to a prospective robust identification and management of risks. Pharmacovigilance in children is lagging behind and the reasons are complex.

- Adverse effects are not readily identified by younger children or parents and caregivers.
- Adverse effect profiles in children may differ substantially from those seen in adults.
- Prescribers fear liability if reporting adverse effects from off-label use.
- It is extremely difficult to detect and attribute to a particular medicine long-term adverse reactions that are sometimes only detectable in adulthood.
- Adverse effects are under-reported in children [10].
- Only limited medicines have approved use in the paediatric age group. In most cases validated safety information is lacking.

Because of maturation and growth, some adverse reactions occur mainly or only in children, for example, liver toxicity with valproate, or paradoxical psychotropic effects of diazepam. There are initiatives to develop prospective approaches to detect and prevent adverse effects, for example, in paediatric rheumatology with the unprecedented use of monoclonal antibodies; [8] regulators do analyse paediatric signals from recent databases [11]. In parallel, more reasoned approaches are used to try to predict paediatric adverse reactions through studies of juvenile animals and models [12].

In their often weak regulatory environment and because of insufficient funding and staffing, pharmacovigilance may be nonexistent in many LMIC and limited to adverse effects reporting. Paediatric-specific activities are rarely mentioned. This is paradoxical as the most used medicines, vaccines, anti-HIV or anti-malarial products are all for paediatric diseases [13]. In addition to differences in pharmacology, maturation and growth already mentioned, major differences in disease burden and health care settings in LMIC compared to HIC make it impossible to extrapolate the clinical efficacy and safety profiles of medicines used in adults to use in children. In HIC, there is very limited experience of antimalarials, very few ‘naïve’ children with HIV infection and materno-fetal transmission of HIV is systematically prevented. Specific paediatric safety studies and pharmacovigilance investments have to be made and maintained to ensure that adverse effects of medicines used in children are prevented or mitigated, but in a resource-poor environment, cost-effectiveness of these investments is even more essential. Progressing regulatory science will eventually benefit medicines development, approval and monitoring, lead to more robust decision-making on their benefit/risk and increase the number of quality medicines available for children in LMIC (Box 10.1).

Box 10.1: Useful References on Regulatory Science

Paediatric pharmacology

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Usefulness of HIC Activities for LMIC

The impact of what has changed in HIC, following the legislative changes in the USA and subsequently in the EU, is only beginning to be detectable, but little has changed for LMIC. In 2013, almost 6 of the 7.1 billion world population lived in LMIC [14]. Whereas children (less than 15 years) represent only 16 % of the population in HIC, in LMIC they represent 30–40 %, and up to half of the population in Africa. Children accumulate a very high burden of infectious diseases from curable causes, in particular in those aged less than 5 years (7 million deaths/year). The other main killers of children in LMIC are complications around birth and pregnancy. The WHO Essential Medicines Model List for children shows that most essential active substances have existed for a long time, but children still lack access to age-appropriate medicines [15]. A notable exception is vaccines, which have been well studied and used in these countries, because availability has been ensured by global initiatives. One example of success in paediatric immunization is the Global Alliance for Vaccines Initiative (GAVI), a public–private partnership, which has reached 440 million children in the poorest countries since 2000 [16].

Availability for children means having multiple doses and innovative forms and formulations of high manufacturing quality, meeting the conditions of most LMIC where humidity and heat are high [17]. For these reasons, LMIC need solid scored forms rather than cumbersome, poorly stable liquid forms, which also require access to clean water. Dosing based on weight must cover a range of 2–70 kg. Pharmaceutical quality and innovation unfortunately have a high(er) cost and maybe unaffordable. Local pharmaceutical businesses may not be able to deliver such quality.

In addition, as for other populations, children's medicines may be of substandard quality, diverted into the black market or falsified. This has been documented especially in countries with limited resources for controls and enforcement of importation, wholesale distribution and manufacturing [18–20].

Beyond the Scope of Regulatory Science

There are issues in LMIC that will not be solved by progress in regulatory science. How might it be possible to ensure that there is commercial interest in paediatric medicines intended to treat the specific diseases of the LMIC? Can solutions or other models be found to ensure that these unmet needs are covered? Some models have been developed. Examples are the financial approach of UNITAID, brokering for larger quantities, therefore better priced medicines; that of the Patent Pool (pooling IP rights); or drug development through alternative business models such as the Drugs for Neglected Diseases Initiative. This is also one of the three aspects addressed by the implementation plan of the UN Commission on Life-Saving Commodities for Women and Children in 2012 [21]. The UN Commission was aimed at stimulating and implementing measures to reach the 2000 Millennium Development Goals (MDG) on reducing childhood mortality (MDG4) and improving women's health (MDG5). Financed by some countries and donors such as the Bill & Melinda Gates Foundation, this initiative focused on three aspects: innovative financial approaches to make medicines affordable, decreased regulatory hurdles and innovative technologies to ensure access to 12 essential medicines and some devices. The implementation plans are ongoing [21].

The Role of Regulators in Addressing Needs for Paediatric Medicines in LMIC

Regulatory focus on paediatric medicines by regulators in LMIC needs to be further stimulated.

Many essential paediatric medicines do exist as active substances. The 12 essential medicines chosen by the UN Commission to address the main causes of morbidity and mortality of children aged less than 5 years old and of women around pregnancy are widely available in HIC, including paediatric forms and formulations. In LMIC countries, however, there is a general lack of approved and adapted paediatric forms, in particular fixed-drug combinations, of good quality. These combinations are essential for the long-term treatment of HIV infections and tuberculosis. Regulatory collaboration on paediatric needs for fixed-drug combinations of anti-HIV medicines is ongoing with a group of experts and generic companies (Paediatric Antiviral Drugs Optimization initiative of WHO, with the Drug for Neglected Diseases Initiative (DNDi) and nongovernmental organizations)

(see Chap. 13). Despite joint efforts of WHO (Stop-TB) and the TB Alliance, the treatment of tuberculosis in children (coinfected or not by HIV) is still lacking appropriate fixed-drug combinations. The currently available form is too large (15-mm diameter with 5-mm thickness), unpalatable and its ratio of active substances is outdated [22].

The recent growth of collaborative approaches and regional harmonization initiatives in LMIC such as the East African Community (EAC) and the African Medicines Regulatory Harmonization (AMRH) programme offers some cause for optimism, although these initiatives are not focused on paediatric needs. With the collaboration of WHO, and partly funded by donor organizations, these initiatives are the product of a growing realization of the need to better use scarce resources and of the potential to adopt collaborative approaches to regulatory approval, sharing expertise and reducing parallel evaluations, all of which help to speed up processes and facilitate access. The EAC, established in 2012, has already developed processes for the joint registration and evaluation of medicines for marketing authorization; joint good manufacturing practices (GMP), inspections for pharmaceutical manufacturing facilities; regulatory information exchange; and harmonization of quality management system requirements for Partner States' regulatory authorities [23, 24]. These build upon the approach used in the European Union and are intended to ensure that adequate quality standards are maintained, so as to achieve consistency in regulatory service delivery and facilitate mutual trust, confidence and recognition. The AMRH has recently announced the selection of ten Regional Centres of Regulatory Excellence (RCOREs) with specific regulatory science expertise as well as training capabilities to help strengthen regulatory capacity development in Africa. In the area of clinical trials, successful work was done by the European & Developing Countries Clinical Trials Partnership (EDCTP) and the African Vaccines Regulatory Forum (AVAREF) bringing together expertise in the evaluation of clinical trials of vaccines [25, 26]. Similar initiatives in Asian and Latin American countries are also emerging.

Stringent regulatory authorities play a role in many areas of capacity building, training and cooperation. The US FDA has very successfully implemented the PEPFAR programme on HIV medicines [27]. The European Medicines Agency, in collaboration with WHO, has issued scientific opinions on new medicines intended for use outside of the EU on behalf of other regulatory authorities (so-called 'article 58' opinions). Most are for medicines for paediatric use such as vaccines and antimalarials [28].

With respect to capacity building in LMIC for paediatric medicines, WHO has led initiatives [29] and hosted several regulatory meetings on paediatric medicines. The highest needs identified were for training and capacity building in particular the assessment of paediatric clinical trial protocols for regulatory approval, ethical guidance on paediatric trials and paediatric forms and formulations guidance. Most LMIC regulators do not have paediatric expertise. Therefore to combine expertise and experience, in 2010, WHO decided to create a forum of exchange by creating the network of Regulatory Authorities for Paediatric Medicines (PmRN), which is chaired by the EMA. It has a membership of 26 countries. The network output

includes a systematic review of paediatric ethics guidance, and guidance for assessors of paediatric trials and on paediatric formulations. At this point in time, the network focuses on providing training relevant to paediatric medicines development either face-to-face or via webinars [27].

There is still a high need for integration and awareness of paediatric medicines in regulatory processes. Experience from the review of a Regulatory Authority in a country in Africa showed that the general regulatory framework was only partly set up, sometimes outdated or lacking implementation measures and training resources were insufficient. Importantly, potential conflicts of interest were insufficiently addressed. From the paediatric-specific perspective and despite the size of the paediatric population in that particular country, access to paediatric expert and academic advice, as well as internet and library support were limited or underused. The templates for evaluation reports or pharmacovigilance did not take age and other paediatric characteristics into consideration, and the drug expert committees did not include paediatric expertise. Many of these aspects could be improved without the need for significant resources, by increasing the regulators' awareness of the needs of children.

An interesting example of multi-stakeholder collaboration in capacity building is represented by the GRIP partnership, funded by the European Commission under the 7th Framework Programme (2010–2015) [30]. GRIP aims at providing training on paediatric clinical trials and paediatric pharmacology and is supporting the development of the tools necessary to the training. This includes paediatric pharmacovigilance, pharmaceutical forms and formulations, outcome measures, trial methodology and neonatal aspects. GRIP includes academic partners, the EMA, WHO, the NIH and patients organizations. The training will, in most cases, be provided remotely and through a Virtual Learning Environment. Since it is modular in its approaches non-paediatricians, in particular health care providers from LMIC involved in paediatric trials at various levels will have an opportunity to develop competence. GRIP will also deliver an appropriate Master's degree curriculum.

Conclusions

Paediatric medicines benefit widely from regulatory science and its progress; in many areas the needs for medicines appropriate for use in children are stimulating new approaches and changing paradigms. The needs encompass forms and formulations, nonclinical studies in juvenile animals, higher quality clinical trials and better proactive pharmacovigilance. Progress and innovation are needed for products of LMIC even if they are not immediately affordable by LMIC. Eventually innovation will become routine and less expensive, and will improve the imperfect way we treat children today. Regulatory authorities must cooperate to suppress hurdles, and to ensure robust benefit–risk decisions and monitoring of paediatric medicines. Regulatory authorities have a responsibility in embracing change and ensuring that progress is benefiting children of the world, a majority of whom live in LMIC.

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Chapter 11
Enabling Equitable Access to Essential Medicines

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Essential medicines are intended to be available within the context of functioning health systems at all times, in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and community can afford.

Background

Essential medicines are medications that meet the majority of the health needs of the population and are usually tailored to an individual country based on national assessments of disease prevalence, effectiveness, safety, and cost-effectiveness. The World Health Organization (WHO) drafted the first essential drug list in 1977 containing 220 drugs. Over 30 years later, Health Action International states that fewer than 350 medications are needed for most countries to manage 90 % of health issues requiring medicines [1].

Access to essential medicines is a core component of the 'right to health' [2] and is considered by the World Health Organization as one of the six essential components

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of a health system [3]. With the recent shift in global focus to support the strengthening of national health systems [4, 5] as well as a specific Millennium Development Goal target of providing affordable essential drugs in developing countries (target 8.E), it might have been expected that more medicines of good quality would be available to more people throughout the world. However, the United Nations notes that 'there has been little improvement in recent years in improving availability and affordability of essential medicines in developing countries' [6].

Improving access to medicines remains a critical issue for all health systems and is particularly challenging in developing countries where, for many reasons, a prescription may not lead to the prompt dispensing of the appropriate medication: poor people and poor governments may not be able to afford to buy essential medicines; people may be unaware of available medical treatments or how to take prescribed medicines correctly; a lack of trained health staff can impede drug purchasing, distribution, and storage, as well as impair rational prescribing and dispensing; national systems may hinder procurement or add costs to essential medicines and may be inadequate to assure quality; hospital services may be unable to support drug monitoring in individual patients; and substandard and counterfeit drugs may predominate. This chapter outlines the major constraints to optimising drug treatment in developing countries and highlights the need for a comprehensive approach to tackle the numerous challenges.

Availability

In resource-poor settings, the manufacturing, procurement, distribution, delivery, and storage of medications is unreliable limiting their availability to patients who need them. For low- and middle-income countries, the average regional availability of generic medicines in the public health sector ranges from 29.4 % in Africa to 54.4 % in the Americas [7]. Similarly, wide differences are seen in the private sector with average availability varying from 14.8 % in Chad to 97.5 % in Syria.

Issues of availability relate to the available stock in public or private pharmacies and warehouses, the time a medicine is out of stock (stock-out duration), and the quality of storage of medicines. A number of studies have employed the WHO survey methodology to assess the pharmaceutical landscape in their country. In Malaysia, there was poorer availability of essential medicines in public district drug stores compared to public health clinics (89.2 % vs 95.4 %) with an average stock-out duration of 32.4 days in district drugs stores [8]. In Rajasthan, India, the availability of medicines, particularly generic medicines, was highest in the private sector followed by the NGO sector. Notably, only 2/36 essential medicines were available as generic versions in the public sector [9]. In Sudan, only 85 % of medicine prescriptions led to dispensing of the medication and the quality of medication storage was poor in 56–65 % of sites [10].

Several organisations are working towards improving the availability of medicines in developing countries through international mechanisms such as the framework for protecting public health interests provided within the 2001 Doha Agreement on Trade-

Related Aspects of Intellectual Property Rights (TRIPS) [1, 11]. One example is Medicines Patent Pool, a United Nations-endorsed organisation that works with manufacturers to negotiate licensing of inexpensive preparations of antiretroviral medications as well as appropriate formulations to allow ease of dosing [12]. Some countries such as Brazil, India, and Thailand have used the TRIPS agreement to produce low-cost versions themselves to improve access to key medicines such as antiretroviral drugs.

Affordability

The large majority of people in developing countries access medications through out-of-pocket payments [13]. Although in many countries medications are ostensibly free (or with only small copayments) in most public sectors, many essential medicines are frequently unavailable [14] with consumers forced to purchase them from the private sector. The costs of medications are typically evaluated relative to the patient's ability to pay (for example, daily income) or the median price ratio (MPR) [15].

The MPR evaluates the local price of a medication relative to the international reference price (IRP) and is a useful means of evaluating the local cost of medicines. The MPR varies significantly between countries and has been reported to be more than four times the IRP in the public sector in countries such as the Congo, the Philippines, and Moldova. The MPR also varies in the private sector and has been recorded as 27 times the IRP in El Salvador [16]. These figures highlight the continued high price of medications in settings where people are least able to pay for them.

There is an urgent need for improved access to medicines for the treatment of chronic disease due to the high burden of non-communicable diseases (NCDs) in developing countries. While acute illnesses often require a one-off course of medication, long-term access to medications for the control of chronic diseases is often unaffordable in developing countries [17]. The MPR of generic and original brand medicines required for chronic diseases fluctuates significantly across private and public health sectors. For example, the MPR of generic-brand glibenclamide in the private sector across WHO regions ranged from 13.0 to 67.6, and in the public sector from 3.2 to 57.0. For original brands, the variability in the private sector was greater, 12.8 to 211.9 [18]. The variability in pricing of these medications means that continued access to prescribed products throughout the course of a person's illness is unreliable and unaffordable in many countries.

However, there has been a recent increase in multinational efforts for better access to chronic disease treatments. In 2011, the UN General Assembly Political Declaration on the Prevention and Control of NCDs called for greater commitment on a range of measures to improve access to medications to manage NCDs [19]. In 2012, the World Health Assembly set a target of a 25 % reduction in NCD mortality by 2025 with improved access to medicines an inherent part of achieving this goal [20].

To address the issue of affordability, countries have implemented a policy to remove duties on medicines. However, such policy changes require stringent

regulation to ensure that this price reduction is passed onto the consumer [18]. Ensuring quality of and access to cheaper, generic-brand medications enhances patient and prescriber use of generic formulations. Other potential approaches to improve government affordability include national-level pooled purchasing or differential pricing based on the income level of the country [18, 21].

Quality Control

The infrastructure for quality control for manufacturing and regulation of medication standards in developing countries is often inadequate. Lack of legislation, the high cost of medications, the absence of a reliable supply chain, and limited infrastructure for drug quality surveillance contribute to an escalating problem of counterfeit and substandard medications (see Chap. 9).

Substandard medications are those that do not meet national quality specifications [22]. WHO has published the International Pharmacopoeia (for adults and children) to standardise and ensure the quality of drug formulations in developing countries. Furthermore, the WHO prequalification programme provides 'standards of acceptable quality, safety and efficacy' of medications through surveillance of manufacturing, quality laboratory control practices, and building the capacity of national regulatory authorities [23].

Counterfeit medications are an imitation of the original drug with an alarming 'market share': an estimated 25 % of all dispensed drugs globally are counterfeit [24], with up to half of the drugs dispensed in Asia and Africa thought to be counterfeit. There is an absence of functional regulatory agencies in many countries to enforce quality and safety standards for medications. There is also a lack of consumer awareness and there is a paucity of reliable information systems to compile data on the type and location of counterfeit medications to facilitate countermeasures [25]. The US FDA has suggested the use of 'track and trace' technology such as employing radiofrequency identification to follow medications from the point of manufacture through the distribution network to final delivery to the patient [26]. WHO has designed a BE AWARE toolkit for health professionals to inform clinicians of methods for identifying and reporting counterfeit medications and have highlighted the current issues with counterfeit medications [27].

Rational Prescribing

Self-medication, polypharmacy, and the inappropriate use of medications are common issues in developing countries [28]. Promotion of rational prescribing is multifaceted and includes the development of procedures for writing and revising treatment guidelines by reputable committees [29, 30]. However, guidelines alone

do not suffice [31], and public health and educational approaches are also needed to influence prescribing practice – the doctor, pharmacist, other health workers, and the patient all need to understand the rational use of medications. Such approaches include educational programmes for prescribers, empowering pharmacists to take an active role in the treatment team, and establishing hospital committees that promote appropriate prescribing [30]. Polypharmacy and inappropriate use of medications can be addressed by employing strategies such as setting a maximum limit for the number of drugs per prescription and a maximum (or minimum) treatment duration, creating a list of restricted drugs that need committee approval before use, and specifying minimum qualification requirements for those writing certain prescriptions [28].

Monitoring of drug use requires a standardised method of assessment with specific indicators related to the appropriate use of medications [32]. One example is the 'Core indicators for monitoring and assessing country pharmaceutical situations', a low-cost tool developed by WHO that permits easy implementation [33].

Local practices of using traditional medicines as complementary or alternative treatments for common conditions are infrequently addressed under strategies to improve the rational use of medications. However, efficacy and safety data for these agents are often limited. Ideally, such therapies should be subject to the same strategies to optimise treatment as essential medicines, and guidelines for their rational use should be developed [10].

New Technologies

The increasing availability of mobile phones as well as improved telecommunication networks in resource-poor settings provides a means of overcoming some of the many challenges [34]. Clinical pharmacology applications for smart phones have been developed that allow remote access to accurate drug information allowing health workers of all levels to prescribe appropriate medications, doses, and durations of treatment. A mobile pharmacy service system in China has been used to individualise patient care through Short Message Services (SMS). This service provided drug information to patients, prompted them when medications were due, and reminded them to renew their prescription at the end of the treatment course [35].

Mobile phone reminder systems that target patient compliance have been extensively studied in the treatment of HIV and tuberculosis [27, 28] and have been associated with improved compliance with ART, notwithstanding various technical difficulties with mobile phones [36, 37]. Despite rapid improvements and availability of mobile phone technology, limited infrastructure to support mobile reminder services persists in many rural and remote settings, and the acceptability and reliability of the technology has been challenged because of concerns about patient confidentiality and data security [38].

Conclusions

The use of medicines in the developing world remains suboptimal. Drug treatment must be improved through strict regulation and monitoring of pricing and drug quality. Better staff training is needed to overcome system limitations of distribution and storage, improve prescribing and dispensing, and to enhance detection and reporting of substandard and counterfeit medications; numerous tools tailored for developing settings are now readily available [39, 40]. Emerging technologies such as mobile phones and other smart devices offer scope to overcome some of the challenges faced in resource-limited settings but their success is still largely contingent on trained health personnel, an engaged public, reliable infrastructure, and affordable communications. Actions at the international through to the local level are required to realise the goal of individualised patient care and rational prescribing in all healthcare settings.

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Chapter 12
Clinical Pharmacy and Pharmaceutical Care

Sara Arenas-Lopez and Stephen Tomlin

Clinical Pharmacy and Pharmaceutical Care

The goal of pharmaceutical care is defined as "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life" [1]. The process of pharmaceutical care includes identifying, resolving, and preventing drug-related problems. The underlying principles apply to all populations, including infants and children, although the provision of pharmaceutical care to children presents additional unique challenges and these are particularly amplified in the developing world. Nonetheless, even in settings with limited resources, pharmacists can aspire to be responsible for improving drug therapy of their patients. In this effort, clinical pharmacy provides one of the most important tools for achievement of optimal therapeutic outcomes through pharmaceutical care.

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Off-Label Use of Drugs in Children

The Situation

Many drugs that are prescribed for children are not specifically licensed for pediatric use. These drugs frequently are designed for adults, but are also used in children (off-label use). There is often a lack of data to support dosing choices, and there may be only limited evidence for efficacy and safety. For the past two decades consistent efforts have been made to overcome this problem, as described in Chap. 10. The Best Pharmaceuticals for Children Act was passed in the United States in 2002, with subsequent amendments in 2007 [2]. In 2007 the European Parliament also approved legislation mandating the pharmaceutical industry to produce a Pediatric Investigation Plan at the same time as a pharmaceutical development plan for adults is submitted [3]. Currently, only a relatively small percentage of new or old drugs are commercially available in age appropriate pediatric formulations. A survey looking into the licensed products available in the British National Formulary for Children (BNF-c) 2008 edition highlighted the fact that nearly 70 % of the products licensed for children were formulated as oral solid dosage forms even when intended for use from birth [Tuleu C, personal communication].

However, it will take much time and effort before these regulations significantly impact clinical practice. In the meantime professionals will need to draw upon clinical experience, a variety of information resources and professional networks to ensure the most effective and safest therapeutic choices for children [4]. This is especially pertinent to low-income countries (LICs), which may lack adequate drug information resources, internet accessibility, and availability of clinically trained pharmacists.

Implications for Clinical Practice

The general lack of suitable, licensed formulations for children carries an increased risk of medication errors. For example, it is often the case that only a small portion of a vial is required for administration of the correct dose. It is not difficult to err and to measure a ten times or even one hundred times overdose for a small baby from one single vial [5]. In many countries in house formulations (i.e., those that are prepared extemporaneously in pharmacies) will vary in production from pharmacy to pharmacy. This situation can only be worse in low-income countries, which may lack trained individuals, basic ingredients, and appropriate utensils to prepare such formulations. Even access to clean water or adequate refrigeration may be problematic.

In some countries the use of central intravenous additive services (CIVAS) in hospitals, where individual patient doses are prepared following standard operating procedures by the pharmacy department, can greatly assist in minimizing errors in neonates and children. Still, in many countries, due to their economic situation or

lack of trained staff, it is likely that such services will be less than optimal. The impact of even a single pharmacist or pharmacy technician, trained in aseptic technique, on a hospital or a clinic in low-income countries could be dramatic. Experienced pharmacists and technicians in this field could provide supplemental teaching and training in resource poor countries.

Most pediatric doses are calculated based on the child's weight. However, this often results in doses which are extremely difficult to measure from the preparations that are available or which must be specifically formulated. Basic amenities must be in place before formulation of special pediatric products can even be considered. A trained pharmacist, with education and experience, can provide guidance regarding accurate dosing, alternative preparations, a sensible approach to rounding doses to measurable quantities, advice on clinically appropriate and practical administration frequencies and knowledge concerning drugs that have the narrowest therapeutic indices.

Key Principles for Drug Supply and Administration

- Ensure stock drugs in the hospital are appropriate for pediatric clinical use.
- Dispense the correct quantities of medicine and in appropriate packs. Avoid wherever possible decanting of tablets in plastic bags in hot and humid countries as they can disintegrate.
- Provide medicine in child-resistant containers when possible.
- Avoid decimal points where possible (e.g., 10 mcg, not 0.01 mg).
- Avoid trailing zeros (e.g., 2 mg, not 2.0 mg).
- If a decimal point is really needed, put a 0 in front (e.g. 0.2 not .2).
- Provide clear labeling for parents and caregivers (e.g., phenytoin liquid 6 mg/mL – give 4 mL {24 mg} twice daily).
- Overall oral syringes are the best medical devices for administering medicines to children in small volumes <5 ml.
- Be aware of how to measure and administer medicines in oral and IV syringes, select the right size syringe for the right dose volume and avoid using the same syringes for oral and IV use as fatal errors have occurred with oral drugs mistakenly given intravenously.
- Perform Medicines Reconciliation in order to ensure that patients understand their medicines and identify the medicines that are brought from home as in many countries patients bring their own drugs into hospital or have to buy their own in the community pharmacy in order to be treated at the hospital [6].

Adverse Drug Reactions (ADRs): Detection and Prevention

Many ADRs do not become evident until drugs have entered the market and are used by tens of thousands of patients. Consequently, it is important that people are taught to report any potential adverse effects to their doctor, nurse, or pharmacist. This is clearly

a role in which pharmacists in low-income countries can take a lead. Pharmacists can also become active in formally reporting any ADR to their local health authority. These activities should not require any additional resources, other than an adequate source of drug information and appropriate channels of communication.

Counseling of Parents, Caregivers, and Children

Part of pharmaceutical care is the process of counseling. Parents and other caregivers should be taught about the medication for their children. Basic information, including the name of the drug, what it is used for, how to correctly administer and potential, common side effects should be clearly communicated both verbally and in writing. If the child is old enough, he/she should also be included in the counseling session. Irrespective of age, it is important to involve the child as much as possible in any discussions about taking medication. Young children tend to like routine, and this approach should be encouraged. Similarly, teenagers do not like to be ignored, even if they may appear disinterested at the time of discussion.

Enteral Drug Administration

In some situations drug palatability could have an effect on adherence by the child. Oral dosage forms may be mixed with food or beverages to increase acceptability, ease of administration, and adherence. However, certain foods or beverages may affect the palatability, bioavailability, and/or therapeutic action of the medicine and it is important to bear this in mind at the time of administering some medicines with beverages or food. In some cases the manufacturer may have appropriate recommendations. It is also important to add the drug dose to a small portion of the food and not to the full amount as if the child does not eat the entire portion of food he/she will not receive the full dose [7].

All of the above is clearly within the scope of what pharmacists in LMIC settings should be able to do, provided that they have an adequate and current source of drug information and sufficient time to permit full engagement in care of their patients.

Factors Affecting Medication Adherence in Children

- Age
- Number of doses per day
- Side effects
- Palatability and formulation
- Lack of information
- Empowering the child, for example:
  - Rounding of doses so that tablets can be taken if liquids are not acceptable
  - Allowing an asthmatic child to choose a preferred inhaler spacer device

IV Administration

In some situations drugs must be administered by the intravenous route, especially when neonates and children are clinically unstable. When this is necessary some clinical considerations are required. Children and specially neonates have very fragile vasculature and it may be very difficult to obtain appropriate peripheral or central access. Neonates may only have a small number of IV lines to administer all medicines, as well as blood products, total parenteral nutrition (TPN), and maintenance fluids. Concomitant administration with TPN using the same IV access is discouraged, although sometimes it must be done, and drugs must then via a Y site connector that may allow brief mixing with the TPN solution.

When using preparations designed for adults, administration to neonates and children is likely to involve a multiple manipulation process using open systems (non-aseptic conditions). The need for additional dilution and or flushing may be important for effective administration and to avoid local (i.e., thrombophlebitis) and or acute systemic adverse events such as acute hypotension or hypertension. Fluid and electrolyte balance must be carefully considered (e.g., hypernatremia may be caused by flushing with sodium chloride solutions). Environmental conditions in neonatal units and other pediatric areas (i.e., temperature, humidity, phototherapy) may affect medicinal product stability and should not be ignored.

On a practical note infusions and fluid bags should be labeled clearly with the drug, additive, amounts, name of patients, time of preparation, and details on who prepared it to prevent errors.

The pharmacist can work closely with the nursing staff to ensure a safe and effective use of IV drugs.

Seamless Care Between Care Settings

It is essential that the transition of care for any child (e.g., between hospital and home) is dealt with in a sensitive, logical, and timely manner.

Clinical pharmacists in LMIC settings can take the lead by discussing issues such as the length of therapy, how to monitor for efficacy and side effects, as well as monitoring the logistics of obtaining medication supplies and ensuring that the pharmacist in the community understands the medication requirements of the patient. This is particularly important when, as is commonly the case, unlicensed and off-label medicines have been prescribed. The usual drug information sources available to healthcare professionals may not contain information on such drugs. The situation is exacerbated in many low-income countries when even basic drug information resources are often lacking. Whenever possible, pharmacists must act to see that caregivers providing continuing care to children are supported with adequate and timely information, including details of the drug, dose, dose information source, potential changes in dose, formulation provided, and source. If an extemporaneous product is dispensed, the formula, method of preparation, expiry date, and storage details should be supplied.

It is in any patient's best interest to have a completely seamless transfer of medicines management when changing care settings. With unlicensed medicines the child should be maintained on a consistent formulation and strength, made in the same way, to reduce the potential for variations in dose. Whether initial communication is via email, post, telephone, or text messaging, thorough communication of any problems, including need for special formulations or unusual doses, must occur. This requires knowledge of where a child is taking his/her medication (e.g., home, care-home, boarding school) and who is involved in his/her care. A breakdown of communication at any point can lead to unacceptable errors or delays in obtaining medication.

Reconciliation of medicines both when a child enters and leaves the hospital is known to be very poor. Pharmacists are ideally suited to ensuring that medicines are correct at the point of transfer between settings and should try to use these times for medicines review.

It is important that patients are able to obtain their medicines from a location suitable to their needs. These arrangements should be agreed prior to transfer of care. The most appropriate method of supply will depend on the drug, source of supply, formulation, shelf-life, local circumstances, and logistics. Every effort should be made to minimize parental inconvenience whilst ensuring supply of appropriate medicines. Information should be made available and arrangements made prior to discharge to ensure that continuation of supply is seamless. This can be achieved by requesting a copy of the product specification from the initial prescriber or pharmacy, often a referring hospital. This specification should detail the strength, formulation, constituents, method of preparation, and source.

Resources to Support the Pediatric Pharmacist

Pediatric Formularies

In the last 30 years several formularies around the world have emerged; some of the guidance books, such as *Drug Doses in Paediatric Intensive Care* by Frank Shann [8], provide information only on drug dosage and indications to treat in a very specialized area others go beyond and provide details on pharmacology/toxicology in children with references, information on the formulations, on manipulations of dosage forms and indication of whether the drugs are licensed or not (e.g., Paediatric and Neonatal Dosage Handbook by Taketomo [4]). Many of these formularies are applicable to a local area such as hospital formularies (e.g., Guy's & St Thomas, Lewisham and King's College Hospitals Paediatric Formulary) [9] and others are of national scope.

In 2005, the United Kingdom published for the first time an annual national formulary for children, the British National Formulary, which was a joint initiative from the Royal College of Paediatrics and Child Health, The Royal Pharmaceutical Society, and The Neonatal and Paediatric Pharmacist Group. It is a compendium of drugs used in the pediatric population with information about licensing, products, treatment guidelines and dose adjustments in different conditions such as renal or

liver failure, pregnancy, or lactation. It also serves as a very useful reference to drug interactions [10].

In 2007, The World Health Organization also published the first Essential Medicines List for Children and its current (fourth) edition was approved in April 2013 [11]; this list provides information on different therapeutic areas and the essential medicines that countries should have to provide care. This Essential Medicines List should be used as a guideline in the production of National "Essential Drug Lists" in low-income countries.

Pediatric Networks

The pediatric clinical pharmacist often seems to be working in isolation. Networks have the potential to play an important role to support the daily work of the pharmacist and to provide the necessary exchange of information and skills with continuous professional development activities.

In 2008, Knoppert and his colleagues described the emergence of an international pediatric pharmacy community and explored all the initiatives from different organizations to support the pharmacist working with children [12]. Some organizations, such as the American College of Clinical Pharmacy (ACCP) [13] and the European Society of Clinical Pharmacy (ESCP) [14], have special interest groups, which include pediatrics. Other organizations, such as the Pediatric Pharmacy Advocacy Group (PPAG) in North America [15] and the Neonatal and Paediatric Pharmacy Group (NPPG) in the United Kingdom [16], are exclusively dedicated to the discipline of pediatric pharmacy.

Both PPAG and NPPG aim at improving the care of neonates, infants and children. Any pharmacist, pharmacy technician, or corporate body with a pharmaceutical interest in pediatric or neonatal pharmacy is encouraged to join one of these organizations, which welcome international members.

Pediatric pharmacy as a specialty is less developed in Europe than in North America (with the exception of Great Britain where there is a very robust network). The development of clinical pharmacy in low-income countries is at the stage where North America was about 30 years ago. This is mainly a result of inadequate funding for education of pharmacists and technicians, as well as a general lack of an adequate infrastructure. However, with assistance from pharmacists trained in clinical pharmacy, pharmacists in low-income countries should be able to aspire to, and achieve, the provision of pharmaceutical care at the highest level for their patients.

Professional Development Programs

In North America and the United Kingdom efforts are being directed at defining the specialty of pediatric pharmacy. Recently the Royal Pharmaceutical Society of Great Britain launched its Faculty [17]. This is a body to support the Professional

Development of Pharmacists in the United Kingdom and to assess the level of competency of individuals in a peer review context. At present, colleagues from several fields, academia, hospital, community, and industry are undergoing the assessments. Pediatric pharmacy competencies have already been defined to support this work.

Among the work conducted was the production of the self-directed learning pack "Introduction to paediatric pharmaceutical care" by NHS Scotland and the English version led by the CPPE accessible online via NPPG website. The NPPG is committed to other education activities such as the production of the learning pack by the Paediatric Intensive Care Pharmacists Subgroup or annual study days such as the beginner's day which is attached to an annual autumn conference.

In addition, at King's Health Partners a 6-week program specifically designed for international pharmacists has been developed as a Master Module in order to provide interested pharmacists with the necessary skills to provide a pediatric clinical pharmacy service in their own country setting. One of the main objectives from this "hands on" course is to enable the participating pharmacist to identify an appropriate area of service development based on their learning experience and implement change. In this way the referral country benefits from the 6-week placement by retaining the learners [18].

In North America, the specialty of Pediatric Pharmacy practice has been recognized by the Board of Pharmaceutical Specialties. Much work is currently being done to organize preparatory courses and the creation of the specialty exam.

Summary

This chapter has briefly described some of the major issues in professional practice that are faced by pediatric clinical pharmacists. In low-income countries these challenges are compounded by poverty, and a subsequent lack of adequate resources and a supporting infrastructure. Pediatric pharmacists in some better resourced countries are advancing their specialty, and have the opportunity to assist their colleagues in low-income nations. Targeted financial support from government or other international agencies would help to make this possible.

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Chapter 13
Promoting Drug Development and Access: The Role of International Networks and Organizations

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Acronyms

3TC	Lamivudine
ABC	Abacavir
ART	Antiretroviral therapy
ARVs	Antiretroviral drugs
AZT	Zidovudine
d4T	Stavudine
DNDi	Drugs for Neglected Diseases initiative
EMA	European Medicines Agency
FDA	US Food and Drug Administration
FDCs	Fixed-dose combinations
GRiP	Global Research in Pediatrics – Network of Excellence
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials
LPV	Lopinavior
NIH	US National Institute of Health
NVP	Navirapine
PDP	Not-for-profit Product Development Partnership
PENTA	Paediatric European Network for Treatment of AIDS

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PEPFAR	President's Emergency Plan for AIDS Relief
R&D	Research and Development
RTV	Ritonavir
SRA	Stringent regulatory authority
WHO PQ	WHO Prequalification Program

Background

Just 20 years ago, research and development (R&D) for the treatment of diseases disproportionately affecting developing countries was negligible. Over a period of 25 years (1974–1999) only 1 % of new drugs were approved specifically for so-called neglected diseases, which broadly indicates diseases prevalent chiefly in low-income countries or other low-resource settings and for which no or limited health technologies are available or in development [1], despite the fact that these diseases represented over 12 % of the global disease burden in terms of mortality, chronic disability and poverty [2, 3]. The need for greater political commitment to fight these conditions has been recognized by the United Nations and included in the Millennium development goals (target 8E) [4].

Over the past decade, several major initiatives and innovative research and development (R&D) models have emerged to address neglected diseases. Despite objective progress and acceleration in new drug development, there is still a major gap between the needs and the treatments available for these diseases. Of the 850 drugs and vaccines approved (40 % new chemical entities) from 2000 to 2011 only 4 % were for neglected diseases. Furthermore, of the 150,000 clinical trials registered for new therapeutic compounds, only 1 % were for these disease areas and less than 0.5 % of them included children [5].

The lack of R&D investment for neglected diseases and for paediatric drugs has been attributed to the very low financial return for pharmaceutical companies. However, public institutions also failed to establish effective enabling policies and have not prioritized neglected diseases and thus also share responsibility for the current situation [6]. New approaches and alternative R&D models to address market and policy failures have been launched and include a broad range of actors, including academic groups, pharmaceutical companies, governments from disease-endemic countries and emerging economies, and others [2]. One of the results of this evolution was the not-for-profit product development partnership (PDP) model, an example of which is the Drugs for Neglected Diseases initiative (DNDi).

In this chapter, we briefly describe the DNDi model, and give an example of the paediatric HIV project it has undertaken in support of the HIV response. We highlight the role that research networks, public-private partnerships and strategic mobilization of key stakeholders have played in drug development and drug/formulation access for children.

Looking Back: A Brief Sketch of Public Health Achievements in Antiretroviral Drugs

One of the most successful achievements in the history of public health intervention has been the rapid implementation and use of antiretroviral drugs (ARVs) in countries with high HIV prevalence. In Africa, the region with the highest HIV burden, an estimate of nearly ten million people were receiving ARV treatment at the end of 2013, compared with only 50,000 a decade earlier [7]. However, only about 25 % of African children in need of ARVs are receiving them today [7]. There are major challenges in the implementation of early infant diagnosis and in the development and provision of appropriate paediatric formulations. Thus far, the progress made in scaling up ART for Africa has been enabled by an effective 'model' of public and private partnerships, which have mobilized international organizations, multilateral partners, research networks, non-profit organizations, philanthropic entities and industries in high- and low-income countries (see also Chap. 3).

The DNDi Model

DNDi, an independent international non-profit, patient-needs driven R&D organization, was established in 2003 to fill R&D gaps for neglected diseases [8]. Its mission is to deliver new treatments for its targeted diseases by developing entirely new drugs and re-formulations or new combinations of existing drugs, to optimize treatment and improve outcomes. In doing so, it also aims to develop sustainable research capacity in disease endemic countries and advocates for public responsibility globally [8] (see Chap. 18).

In 10 years of activity, DNDi was able to deliver six new treatments for neglected diseases and establish a solid drug pipeline including 13 new chemical entities in pre-clinical and clinical development. With its many partners, DNDi has conducted more than 25 clinical studies from phase I to phase IV, including implementation and pharmacovigilance studies, enrolling more than 33,000 patients often in very remote and unstable areas. To do that, DNDi established partnerships with a wide range of organizations including funders, academia, public sector research institutions and networks, pharmaceutical companies, non-governmental organizations and governments worldwide (including some 350 collaborations in 43 countries, 20 pharmaceutical and biotechnology companies, and 50 universities and research institutes). North-south and south-south technology transfer projects and disease specific clinical research platforms were formed to strengthen research capacity in neglected disease-endemic countries. In 2010, while maintaining its core focus on the three most neglected tropical diseases, DNDi responded to a call by various organizations, including Médecins sans Frontières, WHO, and the global health initiative UNITAID, to apply its expertise to the development of paediatric HIV drug formulations.

Although from the R&D perspective, HIV is not seen as a neglected field, the fact that paediatric HIV has been virtually eliminated in wealthy countries has left pharmaceutical companies little incentive to develop child appropriate formulations [9]. While the same neglect can be seen to apply to the development of paediatric formulations in general, the lessons learnt in the paediatric HIV field are worth documenting and may provide insight to paediatric drug development in general.

The 'AIDS Response'

The AIDS exceptionalism in the west rose in the 1980s and ended at the end of 1990s when technical solutions of testing and antiviral treatments were made available. However, the same struggle for access to treatment in developing countries did not happen at the same time. In 1996, during the International AIDS Conference in Vancouver, the first studies showing how combination antiretroviral therapy (ART) can reduce HIV disease progression were presented. This scientific breakthrough was, however, restricted to high-income countries which had all the needed financial and health care resources to mobilize and control the epidemic. Realizing the gap in response and the imminent rise in the HIV/AIDS epidemic in sub-Saharan Africa, the issue gained momentum in the international community and in 2001, UN Secretary General Kofi Annan called for a 'war chest' of $7–10 billion to address the global HIV/AIDS crisis. Mobilization from different angles such as price of treatment which is linked to intellectual property rights, positioning of the inequity of treatment access as an international human rights cause, implementation of successful treatment programmes in resource poor countries, setting up of the Global Fund to Fights AIDS, Tuberculosis and Malaria in 2002 and President's Emergency Plan for AIDS Relief in 2003 all led to the needed access to treatment in many developing countries, and sub-Saharan Africa in particular. The story is very compelling and almost unique for a single disease. A subset of this story is the one experienced by children living with HIV/AIDS [10].

Despite the success in bringing antiretroviral treatments to the developing countries, efforts are mainly concentrated on adults, while children with HIV/AIDS suffered the neglect of tools (diagnostics and medicines) and political will in the early years. As early as 1982, cases of children with HIV were reported in North America and Europe, a few months after AIDS had been described as a new disease in the adults by the US Centers for Disease Control. When the epidemic heightened in the 1990s in sub-Saharan Africa, so did the perinatal transmission of HIV to the babies. Many deaths in children with HIV/AIDS were not accounted for and many children were orphaned as a result of losing their parents to the same disease. Today, thanks to the effective implementation of the use of ARV during pregnancy for prevention of mother to child transmission of HIV, perinatal transmission in the developed countries including some emerging countries such as Thailand and Brazil, has been eliminated [11]. However, despite a decrease in the number of new cases, the number of children living with HIV/AIDS continue to be highest in sub-Saharan Africa and treatment coverage remains low, at 25 %, half that of adults [7].

When the ART scale-up started in developing countries, treatment programmes struggled with demonstrating feasibility of such programmes in resource poor settings. It was a major challenge to treat children with HIV partly because of lack of diagnostic facilities and optimal drugs. Infants and children infected with HIV had to take large amounts of liquid formulations and to use split adult tablets. When fixed-dose combinations (FDCs) were made available for adults, some programmes resorted to breaking these adult tablets for use in children due to the simplicity it offers to the caregiver and management of drug supply as liquid formulations are bulky, difficult to store and may cause stigma in the community. There was a clear need to develop adapted paediatric HIV formulations for developing countries but it was a gruelling battle to fight against the disincentive that the paediatric HIV market offers the pharmaceutical industry. Ninety percent of children living with HIV are in sub-Saharan Africa. It was not one but a series of actions or initiatives by a collective number of actors representing a wide range of organizations and companies which made it possible. The story of access to HIV medicines for children is a fascinating one to tell, with many lessons learnt which can provide a useful case study for other diseases as well.

Role of HIV Treatment Guidelines for Developing Countries

Treating children with HIV through a normal programmatic approach proved challenging in the early 2000s. There was a lack of trained skilled health personnel and expertise in treating children with HIV. Diagnosing and treating children living with HIV appeared to be complex due to the lack of simplified guidance for resource limited settings. The first Guideline on Scaling up ARV Therapy in Resource Limited Settings was published by the World Health Organization in 2002 [12]. The guideline was aimed at scaling up ARV treatment using a public health approach which promoted rational and safe use of medicines. This technical guidance was developed with the support of US National Institutes of Health which recommended standardized regimens and simplified monitoring. The first guidelines included a section on diagnosis and treatment of children with HIV, but at that time there was a clear lack of diagnostic tools and drugs to enable treatment scale-up and achieve global targets.

Despite these simplified guidelines, programmes struggled to implement paediatric care because of poor capacity among health care workers who had limited experience in treating children and were hesitant starting treatment in those in need. Additional challenges were offered by the almost complete lack of age-appropriate paediatric ARV formulations suitable to supply in resource limited settings; no FDCs were available for children, no simplified dosing procedures had been provided to ease dose adjustment and provision by health care workers, paediatric ARV formulations were remarkably expensive and diagnosis in infancy was impeded by the lack of simple and affordable HIV-diagnostic tests for children under 18 months [13]. One of the leading implementers of HIV programmes in resource limited settings, Medecins Sans Frontieres, described the challenges faced between 2001 and

2005 in treating children with adult FDCs. These tablets had to be broken or crushed and dosing were provided based on weight bands. Programmes had no access to HIV viral loads assays at that time but, reassuringly, survival and clinical or immunological outcomes were similar to those observed in adults.

The revised 2006 WHO recommendations [14] were subsequently collected in stand-alone comprehensive guidelines that focused on providing care and treatment to infants and children. This guideline introduced more detailed information to guide diagnosis and management of children living with HIV including drug dosages, side effects, WHO staging and classification of HIV/AIDS in children. The paediatric formulation dosages were particularly complex and the need was apparent for development of a simplified weight-based dosing approach to facilitate prescribing by non-specialized personnel (see Chap. 6). The development of a generic tool to combine different drugs based on the US Food and Drug Administration (FDA) approved target dose enabled, for the first time, the establishment of a pragmatic approach to dosing and the development of FDCs containing 2 or 3 drugs in the same tablets [15]. Validation of these products that were developed in response to WHO recommendations by generic companies (via an advisory board of experts, the Paediatric ARV Working Group) occurred through the efforts of a research network committed to investigating feasibility, acceptability and PK of these products as nested sub-studies of bigger paediatric trials underway in resource limited settings.

The 'treatment 2.0 initiative' that included a key pillar, 'treatment optimization', leveraged these concepts and promoted further efforts in developing normative guidance that could result in simplification and harmonization of the deployment of more effective and less toxic drugs. Alignment of paediatric with adult treatment options and the development of these key products has been one of the central messages emerging from the WHO 2013 consolidated guidelines [16]. These guidelines, significantly forward looking, have called for urgent development of key paediatric formulation that would be critical to allow country implementation, such as the '4-in-1' FDC that includes LPV, RTV, 3TC and ABC or AZT as optimal regimen for children less than 3 years.

While the development of the WHO guidelines entails a very rigorous evidence-based approach that takes into account feasibility and cost implications, these guidelines also provide a powerful advocacy tool to catalyse attention and mobilize resources towards development of new paediatric drugs and formulations for resource limited settings.

Development of Adapted Formulation for Children Living With HIV

The last decade has been hailed as the golden decade of ARV development despite claims that the HIV drug pipeline is drying up [17]. An impressive 34 % of the new drugs or combinations (16/49) were approved by US FDA since 2000, representing

an active pipeline. However, of the ARVs which are approved by US FDA, only 12 are approved for use in children below 2 years of age [18].

Paediatric studies are required as part of new drug application to US FDA since 1997 and incentives for pharmaceutical companies are offered through marketing exclusivities. The European Parliament in 2007 issued the Paediatric Regulation, requiring the marketing authorization holder to present a Paediatric Investigation Plan (soon after the results of phase 1 trials in adults) to be evaluated by the Paediatric Committee at the EMA, including paediatric studies to be developed (see Chap. 10). Although this process is compulsory for new marketing authorization holders, EMA offers an incentive by granting patent extensions. These legislative measures have forced and incentivized R&D companies to plan early paediatric development strategies.

In an analysis of the time needed from adult ARV approval to granting of paediatric exclusivity following submission of all US FDA required paediatric studies, there was an average of 6.5 years (range <1 year to 14.9 years) [17]. Since drug studies in children are usually done in a de-escalating age bands, evidence-based treatment takes longest to reach the youngest age groups. The formulations were initially formulated in syrups and intended for the developed world. However, it became evident very quickly that the majority of HIV infected children are living in sub-Saharan Africa and that health care workers and caregivers in these countries were struggling with the burden of managing bulky syrups from the supply chain perspective as well as difficulties in administering multiple syrups with different dosages. Soon activists were calling for FDCs for children. Some started to use adult FDCs by breaking or cutting them.

In response to the need for paediatric FDCs, a WHO/UNICEF consultation in 2004 established a priority list of missing formulations and discussed ways to encourage pharmaceutical companies to produce them [19]. As a result of this WHO developed a generic weight band dosing tool to facilitate the development of paediatric FDCs in 2006. The fact that the WHO Expert Committee on the Selection and Use of Essential Medicines recommended and endorsed the use of such products and encouraged their development since 2005 also helped countries to prioritize selection of FDCs in national formularies. From the technical perspective, since paediatric combinations usually do not often exist in the original formulations, further guidance was needed to assist generic manufacturers in developing them, especially with regard to dosages and dosing. The WHO Paediatric ARV Working Group was tasked to do this and in 2007 issued a report prioritizing preferred ARVs for treating HIV in younger children and grading them as ‘urgent’, ‘high’ and ‘important’ in order to give guidance to manufacturers [20]. The entry of Indian generic manufacturers into the paediatric HIV market started around this time and UNITAID started to fund paediatric HIV commodities in 2006. In August 2007, the first paediatric FDC (d4T/3TC/NVP) was tentatively approved by US FDA. The commitment from UNITAID to fund this market was the main driving force for the entry of generic manufacturers. In an analysis of the global paediatric ARV market, UNITAID was the largest

donor for paediatric ARV products with 97–100 % market volume in 2008–2009 [21].

From the regulatory perspective, it was important to note that the WHO Prequalification Program (WHO PQ) was set up in 2001 to facilitate access to medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis. Regulatory dossiers from manufacturers can be submitted to WHO PQ and this has helped UN agencies to buy quality medicines and countries with limited regulatory capacity, to expedite the dossier review process. In parallel, the US FDA set up a similar initiative which allowed ARVs to be reviewed and receive 'tentative approval' under a special programme associated with the President's Emergency Plan (PEPFAR) even if products have intellectual property protection in the country. As a result, the use of generic ARVs under PEPFAR increased.

By 2012, there were 33 paediatric ARV formulations used in developing countries [22]. This created market fragmentation and clinical confusion since multiple dosage forms exist for the same ARV. Due to the small volume of certain paediatric ARVs and the small purchasing volume of certain countries, there is a considerable delay in the production of needed ARVs. A few initiatives were taking place at the global level to protect this market. The Paediatric ARV Procurement Working Group was formed by UNITAID, the Global Fund, PEPFAR, UNICEF and other stakeholders to align procurement, promote product optimization, secure financing, engage with manufacturers and provide in country support. In May 2011, a special paediatric working group from the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children produced a list of optimized paediatric ARV formulations to guide donors, ministries of health and procurement agencies to prioritize purchase of paediatric formulations.

Figure 13.1 summarizes how an efficient drug development process for FDC can be achieved. The first step includes the identification of the right target dose to be included in the FDC in different age groups. This is often not a straightforward exercise since entities with different PK/PD profiles are being combined. Biostability and PK studies are then needed before a prequalification approval is sought. In order to be successful a comprehensive collaboration of different stakeholders including WHO, researchers, pharmaceutical companies and international organization is needed. An important role is also played by clinical research networks who are the ones producing the scientific evidence.

Role of International Clinical Research Networks

Multi-centre international collaboration has been vital for paediatric HIV research, at least in most industrialized countries, where a large number of clinical centres each care for a relatively small number of children. In the early nineties both in the United States and Europe large independent clinical trials network, such as PENTA in Europe and PACTG/IMPAACT in the United States, were established to

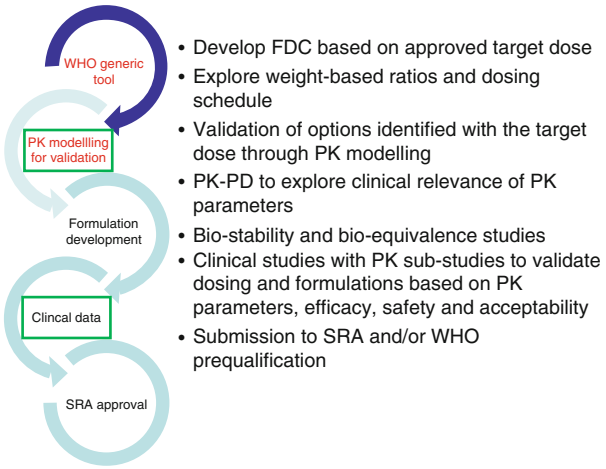

Fig. 13.1 Informing drug development

undertake trials to address questions about ART in HIV infected children where answers could not be extrapolated from trials in adults. The activities and the studies run by these networks have been essential for the implementation and scaling up of ARV treatment in developing countries.

The Paediatric European Network for Treatment of AIDS (PENTA) was established in 1991 as collaboration between paediatric HIV centres in Europe Core funding for PENTA activities have been provided by the European Commission for more than 20 years through several research programmes [23]. Additional support for specific research activities were given by governmental and regional bodies in France, the United Kingdom, Italy, Spain and Germany and from pharmaceutical companies. Since early 2000 PENTA activities extended beyond clinical trials, to include cohort studies collaboration, pregnancy studies (including phase 1 trials in pregnant women), treatment guidelines and training/educational programmes. The PENTA network now comprises more than 80 clinical centres and research laboratories in 22 countries in Western and Eastern Europe, Africa, Asia and the Americas able to recruit and follow HIV-infected children both in clinical trials and cohorts carried out according to good clinical practice. By 2014, 16 major clinical trials had been completed and almost 2000 children had been enrolled. Most trials aimed to address strategic questions not just on specific drugs or drug combinations, but on what is the optimal strategy for treating HIV infection in children. Large studies on structured treatment interruptions, simplification strategies, management strategies and best initiation approaches have been carried out. Also, several PK studies have been performed allowing identification of the right dosing for paediatric patients in different age groups [23].

The National Institutes of Health (NIH) funded International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network [24] is a global collaboration of investigators, institutions, community representatives and other partners

organized for the purpose of evaluating interventions to treat and prevent HIV infection and its consequences in infants, children, adolescents and pregnant/postpartum women through the conduct of high quality clinical trials. IMPAACT has a comprehensive research agenda including: (a) evaluation of new and existing anti-HIV drugs and formulations, (b) novel approaches for addressing tuberculosis in HIV-infected or at-risk populations, (c) biomedical/behavioural interventions to prevent mother-to-child HIV transmission, (d) immunogenicity, safety and efficacy of high priority vaccines, (e) potential for HIV cure through therapeutic interventions, (f) new drugs and drug combinations to treat hepatitis in HIV-infected populations and (g) development and validation of methods to prevent and manage complications of HIV infection and its treatment. More than 40 studies have been completed and several are ongoing in more than 90 sites from 14 countries worldwide.

Studies run by PENTA and IMPAACT, which included sites in both developed and developing countries have been very informative and instrumental for the implementation of the use of ARV in developing countries and key publications for the development of WHO guidelines (2002–2013) [12, 14, 15]. Also the involvement of clinical sites in resource constrained settings in clinical trials has an important role in 'capacity building'.

Community participation and engagement are critical in the conduct of scientific research especially in developing countries settings. There is mutual benefit to communities and researchers when both parties work together throughout the scientific research process. Both in the PENTA and IMPAACT networks community participation occurs throughout the network, community and site levels through various mechanisms that include representation on the network committees, protocols teams and cross-network community activities.

Beyond specific disease research networks other more general initiatives/networks focusing on paediatric drug research have an important role in facilitating the development and safe use of medicine in children in both developed and developing countries. With this mission the Global Research in Pediatrics – Network of Excellence (GRiP) was funded by the European Commission in 2010 [25]. The main reason for the existence of GRIP is the recognized lack of appropriate testing of paediatric drugs, with most marketed drugs having inadequate information about dosing regimen, dose adjustment and administration. The GRIP consortium is currently made up of 21 main partners from Europe, Asia and North America, including academia, research networks, regulatory agencies (EMA), international organizations (WHO, NIH) and parent advocacy groups. By linking the existing paediatric research networks, GRIP involves and mobilizes more than 1000 institutions worldwide including many active in developing countries. Partners are working to build and maintain an infrastructure matrix, which has the core aim of reducing the current fragmentation of efforts to achieve safe and effective use of medicine in children. The GRiP infrastructure matrix promotes the sharing of best practices, strategies and plans. Key points of these efforts are to harmonize methodologies and standardize research recommenda-

tions. GRiP produces guidelines reflecting the needs of researchers (including those in industry) and patients, facilitating interoperability in paediatric research to improve efficiency in clinical research in both HIC and LMIC settings. New protocol designs, procedures and methodologies for clinical trials in children are also explored and validated to fill the important 'gaps' that currently exist in paediatric medicine.

Paediatric studies require well-trained researchers, investigators and other experts in greater number and capacity than currently exist. Since the project aims to reduce fragmentation, one of the key components of GRiP is the development and implementation of a Joint Paediatric Clinical Pharmacology Training Program in collaboration with international stakeholders. This will include a Master Program in Paediatric Pharmacology which is to be launched in November 2014. The training programme will build on the existing experience and capacity of the partners and will aim to prepare more highly qualified personnel in paediatric clinical pharmacology able to work both at regulatory and clinical research levels in a variety of settings.

Conclusion

In this chapter we have described different experiences and networks that were involved in the successful implementation of the scaling up of ARVs in developing countries. We have presented the activities of DNDi a very efficient and innovative model for the development of new and affordable medicine for neglected diseases and have described its role in developing new ARV formulations. We briefly reviewed the fundamental role of WHO in coordinating efforts of various organizations to develop integrated guidelines to facilitate the scaling up of ART in resource constrained settings. Finally, we have described two different types of clinical and research networks: those HIV-specific, such as PENTA and IMPAACT, and the more general, focusing on the challenges of paediatric therapeutics, such as GRiP.

The common thread lacking in these initiatives is the development of a new global framework to stimulate research on paediatric drugs, prioritizing the specific needs of children in developing countries at the start of the drug development process. The important and effective achievements obtained in scaling up ARV deployment in resource limited settings shows the importance of consolidating public and private partnership, including WHO, both innovative research intensive and generic pharmaceutical companies, and international initiatives such as DNDi, to work with partners from countries where diseases are endemic. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases said a few years ago that 'We need to use HIV networks to study other disease'. We believe that we should continue to emphasize this statement and to use the HIV networks as effective models to ensure that the output of new drug development will reach people and particularly children in need.

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Part III
Research Challenges

Chapter 14
Standards of Research for Clinical Trials in Low- and Middle-Income Countries

Zulfiqar A. Bhutta and Martin Offringa

Introduction

The increasing conduct of clinical research in low- and middle-income countries (LMIC) is motivated by the desire to promote host country access to biomedical research, to enhance LMIC access to modern clinical care, and to create opportunities to conduct research with simpler regulatory requirements and at lower cost. Yet, clinical research in LMIC seems to be associated with ethical and scientific risks beyond those of clinical research conducted in high-income countries (HIC). Scientific challenges of clinical research in LMIC include containing certain risks of trial bias related to attrition and blinding, definition of the role of data monitoring committees, valid measurement of relevant and standardized outcomes, and inclusion of the appropriate paediatric age sub-groups. Ethical challenges particular to clinical research in LMIC include the conduct of placebo-controlled clinical trials in LMIC despite HIC availability of effective comparator interventions, obtaining informed consent despite power inequities, and the obligation of HIC researchers to redress health disparities in LMIC. This chapter addresses challenges of clinical research in LMIC, and proposes ways to navigate these challenges through awareness, regulatory oversight, consultation, and strengthened collaboration with LMIC investigators and community representatives.

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More and Better Research in Children

Historical consideration of the vulnerability of children has led to an environment where between 50 and 90 % of medicines prescribed to children in hospitals do not have a sufficient evidence-base for dosing, safety, or efficacy [1, 2]. While providers rely on information extrapolated from adult trials, evidence has shown that this practice may be ineffective for children and may put them at increased risk of adverse effects [3]. Thus, this paucity of paediatric pharmaceutical research means that, on a daily basis, child health care providers around the world must make decisions without age and developmental stage-appropriate information on how their treatments will change short-term and long-term health outcomes in young patients. In recent years, the international scientific community, along with regulators, parents, and funders, has acknowledged that research in children is not only necessary, but also morally imperative to provide children with safe and effective treatments. This acknowledgement is reflected in the recent increase in registered trials. Still, research involving children continues to demonstrate a substantially lower quantity, quality, and relevance compared to research involving adults [4].

The current shortcomings of paediatric clinical trials stemming from particular methodological and practical challenges of conducting research in children have been highlighted [3, 5]. Many of these methodological shortcomings are threats to scientific validity and impact the science that is used by decision makers who determine children's access to existing and new therapies. Thus, research that is not conducted in the best or safest ways possible, pose a threat to the health of children across the globe. Therefore, as the need to enhance high-quality research in children is more pronounced than ever and clinical researchers, funders, medical ethical committees, and journal editors are seeking quality standards, there is an urgent need for standardization of research protocols, research conduct, and reporting standards for child health trials.

Quality Standards: The STaR Guidelines

Standards for Research (StaR) in Child Health [6] was founded in 2009 to address the paucity and shortcomings of paediatric clinical trials conducted around the world [7]. This global initiative involves methodologists, clinicians, patient advocacy groups, and policy makers dedicated to enhance the reliability and relevance of paediatric clinical research. The aims of StaR Child Health are to improve the quality, ethics, and relevance of clinical research in children by developing and disseminating evidence-based standards and guidance for the design, conduct, and reporting of clinical trials with children. It is achieving this objective using a systematic process which includes identifying relevant problems, reviewing existing appropriate knowledge, generating guidance where gaps exist, adapting knowledge to the relevant context, facilitating the implementation of new knowledge, and promoting best

practice. The impact of StaR's work is reviewed through evaluation of the knowledge uptake and the effect on practice.

In 2009, a systematic review of available guidelines for the design, conduct, and reporting of research in children found few relevant guidelines [8]. For instance, guidance on appropriate stratification according to age, the relevance of development, and the choice of child-specific outcomes was not available. The review, sponsored by WHO, found that guidance emphasized what should be done but had less focus on how to achieve this.

In October 2009, on the eve of the 20th anniversary of the adoption of the United Nations Convention on the Rights of the Child, StaR Child Health hosted its first summit in Amsterdam. This meeting convened in conjunction with WHO, involved approximately 180 participants including representation from the WHO, the US food and Drug Administration, and the European Medicines Agency. The aim for StaR was set to provide a global forum to develop and facilitate the use of better guidance on methodology in children's research. Following the systematic review and extensive discussion at this multidisciplinary inaugural conference in including child health professionals, methodologists, and regulators, priorities relating to the design, conduct, and reporting of paediatric clinical trials were agreed. The first six topics were as follows: Consent and recruitment; Containing the risk of bias; Data Monitoring Committees; Determining adequate sample sizes; Selection, measurement, and reporting of outcomes; and Age groups for paediatric trials (see Box 14.1) [6].

Box 14.1: The First Six StaR Child Health Reports

1. *Consent and recruitment* Recruiting children into clinical trials is influenced by multiple factors, including parental (beliefs, knowledge), the child (condition, choices), the trial (use of placebo or other comparators, specific trial requirements), and doctors (treatment preferences, influences on parental consent). Improving communication, education, and optimizing the risk-benefit ratio of participating can enhance children's participation in trials. Reaching agreement on how to best recruit children in an efficient and ethical manner is a prerequisite for adequate and timely recruitment. The standard uses clinical scenarios to discuss and provide guidance on (1) who should give consent for children in research, (2) which information is necessary to obtain consent, (3) how we can make sure that research in extra vulnerable children means equitable opportunity, not exploitation, (4) whether payment for research is justified or unethical, (5) whether the child's clinician can also be the investigator, and (6) who decides which eligible patients are invited to participate in a trial.
2. *Containing risk of bias* Trials with a high risk of bias tend to overestimate treatment effects. This StaR paper addresses how best to minimize or contain bias, including (1) sequence generation and allocation concealment,

(2) blinding of key study personnel particularly outcome assessors, (3) adequate follow-up and handling of missing outcome data, (4) selective outcome reporting, and (5) other sources of bias. Guidance is discussed in the context of both trial registration and existing guidelines for development and reporting of randomized controlled trials. The report suggests that more work is needed to improve the implementation and uptake of best methodological principles, especially in child health research.

3. *Data Monitoring Committees (DMCs)* DMCs should be considered for trials with vulnerable populations such as children. In a review of 739 paediatric trials performed until 2002, only 2 % reported having a DMC, while 71 % reported an adverse event (AE), and 20 % reported a serious AE. While an independent DMC ensures the safety of study participants, decisions made by DMCs regarding interim analysis and early stopping of clinical trials can have consequences for the scientific validity, results, and clinical impact of a trial. Two recent systematic reviews showed that only 17 % of 648 recent paediatric trials reported on DMC activities, interim analysis, or early stopping. This StaR article defines a set of minimum requirements to which DMCs should adhere to best serve paediatric researchers as well as trial participants. It explains criteria to determine whether a DMC is required for a particular study, both clinical (e.g. trials addressing major morbidity or mortality end points, a novel intervention with little existing safety data) and methodological (e.g. planned interim analyses, large and/or multicentre trials). When convened, DMC membership should be broad enough to include individuals with clinical and methodological expertise and knowledge of local context, and the operations of these committees should be guided by a detailed charter. The authors provide recommendations for reporting on DMC operations in manuscripts, as this will inform the reader in interpretation of trial results.
4. *Determining adequate sample sizes* Evidence demonstrates that paediatric trials are generally smaller than adult trials, more often single-centre, and sample size calculations are rarely reported. An important explanation for smaller sample sizes in paediatric research is the relative scarcity of many medical conditions in children. Whilst it is unethical to recruit more participants than is necessary (no unnecessary experimentation should be done), it is also vital that any research aims to recruit an adequate number to answer the designated objective. Failure to achieve the required sample size may prejudice the chance of answering the original research question and thus potentially waste the participants' voluntary efforts as well as the study costs and resources. Best practice in achieving the right number of subjects in a trial may be achieved by conducting more pilot studies to establish variance in outcome parameters, and applying interim analyses and other methods like triangular tests in the context of a adaptive sequential design

to make paediatric trials ostensibly more efficient than adult trials. This StaR guidance covers (1) optimal sample size (including simulation and modelling techniques), (2) stopping criteria, and (3) novel approaches to conducting research when the number of available participants is small (e.g. adaptive protocols, use of historical data).

5. *Selection, measurement, and reporting of outcomes* Clinical research should provide answers that in turn enable better information, optimal care, and well-being. To achieve this, the study must have the right outcome measure. Surrogate endpoints may be measured instead of the variable of interest for reasons of efficiency and practical considerations. A recent systematic review shows that few studies address the appropriate choice of outcomes for clinical research with children. Various different methods and tools are used to measure the same outcome (e.g. pain, behaviour, quality of life), often using instruments that have not been validated in children. This heterogeneous approach presents a challenge when assessing the totality of evidence based on different trials, for example, to inform decision-making regarding health care interventions. This StaR paper discusses the use of relevant outcomes and standard approaches to measuring outcomes as essential factors in estimating the relative effects on outcomes which matter to children and families. A model for developing core sets of trial outcomes is presented.
6. *Age groups for paediatric trials* The response (and thus the degree of benefit versus harm) of adults and children to the same medication may be similar but also very different. Even within childhood, there may be wide variation in response between a preterm neonate and an adolescent. However, large variability exists in the age ranges and age-subgroups of children considered appropriate to be included in paediatric trials and meta-analyses; the rationale for the selection of particular age-subgroups is often unclear. This variation impairs inter-trial comparison and data synthesis of information about treatment effectiveness and safety. It also signals a knowledge gap concerning legitimacy of age groups in existing guidance, which limits current research examining specific differences between and within age groups. This StaR report offers guidance on (1) age groupings, based on existing best practice, (2) justification for subgroups or combining age groupings, and (3) the need to ensure biological, developmental, psychological, and social variables are appropriate for trial design for the included ages. The paper also provides an agenda for further research on age groupings.

These topics have been systematically addressed through standard development groups (SDGs). Led by a nominated convenor, these are multidisciplinary groups that act as a forum for individuals interested in improving evidence in the specific

topic. Membership is by invitation and voluntary subscription, aiming for representation from developed and developing nations. SDGs perform a thorough literature review, summarize best and weaker evidence in the topic and develop draft reports in standard format. These reports are then reviewed by a wider group of researchers, as well as regulators and representatives from the pharmaceutical industry and other interested organizations. A programme of revision and updating of current standards should ensure that guidance remains up-to-date. StaR has developed web-based tools, seminars on methodology for presentation at large academic meetings, specific trial design courses, and conferences open to all stakeholders such as patients and parents, researchers, research funders, regulators, and journal editors. To date, StaR has hosted four global summits (video materials can be found on the StaR website), writing weekends, and workshops as a result of which six priority issues have been addressed and published in open access, as summarized below. With its work, StaR Child Health aims to evolve into a global child health research network with an ongoing research agenda of empirical research to inform decisions regarding design and conduct of clinical research in children; a repository of guidance documents and supporting materials; and engagement in knowledge transfer activities and training to optimize uptake and implementation. In a report of the Council of Canadian Academies (2014) [9], an entire chapter is dedicated to consideration of how current approaches to paediatric efficacy studies can be improved; the first six StaR reports are used to inform the recommendations.

Trial Protocol Development and Reporting Standards

Current paediatric research suffers from a lack of standardization of research protocols and practice, and reporting standards for child health trials. Two recent developments aim to improve this situation. The protocol for a randomized trial is the foundation of the study's conduct and reporting. The SPIRIT 2013 initiative defined 33 key items to be addressed in trial protocols aiming to improve the quality of protocols enabling accurate interpretation of trial results [10]. However, SPIRIT does not offer specific guidance on crucial and unique issues in paediatric randomized controlled trials (RCTs). Without integrated guidance for paediatric trial design/conduct we face a critical gap in our ability to advance child health research. Paediatric trials require additional and modified items because across the spectrum of ages and developmental stages, children have highly different developmental physiology, pharmacokinetics and pharmacodynamics, and short- and long-term benefits and harms. Interventions impacting growth and development need tailored instruments to assess outcomes. Therefore, the generic items of the SPIRIT 2013 Statement were tailored and refined adding evidence-based guidance on essential items to include when developing a protocol for a paediatric trial. In early 2015 *SPIRIT-Children* will be published.

Only with complete, clear, and transparent information on its methodology, ethical considerations and findings can a study be fully assessed and placed into proper context. The well known CONSORT Statement has resulted in improved reporting and better implementation of trials [11]. Yet, specific elements for trials with children at various different ages, such as detailing the intervention, validity of the outcomes studied, etc. are not included. Like SPIRIT, CONSORT does not cover crucial issues in paediatric RCTs. In 2014, CONSORT was extended into a checklist of essential reporting items for paediatric clinical trials. In early 2015 *CONSORT-Children* will be published. Both new standards will consist of a checklist and explanatory paper providing the rationale and evidence supporting each recommended protocol and reporting item for SPIRIT-C and CONSORT-C, respectively, along with exemplars from actual protocols and published trial reports.

Ethics of International Biomedical Research

Recent debate and controversy in international bioethics has stemmed from regulatory processes and international guidelines for the conduct of research. As a concept, the pre-eminence of the rights and safety of patients has been recognized since the time of Hippocrates, but they were first enunciated in the context of experimental therapy by Claude Bernard in the nineteenth century [12]. Events during the Second World War, with widespread atrocities committed by Nazi scientists and physicians under the guise of medical experimentation, led to global outrage and dictated the need to put forward a code of conduct for human research, namely the Nuremberg Code [13]. In 1964, the World Medical Association Declaration of Helsinki took this process a step further and underscored 12 basic principles for the conduct of human biomedical research. However, these principles were largely physician-oriented and did not directly address the issue of research in developing countries, which has been subsequently included through a series of inputs at its meetings in various parts of the world [14].

The issue of research in developing countries was eventually taken up by the Council for International Organization of Medical Sciences (CIOMS) [15], which, in collaboration with WHO, proposed guidelines for international research. The guidelines were further amended in 1993 as the International ethical guidelines for biomedical research involving human subjects and substantively revised [15]. In another follow-up by concerned agencies in the United States, the Belmont Report [16] drew upon the existing Helsinki Declaration and highlighted three principles: respect for individual autonomy; beneficence; and justice. Over the last few years these guidelines and amendments to the Helsinki Declaration have also been complemented by efforts in industrialized countries, such as the consultations of the Nuffield Council for Bioethics in the United Kingdom (1999) [17] and the National Bioethics Advisory Commission in the United States (2000) [18].

Specific Issues in the Ethical Conduct of Research in Developing Countries

Responsiveness to Subject/Public Priorities

Research needs to respond to community needs and national priorities, and the development of a national research agenda in developing countries must be firmly grounded in a process of national and local priorities. However, a larger and more difficult challenge is to involve the communities themselves in the research questions and to link the research to their own development. Such a participatory process with the community is a continuum that includes community consultation in protocol development, appropriate information disclosure and informed consent, protection of confidentiality and right of dissent, and community involvement in the conduct of research [19]. At the level of researchers, striking the balance between individual and population benefits remains an important aspect of planning research.

Prior Agreements and Benefits of Research

Prior agreements and assurances about the benefits of research products have received less attention than the practical aspects of protocol development and study design. The commentary on CIOMS guidelines 8 and 15 [15] explicitly states that "As a general rule, the sponsoring agency should agree in advance of the research that any product developed through such research will be made reasonably available to the inhabitants of the host community or country at the completion of the successful testing. Exceptions to this general requirement should be justified and agreed to by all concerned parties before the research begins."

The most recent revisions of the Helsinki Declaration [14], however, take a less stringent position, but declare that "Medical research is only justified if there is reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research." Others have criticized the CIOMS guidelines as being soft and have argued that agreements need to be explicit and that funding needs to be identified prior to undertaking the research [20]. In its most simplistic interpretation, these requirements preclude any large-scale public health research in developing countries, unless these assurances could be provided. The proponents of this approach argue that it would avoid unnecessary and curiosity-driven research, as well as undue exploitation of vulnerable populations in underdeveloped communities. Those exposing themselves to the risks of research must, at the very least, be assured of access to the fruits of the research.

These assured availability agreements only apply to a narrow band of drugs, vaccines, and other products. They cannot be readily applied to phase I and II drug trials, nor to vaccine trials, and epidemiological and social science research. Another important consideration is the usual time lag before the robustness of research find-

ings can be assured, frequently by replication elsewhere. The benefits of participation in research may also extend beyond the narrow definition of end products, as there may be other significant improvements in the health care system as part of the project. It is also possible that the assurances of such benefits may offer inordinate inducements to poor and impoverished populations, thus representing another form of exploitation. Moreover, a broader definition of benefits as something other than the product of research may be required, since the availability of a product within a dysfunctional health system is no assurance that the product will reach those who need it most. In some developing countries, political doctrine may demand that either all or none of its citizens should have access to a particular product, which makes it almost impossible to make an economic argument for the pharmaceutical industry to pursue research of relevance to developing countries. However, placing such issues at the forefront of research planning, especially if the research has international sponsorship, can expedite making the benefits of research available to the very populations that helped in the development of the benefits.

Given the limited resources for research in most developing countries, stringent application of these criteria and guidelines might make it almost impossible to provide such long-term assurances of benefits or availability of products. This would effectively stop much-needed public health and epidemiological research that often generates precisely the information that might influence future public health policy. The groundbreaking way in which research on hepatitis B [21] and *Haemophilus influenzae* type B vaccines [22] was undertaken in Gambia points the way. A participatory process involving donors, researchers, and the Gambian Ministry of health ensured that the vaccination programme could be sustained well beyond the trials. In contrast, evaluation of hepatitis A vaccination in Thailand [23] or the more recent typhoid conjugate [24] or Dengue vaccine trials [25] were not accompanied by any such agreements or plans to introduce the vaccine, nor were such agreements part of other evaluations of pneumococcal conjugate vaccines in other parts of South-East Asia Asia and Africa [26].

It is therefore evident that the concept of "reasonable availability" does not settle the issue of responsibility to the community. In its narrowest definition, the concept indicates a simple assurance of the availability of a research product within the local market and includes responsibilities for the care and well-being of the community for a long time. The requirement for extended community care may place an inordinate burden on both governments and other sponsors, effectively stopping all large-scale trials in developing countries, whereas the former situation may open opportunities for exploitation. Actual practice probably lies somewhere in between, with a broader interpretation of the responsibilities and benefits of participating in research.

Informed Consent

Although a relatively recent phenomenon, the role of informed consent in human research is central to its ethical regulation and conduct. However, guidelines often recommend procedures for obtaining informed consent (usually written consent)

that are difficult to implement in developing countries. Although a relatively recent phenomenon, the role of informed consent in human research is central to its ethical regulation and conduct. Several innovations are necessary to obtain truly informed and "understood" consent. These include the use of culturally acceptable and understandable tools and information sheets and a consent process that is understandable. Although guidelines often recommend procedures for obtaining informed consent (usually written consent) that are difficult to implement in developing countries, it is important that the consent process be carefully explained, witnessed, and appropriately documented in all cases involving drug and vaccine trials or invasive procedures.

Standard of Care and the Use of Placebos

A major issue in the earlier controversies surrounding the HIV/AIDS drug and vaccine trials in LMIC pertained to the use of a placebo arm instead of standard therapy, which had only recently been introduced in high-income countries. Earlier revisions of the Helsinki Declaration clearly stated in Section 29 that "… the benefits, risk, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists."

Although some have argued in favour of retaining placebos as the most efficient means of obtaining requisite scientific information [27], their overall value in health research may be overestimated. Perhaps the most pervasive argument supporting the continued use of placebos is based on efficiency and economics. The scientific rigour of a placebo-controlled design can be balanced against alternative models of scientific enquiry, which, though longer and more expensive, are ethically sound. If journals were willing to accept reports of studies with quasi-experimental designs, and funding agencies were willing to support studies for longer durations, several alternatives to placebo controls would likely emerge.

Although not clearly specified in the Helsinki Declaration, the standard of care can be interpreted in the context of the study location. Others have expanded the definition of standard of care to include additional aspects such as provision of care by a research team with qualifications, training, and expertise equivalent to as those in industrialized countries; and research carried out by a team with the same culture and language as the study subjects, to assure effective communication and informed consent [28].

The issues surrounding standard of care have been the subject of much **rancour** and debate, and they highlight the wide disparities that exist in health and economics globally. Some scientists in developing countries have argued that given the inadequate state of health and facilities in many developing countries, the local therapy for HIV infection may well be no treatment, a point clearly refuted by the subsequent introduction of highly active antiretroviral therapy through global pro-

grams like PEPFAR and UNITAID. Others have questioned the very notion of a global standard of care, given that standard therapy in one health system, with profligate expenditure on defensive medicine, may be totally inappropriate in another system with limited resources. On the other hand, the development of protocols for managing acute respiratory infections among children in developing countries has been a tremendous benefit. It can be argued that none of these developments could have taken place had studies employed the western standard of care for treating pneumonia with injectable third-generation cephalosporins. More recent modifications of the Helsinki Declaration include a Note of Clarification which lists two situations where placebo is acceptable: where there is a scientifically compelling reason, or where the condition under study is minor and the subject at no increased risk of serious or irreversible harm.

The Way Ahead

Although recent debates on the scientific and ethical dilemmas of health research in developing countries have focused on regulatory issues and have lamented the polarization of views, many see a silver lining. At the very least, the debate has focused attention on the needs of developing countries and the vast inequities in health and human rights. A pragmatic approach towards bridging the gaps necessitates the introduction of several measures, some of which are discussed below and others have been addressed in a meeting in Copenhagen on Paediatric Drug Development in Low and Middle Income Countries in 2010 (see Box 14.2) [29].

Box 14.2: Ten Priority Issues for Future Development*

1. *Code of conduct* A generalizable code of conduct to apply to academic researchers, private sector contract researchers, industry researchers, and drug regulators who are initiating, conducting, or supporting paediatric clinical trials in low- and middle-income countries (LMIC) is needed.
2. *Standards of informed consent* It is understood that ethical review of paediatric trial protocols across international boundaries is problematic because of legal and cultural variation. Nonetheless, standards for the obtaining of informed consent could be agreed and a template developed suitable for baseline application in different jurisdictions. The fact that a study population is poor and/or illiterate should never be a reason for waiving written consent. Agreement should be sought on a checklist of requirements for ethical conduct of paediatric trials.
3. *Trial design* It is recognized that detailed randomized, double blind, controlled trials are unlikely, in future, to be the normal standard for clinical research in low-income settings. As an alternative, standards are required

addressing the use of large and simple pragmatic trials, and different approaches to randomization, including cluster randomization. Adaptive trial methods should be further explored in order to minimize the numbers of children unnecessarily exposed to risk in prospective trials.

4. *Trial registries* The WHO International Clinical Trials Registry Platform (ICTRP) has a filter to identify paediatric clinical trials world-wide http://apps.who.int/trialsearch/AdvSearch.aspx; however, the entry of trials from many countries is below expectations. Partnerships should be developed to support efforts of low- and middle-income countries to improve the registration and characterization of paediatric clinical trials.
5. *Standardized outcomes* Further work is needed to achieve agreement on standardized outcome measurements and outcome indicators for use in paediatric trials in low- and middle-income countries. This would include efforts to achieve consensus on measurement of value added by new treatment modalities. Exploration of the use of QALYs, DALYs, and health utility indices in paediatric trials would be helpful.
6. *Safety standards and evaluation of serious adverse drug reactions* There seems to be insufficient agreement on appropriate safety standards for paediatric trials generally and in particular for those trials conducted in low resource settings. The use of data safety monitoring boards in international clinical trials is gradually improving but is still at an unacceptably low level. A comprehensive statement on the appropriate roles for DSMBs needs to be implemented worldwide with international endorsement. Not all jurisdictions have a system in place for evaluation of SADRs. In some cultures, autopsies are discouraged and burial practices require immediate burial, which prevents full investigation of SADRs. Verbal autopsies are frequently used for this purpose but there is no consistent approach and the conclusions are likely to be invalid in the absence of appropriate supportive laboratory and autopsy testing.
7. *Human capacity/paediatric clinical research* There still is a distinct shortage of highly qualified personnel available to conduct paediatric clinical trials in low- and middle-income countries. A forward-looking structured human resource plan to meet the needs of all interested countries is required. This plan will require endorsement by international agencies, including WHO. A standardized curriculum for training in paediatric clinical research should be open to interested parties from low- and middle-income countries.
8. *Networks* The improved use of research networks to optimize the information to be garnered from limited patient numbers should be encouraged. Procedures and standards must be developed to guide the linkage of data within jurisdictions and across jurisdictional boundaries wherever possible.

9. *Patient engagement* Current standards guiding clinical research in low- and middle-income countries are often not driven by patient needs. Mechanisms should be developed for engagement of patients and families in support of paediatric clinical investigation. Such engagement should go beyond the informed consent paradigm and include relevant knowledge transfer and improvement in public health literacy.
10. *Knowledge transfer* The key outcome of paediatric clinical research is knowledge translation into improved patient/family information and treatment approaches that will improve child survival and child health outcomes. This is the expected deliverable from all clinical research undertaken. Medical publication authorities should do everything possible to facilitate the dissemination of results from paediatric studies, either through print publication or electronic means.

*Adapted from the report of the 2010 Copenhagen meeting on paediatric clinical trials development in LMIC [29]

Developing Local Capacity

Strengthening models for reviewing the ethics of research could develop local capacity, since the capacity for undertaking research must include the capacity to undertake ethical review of the planned research and its conduct. Developing partnerships could also strengthen local capacity, although international and regional networks or partnerships in bioethics are no substitute for local action. In the words of Abdallah Daar "So long as all the ethicists are in the North, and the South is just the recipient of ethical principles, nothing will change!" [30].

A review of the existing capacity in bioethics and in ethical review of research in developing countries reveals major gaps [31, 32]. Bioethics training must be strengthened in undergraduate medical education, and in postgraduate and public health training programmes. This will require a major investment in manpower and a new approach to the teaching of bioethics, such as training programmes in bioethlics in the United States National Institutes of Health, Fogarty. The immediate need, however, is to strengthen local capacity and manpower by developing innovative training models for ethics that are cost-effective and sustainable. The opportunities afforded by the Internet for learning and education in ethics should also be utilized.

Conclusions

Research to support the effectiveness and safety of medications in young children can only be generated if high-quality randomized controlled trials are designed, conducted, and reported appropriately. As discussed in this chapter, recent years

have seen a number of actions to encourage research involving children and help investigators cope with the many methodological, practical, and ethical challenges of paediatric studies. These advances mean that it is no longer "too difficult" to conduct trials with children. StaR Child Health is dedicated to improving child health across the globe by enabling better drug treatment for children through the development of guidance in paediatric clinical research.

The last few years have also been a watershed in international bioethics and the heightened debate has pushed ethical issues surrounding health research in developing countries into the limelight. The challenge now is to develop a sound plan for expanding the ethics debates to the larger issues of global equity and justice, and to make the process as participatory and democratic as possible. It is critical to link issues of health, health research, ethics, and equity as vital components of the same equation. The actions required to move ahead in this field include strengthening bioethics capacity in developing countries; linking health research to community needs in a transparent and participatory process; and increasing communication between scientists and ethicists in industrialized and developing countries. The clear goal in all these activities must be the reduction of global inequities in health. This may take time, but it is the only way to bring about true change in the ethics of international health research, far preferable to having a superficial and perhaps endless debate on the language of regulations.

Strong methodological and ethics guidance from a multidisciplinary collaborative is required to produce evidence that can bring safe and effective drug treatments to children. Advances in both areas have the potential to improve of quality of life for children across the globe.

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Chapter 15
Ethical Considerations in the Design of Pediatric Clinical Trials in Low- and Middle-Income Countries

Robert M. Nelson and Michelle Roth-Cline

Historically, the exclusion of children from clinical trials has been a consequence, in part, of the belief that children should be protected from the risks of research. The result was a paucity of safety and effectiveness data that made the use of therapeutic agents a virtual uncontrolled experiment whenever they were prescribed for children [1]. More recently, legislation in both the United States and Europe have established requirements and provided incentives for the pharmaceutical industry to conduct pediatric clinical trials so that new drugs and biologics are adequately labeled for use in children [2]. Due to the need to recruit sufficient patients, many of these trials are multinational, even if the eventual goal has been regulatory approval in the United States and Europe. The requirement for pediatric data to support the safe and effective use of drugs for children reinforces our responsibility to ensure the children are only enrolled in research that is both scientifically necessary and ethically sound. Children are widely considered to be vulnerable persons who, as research participants, require additional protections beyond those afforded to competent adults [3].

Four principles serve as the basic ethical framework for the additional protections for children who are enrolled in clinical trials [4, 5]. First, children should only be enrolled in a clinical trial if the scientific and/or public health objectives cannot be met through enrolling subjects who can provide informed consent personally (such as adults). In addition, the scientific and/or public health objective must be important to either understanding or ameliorating the enrolled child's disorder or condition. Second, absent a prospect of direct clinical benefit, the risks of an intervention or procedure to which a child may be exposed must be low. In other words, the knowledge to be gained from a clinical trial does not, by itself, justify exposing a child to more than low risk. Third, children should not be placed at a disadvantage

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by being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care. Fourth, vulnerable populations who are unable to consent for themselves (such as children) should have a proxy to further protect them from harm (usually a parent or guardian) who may give permission on behalf of the child for the child's participation [3].

The first principle, which we refer to as the principle of scientific necessity, is grounded in the ethical tenet of justice [6]. The basic premise is that one population (e.g., children) should not be asked to bear a disproportionate share of the risks of research unless that population also benefits from the research. In articulating the principle of justice, the Belmont Report states "the selection of research subjects needs to be scrutinized in order to determine whether some classes … are being systematically selected simply because of the easy availability, their compromised position, or their manipulative ability, rather than for reasons directly related to the problem being studied" [7].

The global redistribution of clinical trials from high-income to low- and middle-income countries has raised concern that the populations of less developed countries are being exploited in order to provide data for marketing approval in developed countries, as may be true if a drug were not available in the less developed country after marketing approval [8, 9]. The factors that make clinical trials in less developed countries attractive to pharmaceutical sponsors also apply to pediatrics. Recruitment may be easier given a higher prevalence of disease, with many treatment-naïve patients, who have fewer treatment options [8, 10]. Conducting a clinical trial may be cheaper [10]. Regulatory oversight may be less burdensome [11]. Access to drugs and other treatments for underprivileged populations may be insufficient or nonexistent, making clinical trials an attractive option for individuals seeking treatment [12].

The limited data that are available, however, suggest that pediatric clinical trials have not experienced the same redistribution to lower- and middle-income countries as have trials in adults. Trial site data appear to overestimate the contribution of developing countries to pediatric research being conducted under the US exclusivity incentives. Based on clinical trial registry data, approximately one-third of phase 3 clinical trials sponsored by US-based pharmaceutical companies are being conducted solely outside of the United States, with the majority of study sites for the remaining two-thirds of clinical trials located outside of the United States (including many in developing countries) [13]. These observations were extended to published pediatric trials conducted in response to the US exclusivity incentives, finding that the majority of these trials included trial sites outside of the United States, and 38 % included sites in developing countries [14].

However, this report did not include the number of patients enrolled at each location. When patient enrollment data were examined, only 26 % of the total number of enrolled children was from sites outside of the United States, and only 10 % were enrolled in developing countries. Vaccine studies were an exception, with sites outside of the United States contributing 78 % of pediatric subjects, with 52 % from developing countries. In addition, there does not appear to be a shift over time towards pediatric clinical trials being conducted in developing countries [2]. Thus,

existing data do not support the view that pediatric clinical trials are being conducted in low- and middle-income countries exclusively in support of registration and marketing in high-income countries [2]. The lack of necessary healthcare infrastructure and resulting concern about generalizability to children living in high-income countries may partially explain the lack of pediatric-specific data indicating a shift in pediatric clinical trials to low- and middle-income countries.

Concern has also been expressed that the pediatric products developed under initiatives in the US and Europe are primarily responsive to the health needs of children in high-income countries, with inadequate attention paid to the burden of pediatric diseases in low- and middle-income countries. The increase in pediatric clinical trials and subsequent pediatric labeling has largely been driven by market forces and thus neglects the large burden of pediatric diseases in low-and middle-income countries [15–18]. However, even in high-income countries, there is only a moderate correlation between the number of trials conducted and the burden of pediatric disease. Low-income countries bear the majority of global disease burden (73 %), but were represented in only 7 % of clinical trials. Finally, the lack of clinical trials in low- and middle-income countries may limit the adoption of evidence-based treatments that have been developed in high-income settings [15].

This chapter will start with an overview of the concepts of vulnerability and exploitation, followed by a discussion of how equipoise and the appropriate standard of care are important to the analysis of clinical trials in developing countries. Following this discussion, we present contrasting case examples. The first case study involves a placebo-controlled trial of a vaccine for preventing invasive disease due to Haemophilus influenzae type b that was conducted in The Gambia. This clinical trial, although placebo-controlled, was responsive to the health needs of the local population. This case is contrasted with the second case study of a proposed placebo-controlled trial of a synthetic surfactant in Latin America that was not responsive to the health needs of the local population. The four themes of the choice of an appropriate standard of care, justice and the provision of fair benefits, decisions on fair protocol design, and capacity building are highlighted in these case studies. Finally, the implications of each of these themes for pediatric trial design are considered.

Vulnerability and Exploitation

The concept of vulnerability has been criticized as being both too broad and too narrow. The definition of vulnerability may be overly broad when many groups of individuals are considered vulnerable without a clear specification of what special protections ought to be provided. Vulnerability also may be construed too narrowly if vulnerability is understood only as the lack of capacity to give informed consent. Generally vulnerability can be understood as “being under threat of harm” [18]. As described below there are additional allocational vulnerabilities that risk harming a research subject, even if the subject fully understands the risks, benefits, and

alternatives of study participation. Thus, one can reframe vulnerability in the research context as the conditions under which exposure of a person to research risk becomes permissible.

Kipnis identifies seven distinct vulnerabilities of a child who is a potential research subject, building on the distinction between features "that either call into question the efficacy of consent in affecting the permissibility of proposed research, or that somehow nullify the ability to give or withhold informed consent" [19]. Three of these vulnerabilities (i.e., lack of capacity, subject to the authority of others, and given to deferential behavior) are features specific to a child, and are addressed by the requirement for parental permission. However, the other four of these vulnerabilities are allocational: belonging to a socially disvalued group, facing an emergent medical situation, lacking satisfactory remedies for a serious health-related condition, and lacking important social goods that would be provided in the research. These allocational vulnerabilities may compromise the ability of a parent to give effective permission. Kipnis points out in a later commentary that there is a subtle yet important distinction between "(1) compromising the ability to give informed consent and (2) compromising the power to give effective permission" [20]. Even if a parent is capable of giving permission, Kipnis calls our attention to whether this agreement to participate in the research is "fair to the party in the weaker position." Thus, the identification of allocational vulnerability raises important considerations of the fairness of the clinical trial protocol that is being offered. In the pediatric setting, parental permission does not establish that the enrollment of a child is permissible unless the design of the study itself is ethical; the protocol must have an appropriate balance of risk and potential benefit, as reflected in the second and third ethical principles outlined above. As such, children can be harmed by enrollment in clinical trials that "unjustly allocate benefits and burdens" regardless of whether informed and voluntary parental permission and child assent have been obtained [20, 21].

The concept of allocational vulnerability may lead to questions about whether the design of the protocol is exploitative. Exploitation can be defined as a transaction where one party A takes "unfair advantage" of a second party B, such that B receives an unfair level of benefits as a result of the interaction [21–23]. A clinical trial may exploit (i.e., take advantage) of the fact that a targeted population lacks adequate healthcare, such that the rational choice of an individual would be to enter the clinical trial even if, for example, the possibility exists that they may be randomized to an inadequate standard of care. The Belmont Report specifically cautions against the enrollment of vulnerable groups solely "because they are easy to manipulate as a result of their illness or socioeconomic condition" [7]. Similarly, paragraph 20 of the 2013 WMA Declaration of Helsinki states that enrollment of a "vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group" [24]. In other words, the research must focus on the health needs of the population, and the population should benefit from the research.

However, the fact that economically disadvantaged individuals may preferentially enroll in a clinical trial in order to obtain access to otherwise unavail-

able medical resources is not a sufficient reason to conclude that the trial is exploitative. Rather, there needs to be an assessment as to whether the level of benefits offered as a result of trial participation is fair and reasonable [22]. The challenge then is to distinguish between a clinical trial that offers an *unfair* benefit versus a trial that offers a *fair* benefit but enrolls economically disadvantaged participants [22].

Can we truly divorce the question of whether a clinical trial offers a "fair deal" if that offer is only a "deal" due to the "unjust" circumstances in which the economically disadvantaged find themselves? Emmanuel and colleagues offer the ethical principle of "collaborative partnership … to minimize the possibility of exploitation by ensuring the developing country determines for itself whether the research is acceptable and responsive to the community's health problems" [23]. Although collaboration is an important ethical principle, as a procedural solution it leaves open the possibility that the broader community may "sell out" their disenfranchised members in order to obtain valuable benefits (i.e., healthcare capacity). Alternatively, a clinical trial that offers a "fair deal" generally should be designed in a way that would not unduly induce a disenfranchised population to enroll. For example, the study could be designed so that lack of financial and medical resources was not relevant to the objective of the study. This approach, however, risks labeling as "unethical" clinical trials in low- and middle-income countries that are designed to answer legitimate health policy questions given limited healthcare resources. As argued below, a broader understanding of the principle of equipoise may allow for the incorporation of limited healthcare resources into the ethical justification of a clinical trial.

Equipoise and the Appropriate Standard of Care

The concepts of equipoise and standard of care are important to discussions of clinical trial design in developing countries. The term "standard of care" can be used in either a descriptive or normative sense. Descriptively, it simply refers to the clinical care that is usually provided for patients by health care providers in that setting. Normatively, it refers to the clinical care that ought to be provided. One definition of the principle of equipoise is similar, that is, the ethical norm that no one enrolled in a clinical trial should receive an inferior treatment. Here equipoise is seen as a specification of the "duty of care" [25]. Additionally, equipoise can be understood as the requirement for sufficient "uncertainty" about which treatment in a clinical trial is best [3].

In the research setting, the debate about equipoise centers on what treatment should be provided to the control group in a randomized controlled trial [26]. Two questions are central to this debate. The first question is under what circumstances, if any, it would be appropriate to withhold a known effective treatment from the control group in favor of a placebo or no treatment. The second question is whether there should be a different standard of care for the control group in clinical trials conducted in developed versus developing countries [26].

There is a general agreement, with some exceptions, that a known effective treatment should only be withheld if there would be no additional risks of serious or irreversible harm (such as death or irreversible morbidity). On this point, the 2013 Declaration of Helsinki and the FDA guidance on choice of control group are largely harmonized, with two caveats. First, the Declaration of Helsinki states that the "best proven intervention" must be used unless there are "compelling and scientifically sound methodological reasons" to use a different intervention [24]. The FDA document is more permissive, provided that there would be no risk of serious harm [27]. However, the Declaration of Helsinki does not qualify the phrase "best proven intervention" with the notion of availability, as does the FDA document. As such, the Declaration of Helsinki clearly supports a single standard of care regardless of the location of the trial, while the more ambiguous FDA language of "available treatment" opens the door to a double standard. This ambiguity can be found in other international documents where a universal standard (e.g., "available anywhere in the world") is then qualified by "available … as part of the national public health system" if the universal standard cannot be met [26]. In addition, there is a lack of clarity about the evidence that may be necessary to claim that a treatment is "known," "proven," or simply "established" as part of a professional standard of care [26].

A single standard that nevertheless would allow for "morally relevant differences" has been proposed. Specifically, "In a randomized controlled trial, the control group shall not be denied a superior medically established procedure that has net clinical relevance for a specific condition that is under study for the population that the control group represents" [26]. There are two features of this definition that should be noted. First, the phrase "medically established procedure" sets the evidentiary standard for the treatment of the control group to what is "considered acceptable within the professional medical community." Second, the phrase "net clinical relevance" is meant to render the standard "context-sensitive" so that considerations of what may be attainable and sustainable in the local context can be taken into account [26]. This proposal, however, does not adequately deal with the question about the level of evidence that may be necessary to establish a medical procedure as superior. Absent data in support of the claim that the control treatment will be effective under the conditions of the clinical trial (referred to as "assay sensitivity"), a noninferiority comparison would be uninformative. One solution to this problem would be to always require that the experimental treatment is shown to be superior to the control treatment. This approach may be appropriate in some circumstances, but it is not clear that it should be the required approach in all circumstances as this may hamper the development of many promising products. In addition, this proposal appears to assume an obligation to provide care in the research context that has been "medically professionally accepted" in the clinical context (regardless of the data in support of that standard).

The above proposal builds on a broad interpretation of clinical equipoise proposed by Alex London [28]. London starts with the observation that: "If we assume that some intervention (I) has been shown to be effective in treating patients with some condition (C) in one treatment setting (S), then in order to infer that no doubts

exist about the benefits of I for treating patients with C in some other treatment setting (S∗), we must be confident that S and S* are sufficiently similar that causal relationships that exist in the former will obtain in the latter" [28]. Although there are other factors than the treatment setting, this observation is similar to the concerns about assay sensitivity when taking a drug shown to be effective in one context and using it in another context. As a result, there may be sufficient uncertainty (i.e., equipoise) as a "necessary condition for the initiation of clinical trial" even though the experimental intervention has been shown to be effective in another setting [28]. London is quick to point out, however, that such uncertainty is not a sufficient justification for conducting a clinical trial where the available treatments are constrained by socioeconomic factors. Rather, the "proper response to this difference" may be to change the features of the new setting so that it is more similar to the setting in which the intervention has been shown effective. The moral obligation to make such changes may not derive from the "role-related obligations of physicians" (which is often an argument heard from those who favor a broad interpretation of the principle of equipoise), but rather from "a systematic and explicit treatment of the fundamental questions of distributive justice that routinely arise in the context of international clinical research" [29]. In this context, London has proposed a "human development approach to international research" which ensures that "clinical trials are adequately responsive to the health needs of individuals in the developing world" by focusing on "the gaps that exist between the basic interests of community members and capacity of basic social structures in that community to meet those needs" [28, 29].

London's proposal provides a single standard for the choice of an appropriate control group, with sufficient flexibility to account for biological and nonbiological factors influencing the effectiveness of an intervention when tested in a new setting. In doing so, he seeks to avoid the more limited claim that participants only need to be protected from being made worse off [30]. There are a number of challenges with this approach. First, the "scientific" reason why interventions that have been established as effective in the developing world cannot be used as a comparator is often economic [31]. Second, nonbiological factors may vary between local communities, regions, or nations. If we link availability to a "national standard of care," considerable efforts (i.e., capacity building) may be necessary to bring local standard of care up to that national level even if that national level in a developing country is different from a developed country [30]. Third, it may be difficult to draw a clear line between biological and nonbiological factors in some cases. For example, there were doubts as to whether vaccines against Haemophilus influenzae type b would be effective at preventing meningitis in developing countries in spite of data demonstrating efficacy in Europe and North America. Factors such as the severity of disease in young infants, the intensity of pathogen transmission, and the effect of malnutrition and malaria on vaccine efficacy are a complex mix of both biological and nonbiological factors that are not easily disentangled. It was also plausible that the vaccine might protect against meningitis but not pneumonia, a question that was important during the design and conduct of a clinical trial in The Gambia [32].

Case Study: Clinical Trial of Hib Vaccine in The Gambia

Haemophilus influenzae type b conjugate vaccine was approved by the Food and Drug Administration in 1990 for the prevention of invasive disease following a placebo-controlled trial demonstrating safety and efficacy among Navajo infants [33, 34]. Overall, the introduction of effective conjugate vaccines in the United States (and elsewhere) led to a marked decrease in the incidence of invasive disease secondary to Haemophilus influenzae type b (HIB) [35]. While some HIB vaccines were found to be effective in countries such as Finland [36, 37] and the United States [38], in other populations they were not effective [39].

Shortly thereafter, a randomized placebo-controlled trial of a HIB vaccine was conducted in The Gambia [40]. Globally, the most common manifestation of disease secondary to Haemophilus influenzae type b is pneumonia. As such, proven efficacy against pneumonia was identified as "an essential prerequisite for introduction of the vaccine into The Gambia and most other developing countries" [32]. However, the diagnosis of pneumonia is subjective, introducing a potential source of ascertainment bias that could only be adequately controlled through use of a double-blind study design. In addition, there were doubts that the vaccine would be effective in preventing pneumonia as opposed to other forms of invasive disease, such as meningitis, cellulitis, or arthritis [32, 40]. The majority of cases of invasive disease that occurred in vaccine studies conducted in the United States and Finland were meningitis [34, 36, 37]. In addition, given the vaccine's lack of effectiveness at preventing meningitis among Alaska Native infants [32, 39], concerns were raised about whether it would be effective for this indication in developing countries. It was also plausible that the vaccines might protect against meningitis but fail to protect against pneumonia [32].

However, the trial was controversial, and questions were raised about whether a placebo group in this trial was justified. A vaccine that was known to be effective in preventing invasive disease in developed countries was withheld from infants in a developing country. The withholding of this vaccine appeared to violate the Declaration of Helsinki. Depending on the interpretation of the phrase "available treatment," the withholding of the vaccine may or may not have violated the FDA guidance on choice of control group, because a HIB vaccine was not available at the time in The Gambia. However, consistent with London's proposed understanding of the principle of equipoise [28], it also appeared reasonable to be concerned that a vaccine shown to be safe and effective in the United States and Finland may not be effective in The Gambia.

There was, however, a second feature of the trial design that illustrates the impact of policy decisions. The steering committee for the clinical trial (which included representatives of the Gambian government) believed that efficacy against pneumonia must be demonstrated in order to justify introduction of the vaccine into the Gambian vaccination schedule. The Gambian Ethical Committee concurred with this assessment, supporting the use of a placebo control as "ethically acceptable" given the importance of pneumonia as an endpoint and the lack of availability of Haemophilus influenzae type b vaccines in The Gambia during the trial [32].

The selection of pneumonia as an endpoint had an important secondary consequence. Due to multiple causes of pneumonia other than HIB, the possibility existed that efficacy against meningitis would be demonstrated prior to efficacy against pneumonia. However, due to the importance of the pneumonia endpoint, the decision was made that interim effectiveness assessments would not consider meningitis. Therefore, the Safety Monitoring group performed an interim analysis based only on the pneumonia cases, despite the possibility that (at the time of the interim analysis) the vaccine may have demonstrated efficacy regarding the prevention of meningitis. Based on this analysis, the Steering Committee decided to extend the enrollment of the trial for an additional 6 months to collect additional data regarding prevention of pneumonia [32].

After the trial was completed, a post hoc analysis was conducted of the meningitis data. Had efficacy against meningitis been used as an interim stopping rule, the trial would have been discontinued earlier, prior to demonstrating efficacy for the prevention of pneumonia. Therefore, the policy decision that demonstrating efficacy against pneumonia would be necessary prior to the widespread introduction of the vaccine meant that there were more cases of meningitis that occurred during the extension of the clinical trial than would have been necessary if meningitis had been the endpoint. This decision illustrates the complexity in ethical decision making when considering both biological factors that may impact efficacy in a particular subpopulation, and policy decisions that may justify alterations in trial design.

Finally, some commentators expressed concern about whether the trial was justified, given the high cost of the vaccine, because it would "have no future beneficial impact on that community" [32]. Although the Gambian government sought an agreement that the clinical trial, if successful, would result in a donation of vaccine to allow for broader vaccination of the Gambian population, such an agreement was not in place during the clinical trial (although was negotiated subsequently) [32]. To the extent that the results of the clinical trial were an important factor in stimulating programmatic efforts to make vaccine more widely available, a demand by the Gambian government that an agreement be in place prior to the start of the clinical trial may have undermined the ultimate success of their public health efforts.

This case, however, differs significantly from the proposed Surfaxin trial in Latin America. The Gambian authorities collaborated closely on the design and implementation of the clinical trial, and were able to articulate quite clearly the public health policy objectives that should be met by the overall development program. In contrast, the proposed Surfaxin trial was designed to satisfy US regulatory requirements, and an informative trial arguably would not have required a placebo control.

Case Study: Clinical Trial of Surfaxin in Latin America

A multinational, double-blind, randomized, two arm, placebo-controlled trial of Surfaxin, a synthetic surfactant for the treatment of respiratory distress syndrome in premature infants, was proposed to be conducted in four Latin American countries. The primary purpose of the Surfaxin study was to satisfy US regulatory

requirements. At the time that the trial was proposed (2000), an animal-derived surfactant was approved for use in some countries in Latin America, but was costly and thus not widely available. Another synthetic surfactant was approved in the United States, but often was not used due to the superiority of the animal-derived product. Surfaxin was thought to be equivalent to the animal-derived surfactant, and superior to the other synthetic surfactant, due to the addition of a recombinant form of a surfactant-associated protein that facilitates distribution of surfactant throughout the lung.

Although the proposed trial may have offered a higher standard of care than was otherwise available for the enrolled premature infants (e.g., improved ventilator support for all, access to otherwise unavailable surfactant for some), the withholding of a known effective treatment (surfactant) in favor of a placebo would have been considered unethical in the United States and other developed countries [41]. However, the sponsor did not want to conduct a superiority trial of Surfaxin against the already approved synthetic surfactant due to concerns that Surfaxin may fail to demonstrate superiority in that setting [42]. In addition, a noninferiority trial would not be informative given the concern that the approved synthetic surfactant may not have the same treatment effect in Latin America due to differences in the standard of care compared to the United States.

At the time that this clinical trial was proposed, FDA guidance (published in early 2001) on the choice of control group stated: "In cases where available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally inappropriate to use a placebo control" [27]. The document, however, does not consider what "available therapy" means in the context of limited medical services due to economic constraints.

Arguing in favor of the proposed placebo-controlled trial in a published commentary, Robert Temple discards as unpersuasive arguments "using the evocative language of social justice at the expense of rational consideration of the real interests of potential participants in the trial" [42]. Temple offers a utilitarian justification for the proposed placebo-controlled design, arguing that an actively controlled trial would not be conducted in Bolivia due to concerns about the applicability of these data to the US population. If the trial were not conducted, premature infants born in Bolivia "would not have received either ventilator support or surfactant," possibly resulting in "more than the 17 deaths … that advocates of an active-control trial claim a placebo-controlled design would produce" [42]. Thus, he argues that no enrolled infant would have been worse off than they were before the study, and most or all of them would have been better off given the overall improvement in neonatal care offered by the trial. Favoring rational choice over considerations of social justice, Temple concludes that taking advantage of inequalities in health care is not exploitative, unless participants would be worse off than they were before the study.

An internal FDA presentation with the provocative title "Use of Placebo-Controls in Life-Threatening Diseases: Is the Developing World the Answer?" that included the proposed placebo-controlled design was leaked to Public Citizen in late January 2001. In a February 22, 2001 letter to Health And Human Services Secretary Tommy Thompson, Lurie and Wolfe argued that such a placebo-controlled trial was

unethical. Instead, they proposed that the premature infants should receive the "best scientifically proven intervention" regardless of economic status and study location [43]. This language mirrors that of the 2013 Declaration of Helsinki, paragraph 33, which states: "the benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven interventions" [24].

Temple's support of a placebo-controlled trial notwithstanding, it is not clear that such a design had widespread support within FDA. Agreement between FDA and the sponsor was reached in March–April, 2001, on a single superiority study to be conducted in Europe and Latin America that would compare three treatment groups (the experimental Surfaxin, the approved synthetic surfactant, and an approved animal-derived surfactant). Although not public until after the letter by Public Citizen, the design was proposed by FDA in late January 2001. The results of the clinical trial were submitted in April 2004. Surfaxin was found to be superior to the approved synthetic surfactant, and comparable to the animal-derived natural surfactant.

Was the proposed clinical trial of Surfaxin responsive to the health needs of the local community? Clearly, premature infants in Latin America are dying from lung disease secondary to surfactant deficiency. There would have been no reason for the sponsor to propose conducting a trial in Latin America if they did not believe that sufficient numbers of patients would be available who would meet the eligibility criteria. The sponsor apparently was willing to invest in developing the capacity for providing neonatal intensive care, a capacity which presumably would have been available to others both during and after the clinical trial. The sponsor was willing to make the product available for a limited time at a reduced price after the clinical trial was completed. However, continued access to the product would not be sustainable for the host country, and questions could be raised about the ability to support and maintain the capacity to deliver neonatal intensive care. In addition, whether this new synthetic surfactant worked was not a research question that was important to the host community, given the availability of already approved animal-derived surfactants and the fact that the new synthetic surfactant would not have remained available. In retrospect, there was no need to use a placebo control in order to conduct an informative clinical trial. The clinical trial that was performed provided an active product to all of the research subjects, and thus could be considered a better deal or a more "fair" deal than the placebo-controlled design.

Justice and "Fair" Benefits

As noted earlier, the majority of pediatric clinical trials conducted for regulatory approval in the United States appear to be conducted in developed countries, with the exception of vaccine studies [2]. Although reassuring with respect to possible exploitation of populations in developing countries, this observation also reflects the fact that there appears to be only a moderate correlation between the number of pediatric clinical trials for a given condition and the global burden of that disease [15].

The pharmaceutical industry does not have a moral obligation to focus their research efforts on diseases that primarily affect low- and middle-income countries. Rather, the primary responsibility for ensuring that research being conducted within a developing country is responsive to the needs of the local population rests with the regional government and other institutional structures within those countries [44]. However, research sponsors do have an obligation to make sure that participation in the clinical study represents a "fair" deal for both the individual participants as well as the community within which that clinical trial is being conducted. Thus, we should distinguish between an obligation to conduct clinical research in low- and middle-income countries that addresses those diseases that have the largest impact on the local burden of disease, and an obligation to conduct "just" or "fair" clinical research in low- and middle-income countries on diseases that may contribute to the burden of disease in high-income countries. Even if the disease being studied does not contribute significantly to the burden of disease in the host country, presumably the research sponsor would not conduct the study in that setting absent the possibility of enrolling sufficient subjects within a reasonable timeframe to make the investment of resources worthwhile.

The National Commission identified the principle of justice as one of the three core principles of research ethics. "Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly" [7]. The principle of justice grounds the moral requirement that "there be fair procedures and outcomes in the selection of research subjects." For example, research subjects should be selected based on reasons related to the research objective and not "simply because of their easy availability, their compromised position, or their manipulability." Even if the selection of individual subjects is fair, "unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research." For example, "research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research" [7].

The moral requirements that derive from the principle of justice extend beyond the clinical benefits that individual subjects may experience from enrollment in a clinical trial to encompass the requirement that there must be some benefit to the host community. This requirement has been articulated in at least two different ways. First, as noted earlier, the research must be responsive to the needs of the host community [10] so that the results of the research can be applicable practically to that community [45]. For example, a new treatment that is found to be both safe and effective should be incorporated into the local healthcare delivery system. Second, there should be benefits to the broader community in addition to the knowledge that may be gained from the research [46]. Such benefits might include employment, training of local healthcare workers, sharing in sources of financial profit resulting from the clinical trial, or authorship [23]. In general, benefits to the broader community fall under the rubric of capacity building.

Some commentators appear to assume that sponsors are only required to provide benefits to the broader community if the results of the clinical trial would not be locally available following the trial [10]. Others argue that the local availability of the new treatment following the research is an essential aspect of whether conducting a clinical trial in that setting is morally justified [45]. Some assert that it is common for drugs to be developed through clinical trials performed in developing countries which may not be substantively available in local healthcare systems [12]. Others, writing from an industry perspective, argue that clinical trials should only be performed in countries where "there is an intention to pursue registration and make the product available once it is approved" [47].

How does one balance what may be considered a "fair" deal for the community with what may be considered a "fair" deal for the individual research participants? For example, does the commitment to build clinics or renovate hospital facilities that would then be used by the local community after a clinical trial has ended (i.e., perhaps a "fair" deal for the community) justify a clinical trial design that would otherwise be considered "unfair"? The unequal distribution of access to healthcare resources internal to a developing country can also create the opportunity for exploitation. Concerns about exploitation are particularly salient when the technology that is being developed would not be sustainable in the setting of the host country. This is not to say that socioeconomic considerations do not play a role in deciding whether a treatment demonstrated effective in one setting would be effective when tested in another setting, consistent with London's proposed approach to equipoise. The question is when these socioeconomic differences should serve as a legitimate justification for making modifications to the design and/or conduct of a clinical trial, or motivate social and economic change to eliminate these disparities.

Concluding Remarks

The legislative initiatives in the United States and Europe that have stimulated pediatric drug development have not resulted in an adequate focus on the burden of pediatric diseases in low- and middle-income countries. The data that are available may be reassuring that pediatric clinical trials in support of marketing authorization in developed countries are not yet being exported to developing countries. Nevertheless, the risk of and thus need of protection from exploitation of economically vulnerable populations exists. The FDA good clinical practice guidelines do not provide sufficient advice about how to pay "special attention" to these vulnerable subjects [16]. The development of collaborative partnerships that provide a framework for engagement between the researchers, sponsors, policymakers, and host communities would help "minimize the possibility of exploitation by ensuring that a developing country determines for itself whether the research is acceptable and responsive to the community's health problems" [23]. Two aspects of such a collaborative partnership are worth emphasizing. First, capacity building may be necessary to strengthen institutions within the host country such as the national drug

regulatory agencies and other research oversight structures such as independent ethics committees and data safety monitoring boards [8, 11, 48]. Such capacity development should also focus on strengthening the opportunity for ethical dialogue and truly representative consultation among the parties that would most be affected by the design and conduct of a clinical trial in the host community [31]. Second, "as academic groups and institutions in low-income countries become stronger," the ability of researchers within the host country to contribute to the study design, including the choice of an appropriate intervention, should be improved [46]. Finally, the development of research oversight and capacity in low- and middle-income countries to promote collaborative partnerships may limit exploitation through the development of normative ethical and regulatory instruments that reflect the socioeconomic and cultural context of these countries [12].

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Chapter 16
Micronutrient Deficiencies: Impact on Therapeutic Outcomes

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For health and well-being, humans must consume adequate quantities of key essential nutrients, such as protein, carbohydrates, fats, vitamins, and minerals to meet the biological requirements of the body. Many of these nutrients are considered essential since these cannot be manufactured within the body and are reliant upon dietary intake to meet requirements. At a basic level, malnutrition arises from decreased nutrient intake, or as a result of nutrient imbalances, i.e., a failure to meet nutrient requirements, an increase in nutrient losses, and/or alterations in nutrient utilization [1]. Malnutrition (undernutrition) in children has been recently defined as "an imbalance between nutrient requirements and intake that results in cumulative deficits of energy, protein, or micronutrients that may negatively affect growth, development, and other relevant outcomes" [1]. Stunting or achieving the height that is "less than 2 standard deviations of the median age height in the reference population" [2] may be used as a broad indicator of inadequate dietary intake and malnutrition [3].

Malnutrition is directly or indirectly responsible for 45 % of global deaths among children who are under 5 years of age [4]. Malnutrition is classified as acute or chronic in nature. Acute malnutrition may arise from starvation, sometimes associated with humanitarian crises, sudden catastrophes, or seasonal food shortages [5]. *Severe* acute malnutrition, defined by a very low weight for height, by visible severe wasting, or by the presence of nutritional oedema, affects approximately 20 million children, mostly living in south Asia and sub-Saharan Africa [6].

Severe and/or acute malnutrition is also referred to as protein-calorie malnutrition (PCM), which is a result of low ingestion of protein and calories. Protein is an essential nutrient that has both structural and functional roles in the body. PCM has been identified as a contributor to higher mortality rates in infectious disease resulting from the negative impact on the immune system [7]. Some of the immunologi-

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cal changes that have been identified include altered immune cell populations, decreased natural killer cell activity, and decreases in immunoglobulin A as examples [7, 8].

Stemming from an interplay of socioeconomic disparity [9], poverty, chronic food insecurity, poor feeding practices, and illness [5], more than two billion individuals worldwide are chronically malnourished and suffer from micronutrient deficiencies. Chronic malnutrition may be more subtle in its manifestations, but can nonetheless have major health implications for populations. In early childhood, chronic malnutrition as a result of micronutrient deficiencies can lead to significant morbidity, given the impact on motor and mental development [10–13]. Micronutrient deficiencies which have an increased prevalence in children of developing countries are Vitamin A, zinc, and iron. A deficiency in one or several of these essential nutrients has been demonstrated to have an impact on the growth, development and immune status of children, and increase the susceptibility to several diseases [14].

Deficiencies arise in micronutrients for a variety of reasons. In developing countries, food choices are limited due to overwhelming poverty and poor agricultural yield. There is a reliance upon carbohydrate rich foods, such as rice or maize, as dietary staples, which are inherently poor sources of these essential nutrients [15]. A lack of adequate access to protein sources, such as meats, eggs, and dairy products, compounds the problem since reduced protein intake can also lead to a concomitant reduction in vitamin A, zinc, and iron [8, 16]. Illness can further exacerbate the malnourished state since dietary intake is reduced. Fever will necessitate an increase in catabolic processes and, in the case of diarrhea, increases the excretion of zinc. All of these factors can result in the vicious cycle of further depletion of essential nutrients from which the child may not be able to recover [14]. In the following sections, we will describe the role of these essential nutrients in health and illness.

Vitamin A

Vitamin A is a lipid soluble vitamin that is derived from preformed retinoids and provitamin carotenoids. Retinoids, such as retinoic acid and retinol, are available from animal sources such as liver, eggs, and dairy products, while leafy green or yellow vegetables and carrots are a source of the provitamin carotenoids of which beta-carotene has the greatest Vitamin A activity [17, 18]. Beta-carotene's bioavailability from plants sources ranges from 7 to 65 % and is converted to Vitamin A in the intestinal mucosa upon absorption [18]. The various forms of Vitamin A, retinoic acid and retinol, have roles in many areas of the body. Retinol is integral to the function and health of the eyes by acting in the differentiation of the corneal and conjunctival membranes and as an essential component of the rods of the retina [19]. Vitamin A regulates gene expression of structural proteins, enzymes, extracellular matrix proteins, and retinol binding proteins and receptors. Its involvement in cellular

differentiation and proliferation also impacts not only the integrity of the epithelium but also immune function [19]. Adequate levels of circulating natural killer cells, which have both antiviral and anti-tumor activity, require adequate levels of retinoic acid. Maturation and activation of B lymphocytes and production of inflammatory cytokines which stimulate T and B cell production require adequate levels of retinoic acid [19, 20]. Vitamin A improves iron absorption and metabolism [21].

A deficiency in Vitamin A can negatively impact both immune system function and the integrity of the epithelial barriers increasing susceptibility to infection. Vitamin A deficiency can also cause blindness. In accordance with WHO standards the prevalence of vitamin A deficiency has been measured indirectly by assessing the prevalence of night blindness (xerophthalmia) and a serum retinol concentration of <0.70 μmol/l. Night blindness has been found to affect 5.2 million preschool-age children (CI95%: 2.0–8.4 million); serum retinol concentration <0.70 μmol/l affect an estimated 190 million preschool-age children (CI95%: 178–202 million). In total, Vitamin A deficiency is determined to affect one-third of preschool-age children globally with Africa and South-East Asia being the most affected [22].

Zinc

Zinc is an essential mineral and has three distinct roles in the body: structural, catalytic, and regulatory [17]. Zinc is involved in catalyzing over 100 different enzymatic reactions and, structurally, in the correct folding of proteins [17]. Finally, zinc is involved in regulating gene expression through the activation of gene transcription, is involved in apoptosis, regulating normal synaptic processes, and cell-mediated immune function [17, 20]. In sum, zinc is key in physical growth and development, the functioning of the immune system, reproductive health, and neurobehavioral development [20]. The food sources of zinc are broad and include meat, beans, grains, and nuts; however, the bioavailability of zinc is highest in animal sources, since it is bound to protein. In grain sources, zinc is bound to phytates which inhibit its absorption [23]. A deficiency of zinc has been demonstrated to negatively affect the immune system through the decreased activity of both natural killer and T-cytolytic cells and a reduction in both the secretion and function of cytokines [24].

Based on demographic data, physiological requirements, and absorbable zinc content in national food supplies, it is estimated that approximately 15–20 % of the world's population is at risk of inadequate zinc intake [25]. In particular, the regions of sub-Saharan Africa and South Asia may be most affected. Moreover, it is estimated that the prevalence of zinc deficiency is higher in children less than 5 years of age than in the general population, owing to high nutrient density needs and rates of infection [25]. It is suggested that the prevalence of stunting among young children may be an indirect indicator of inadequate zinc intake, as zinc supplementation has been shown to increase both linear growth and weight gain in children [25, 26].

Iron

Iron is an essential mineral and has roles not only in the hemopoietic system but is also required for cell proliferation and oxidative metabolism [17, 20, 21]. Iron is available from both animal and plant sources, with animal source providing the more absorbable form of heme-iron. As with zinc, plant sources of iron are bound either to phytates or oxalic acid which inhibit its absorption [23]. Iron deficiency has been associated with reduced immune function, negatively impacting T-cell response, phagocytic activity, and immunoglobulin levels [8, 27, 28]. In addition, iron deficiency has been associated with reduced Vitamin A and carotenoid absorption [21].

In children, iron deficiency may arise from an inadequate diet, poor iron absorption, enhanced iron requirements during growth, and chronic blood loss resulting from parasites like hookworm. Young children have very high dietary iron requirements due to the rapid growth and expansion of red blood cell mass [29]. Iron deficiency can have major health implications, including impaired physical and cognitive development, increased risk of morbidity in children, and also accounts for approximately 20 % of maternal deaths [30]. Anemia affects 293 million children globally and is used as a surrogate indicator of iron deficiency. Almost half of all pre-school children (age 0–5) are affected by anemia; the highest prevalence of anemia is in Africa (68 %) and South-East Asia (66 %) followed by the Eastern Mediterranean (46 %) [31]. Country-specific information on the prevalence of anemia can be accessed by referring to the WHO's Vitamin and Mineral Nutrition Information System database [32]. Serum ferritin concentrations have also been measured for assessment of iron status and are the preferred method for determining the prevalence of iron deficiency in a population [33].

Iodine

Iodine is a mineral found in seafood, kelp, dairy products, and in plants which are grown in iodine-rich soil. The most common dietary source, however, is iodinated salt. Although it is estimated that 71 % of the world's population use iodized salt [34], iodine intake of 285 million school-age children worldwide is still deemed insufficient, as defined by urinary iodine concentrations below 100 μg/L [35]. The largest number of children affected is in South-East Asia, Africa, and the West Pacific. The highest proportions of iodine insufficiency, albeit mild, are found in Europe (59.9 %) and South-East Asia (39.9 %) [35]. Deficiencies in iodine are associated with a wide range of physical and cognitive deficits in children [36] and are the greatest cause of preventable brain damage in childhood [37]. It has been shown that people living in areas affected by severe iodine deficiency may have an intelligence quotient (IQ) of up to 13.5 points below that of those from comparable communities in areas where there is no iodine deficiency [38]. Moreover, a range

of iodine deficiency disorders, related to hypothyroidism resulting from insufficient iodine intake, can plague the growth and productivity of whole communities who are not receiving enough iodine as part of their diets [38]. While significant progress has been made due to salt iodination, moderate to severe iodine deficiency was still reported in 14 countries in 2004 [37]. The WHO has mapped population iodine status in school-aged children over a 5-year period by measuring iodine excretion in urine. The prevalence of iodine deficiency, based on goiter prevalence and/or urinary iodine, in over 150 countries worldwide can be accessed through WHO [32].

Addressing Key Nutrient Deficiencies and the Resulting Impact on Therapeutic Outcomes

Globally, the leading causes of death in children less than 5 years of age are pneumonia, preterm birth complications, birth asphyxia, diarrhea, and malaria [39]. It is also recognized that both maternal and child malnutrition are exacerbating factors in about half of these childhood fatalities. In children with diarrhea, measles, and malaria, vitamin A deficiency increases the risk of mortality by 20–24 %, while a zinc deficiency increases this risk by 13–21 % [10, 12, 40]. These nutrient deficiencies are believed to not only compromise child health but can also reduce a country's economic advancement by 8 % [13].

A variety of different strategies have been undertaken to improve the nutritional status of children in low and middle-income countries. In 2010, a framework entitled, Scaling Up Nutrition (SUN) was developed to deliver 13 different nutrient interventions in 36 different countries aimed at reducing undernutrition targeting children under 2 years of age, however; the program also provided benefits to children up to the age of 5 years and included interventions targeting maternal nutrition [41]. The interventions identified in the framework leveraged supplementation strategies for Vitamin A and zinc, iron fortification of staple foods, and multiple nutrient powders [41, 42]. Since its inception, the number of countries participating in the program has grown to 46 [43].

The WHO has created a central database which consolidates the nutrition initiatives undertaken by countries and various groups worldwide. The Global database on the Implementation of Nutrition Action (GINA) accepts data from many different organizations such as Flour Fortification Initiative, Mapping Actions for Food Security & Nutrition, FAOLEX, SUN movement, IBFAN World Breastfeeding Trends Initiative, Micronutrient Initiative, Global Alliance for Improved Nutrition, Iodized salt consumption, Vitamin A supplementation coverage, Coverage Monitoring Network, World Vision International, and 1,000 days [44]. The scope of the database is much broader and goes beyond the supplementation and fortification programs to help children under the age of 5 years, and is designed as an interactive platform for sharing nutrition policies and actions.

Vitamin A

Mayo-Wilson et al. conducted a meta-analysis of randomized controlled trials on Vitamin A supplementation versus either placebo or no treatment and the impact on all-cause mortality and cause specific mortality in children under 5 years of age. The dosing strategies were variable in the studies, both dose and duration. The meta-analysis showed that Vitamin A supplementation was associated with a 24 % reduction in all-cause mortality (risk ratio: 0.76, CI95%: 0.69–0.83), with moderate heterogeneity [45]. Additionally, there was a 27 % reduction (risk ratio: 0.72, CI95%: 0.57–0.91) in mortality from diarrhea; with respect to measles, there was a non-significant reduction in mortality (risk ratio: 0.80, CI95%: 0.51–1.24) but a significant reduction in the incidence of measles (risk ratio: 0.50, CI95%: 0.37–0.67) [45]. The result of the cumulative meta-analysis demonstrates that Vitamin A supplementation contributes to the reduction of mortality in children under 5 years; however, the most appropriate dosing strategy to maximize this benefit requires further investigation [45].

A meta-analysis on the impact of 100,000 or 200,000 international units (IU) of Vitamin A administered quarterly to HIV infected children between 1 and 5 years of age ($n=267$) found a 45 % reduction in all-cause mortality (risk ratio: 0.55, CI95 % 0.37–0.82) [46]. The supplementation and follow-up period ranged between 17 and 24 months in these studies. A positive impact on reducing the persistence of the cough associated with pneumonia [47], diarrhea [48], and AIDS-related deaths [49] were also reported.

In the case of sickle cell disease (see Chap. 27), there is some evidence that children affected may have lower micronutrient levels [50]. Despite similar dietary intake, children with SCD had lower red blood cell zinc levels, lower serum vitamin A levels, and lower urine nitrogen levels versus controls [50]. However, a 12-month vitamin A supplementation program in US children with SCD did not improve serum retinal values in a randomized, double-blind, placebo controlled trial, suggesting that (1) further research is needed and (2) higher doses than the recommended dietary allowance of vitamin A may be required to achieve adequate Vitamin A status [51].

Zinc

Yakoob et al. completed a meta-analysis of zinc supplementation randomized controlled trials in children less than 5 years of age to determine the impact on diarrhea, pneumonia, and malaria [52]. The median dose of zinc reported in the meta-analysis was 10 mg/day for at least 6 months. The results suggest a non-significant decrease in all-cause mortality (risk ratio: 0.95, CI95%: 0.88–1.02), and mortality from diarrhea (risk ratio: 0.91, CI95%: 0.76–1.09) with zinc supplementation at this level. There was a significant reduction in the mortality from pneumonia (risk ratio: 0.80,

CI95%: 0.67–0.96) and in the incidence of both diarrhea (risk ratio: 0.87, CI95%: 0.81–0.94) and pneumonia (risk ratio: 0.81, CI95%: 0.73–0.90). A subsequent study that was published after the meta-analysis completely investigated the impact of zinc supplementation at a dose of 20 mg of zinc gluconate daily for 7 days ($n = 127$) versus placebo ($n = 129$), as an adjunct therapy to standard treatment in children admitted with pneumonia in Uganda. The findings suggest that there was no impact on clinical recovery; however a non-significant reduction in the number of fatalities was reported in the zinc supplemented group (risk ratio: 0.7, CI95%: 0.2–2.2) [53].

Studies of zinc supplementation in both acute and chronic diarrhea in children under 5 years of age have been completed. Lazzerini et al. found that zinc supplementation of 5 mg/day significantly reduced the duration of acute diarrhea in children between the age of 6 months and 5 years at all time points evaluated (Days 3, 5, and 7) [54].

The impact of zinc supplementation in children with SCD has been systematically reviewed. In SCD, there is an increase in urinary zinc excretion that, in combination with inadequate dietary intake, can contribute to zinc deficiency [55]. Dekker et al. concluded that zinc supplementation could possibly reduce the incidence of infection and vaso-occlusive crises when zinc was given for at least 1 year [56]. However, further research is required to determine whether zinc supplementation could have an impact on reducing mortality in children with SCD.

In HIV+ children, the impact of zinc supplementation appears limited. One study investigated the effect of 10 mg of zinc sulfate for 6 months. There were no negative effects found; no increase in viral load occurred and there was a reduction in the incidence of diarrhea in the children receiving supplementation [46, 57]. A subsequent study investigated the impact of zinc supplementation at a dose of 20 mg of zinc gluconate daily for 7 days ($n = 27$) versus placebo ($n = 28$), as an adjunct therapy to standard treatment for those HIV infected children admitted with pneumonia in Uganda. There was a reduction in the number of fatalities in the zinc supplemented group (risk ratio: 0.1, CI95%: 0.0, 1.0); however, zinc supplementation had no impact on clinical recovery times [53].

Iron

The impact of iron supplementation programs on nutrition and development in children under 12 remains uncertain [58]. A 2009 Cochrane review on the impact of iron supplementation on mortality and morbidity outcomes in HIV infected children was inconclusive [59]. While there is evidence to support the reduction of anemia and iron deficiency with both daily and intermittent iron supplementation, in malaria endemic areas the supplementation of iron in children can result in an increase in the severity of the illness and perhaps death [60, 61]. The WHO recommends that malaria prevention and treatment programs be in place in malarial endemic areas prior to the administration of iron supplementation [62].

Multiple Nutrient Supplementation

A recent randomized controlled trial compared zinc supplementation or placebo with vitamin A, in 852 apparently healthy 2–5 year-old children in Indonesia, on the incidence and duration of upper respiratory tract infections (URTI) over 4 months [63]. Children in the study were randomized to receive either 10 mg of elemental zinc ($n=399$) or placebo ($n=399$) daily in syrup for four months. All children in the study receive 200,000 IU of vitamin A at month 2 after recruitment as part of a bi-annual national supplementation program. Findings from the study suggest that the combination of zinc and vitamin A reduced the duration of the URTI by 20 % ($p=0.01$), producing a greater reduction versus zinc supplementation alone (12 % reduction in duration ($p=0.09$)). The authors suggest that the interaction effects of these two nutrients could result from the impact that these nutrient have on improving epithelial integrity and immune response.

The impact on therapeutic outcomes from the use of multiple nutrient supplementation powders which combine several essential nutrients together in a format that can be mixed with prepared food in the home requires more investigations. Evidence suggests that this form of supplementation can improve both iron and vitamin A deficiency; however, there is also evidence to suggest that the use of multiple micronutrients formulation increases the incidence of diarrhea [61, 64].

Conclusions

Undernutrition contributes to 45 % of the global deaths of children under 5 years of age. Supplementation programs in developing countries for Vitamin A and zinc have been shown to reduce all-cause mortality, mortality from diarrhea in both HIV infected and uninfected children, and the incidence of measles in HIV negative children. Zinc, as an adjunct therapy to standard treatment for pneumonia, also reduced the mortality rate in both HIV infected and uninfected children. There are gaps in our understanding of the most appropriate dosing strategies for Vitamin A to maximize the benefits associated with supplementation. What, if any, synergies may result from multiple nutrient supplementation or fortification strategies require further investigation.

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Chapter 17
Clinical Pharmacology and the Individualized Approach to Treatment

Michael J. Rieder

Introduction

While health care workers have prescribed therapy to children for thousands of years, this was on the basis of anecdote and traditional wisdom rather than evidence of either efficacy or safety. This was relatively inexpensive, frequently unsafe, and infrequently effective. "Specific Therapy," which began in 1935 with the demonstration of the antimicrobial activity of sulfanilamide, produced both great gains but also great challenges in the care of children [1]. The discovery that drugs could combat infection on an ambulatory basis was a true paradigm change in the practice of medicine [2]. Prior to the introduction of vaccines and effective drug therapy the mortality rate for children under five was roughly 25 % [3]. The vast majority of deaths, in fact for most ages, were due to infection. With the introduction of Specific Therapy, vaccination, and better public hygiene the mortality rate among children fell dramatically, such that the rate for children under five in most developed countries now approximates 0.6 %, with mortality being largely due to congenital problems, accidents, or cancer. This benefit in reduced child mortality has not been achieved in many developing countries, where infectious, and frequently preventable, deaths remain regrettably common (Table 17.1) [4].

Drug utilization for children is an area in which myth has consistently denied reality. There is a myth that drug therapy for children is uncommon and confined to antibiotics. In fact, while drug therapy is less common among children than adults, age being a major factor driving drug utilization, it is clear that, in the developed world, drug therapy among children is a common occurrence [5, 6]. While antibiotic use is certainly common, many children receive therapy with a broad range of

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drugs, notably for complex or chronic diseases such as cancer or epilepsy [7, 8]. For such children pharmacotherapy is a major component of care.

To illustrate, the 20 % of children with complex and chronic disease in the developed world account for 70 % of drug utilization [3]. These include children with cancer, asthma, or seizures. During the first several years of therapy children with refractory epilepsy receive on average seven different prescription antiepileptic drugs [3]. In the developing world, while antibiotics for infectious disease remain the primary drivers of drug use in children, the rising incidence of chronic disease suggests that patterns seen earlier in the developed world are likely to be followed [9]. In many developing countries chronic diseases now account for more than 50 % of deaths, and efforts to prevent or control these problems are of great significance, notably if cost-effective preventive strategies can be started in childhood (Fig. 17.1).

Table 17.1 Mortality rate for children in selected countries

Country	Infant death rate per 1,000 live births	Child under-5 death rate per 1,000 live births
Afghanistan	165	257
Haiti	60	80
Niger	148	253
Pakistan	78	97
Canada	5	6
Cuba	5	7
United Kingdom	5	6
United States	7	8

Data from Work Health Statistics (2008), World Health Organization [62]

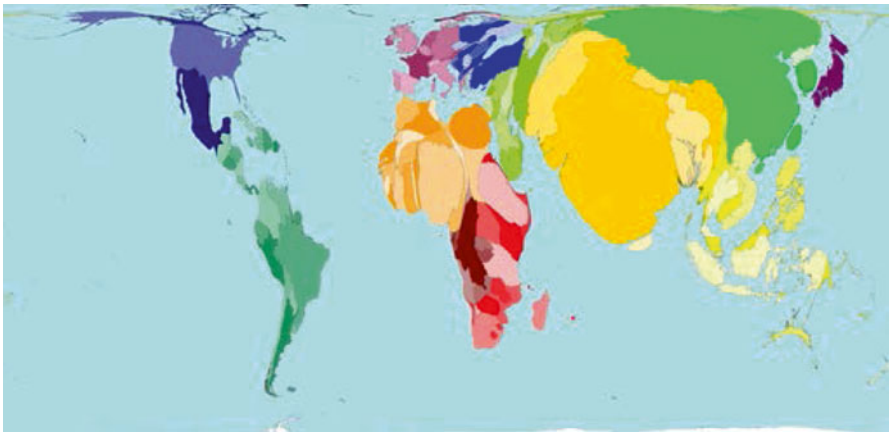

Fig. 17.1 Distribution of children across the world. The size of each country is shown relative to the number of children (Worldmapper Project, © Copyright Benjamin D Hennig) www.worldmapper.org

Challenges in Drug Therapy for Children

There are many challenges in providing optimal therapy to children in the developed and the developing world. Common challenges include the need for robust and accessible data on efficacy and safety of drugs in children [10, 11]. The appreciation that children, especially infants, are not small adults is not new and the importance of understanding how developmental pharmacology influences drug safety has been emphasized for many decades [12]. However, while the issue of developmental pharmacology and drug safety was clearly articulated in 1959 in relation to gray baby syndrome and chloramphenicol, it has only been over the last three decades that substantial progress has been made in understanding these differences mechanistically [13, 14]. While attempts to address the knowledge gap in pediatric pharmacology have focused largely on changes in drug disposition and clearance in infants, it is increasingly apparent that more information on efficacy and safety is needed for children in other age groups [15]. This problem applies to children in both developed and developing countries, but most of the world's children live in the developing world [3, 16]. This situation is unlikely to change in the immediate future. For example, the percentage of the population under age 15 is 50 % in Uganda, but only 14 % in Japan. The children of the world mostly live in countries that are economically and frequently structurally challenged to provide health care for their citizens. Additionally, many diseases that are common and important in the developing world, for example, malaria, are uncommon in the developed world, resulting in limited commercial interest in developing therapies [17]. While this has been a problem with conventional drugs, introducing vaccines into the developing world has often been associated with fewer problems and with considerably more success [18].

Germane to this is the fact that most drug development and drug research for children has been conducted in the developed world, focusing on children of northern European and, more recently, African-American ancestry [19]. There are also important differences in many key pathways in drug disposition and clearance that vary among populations, and as the world becomes more multicultural these differences can translate into therapeutic tragedy.

Perhaps one of the clearest examples is codeine, a prodrug (3-methylmorphine) that is demethylated to morphine, and produces analgesic effects. Conversion of codeine to morphine and subsequent glucuronidation of codeine are both subject to genetically determined variations [20]. For demethylation, the major isozyme of cytochrome P450 responsible, CYP2D6, is polymorphic, with at least three well described phenotypes known: (1) extensive metabolizers, most common and for which dosing recommendations for codeine are based, (2) poor metabolizers (PM, in which codeine's analgesic efficacy is blunted), and (3) ultra rapid metabolizer (URM, with very rapid and extensive conversion of codeine to morphine) (Fig. 17.2) [21]. While the URM phenotype is relatively rare in northern European populations, this phenotype is common in the Mediterranean littoral and is very common in the horn of Africa and southern India (Table 17.2). In the case of glucuronidation,

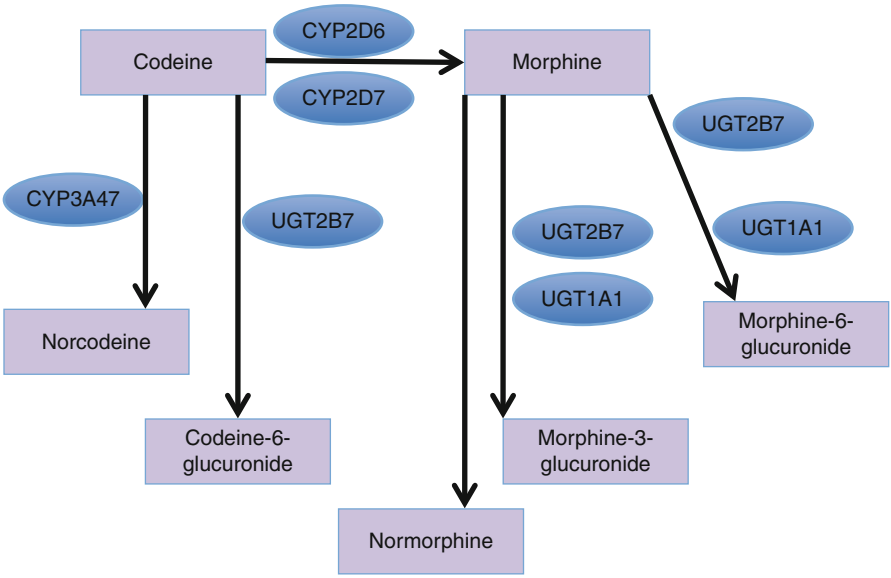

Fig. 17.2 Metabolism of codeine. Codeine undergoes metabolism by pathways subject to genetic variation

Table 17.2 Percentage of CYP2D6 poor metabolizer (PM) and ultra rapid metabolizer (URM) phenotypes in different populations

Population	PM %phenotype (%)	URM phenotype (%)
Northern European	9	1
Mediterranean littoral	2	8
Horn of Africa	2	29
South African	19	
Han Chinese	1	1
Saudi Arabian	1	21

Data extracted from Neafsey et al. [61]

polymorphisms can alter the balance of metabolites produced, which normally favor production of morphine-3-glucuronide, which has no opiate activity, to morphine-6-glucuronide, which is pharmacologically potent [22]. This is clinically important as therapeutic tragedy has accompanied the use of codeine in children and nursing mothers [23, 24]. Given North-South immigration and migration patterns, these variations in drug response are of importance to pediatric pharmacologists and health care providers in both the developed and developing world [25].

A challenge faced by all countries is access to medications. In the developing world, the issues of access are clear and obvious. When annual per capita health care spending is less than $50 US per year, the case for many developing countries, hard choices are required as to which drugs are made available and which are not. A stark illustration of this is that, in 2002, the United Nations estimated global

revenues for the pharmaceutical industry, $400 billion, were larger than the combined GDP of the poorest 95 countries at $388 billion. This was further exacerbated by the fact that consideration of which medicines are important for children globally has not been actively pursued by international agencies until recently. The current WHO Essentials Medicine for Children list (April 2013) is only the fourth such list, the first dating to 2007, while the WHO List of Essential Medicines as applied to adults was first issued in 1977 and is currently in its 18th iteration (http://www.who.int/medicines/publications/essentialmedicines/en/). As well, drug availability also often requires involvement of health care workers and always requires infrastructure to ensure that there is a supply of medication available.

Beyond cost, an additional concern relates to drug development. This is driven largely by the therapeutic needs of the developed world and, in turn, by the therapeutic needs of adults [3]. This is not surprising given that the single most important driver for prescription drug use is age. This results in a lower priority for drug development for children and a much lower priority for drug development in developing countries. This has been identified as the 10/90 gap, in which globally 90 % of research funds have been spent on diseases affecting 10 % of the population [26]. While the increasing burden of chronic disease in the developing world is now changing the dynamics of this equation, this has so far been much less marked with respect to the development of drugs for children.

The issue of cost and availability of drugs in the developing world has been addressed by a number of approaches, some more successful than others. Targeted donation programs have problems with sustainability. Furthermore, restrictive infrastructure requirements have arguably been counterproductive in that scant logistical resources may be directed to a goal that, from a systems perspective, is more important to the donor than to the recipient country. Agreements between industry, governments, and international agencies on cost relief for developing countries have been more successful for longer-term solutions, while the development of a robust generic drug industry in developing countries also offers promise. Although the development of such generic drug companies has not been without problems, a number of countries have done this, for example, India, Brazil, and Argentina. However, the development of a global generic drug industry is in part responsible for drug shortages, an issue that applies both to children and adults. Because of centralization of generic drug production, quality control or import issues now have a more substantial impact than they would have had when there was more distributed drug production. Now the problems of single suppliers may affect multiple users.

Optimal access to medicines for children is also a problem in developed nations. There are several issues which impact on this, one of which is likely to, over time, become an issue for developing countries. The first issue applies to the fact that most drugs used in children are used off-label, a common issue in the therapy of children [27]. This use often occurs without supporting evidence and may be associated with an increased risk for adverse drug events [28]. While it is common for 75 % of drugs used by children in developed countries to be used off-label, recent data suggests that this may be even more marked in the developing world. A recent

review of more than 5,000 drugs commonly prescribed for children in China revealed that only 4 % had pediatric labeling, the authors concluding that despite economic and social development in China children as therapeutic orphans were "marooned" [29]. In parts of the developing world, many drugs are available without prescription while in the developed world they are only available by prescription; for example, the antibiotic chloramphenicol is available over-the-counter in many countries in Latin America. These issues may influence whether or not the drug is listed in national or local formularies, which may determine whether or not the drug is paid for by private or government drug reimbursement plans.

A second major access issue that is increasingly problematic everywhere is cost. While newly marketed drugs are frequently more expensive than older drugs, notably when generic equivalents exist, the recent revolution in protein and factor therapy has provided novel approaches to childhood disease that can be extraordinarily expensive, even when they are developed for precision targets and are highly effective. While generic drugs and biosimilars offer potential relief from cost pressure, there remains considerable controversy as to how these approaches should be evaluated [30]. Cost of drugs has long been a problem in the developing world and recent direction shifts in therapeutics suggest that the most significant pressures have yet to be appreciated. Given the growing burden of chronic illness worldwide and increasing diagnostic sophistication in identifying specific subsets who respond to therapy, the issue of how to deal with niche therapies and orphan drugs is likely to be an increasing issue in the developing world.

Formulations remain a challenge for medicines for children, an issue that is particularly germane in the developing world [31, 32]. While the majority of drugs are given orally, typically as tablets or capsules, the pragmatic developmental issue limiting this strategy with respect to children is that the majority of medication-naïve children below age eight have difficulty in swallowing solid formulations, while essentially all children younger than five have trouble taking tablets or capsules [33]. The classical solution has been to develop liquid formulations. In the developing world, liquid formulations present some specific problems. Transportation becomes an issue; by far the most abundant element of most preparations is water. Transporting water is relatively expensive, especially when transportation infrastructure is underdeveloped. An alternative is to have the medication in a dry powder form that can be reconstituted near the point of care. This works well in the developed world, but in many LMIC settings the skilled personnel to reconstitute medication and clean water needed for reconstitution are both in short supply and often available only in restricted locations [31, 32].

An additional issue that is rarely considered is palatability: children's medications are very rarely assessed for palatability, a complex blend of taste, texture, and smell [34]. Palatability issues can cause significant difficulty in treatment of children with complex and serious disease. As an example, in the care of children with HIV infection drug delivery has, on occasion, required the use of a gastric tube to offset palatability issues [35]. Creative solutions are urgently needed for these problems.

An important and relatively underappreciated issue impacting child health in the developing world is armed conflict and associated preparations. War is common in much of the world, notably areas where there are many children. As many as 1 in 6 of the world's children live in areas of current conflict and child soldiers are often combatants. This produces physical and psychological injuries, many long-lasting, as well as loss of crucial infrastructure and civil order and diversion of funds from other areas to supporting military, security, and reconstruction costs [36]. In addition to the issue of actual armed conflict, regional and national tensions in much of the developing world have also diverted public funds to military spending at the expense of other priorities.

It is clear that there is no lack of challenges for the provision of safe and effective drug therapy for the world's children. How can these be addressed and what is the potential role of pediatric drug specialists (pharmacists, clinical pharmacologists, pharmacoepidemiologists) in accomplishing this important goal?

The Importance of Pharmacoepidemiology for Drug Therapy for Children in the Developing World

One of the areas in which training and expertise in pediatric clinical pharmacology may be expected to impact on the provision of drug therapy for children in the developing world is pharmacoepidemiology. Pharmacoepidemiology, the study of the use and effects of drugs in large groups of people or in populations, is a relatively new area of investigation in pediatrics [37]. Although a relatively new discipline, pharmacoepidemiology can potentially offer important guidance to drug therapy for children, for example, in the identification of which drugs are most important and relevant to various countries and regions. This can best be accomplished by combining the efforts of epidemiologists, specialists in infectious disease, pharmacologists, and public health authorities in order to address "big picture" issues that are most germane to a particular country or region and to provide guidance as to which drugs are most likely to be effective, safe, and needed.

Pharmacoepidemiology and Drug Safety

Pharmacoepidemiology can also be helpful in identifying drug safety issues, notably when drugs are being used among populations very different from those in which they were developed. This can result in blunted efficacy or in increased rates of adverse drug reactions. Pharmacoepidemology is an essential part of strategies for drug safety, notably for signal identification and validation [38]. This is crucial given real-world experience of drug utilization following marketing. Drug development often does not include children and when it does is often conducted among

children in unique subsets. Given the reality of drug utilization, once drugs are approved, they are used both widely and frequently among populations very different from those in whom the drug was originally evaluated. As experience grows with the drug, so do the circumstances of use, including off-label use. An example is shown in Fig. 17.3, modeled on the experience of the COX-2 selective NSAIDs. Within 6 months of market introduction of these drugs they had been used by more than 500,000 patients. Interestingly, we found that, despite the lack of labeled indication for use in this age group, several hundred of these patients were children [5]. The finding thereafter of an association between these agents and adverse thrombotic events has subsequently been described. This literature suggests how epidemiological data can be interpreted in more than one manner [39].

This points to the importance of robust systems, both for the detection of adverse drug events and also for drug safety [10]. While one approach uses administrative datasets and data mining techniques, this is not suitable for all questions or for all settings and is not readily applicable to many pressing questions regarding drug therapy in the developing world. There are a number of approaches that can be taken, but one of the most important cautions is that strict standards and care must be taken to avoid potential bias and errors in extrapolating signals from epidemiological data [40]. Some approaches that can be taken are decidedly low-tech. These can include collection of data on paper or evaluation of data from published sources. As an example, we have demonstrated that hepatic injury associated with pemoline,

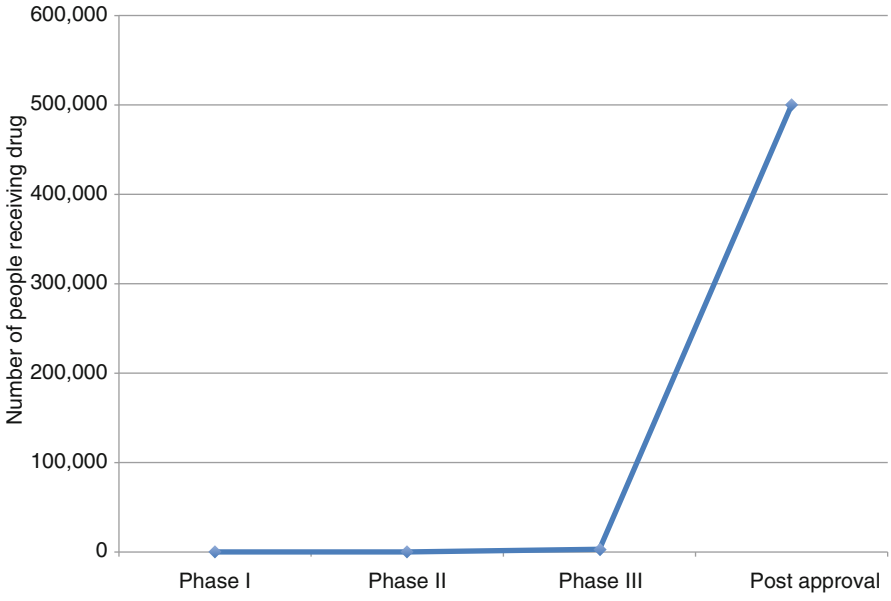

Fig. 17.3 Typical number of people taking a drug through clinical drug development (Phase I – 20, Phase II – 80, Phase III – 3,000) versus number 6 months post-approval (500,000), based on the COX-2 selective NSAIDs

formerly used in children for therapy of attention-deficit disorder, could have been identified by review of the literature years before this concern was raised by drug regulatory authorities [41]. The monitoring of trends and longitudinal assessment of drug use in children is of considerable importance to ensure that therapies being used are efficacious and safe and are addressing significant child health problems [42, 43].

Drug Donation and Aid

There has been a sustained increase in the amount of relief provided to the developing world over the past 50 years, often as drug donations. A major concern is that the interests of the donor may not be coincident with the interests of the country or region receiving the donation [44, 45]. This can significantly distort the outcome of the projects or programs for which the aid or donation was targeted as well as having unforeseen effects on other programs. For example, to meet the infrastructure requirements for some programs, for example, delivering antiretroviral therapy, in some cases countries have needed to create the support for this infrastructure by diversion of resources from other areas such as control programs for other diseases or public health initiatives [46]. It has been suggested that the dramatic eightfold increase in donor funding for HIV/AIDS and other infections from 1998 to 2007 has been accompanied by a decline in funding for the support of health care systems [47, 48].

Individualized Therapy for Children in the Developing World

A major direction in pharmacotherapy in the developed world has been in personalized medicine, where precision diagnosis is linked with understanding of genetic and other variations in drug handling, response, and safety such that the right drug in the right dose at the right time is given to the right patient [49]. This is not new; Sir Archibald Garrod at the start of the twentieth century speculated that variability in drug response was based on genetic differences among patients [50]. One of the first studies in pharmacogenomics, the determination of the role of genetic variations in N-acetylation in isoniazid metabolism by Evans and colleagues, included a number of children [51]. However, for many years these findings were largely considered academic and were not translated into the clinical arena, especially with respect to children. Major stumbling blocks included practical difficulties that included issues of sample size and design as well as the requirement for blood volumes that were unrealistically large in children. Over the past decade, many of these problems have been addressed and research has established that, for many drugs, demonstration of genetic variants can be used to drive safer and more effective drug therapy for children [52].

These developments have led to calls for personalized or individualized medicine for children. This is an important concept and is applicable in many ways in the developing world. In understanding how this applies, it is important to recognize that personalized medicine and pharmacogenomics are not synonymous. In fact, while pharmacogenomics is an important aspect of personalized medicine, there are many other aspects of and approaches to personalized medicine, some of which are well suited for uptake in the developing world [53]. Examples include individualized teaching with respect to problems such as asthma and obesity, with positive results arising from tailoring treatment to patients [54]. Similar results may apply to other chronic diseases in children, an increasing concern for the developing world [55].

One area of personalized medicine that falls clearly in the usual domain of clinical pharmacology involves therapeutic drug monitoring (TDM) [56]. Therapeutic drug monitoring involves determining if the concentration of a drug in a relevant biological fluid, typically blood, is within the therapeutic window between minimal effective concentration and minimal toxic concentration (Fig. 17.4). TDM clinically requires a biological fluid sample in adequate volume for analysis and then being able to correlate the result with known efficacy/toxicity data. While historically TDM has been restricted to a relatively small number of drugs, most of those agents for which TDM is useful are drugs commonly used in children's care. As well, the use of TDM can allow more judicious and prudent use of drugs in resource-limited settings. As an example, once-daily gentamicin in infants and children has offered advantages not only in terms of enhanced safety but also in reducing the need for determination of gentamicin blood concentrations [57, 58]. It has been clearly demonstrated that this is

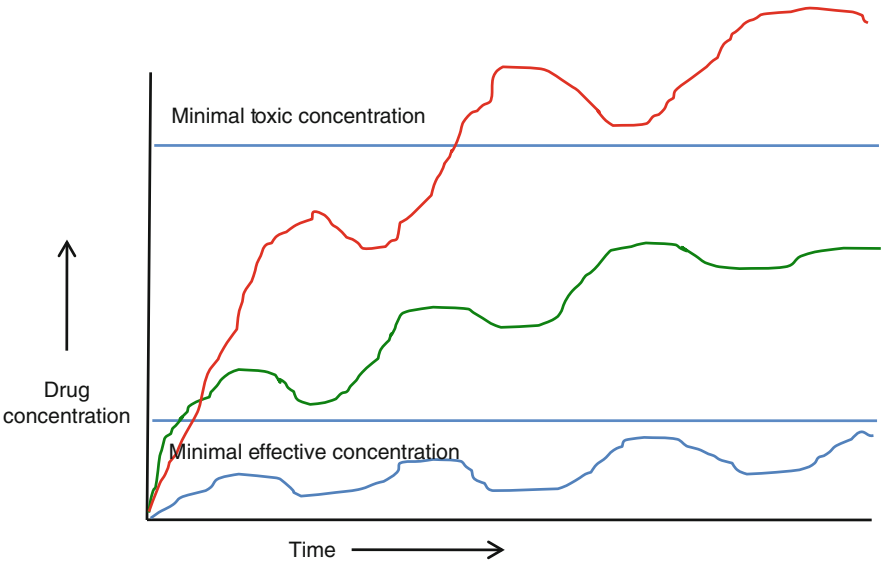

Fig. 17.4 Personalizing therapy by therapeutic drug monitoring. The concentration-time curves show a patient for whom therapy is likely to be ineffective (*blue*), effective (*green*), and associated with significant adverse effects (*red*)

a superior dosing strategy for infants with presumptive neonatal sepsis, an important cause of infant mortality in the developing world. Developing personalized approaches by studying what are optimal strategies for TDM, or in altering dosage schedules such that TDM is not routinely required, offers great promise for children in the developing world, notably as our knowledge of concentration-effect and concentration-toxicity relationships expands and as analytical capacity improves [59] (Fig. 17.5).

Training in Drug Investigation in Children for the Developing World

One area in which input and participation by clinical pharmacologists is clearly needed is in the training of health care workers and health care researchers in the developing world. The ratio of health care workers to patients in most developing countries is heavily skewed compared to developed countries, often with the countries in most need having the least availability of health care workers. While there is a major need in primary health care, it is equally clear that it is important to have local expertise in determining how best to use drugs safely and effectively.

Training of health care providers in pediatric clinical pharmacology has undergone a low key but steady progression over the past three decades. Initially the model, in common with many other training programs for health care workers from developing and low-resource countries, was to bring trainees to centers in the developed world to spend several years in research-intensive training. Training of health care workers from developing and low-resource countries under this paradigm is associated with a set of risks, one being that trainees develop skills dependent on access to technology often unavailable in their home countries, leading to a certain degree of frustration on return, and the second being the chance that these trainees

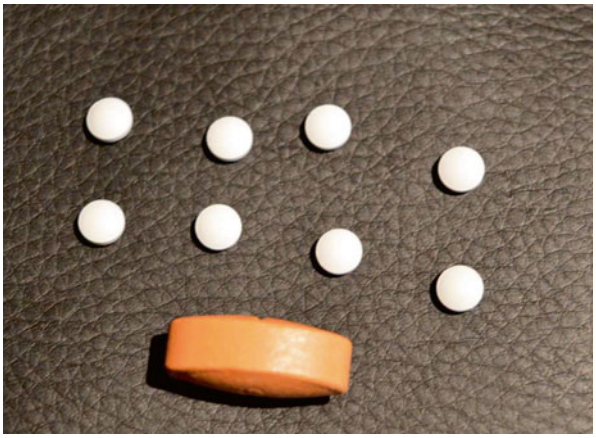

Fig. 17.5 Two ways to give 16 mg of a drug. Relative size of mini-tablets to deliver the same dose as a conventional tablet

will elect to remain in the country of training rather than returning home, producing the classical North-South "brain drain" [60]. An additional issue germane to pediatric clinical pharmacology is that there are relatively few training centers and inadequate access for candidates from the developed world.

Over the past decades, there has been an evolution in the training of pediatric clinical pharmacologists, with clinical pharmacologists from the developing world sharing in the shaping of as well as benefiting from this evolution. One important development has been the creation of consortia such as Global Research in Paediatrics (GRIP), a network of investigators globally focused on the development of better medications for children. GRIP is sponsored by the European Union with the objective of stimulating and facilitating development, and safe use of medication for children. As a multinational initiative GRIP has considered the needs of children in the developing world and has sponsored international collaborations in research and teaching to empower investigators in developing and low-resource countries to pursue studies relevant to children in their regions. This has included the creation of an internationally based training program in pediatric clinical pharmacology and international initiatives for new clinical trials designs in children and for more clinical trials involving neonates. Other groups are also exploring the use of remote and distance education technology for training in pediatric clinical pharmacology, for example, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, part of the American National Institutes of Health, holds an online course on principles of pediatric clinical pharmacology that provides a comprehensive approach to the fundamentals of pediatric clinical pharmacology (http://clinicalcenter.nih.gov/training/training/principles.html). This course is taught by a variety of instructors including academic pediatric clinical pharmacologists as well as staff from the National Institutes of Health and the Food and Drug Administration.

Other important developments have been the evolution of centers for training in pediatric clinical pharmacology with robust and sustainable complements of faculty and the creation of funding streams to support training in pediatric clinical pharmacology. The challenge remains in encouraging well trained health care researchers from developing and low-resource countries to, not only return to their home regions, but also flourish. Work in this area has included efforts to ensure that training is appropriate to the resources and capacity level of the region in question, that post-training linkages are sustained and that there are graduated programs for trainees to return to their home regions. The long-term success of these initiatives remains to be determined.

Clinical Pharmacology and a Brighter Future for the World's Children

While there are many challenges facing children in the developing world, the prospects for safer and more effective drug therapy have never been better. Evolving capacity in addressing these challenges needs to recognize the changing nature of child health and the challenges in developing and low-resource countries, some of

which are generic and some of which are regional. In addition to an adequate fiscal base for child health care, international partnerships, innovation in health care research, and delivery and passionate commitment to optimal child development are all needed to ensure that the fruits of therapeutic discoveries are shared among the world's children.

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Chapter 18
Neglected Diseases: Drug Development for Chagas Disease as an Example

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Neglected diseases (NDs), also known as neglected tropical diseases, are a group of chronic conditions that disproportionately affect the poorest populations in the world [1]. Unfortunately, a universally accepted definition for NDs is lacking, and much discussion is ongoing on the category's actual scope as well as the potential expansion to include non-infectious conditions with a significant impact on the health and well-being of developing populations. These conditions usually share with NDs an underlying basis of poverty and neglect (e.g., reproductive health issues, malnutrition, micronutrient deficits, vaccine preventable diseases, and premature births) [2].

The World Health Organization (WHO) has put together a list of 17 NDs affecting more than one billion people worldwide for which there is overwhelming evidence that they can be effectively controlled with relatively simple measures (Table 18.1). Yet, NDs remain unaddressed at all levels and continue, unchecked, to cause significant morbidity and mortality in the developing world. NDs cause comparatively few deaths, even when they affect and impair, or permanently disable large numbers of people, since many patients have a silent chronic progression that may lead to disability or protracted death.

Largely ignored, children comprise a significant proportion of the voiceless victims of NDs. Unfortunately, the limited efforts to identify new, safe, and effective treatments for NDs, and the even larger void in drug development efforts for

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Table 18.1 WHO list of neglected diseases (http://www.who.int/neglected_diseases/diseases/en/)

Neglected disease	Comments
Chagas disease	An estimated eight million infections, mostly acquired in childhood by congenital or vectorial transmission. Leads to chronic disease with heart and other organ involvement (cardiomyopathy, megacolon, megaesophagus) years or decades after infection
Leishmaniasis	Half a million cases each year, about 50 % children. Visceral leishmaniasis has approximately 10 % mortality rate in children. Cutaneous and mucocutaneous diseases lead to lifelong disfiguring scars
Echinococcosis	Approximately 20,000 new cases every year. Commonly diagnosed in early adulthood. Pediatric prevalence not clearly established
Cysticercosis	An estimated 50 million infections worldwide. Pediatric prevalence not clearly established. Neurocysticercosis commonly causes seizures, headaches, and learning difficulties
Schistosomiasis (bilharziasis)	Approximately 200 million cases, mostly in sub-Saharan Africa. Majority acquired in childhood. Can lead to hematuria, anemia, urogenital disease, bladder cancer, intestinal and liver fibrosis, growth and cognitive delays
Dengue	Over 50 million annual infections. Over 20,000 deaths per year, mostly children
Rabies	An estimated 40 % of exposed humans are children. Tens of thousands of deaths every year worldwide
Soil transmitted helminthiases (intestinal worms)	Approximately 800 million children in the world. Associated to anemia, malnutrition, growth and cognitive delays, poor pregnancy outcome
Blinding trachoma	80 million people affected worldwide. Most prevalent in pre-school children. Leads to blindness
Buruli ulcer	Thousands of new cases each year, 50 % under 15 years old. Disfiguring ulcer
Leprosy (Hansen disease)	Prevalence near 200,000 cases (2013). Few new pediatric cases. Left untreated, leprosy causes permanent damage to the skin, nerves, limbs, and eyes
Dracunculiasis (guinea-worm disease)	Global eradication campaign under way. Significant reduction in cases. Still 50 % are children. Disfiguring ulcers, secondary bacterial infections common
Foodborne trematode infections	Close to 60 million cases worldwide. High prevalence in children. Compromise the overall health status of affected individuals and responsible for specific and severe organ damage
Lymphatic filariasis	Over 100 million people affected. Acquired mostly in childhood. Long-term consequences (adenolymphangitis, lymphedema, hydrocele)
Endemic treponematoses (yaws)	Currently, unclear prevalence, estimated in the tens of thousands. 75 % are children. Disfigurement and disability if left untreated

(continued)

Table 18.1 (continued)

Neglected disease	Comments
Human African trypanosomiasis (sleeping sickness)	Thousands of new cases each year, approximately 30 % children. Untreated can lead to death, seizures, long-term cognitive impairment
Onchocerciasis (river blindness)	Over 15 million affected worldwide, including a varying proportion of children (depending on country). Second most common infectious cause of blindness, after trachoma

children, make young patients with NDs a highly neglected population. Even in situations where drugs are effective, most have been formally tested only in adults, and pediatric use has been introduced out of necessity, as an afterthought to adult therapy. There is usually little scientific research in pediatric populations to guide dose adjustments or even to support claims of therapeutic efficacy in some cases.

Children can be affected by NDs in ways different from adults, as the younger the patient the more developmental processes at play that may be disrupted by pharmacotherapy, affecting their health and development [3]. Starting with fetal development, NDs can lead to congenital infection or other consequences secondary to maternal disease, jeopardizing pregnancy or leading to intrauterine growth restriction. After birth, NDs may affect many areas, depending on the disease and the developmental period affected. Among other things, NDs may affect intellectual and physical development of the infant, causing growth deficits, impaired fitness, impaired cognitive function, impaired test performance, and delayed age starting school [4, 5]. For example, hookworm can cause profound anemia, leading to a multitude of complications capable of significantly affecting the life of children. Moreover, ND effects on children often lead to a profound and long lasting impact on society at all levels. NDs not only affect children's health, but they can also affect other determinants of societal growth and well-being, such as economic activity (e.g., parents of affected children may have to work less to take care of them, they may incur in significant unplanned expenses that may leave less income available for purchasing food, clothes, etc.) and other less evident issues.

Currently available treatments for NDs have a number of drawbacks, may not be practical for use in children, and are often associated with high rates of adverse drug reactions. In fact, the lack of specific pediatric drug studies makes the actual rate of adverse drug reactions and the dose–response relationships largely unknown, leading to significant guesswork when pediatric doses and monitoring schedules are planned.

An astonishing lack of interest on the part of the pharmaceutical industry has characterized the drug development landscape for NDs. A recent study that screened databases of drug regulatory authorities, the WHO and clinical trial registries using a broad definition of "neglected diseases," found that only 4 % out of 850 new therapeutic products and 1 % of 336 new chemical entities approved between 2000 and 2011 were aimed at the treatment for NDs [6]. This grim reality can be explained by the fact that NDs affect mostly poor people from poor countries, explaining the scant resources devoted by the pharmaceutical industry to research and development of new therapeutic agents.

In fact, many developments in the area have come about as a by-product of conflict or western countries' involvement in areas where NDs are prevalent, as exemplified by the advent of antimalarials due to World War II when soldiers from the USA or Europe developed malaria [7]. More recently, development of new drugs for NDs has stemmed from a more general interest in these diseases, and the poverty they promote, by philanthropic organizations and public–private partnerships (such as the Bill & Melinda Gates Foundation, Drugs for Neglected Diseases initiative, PATH, Medicines for Malaria Venture). This interest has prompted many pharmaceutical companies to invest in NDs and/or share knowledge and resources (e.g., compound libraries) with interested organizations, and in some cases to engage directly in ND drug development projects. Unfortunately, the situation is still far from what should be expected for a problem of such a large scope.

A possible solution for the lack of new and significant pharmaceutical industry investment in research and development could be in identifying old drugs, already studied and approved for other diseases, and to assess their activity against the etiological agents of NDs in the hope of finding drugs that are effective. This approach, commonly known as "drug repositioning" [8] or repurposing, holds the potential, once an effective drug for a given ND is found, for significant savings in the preclinical stage (particularly toxicology and ADME) which was already completed when the compound was initially tested on the disease for which it was originally intended.

For many NDs pediatric drug research is significantly lacking, and development of new, safe, and effective therapies has significantly lagged behind the development of medications for other diseases. The main difficulties, and some potential solutions, in the pharmacotherapy of pediatric NDs can be exemplified by Chagas disease, a predominantly pediatric disease with chronic complications that may only surface later in adulthood.

Chagas disease is caused by infection with the parasite *Trypanosoma Cruzi* [9, 10]. This chronic disease currently afflicts over seven million people in the Americas, where it is a significant cause of heart failure and other long-term cardiac and gastrointestinal complications [9, 11–13]. In the past few decades, cases of Chagas disease have appeared virtually worldwide through immigration, with many imported and congenital cases observed in Europe and North America. Chagas disease is most frequently acquired in childhood through vector exposure or congenital infection, and leads to severe long-term consequences [13].

Disease transmission can be vectorial (*Triatoma infestans, Rhodnius prolixus*, and *Triatoma dimidiata*) are the three most important vector species [14–16] or congenital, with other routes of infection such as blood transfusion, organ transplants, and oral ingestion being less frequent. With the advent of effective vector control programs in many South American countries, and the continued migration of infected people from rural to urban dwellings, congenital transmission has become the main route of transmission [17].

The initial, acute phase lasts 4–8 weeks and is usually asymptomatic or associated with non-specific symptoms of fever, malaise, or lymph node enlargement. A minority of acute cases may present with severe multiorgan involvement,

meningoencephalitis, or myocarditis. The initial acute phase is followed by a chronic asymptomatic stage. However, in spite of the lack of clinical symptoms, the parasite lodges in several organs (particularly the heart) leading to a chronic inflammatory reaction and slow tissue destruction that eventually leads to irreversible heart disease in up to 30 % of the infected patients many years later [18–20]. The majority of the deaths, more than 7,000 per year, occur due to cardiac complications in adults infected during childhood [18, 21, 22].

There are only two drugs currently available for the treatment of Chagas disease, benznidazole (BZN) and nifurtimox (NFX), both developed in the early 1970s. Pharmacological research has been slow in the past few decades, but eventually led to the recent clinical testing of a small number of new drugs, including the azole drugs posaconazole and E1224 (a water-soluble prodrug of ravuconazole). Unfortunately, both azoles failed in clinical trials to control parasitemia in chronic Chagas disease patients. Reassuringly, benznidazole, included as control arm in these studies, performed better than anticipated, with over 80 % of patients showing complete parasitological response at 1-year follow up (compared to less than 30 % in the azole arms). Drug combination studies with new (e.g., E1224) and old (e.g., BZN) drugs are presently at the design stages [23].

Benznidazole (Rochagan, Radanil, Abarax) and nifurtimox (Lampit) are nitroheterocyclic drugs developed over four decades ago by Roche and Bayer, respectively. Both drugs have in vitro and in vivo activity against Trypanosoma and Leishmania parasites. The parasitic activity of these drugs is believed to be secondary to the production of reactive metabolites in the parasite that lead to alkylation and oxidative damage of parasite DNA and RNA [24]. Benznidazole and nifurtimox are considered prodrugs, as they need to be activated in the parasite in order to exert their effect.

Pharmacologic treatment is indicated for all cases of acute, congenital, and reactive infections among children up to 18 years of age [25–27].

Treatment of adults in the chronic phase has also recently been recommended, based on findings showing that available treatments lead to persistent destruction of parasitemia [18, 23, 28].

Even though pharmacological treatment of Chagas disease is highly effective during both the acute phase of the infection and in the chronic stage in children and young adults, available medications need to be administered for 30–60 days and are associated with significant toxicity, especially in adults [26–30]. While the prevalence and degree of adverse drug reactions have been often used as an excuse to avoid treating patients, current guidelines emphasize the need to provide all Chagas disease patients, particularly children, with appropriate pharmacological treatment [27, 28].

Both drugs are associated to a high incidence of adverse drug reactions in adults, reaching over 50 % in some series [28, 31]. Children seem to have significantly lower risk of ADRs, but these differences still remain unexplained [9, 26, 27, 29].

Dosing schedules were defined empirically, and transferred directly from adults to children on a weight adjusted basis without further research. Mechanisms of action of both drugs were only recently elucidated [24], but other aspects of their

pharmacology (e.g., extent of absorption, metabolism pathways, mechanisms of adverse drug reactions, etc.) have not been studied in depth to date [27, 31]. Furthermore, pediatric clinical pharmacology information for these drugs is significantly lacking, and pediatric formulations are non-existent.

Altcheh and colleagues described the occurrence of adverse drug reactions (ADRs) in a cohort of pediatric patients treated with BZN. ADRs were clearly age-related, with children older than 7 years being the most affected (77 % of all ADRs) and the skin being the most commonly affected organ (21 %, mostly mild hypersensitivity reactions such as rash, eczema, or pruritus) [32].

Only two pharmacokinetic studies of benznidazole were carried out before the drug came into widespread clinical use, and both were conducted in adults in the 1970s and with very low subject numbers [32, 33]. No pharmacokinetic information was available in children until 2014 [34], when a prospective population pharmacokinetic study in children with Chagas disease observed benznidazole concentrations that were markedly lower than those previously reported in adults treated with comparable mg/kg doses. The pediatric therapy was nevertheless highly effective (100 % parasitological response), and with a significantly lower incidence of ADRs than those observed in adults, suggesting that lower doses could be used for the treatment of adults without loss of efficacy and possibly with a lower risk of ADRs [34].

Non-availability of pediatric formulations is a frequent problem in pediatric pharmacotherapy. Unfortunately, the situation is no different for Chagas disease. BZN has been used in children for decades without a pediatric oral formulation. Treating physicians rely instead on the use of fractioned adult pills that rarely yield the needed dose with any precision. Recently, a pediatric formulation was developed by a Brazilian pharmaceutical company, Lafepe. These 12.5 mg tablets, easily dispersible to facilitate oral administration, would allow the treatment to be adapted to children under 2 years (or <20 kg), avoiding potential errors when fractioning the 100 mg adult strength BZN tablet**.** Unfortunately, the pediatric formulation has not yet reached widespread distribution due to regulatory hurdles.

Nifurtimox (NFX), the alternative to BZN for the treatment of Chagas disease, was manufactured by Bayer (as Lampit©) since 1972. However, near the end of the 1990s, Bayer discontinued its production due to perceived lack of demand and low profitability. Later, as a consequence of clinical trials showing that the drug was highly effective in combination against sleeping sickness, and in response to significant pressure by medical organizations such as Medecines Sans Frontiers, Bayer decided to restart production of the drug and donate it through the World Health Organization (WHO) for the treatment of sleeping sickness and Chagas disease [31]. Access to NFX depends on individual states' agreements and negotiations with WHO and Bayer, and currently seems erratic in many South American countries.

Similar to BZN, NFX is highly lipid soluble and distributes widely to tissues, including the central nervous system. Animal studies have shown that absorption of

the drug from the gut is rapid and virtually complete, but that NFX undergoes significant first pass metabolism (much higher than benznidazole), leading to a small fraction of orally administered NFX reaching the systemic circulation [35, 36]. NFX bioavailability in humans is not known due to the absence of an intravenous formulation. Oral NFX administration produces peak plasma concentrations after approximately 2 h [34, 36]. Hepatic clearance of NFX is rapid and accounts for virtually all the clearance of the drug with unchanged elimination in urine at less than 10 %. Active metabolites have been suggested by isolated (animal) liver experiments [34], but this aspect has not been studied in humans. Data from animal studies also suggest that CYP enzymes are responsible for the metabolism of the drug, but no human data are available to date to confirm this suggestion [35]. The elimination half-life of the drug is 3 h in adults.

The most commonly observed NFX ADRs are anorexia and weight loss, irritability, sleepiness, and other central nervous system signs [37]. NFX is also associated with rash, pruritus, and drug-associated hepatitis, but much less frequently than BZN. Depression, peripheral neuropathy, and psychiatric symptoms have been reported less commonly. Similar to BZN, NFX-associated ADRs seem to be much more common and severe in adults, and are usually mild in children, including neonates. However, data on ADRs in children, including frequency, are much scarcer than for BZN.

After years of intense discussion, Bayer has agreed to restart the development of a pediatric formulation of NFX, as a 30 mg NFX dispersible tablet. Bioequivalence studies of the formulation have been completed (clinicaltrials.gov NCT01927224), with more extensive trials and regulatory approval expected in the near future.

A common theme in the treatment of children with Chagas disease has been the lack of availability of appropriate formulations. For both NFX and BZN, currently marketed formulations were designed for adults, and use in children involves a number of problems and risks. In fact, the degree of dosing error possible with the usual practise of home pill fractioning, sometimes in eight or ten fragments, is unacceptably high as would be expected. Administration of the fragments to small children is not an easy task, and cannot be simplified by dissolution of the pills in water, given the limited aqueous solubility of the drugs. Some researchers have suggested the use of milk to improve dissolution, but the impact of milk on bioavailability of the medications has not been formally tested to date.

Many challenges and roadblocks remain in the treatment of pediatric Chagas disease. The promised pediatric formulations of BZN and NFX hold the potential to notably change the pediatric Chagas treatment landscape. In the meantime, work needs to be done to improve all aspects of the treatment of pediatric Chagas disease, including clarification of the observed high incidence of ADRs in children older than 7 years and in adults, and its relationship to higher plasma levels of the drugs. The pharmacokinetics of both NFX and BZN still remain relatively obscure both in children and in adults, and further work is required to improve treatment and correlate pharmacokinetics parameters to treatment outcome.

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Chapter 19
Health Economic Evaluation for Improving Child Health in Low- and Middle-Income Countries

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Key Messages

- Health care systems require high quality economic evaluations to make wise health care allocation decisions to enhance the health of populations.
- Low- and middle-income countries (LMICs) face the double jeopardy of having very limited resources to produce economic evaluations and highly constrained health care budgets that require funds to be spent judiciously.
- Conducting economic evaluations in children is challenging methodologically – this is exacerbated in LMICs where health care funding and health priorities are influenced by external donor agencies.
- Of 49 economic evaluations of preventative interventions for children published in 2012, 17 (35 %) were performed by or targeted a LMIC. Of 25 economic evaluations of treatments for children in 2012, only 4 (16 %) were performed by or targeted a LMIC.
- World Health Organization (WHO) initiatives such as generalized cost-effectiveness analysis (GCEA) address many methodological issues in child health economic evaluation. Greater collaboration between health researchers from LMICs and industrialized countries can also help to improve the quality of the evidence used for decision-making.

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Countries with well-developed health care systems have relied on a formal process of economic evaluation to assess the cost-effectiveness of new medications for insurance plan coverage decisions for over 20 years [1–3]. Although evidence of cost-effectiveness is not usually required to license a new drug for sale, it is required before publicly funded health insurance programs will pay for it and make it available to plan subscribers. For this reason, the need to demonstrate cost-effectiveness is often referred to as the *fourth hurdle*, in addition to requirements to demonstrate safety, efficacy, and quality [4].

Low- and middle-income countries (LMICs) that seek to make a new drug available to their population face unique challenges above and beyond those faced by other nations. Their limited resources hamper their ability to produce and evaluate cost-effectiveness research and it is precisely in countries with limited health care resources that the need for high quality health economic evidence to ensure judicious resource allocation is greatest. Thus, the lowest income countries face a double jeopardy [5]. LMICs also face numerous contextual challenges related to assigning health care priorities, the availability of data, human resources and infrastructure, and the involvement of external decision-makers, such as nongovernmental organizations (NGO) and donor agencies [6].

In addition to these challenges, the methods for economic evaluation developed and promulgated by agencies in industrialized countries such as the UK National Institute for Health and Care Excellence (NICE) [7] and the Canadian Agency for Drugs and Technologies in Health (CADTH) [8] are not easily applied to health care decision-making in LMICs. This chapter will begin with a review of the basic principles of economic evaluation, present the contextual and methodological challenges of conducting economic evaluations in LMICs, and finally present the results of a survey of the scope and type of pharmacoeconomic evaluations in child health performed by and for LMICs.

Basic Principles of Economic Evaluation

An economic evaluation is defined as a comparison of two or more interventions in terms of both costs and health consequences. Since health consequences, that is, changes in health status, are measured in an economic evaluation it builds upon existing evidence of safety and efficacy.

In a cost-effectiveness analysis, the costs are derived from all health care resources consumed that are relevant to the disease being treated. These health care resources will include not only the medication or vaccine, but also the physician consultations, laboratory tests, technician time, inpatient care, use of medical devices, etc. that occur to treat the disease, manage complications, or treat drug-related adverse events. When local prices are attached to these health resources, such as a negotiated medication sale price or a physician fee, any additional costs for the new treatment are weighed against the changes in health status that are a consequence of using it.

Of particular importance to pediatric economic evaluations is consideration of productivity losses of parents and informal caregivers. Parents and caregivers lose time or reduce their level of productivity from paid and unpaid labor as well as from usual activities in order to provide care to or attend to their child. For chronic pediatric conditions, these productivity losses can be substantial. Failure to include them can lead to falsely concluding that a new intervention is cost-effective when an alternative analysis shows otherwise [9].

Because private or public health plans or individuals are already spending money on health care, health plan decision-makers are mainly interested in the *marginal* cost-effectiveness of new treatments. This is the additional cost above and beyond what is already being spent on usual care, per additional unit of improvement in health status. When the new treatment is more expensive than the current standard of care but provides improved health benefit (which is often the case), the result is expressed as an incremental cost-effectiveness ratio (ICER). The numerator of the ICER is the difference in mean costs between the new intervention and standard care (or another comparator). The denominator expresses the difference in mean outcomes between comparator groups. By subtracting the mean values for costs and outcomes of standard care from the new intervention, one can determine the *incremental* costs associated with the new intervention per unit of *incremental* health improvement achieved [10].

Challenges to Conducting Economic Evaluations in LMICs

Contextual Challenges

The health and treatment priorities of LMICs differ markedly from those in other countries, with a strong emphasis on infectious disease prevention [11]. For the most severely disadvantaged countries, improving infant survival continues to be a priority to meet the Millennium Development Goal 4 (MDG 4), aimed at reducing under-5 mortality by two-thirds between 1990 and 2015 [12]. Yet the bulk of evidence related to safety, efficacy, and cost-effectiveness of new treatments is generated in developed countries where infectious diseases such as malaria and human immunodeficiency virus (HIV) are rare to nonexistent [5]. This results in a smaller health economic evidence base for the interventions that are important to LMICs. To further complicate matters, many LMICs lack the technical expertise and infrastructure to generate and analyze data to perform local cost-effectiveness analysis.

One of the greatest challenges to the ability of LMICs to generate useful evidence of cost-effectiveness is the subsidization of the domestic health care system, and the large decision-making and supplier roles played by external donor agencies. These organizations may have priorities that reflect political factors or their funding base interests, and thus may diverge from the interests of the local government and populace, as well as from each other. External donors often fund discrete health care programs that are mandated by a single or large collective international agency that

may or may not incorporate local needs. For example, the Global Alliance on Vaccines and Immunization (GAVI) disbursed over US$6 billion to eligible countries in cash, vaccines, and vaccine services between 2000 and 2013 [13]. While GAVI has been very successful in increasing immunization coverage rates in LMICs [14, 15], its requirement for receiving national sustainability plans as a funding condition has not been readily fulfilled [16]. Donor agencies may organize health program delivery at a regional rather than country-specific level. They may also rely on already strained local health care administration, personnel and distribution networks for their programs thereby taking resources away from domestic services. While these agencies may inject critical funds and provide health care services to support life-saving treatment or immunization campaigns, this assistance may be time limited and therefore not contribute to local capacity building or the sustainability of the domestic health care system [6].

Methodological Challenges

Taking a closer look at the design of economic evaluations of new treatments for children, there are a number of issues that pose particular challenges when applying these methods to LMICs. These issues include the choice of treatment comparators, setting an analytic time horizon, applying discounting, selecting a payer perspective, and choosing a measure of health benefit.

In a clinical trial that addresses the question of efficacy, the comparator is often placebo. In contrast, economic evaluations require high external validity, and thus the comparator is typically the current standard of care, which may or may not be a medication. Sometimes the intervention represents an entirely novel treatment for a condition for which no treatment previously existed. In this case, the appropriate "usual care" comparator may simply be periodic monitoring with delivery of acute care when the disease progresses. In an economic evaluation, a comparator must always be stipulated even when a standard care treatment does not exist. Both the treatment and usual care arms will have costs and health consequences.

Whereas several alternative treatments may be available for many common children's diseases in developed countries, these products may not be available in LMICs. For some conditions, the proposed new treatment may be the first available. The opposite scenario may also be true – there may be no current relevant treatments in developed countries for conditions that are not endemic to those areas but are common in LMICs. As a result, the standard of care comparator used in an analysis for LMICs will often need to differ from those for other countries.

Economic evaluations must stipulate a time horizon for the study – the length of time over which costs and health consequences are measured. The time horizon typically reflects the nature of the disease being treated, that is, acute or chronic. For preventive interventions that are common in LMICs such as vaccine programs, the time horizon may need to be very long if the vaccine is intended to prevent an adult-onset illness or disability in adult years [17]. The time horizon must also be long

enough to capture clinically significant drug-related adverse events that may be latent or that may occur only after years of treatment. For many interventions, costs are incurred upfront or accrue in a fairly even stream over time. In contrast, health improvements may be delayed well after the start of therapy. Analysts distinguish between costs and outcomes that occur today versus those that are deferred into the future by applying a discount rate to future costs and outcomes when they are measured over a year or more. The same constant rate should be applied to both costs and health consequences and this rate is typically 3–5%, reflecting society's rate of positive time preference [8, 10].

When the time horizon is very long, as is common in vaccination programs in LMICs, discounting can cause deferred health benefits to be reduced substantially compared to costs, which may mostly be incurred upfront. Thus, programs that prolong survival or prevent disability in future decades of life will not appear as favorable as investing in programs with more proximate health benefits. This can greatly disadvantage investment in programs aimed at improving child health and survival in LMICs over the long term. A number of analysts have proposed applying alternative discount rates or equations to address this effect, although this complicates the comparison of costs and benefits to studies that use conventional methods [18].

The precise cost items that are included in an economic evaluation depend on the payer perspective selected for the analysis. The choice of perspective is based on the research question and the target audience – who is asking the question and who will use the value for money information generated by the economic evaluation [10]. As information about cost-effectiveness is used by health program decision-makers to determine whether to pay for a new treatment, a health care system perspective is a common approach. Many analysts use a societal perspective that includes all costs regardless of payer. Only a societal perspective adds the costs associated with time lost by parents and informal caregivers – costs which can be substantial for pediatric health interventions.

The involvement of external agencies in subsidizing or supporting pediatric health interventions in LMICs complicates the ability of analysts to designate the target decision-maker, set the payer perspective, and establish an appropriate set of prices for an economic evaluation. Donor subsidization of health care programs also introduces new costs, such as transaction and implementation costs, that may not be accounted for in the analysis [6]. The involvement of time-limited external resources also poses challenges to designating the scope of health care resources that should be costed in an economic evaluation of a treatment for children in LMICs. The results of economic evaluations that include foreign resources may be difficult for local decision-makers to interpret and to use for long-term planning.

In economic evaluation, a number of analytic techniques can be employed. Cost-effectiveness analysis (CEA) measures health improvements in natural units, such as cases of disease averted or number of life years gained. When the effectiveness of the new treatment is demonstrated to be equal to usual care, then a cost-minimization analysis (CMA), which focuses on incremental costs alone, may be used. A cost–benefit analysis (CBA) monetizes the health improvements so that any

additional costs attributable to the new treatment would simply be subtracted from the monetary value of incremental benefits in a net health benefit equation.

The preferred approach is to use a common measure of health benefit so the value of disparate interventions can be compared across therapeutic areas and patient populations. The quality-adjusted life year (QALY) is a composite measure that considers not only the life years achieved for any given intervention, but also the health-related quality of life that the patient experiences during those life years. The preference for the higher quality of life state, or *utility* for the health state, is used as a *weight* to adjust the observed life expectancy in a cost–utility analysis (CUA). Knowing there is an improvement in QALYs, not just the number of life years, is an important consideration when making an allocation decision [10].

Measuring preferences for health states is a complex task requiring the use of valid techniques and instruments. The cognitive complexity of these tasks and the lack of validity of many tools for use in children and in parent proxies are obstacles to conducting CUA in children [19]. Children in LMICs often present with comorbid conditions and threats to health and survival which cannot be adequately captured with present preference assessment tools.

Recognizing the need for a valid measure of population-level burden of disease in LMICs, the World Health Organization (WHO), along with the World Bank and Harvard School of Public Health, created the disability-adjusted life year (DALY) for the Global Burden of Disease and Injury study [20]. Like the QALY, the DALY is a composite measure of health effects (years of life lost) and morbidity (years of life lived with disability). It can be applied at the person or population level and as a universal metric, allows comparison of disease burden and incremental cost-effectiveness of treatment interventions across disparate patient groups and populations [21]. While the use of QALYs seeks to maximize QALY gains, DALYs measure losses in healthy life, so the desired goal of a new treatment is to avert or minimize DALYs.

In addition to creating the DALY, WHO health economists sought ways to overcome the methodological challenges described above in order to facilitate allocation decisions in struggling economies that will maximize health benefits to a low-income population. The WHO-CHOICE (CHOosing Interventions that are Cost-Effective) approach to sectoral health economic evaluation, termed "generalized cost-effectiveness analysis," (GCEA) is intended to provide a broader application than conventional CEA [22]. GCEA allows decision-making and priority setting at the population, rather than the patient level. It includes the establishment of standardized global methods, region-specific cost databases, and models that can be adapted to specific countries, thereby enabling evidence generation for LMICs with limited resources and technical capabilities [22–24]. Whereas in conventional CEA analysts consider standard care to be the valid comparator, in GCEA every feasible intervention that might be introduced in a country or region is considered and inefficient interventions can be discarded. The GCEA approach allows for simultaneous analysis of multiple single or bundled interventions across the health sector, thus creating a process for prioritization and achieving allocative efficiency on the basis of cost-effectiveness.

The WHO provides regular reports of their GCEA studies [25] and identifies cost-effective interventions that are consistent with strategies to reach the MDGs. These include artemisinin-based combination treatments to address malaria; zinc and vitamin A fortification and measles immunization to address global child health; treatment for HIV/AIDS and a wide range of interventions in various combinations to improve maternal and neonatal health in sub-Saharan Africa and Southeast Asia [26–30].

Present Status of Global Pediatric Health Economic Evaluation

The Pediatric Economic Database Evaluation (PEDE) Project annually compiles data on the volume, type, and study design characteristics of pediatric health economic evaluations conducted globally [31, 32]. In addition to numerous citation databases, a large number of health technology, research, and government agency web site reports are scanned to ensure that the database is comprehensive. The PEDE project assigns a category to all interventions including dental care, detection and screening, diagnosis, educational, health care delivery, health program, health treatment, prevention, and surgical. The findings for the prevention category, defined as "intervention for medical primary, secondary, or tertiary prevention," and the health treatment category, defined as "intervention administered directly to patient for cure or amelioration of a medical condition," are described in this section.

Data for originating or target country, the type of intervention studied, the disease, and the analytic technique were compiled for 2012. These data were compared to results obtained for a previous quality appraisal conducted for 1998–2003 [5].

Economic Evaluations of Prevention Interventions

Table 19.1 displays the global distribution of prevention studies, with the first five rows encompassing mainly LMICs with struggling public health care systems. Of the 49 economic evaluations of this category of intervention published in 2012, 17 (35 %) were performed by or targeted LMICs. This is an increase over the 20 % observed for 1998–2003. There appeared to be less targeting of African countries with a higher proportion of evaluations set in or performed for the Far East and Central and South America.

The LMICs with economic evaluations in 2012 included Bangladesh, Brazil, Thailand, China, Taiwan, Peru, sub-Saharan Africa, Turkey, Uganda, and Vietnam.

Seven of the 17 studies in LMICs were evaluations of vaccination programs for Human Papilloma Virus (HPV), whereas there was not a single economic evaluation of HPV prevention in 1998–2003. Other 2012 studies in LMICs examined vaccination strategies for pneumococcal infectious disease, rotavirus, hepatitis A,

Table 19.1 Global distribution of economic evaluations of prevention interventions by period

	1998–2003		2012	
Region	*n*	%	*n*	%
Africa	20	11.7	2	4.1
Far East	5	2.9	6	12.2
South & Southeast Asia	6	3.5	4	8.2
Central & South America & Mexico	3	1.8	4	8.2
Middle East & Turkey	1	0.6	1	2.0
United States	57	33.3	6	12.2
Western & Central Europe[a]	27	15.8	7	14.3
United Kingdom	12	7.0	4	8.2
Canada	11	6.4	6	12.2
Australia & New Zealand	11	6.4	2	4.1
Eastern Europe	4	2.3	1	2.0
Scandinavia	4	2.3	2	4.1
Netherlands & Belgium	4	2.3	3	6.1
Japan	3	1.8	1	2.0
Other	3	1.8	0	0.0
Total	171		49	

[a]Excluding United Kingdom

Table 19.2 Distribution of analytic techniques for prevention studies by region and period

	CBA		CEA		CUA		Total no. of prevention studies
Region	*n*	Row %	*n*	Row %	*n*	Row %	
1998–2003							
LMIC	2	5.7	24	68.6	9	25.7	35
Developed	28	20.6	98	72.1	9	6.6	136[a]
2012							
LMIC	0	0.0	6	35.3	11	64.7	17
Developed	1	3.1	9	28.1	22	68.8	32

[a]One CMA was included in this total
CBA cost–benefit analysis, *CEA* cost-effectiveness analysis, *CUA* cost–utility analysis

tuberculosis and encephalitis, and prevention of methicillin-resistant Staphylococcus aureus (MRSA) and HIV. Absent were programs for hepatitis B and malaria, which were more frequent in 1998–2003.

There were significant changes in the distributions of analytic techniques observed over time for LMIC and developed countries (Table 19.2).

In 1998–2003, the most commonly used analytic technique for economic evaluation of prevention interventions in child health was CEA. LMICs witnessed a higher proportion of CUAs compared to other regions. This was in large part is due to the application of generalized CEA and the use of the DALY measure [22]. The overall volume of global pediatric CUAs has increased in recent years [33] and in

2012, this was the most common analytic technique, accounting for approximately two-thirds of all pediatric health economic evaluations for both LMICs and developed countries [32]. Thus, LMICs are not disadvantaged by the selection of analytic technique for economic evaluations of prevention interventions.

Economic Evaluations of Treatment Interventions

Table 19.3 displays the global distribution of economic evaluations of pediatric treatments for a medical condition for LMICs and developed countries. There were fewer economic evaluations of medical treatments compared to preventative interventions for both study periods. Of the 25 economic evaluations published in 2012, 4 (16 %) were performed by or targeted LMICs. This is similar to the 14 % observed for 1998–2003. In 2012, there were proportionally fewer studies in South and Southeast Asia and more in Central and South America compared to 1998–2003.

The four 2012 economic evaluations in LMICs were studies of antimalarial treatments (Ghana), antiepileptic drugs (Iran), hydroxyurea therapy (Jamaica), and bovine surfactant therapy (Mexico). Previous years included more studies of antimicrobial and antiretroviral agents.

There were significant changes in the distributions of analytic techniques observed over time for LMICs and developed countries (Table 19.4).

As seen with the prevention studies, the majority of economic evaluations of treatments in earlier years were CEAs. CBAs and CMAs were also reported in

Table 19.3 Global distribution of economic evaluations of treatment interventions by period

	1998–2003		2012	
Region	*n*	%	*n*	%
Africa	4	2.7	1	4.0
Far East	2	1.4	0	0.0
South & Southeast Asia	9	6.2	0	0.0
Central & South America & Mexico	4	2.7	2	8.0
Middle East & Turkey	2	1.4	1	4.0
United States	61	41.8	5	20.0
Western & Central Europe[a]	16	11.0	4	16.0
United Kingdom	27	18.5	1	4.0
Canada	6	4.1	2	8.0
Australia & New Zealand	6	4.1	4	16.0
Scandinavia	4	2.7	1	4.0
Netherlands & Belgium	2	1.4	4	16.0
Israel	2	1.4	0	0.0
Other	1	0.7	0	0.0
Total	146		25	

[a]Excluding United Kingdom

Table 19.4 Distribution of analytic techniques of treatment interventions by region and period

Region	CBA		CEA		CMA		CUA		Total no. of treatment studies
	n	Row %	*n*	Row %	*n*	Row %	*n*	Row %	
1998–2003									
LMIC	0	0.0	19	90.5	1	4.8	1	4.8	21
Developed	6	4.8	90	72.0	13	10.4	16	12.8	125
2012									
LMIC	0	0.0	2	50.0	0	0.0	2	50.0	4
Developed	0	0.0	7	33.3	0	0.0	14	66.7	21

CBA cost–benefit analysis, *CEA* cost-effectiveness analysis, *CUA* cost–utility analysis, *CMA* cost-minimization analysis

1998–2003. In 2012, CUAs constituted half of all economic evaluations for treatments in LMICs and 67 % of those in developed countries.

Discussion

Health economic evaluation involves the use of rigorous methods to produce evidence to facilitate decisions regarding investment in health care resources. The objective of health economic evaluation is to inform health care decision-making so that the greatest health benefits can be achieved for any given investment. The ultimate goals of economic evaluation are to increase efficiency in the selection of treatments to enhance the health status of target populations and achieve a net welfare gain in society.

Previous studies have demonstrated the growing disconnect between health care priorities and needs in developed countries and LMICs [5, 6]. Industrialized nations are increasingly focused on meeting the health needs of an aging population with chronic disease, whereas many developing nations continue to struggle with high child mortality rates. The ability of domestic health care systems to meet the needs of children in LMICs is challenged by these differences. These countries rely on an evidence base largely generated in industrialized nations to make crucial allocation decisions. However, because of the wide gaps in health priorities and illness patterns, the evidence they require is often absent.

Another important concern is that for LMICs, mere evidence of cost-effectiveness of an intervention is not enough. These nations also require an indicator of affordability, that is, the ability of the target payors, such as government or health agencies, to cover the costs of the program. Also needed are plans for program sustainability within a fragile health care system.

LMICs have become increasingly dependent on external sources of support, such as the UK Department of International Development or the Global Fund to Fight AIDS, Tuberculosis, and Malaria [34]. While external donor agencies provide much needed assistance over the short term, they create uncertainty regarding

long-term sustainability and greatly complicate the ability of analysts to generate meaningful health economic evaluations.

Initiatives of the WHO such as GCEA have gone a long way to address many of these issues. Attainment of MDGs also continues to be an international priority to help narrow the gaps in health needs and priorities between low-income countries, emerging economies, and developed nations. Greater collaboration between health researchers from LMICs and industrialized nations can also help to improve the quality of the evidence base used to generate economic evaluations. Agencies such as Health Technology Assessment international (HTAi) and the International Network of Agencies for Health Technology Assessment (INAHTA) are actively fostering initiatives to improve collaboration and the capacity for developing countries to produce high quality economic evaluations to inform decision-making.

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

Shalini Sri Ranganathan and Madlen Gazarian

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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Chapter 21
Perspective on the Role of the Pharmaceutical Industry

Klaus Rose

The challenge of better drug treatment of children in low- and middle-income countries (LMIC) is not just lack of money for the right drug or the fact that diagnosis, prescription, and finally transport of the selected drugs to the respective patient is often hampered. The challenge is more complex. Some lessons learned from the developed world can be used in LMIC as well, such as dosing in children and the development of appropriate pediatric formulations. But society has many dimensions. The fabric of society consists of knowledge learned through education, personal experience, understanding and acceptance of social rules, sufficient law enforcement, existence of social institutions, competitiveness of professional development, freedom to create new institutions, just to name a few. Some countries are historically poor; others were rich in the past. Evolution of modern medicine, modern drugs, and the awareness of the need for better drugs for children did not happen spontaneously in countries that are rich today. There was and is a constant struggle of modern ideas against ideas, rules, and institutions that try to stick to the past or even draw the wheel back. And who defines what is modern or outdated? The challenge faced is not just about transfer of knowledge, experience, and wealth from countries that are rich to countries that are poor. To understand the challenges and to see where the pharmaceutical industry could do more requires an effort to examine struggles below the surface.

There is no country on earth that is not affected by industrialization. Some countries produce a variety of manufactured goods; others offer raw materials. There is mechanical, agricultural, and service industry. Extraction and transport of goods require industrial activity as well. Only a few isolated peoples still live without direct contact with modern civilization. The scientific revolution goes back to the renaissance, when dogmas preached by the church gave place step by step to open

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discussion and scientific experimentation. Eventually this triggered the industrial revolution, which would not have been possible without a framework of freedom of thought and expression.

Industry and Drug Development

The chemical industry started with the production of soda, artificial fertilizer, synthetic dyes, and perfumes. In the beginning of the twentieth century, academic scientists discovered the first potent medicines, which were then produced on an industrial scale. During the twentieth century, development of new drugs became more complex; research and development of new medicines was increasingly taken over by a part of the chemical industry, which transformed itself into the pharmaceutical industry [1].

The obligation to prove safety and efficacy of new medicines by adequate clinical trials dates to the US Kefauver–Harris amendments of 1962. This legislation heralded the birth of modern drug labels as well as of clinical trials performed with the aim of registering the drug with the regulatory authorities. It was also the starting point of pediatric disclaimers that emphasized the fact that drugs had not been investigated in children and led to the famous description of children as "therapeutic orphans" [2–4]. The obligation to prove safety and efficacy by adequate clinical trials was bitterly opposed by the then chemical industry, but also by the American Medical Association. The old standard had allowed "experienced" doctors to declare what was safe and what worked. The new legislation put experts in second place and instead relied on data. Most drugs on the market before this legislation were of dubious value and eventually disappeared [1].

Since 1962, the availability of powerful drugs has multiplied. Development of modern drugs has dramatically changed the landscape of pediatric and adult medicine worldwide. Major killers such as tuberculosis and infectious diseases have almost disappeared from the statistics of developed countries, to be replaced by chronic diseases and cancer in adults and by rare diseases in children. As always in history, these changes had to face bitter opposition from those who preferred to stick with outdated concepts.

In LMIC, the situation for most adults and children is different from that in developed countries. Particularly in LICs, most lack essential ingredients of modern life, including good housing, clean water, and modern communication. Furthermore, most people do not live in a social context where they have options for life and career, freedom to decide and to travel, freedom to choose life partners of whatever gender, freedom of recreational activities as much or as little as they may want. For most people in LMIC setting, child care is embedded in a framework that offers little choice for adults. The potential freedom of personal development for children is as much limited as that of their parents. This is not just a question of available money. Even where good education is available and affordable, parents often remain skeptical because of corrupt structures that disallow career building based on individual efforts and merit.

Industrial-Political Environment in Which Drug Development Occurs

The fundamental difference between industry and government structures is that industry, in general, is mostly private and market-driven. Goods or services must be delivered. Companies that do not deliver or do not meet the customer's taste or requirements will not prosper. Either the top management is replaced and the new one turns the situation around, or the company will be sold, merged, or descend into bankruptcy. The drug market is highly regulated in developed countries, but nevertheless pharmaceutical companies are market-driven. The motivating spirit in pharmaceutical companies is comparable to that in other industries: employees must deliver, and targets must be met. Individual employees are goal-oriented, with the resulting danger that they are likely to develop a department-specific tunnel view.

States and their bureaucracy have a different framework. Even if they do not perform well, they are rarely put out of business. The least successful scenario is industry owned by the state. The service is usually inferior, and the employee's attitudes reflect the fact that they may often receive their salary with or without productive work. Losses will be made up by tax money, representing a poor bargain for the general public.

Industry can only work in a framework that allows business. The pharmaceutical industry has developed in Western countries, with the USA as the pilot in the twentieth century, in part due to its political and innovation-friendly structure, and in part because it is the largest single market worldwide. The pharmaceutical industry today is a global business, with clinical trials being performed worldwide. Nevertheless, sales and research activities must fit within a local framework. On an international level, the research-based pharmaceutical industry is represented by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), situated in Geneva, Switzerland. It represents the official voice of the innovative pharmaceutical industry and has formal consulting status with the United Nations (UN) and its specialist bodies, including the World Health Organization (WHO), the World Bank, and the World Trade Organization (WTO) [5].

Within each country, pharmaceutical companies must abide by local law. They are not required to directly follow the rhetoric of their respective governments, but they must be careful not to attract the wrath of regulatory authorities. On the international level of the UN or the WHO, official representation from the pharmaceutical industry is a continuous balancing act. The WHO is an agency of the UN concerned with international public health. The UN is not a world government. They represent the consensus on healthcare standards that can be found among countries with different governments and different ways of life. The WHO's supreme decision-making body, the World Health Assembly, is composed of the member states' health ministers and meets once per year in Geneva.

There are several types of pharmaceutical industry. The most controversial one is the research-based innovative pharmaceutical industry. Its products have changed the role of conditions such as hypertension, dyslipidemia, infectious diseases,

tuberculosis, HIV, and AIDS [6–8] and resulting profits have traditionally been high. Many practices such as seeking an extension of patent protection through minor new formulations or minor changes in a drug's molecular structure may be strictly legal, but are usually not perceived as legitimate by the scientific and clinical community [9]. This industry is now facing major challenges. Most large companies have dismissed thousands of employees during recent years because their huge R&D machinery was not balanced by adequate output of new products. One consequence is that the focus of research has started to shift away from mass diseases like hypertension or dyslipidemia toward rare diseases, where drugs like tasigna or ivacaftor are potentially life saving and the company can seek a high price once marketing approval is obtained. After the research-based industry has exploited its patented drug for a number of years, a generic industry counterpart will provide the same drug at a lower price. A high-quality generic industry has consequently evolved in both developed and developing countries.

There is also a local pharmaceutical industry that competes with international companies for production of high-standard medicines. How will a minister of health in an LMIC deal with a local producer of an antibiotic if efficacy or stability is far below Western standards? If at all possible, he or she will attempt to have the issues fixed. However, there are several prerequisites: the responsible state control needs equipment and motivation to look into the issue. The local press must be allowed to report about it. Confronted in this situation, the local producer may calculate what is cheaper: to improve the product's quality or to try to circumvent requirements. Furthermore, he or she will emphasize that they offer jobs and pay taxes locally. All these things happened in the past in Western countries, and sometimes still do. Competition between global companies and the local industry is not only based on the quality and price of drugs, but is also subject to the vagaries of local and international politics.

Challenges Particular to Pediatric Drugs

A movement to let children benefit more directly from progress in modern drug treatment started with Shirkey's famous description of therapeutic orphans in 1968 [4]. It was a rather silent movement for decades, limited to specialists in pharmaceutical health care of children, pediatric clinical pharmacologists and other clinicians and officers of regulatory authorities. It culminated for the first time in US pediatric legislation in 1997: FDAMA (FDA Modernization Act) [10, 11] (see also Chap. 10).

Pediatric clinical trials have a long history but both volume of studies and impact have been inconsistent. They were mostly organized by academic clinicians and in some areas, such as pediatric oncology, they revolutionized treatment of children [11–13]. Drugs were developed for pediatric diseases if they represented a sufficient market, for example, growth hormone deficiency, lung surfactant, antibiotics, and vaccines. But these were small successes in comparison to the broad market for drugs in adults. The US legislation of 1997 encouraged additional pediatric

investigations for those drugs that had been primarily developed for adults and where it had become obvious that use in children should be guided by additional data. It brought the machinery of drug discovery and clinical trials of research-based pharmaceutical industry in closer contact with pediatric clinical trials and amplified the idea of drug development for children [3, 10, 14].

Children's health in HIC versus LMIC has some challenges in common but there are many points of difference. There are few children in developed countries that suffer from TB, malaria, or dengue fever. There are millions in LMIC. Essentially, children that suffer from these diseases are in the same situation as their parents: they need access to health care. However, the children not only need drugs, they need them in the right doses and right formulation. If they get fixed dose combinations, the composition of the different drugs needs to be age-adapted. Absorption, distribution, metabolism, and excretion (ADME) evolve with age, and the same composition of three drugs in a fixed dose combination suitable for adolescents and adults cannot just be size-adapted to smaller children. Relative to ADME of each individual component, the composition of a pediatric dose combination must be age-adapted. In this regard, the interests of children in developed countries and LMIC have a broad overlap. Medical doctors, pharmacists, employees of regulatory authorities and employees of the WHO and other international institutions have, in recent years, done everything possible to expand understanding of the basics of pediatric clinical pharmacology.

In the wake of US pediatric legislation, in 2007, WHO started a campaign to "Make Medicines Child Size" [15, 16]. Comparable to the EU pediatric legislation, this initiative was started with good intentions. However, the title chosen for this campaign was not optimal. The size of a medication is not the central issue in discussing pharmaceutical treatment of children. The key issue is correct choice of therapy and dosing, taking into consideration interaction between different drugs given at the same time, and being aware of the development of ADME during individual development. A sachet that contains a combination of two or three water-soluble antituberculosis drugs should not be given to all age groups just in different quantity, for example, one per day for babies, three for children, and six for adolescents and adults. The composition of the sachets needs more sophisticated age-adaption.

The WHO's fact sheet no. 341 "Medicines: medicines for children" (2010) states in a key bullet point: "Worldwide many medicines for children are used 'off-label', that is, their effects on children have not been studied and they are not licensed for use in children" [15]. The success story of modern pediatric oncology evolved because pediatric oncologists systematically tested cytotoxic drugs off-label over decades in systematic international clinical trials. This changed the diagnosis of cancer in children from a certain death sentence to a disease where it is reasonable to hope – over 80% of children with acute lymphocytic leukemia (ALL) survive today, and the survival rate of most other types of cancer in children has considerably increased. Most cytotoxic agents were not licensed for use in children then and are not fully licensed today. But they have been well studied and proven effective. That a drug is used off-label in children does not mean that it has not been

investigated properly. It is encouraging to see that the WHO's newest edition of the essential medicines list for children (EMLc) contains cytotoxic agents for the treatment of ALL [17].

Philanthropic and Other Activities

The best official overview of today's philanthropic activities undertaken by the research-based industry is on the website of the IFPMA [5]. Additional information can be found on each pharmaceutical company's website. According to the IFPMA website, IFPMA member companies currently work on 162 R&D projects targeting neglected diseases, with a focus on developing new or improved medicines and vaccines for 11 neglected conditions, specifically tuberculosis, malaria, human African trypanosomiasis (sleeping sickness), leishmaniasis, dengue, onchocerciasis (river blindness), American trypanosomiasis (Chagas disease), schistosomiasis, lymphatic filariasis, buruli ulcer, and soil-transmitted helminthic diseases. Furthermore, IFPMA members have pledged to donate an average of 14 billion treatments this decade (2011–2020) to fight neglected diseases.

However, not all philanthropic donations and programs of research-based pharmaceutical industry are as exemplary as might appear on industry's brochures and websites [9].

Industry is, for the most part, not government-controlled. The market place has controlled aspects, but it remains a jungle – beautiful and cruel. We love the beauty of the tiger, but we look the other way when it kills and maims. In today's world, economic competition has reached all countries. There is often not enough fairness in the resulting competition, but there is progress. The more countries allow freedom of trade and learn to compete on the world market, the more jobs will be created. Academics in developed countries have a role in supporting their colleagues in LMICs. But their influence is limited. To some degree, the pharmaceutical industry has responded to criticism of overpriced medicines and now offers many modern treatments at a reduced price for those that cannot afford them, both in rich and poor countries. The essence of modern society is the striking of a balance among contradictory factors: competition between companies, freedom of the market, competition between different religions and ideas, and freedom of thought, expression, and communication.

The Way Forward

There are many resources available within the research-based pharmaceutical industry that could be better used in the interests of children in rich and poor countries. However, these resources are often not easily accessible. The pharmaceutical industry's channels of communication with the outside world have priorities that

differ from those of not-for-profit, academic, or philanthropic institutions. Nevertheless, sometimes they respond to good proposals. To reach the right people with the right proposals requires networking, communication, concise project presentation, diplomacy, and more.

The research-based pharmaceutical industry offers opportunities to learn on many different levels in science, marketing, or communication. These lessons can be shared. Many who work, or used to work, in industry teach at universities or outside of academia in commercial or noncommercial settings. The experience that can be shared is potentially valuable for many people living in LMIC, specifically today where modern technology has made distance learning increasingly feasible.

Optimal medical treatment of children and good child education require a fabric of society that allows and encourages this. Societal characteristics determine how much knowledge, experience, and resources can be absorbed in a productive way and not into the pockets of a few. Some elements of this fabric can be imported, but LMIC must build their own institutions and determine their own values. Good intentions from rich country institutions are not a guarantee for good outcomes. The determinants of success are complex. We will need a willingness to help, awareness of our limitations, patience, preparedness to fight for our ideas, and a degree of humility.

Editors' note: In an effort to highlight priority areas for potential pharmaceutical industry engagement in the pursuit of better treatments for children in developing countries, the editors have assembled the suggestions presented in Box 21.1. These do not necessarily reflect the opinions of the pharmaceutical industry.

Box 21.1: Better Medicines for Children in Developing Countries. Priority Areas for Pharmaceutical Company Interactions with Nongovernmental Organizations, Academic Institutions, and Philanthropies

1. Participation in collaborative efforts as described in Chap. 14
   (a) Formalization of guidelines for protocol development, outcome measurement, and publication (e.g., SPIRIT-C and CONSORT-C)
   (b) Support for development of child health research standards, including methodologic innovation
   (c) Contribution to consensus development on research code of conduct and ethical standards
   (d) Collaborative effort to ensure compliance with ethical standards
2. Contribution to development of robust, cost-effective diagnostic methods, including rapid point-of-care diagnostics
3. Full participation in international trial registries and in data sharing/data transparency initiatives
4. Appropriate investment in pharmaceutical sciences necessary for the development of new age-stratified forms and formulations

5. Support for innovative programs in skills development and training of highly qualified personnel for child-relevant drug discovery, clinical trial design and execution, evaluative and implementation sciences
6. Fostering of network approaches that will enhance research efforts to find new treatments for rare and neglected diseases
7. Research partnerships in selected priority areas/conditions, such as:
   (a) Vaccine development
   (b) Neonatal sepsis
   (c) Emergent viral infections
   (d) Infant HIV treatment
   (e) Anti-TB treatment
   (f) Antimalarials
   (g) Pediatric oncology
   (h) Nonaddictive analgesics
   (i) Palliative care therapies
   (j) Micronutrients and vitamins

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Part IV
Clinical Settings

Chapter 22
Optimizing Malaria Treatment in the Community

Michael Hawkes and Lena Serghides

Abbreviations

ACT	Artemisinin combination therapy
CCM	Community case management for malaria
CHWs	Community health workers
HRP-2	Histidine-rich protein-2
iCCM	Integrated community case management
IMCI	Integrated management of childhood illnesses
pLDH	Parasite lactate dehydrogenase
RDTs	Rapid diagnostic tests

Over 200 million cases of malaria per year are reported to the World Health Organization (WHO), including 627,000 deaths [1]. Yet, malaria is an entirely curable infection with currently available medications if treated promptly. It is estimated that 86% of malaria deaths are among children in sub-Saharan Africa [2]. Most malaria infections occur in resource-limited rural settings with poor access to medical care. Therefore, one of the primary challenges in optimizing antimalarial drug treatment is delivery of care to underserved communities. Countries with the highest malaria burden have the fewest doctors (Fig. 22.1), such that alternative strategies to physician-guided, laboratory-assisted, diagnosis and treatment of malaria will be required in order to reach the large number of cases of uncomplicated malaria that arise in rural communities.

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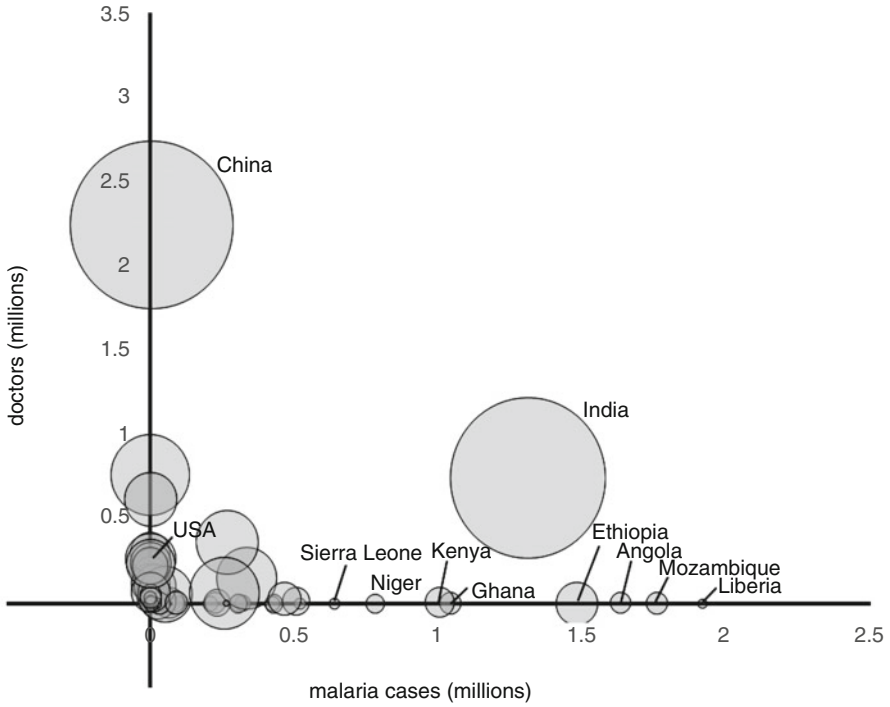

Fig. 22.1 Total number of doctors compared to the absolute number of malaria cases in 150 selected countries. Area of circles is proportional to population size of the country. Of note, countries in sub-Saharan Africa have the fewest doctors and largest number of malaria cases, creating a human resource crisis for malaria diagnosis and treatment. Solutions beyond physician-directed individualized care are needed to meet the demand for malaria case management (Data from World Health Organization, Global Atlas of the Health Workforce (http://data.worldbank.org/indicator/SH.MED.PHYS.ZS) and World Health Organization, Malaria Statistics (http://www.who.int/gho/malaria/epidemic/cases/en/))

This chapter focuses on community case management of malaria (CCMm) for children under 5 in sub-Saharan Africa, since this is the population with the greatest burden of illness [3]. We begin by considering the most relevant healthcare delivery systems for malaria treatment: public, informal private, and community health workers (CHWs). We next discuss the use of point-of-care rapid diagnostic tests (RDTs) for malaria, which have revolutionized the diagnosis of malaria globally, providing an inexpensive and accurate parasitologic diagnosis even in settings without laboratory services. We then consider the numerous challenges in implementing and sustaining a CCMm program using CHWs and RDTs. Finally, the use of malaria RDTs has paradoxically highlighted the importance of nonmalarial febrile illness, and we discuss integrated community case management (iCCM) of childhood febrile illness as a recent advance in public health practice.

Malaria is caused by parasites of the genus Plasmodium. *P. falciparum* is the most common and the most lethal species in Africa. The parasite is transmitted by

the bite of the female Anopheles mosquito. The disease is characterized by fever, myalgias, and headache in its uncomplicated form, but may progress to convulsions, altered consciousness, coma, respiratory distress, severe anemia, and even death. Clinical diagnosis is challenging because of the nonspecific nature of the signs and symptoms, which overlap with benign viral infections but also life-threatening bacterial infections like pneumonia, sepsis, and meningitis [4, 5]. Current WHO treatment guidelines recommend artemisinin combination therapy (ACT) for uncomplicated malaria and parenteral artesunate for severe malaria [6, 7].

Barriers to access to medical care in Africa include availability (physical access), affordability (financial access), and acceptability (cultural access) [8].Together these factors interfere with mothers and children across Africa reaching basic medical help for fever management. A community-based survey in Malawi showed that only half of childhood febrile episodes were presented to a clinic for treatment, and only 7% of febrile children received optimal therapy [9]. In Sierra Leone, only 41% of suspected malaria episodes were diagnosed by a health professional [10]. In a survey from western Kenya, presumptive self-treatment of malaria was common: 60% used herbal remedies or medicines purchased at local shops, 18% received treatment at a health center or hospital, and the remainder sought no treatment whatsoever [11].

How Should Malaria Drug Treatment Be Delivered?

At least three models of delivery of malaria care are currently used in African settings: (1) government-sponsored public health care; (2) the informal private sector; and (3) community health workers [12].

The public sector generally provides affordable or free treatment that can be accessed by poor mothers and children, but it often does not reach remote or sparsely populated regions. Large segments of the population at risk of malaria live far from a health center or hospital, and cannot access diagnostic and treatment services in a timely manner. Severe constraints on human resources for health limit the number of facilities that can be staffed in rural communities. Furthermore, stockouts and poor worker morale within government facilities can undermine quality and can color perceptions of the public system [13].

Most early treatments for fever in Africa take place outside the public health system, through self-medication with antimalarials bought over-the-counter from untrained drug vendors. This informal private sector supplies an estimated two-thirds of all malaria medicines in the African context [14]. Vendors will frequently diagnose and recommend treatment for clients. These commercial outlets are at once shop and clinic, legitimate and illegitimate, trusted and distrusted, in the eyes of different players [14]. Malaria care delivered in this manner is not standardized, is difficult to monitor, and may represent a public health risk. A description of antimalarial prescribing practices by private drug shops in Uganda showed that only 39% of clients with malaria received the recommended first-line therapy (i.e., ACT), 33% received quinine, and the remaining patients received non-artemisinin monotherapy, currently

judged likely to be ineffective, based on resistance rates in Uganda. Many patients with nonmalarial febrile illness were treated with antimalarials, and overall only 34% of patients received appropriate therapy [15]. Nonetheless, the private sector offers some advantages over the public system, including responsiveness to client demands and greater penetration into remote villages. The potential role of drug vendors in improving access to early and effective malaria treatment has been explored in several studies. In one Nigerian report, rural drug vendors were trained on appropriate community management of malaria, resulting in improved drug dispensing, advice given, and referral practices [16]. A cluster-randomized trial from Kenya used drug vendors as community distributors of subsidized ACT, and documented an absolute increase of 25% of children receiving ACT within 24 h of fever [17].

Community health workers (CHWs) are increasingly used to deliver antimalarial drugs in remote settings. CHWs are defined as members of the community with minimal or no formal education in nursing or medicine, who undergo a brief training program to dispense medications within their communities. CHWs reside within high-burden communities and are therefore more accessible than caregivers in government health facilities. For example, a report on a CHW-based malaria management program in rural Uganda found that 86% of households were located less than 1 km away from a CHW's home, whereas only 26% were within 1 km of a health facility [18]. CHWs can be mobilized to deliver malaria treatment under a simple fever-management algorithm. A Cochrane systematic review found moderate quality evidence that home- or community-based programs for treating malaria probably improve prompt access to antimalarials and may positively impact on child mortality [9]. Two trials demonstrated that CCMm increased the number of people with fever who receive an appropriate antimalarial within 24 h [18, 19]. In urban Uganda, a randomized trial of home delivery of prepackaged ACT for presumptive treatment of febrile illnesses resulted in double the number of malaria treatments given for fever episodes and reduced parasitemia at the study conclusion (2% vs. 10%), but did not show a mortality benefit, nor an impact on anemia [20]. A mortality benefit attributable to CCMm was demonstrated in a cluster-randomized controlled trial conducted in Ethiopia in 1997. The study examined the impact of a program to teach mothers to promptly treat fever (without parasitologic diagnosis) using chloroquine provided by CHWs. The study found a 40% reduction in all-cause child mortality related to the intervention, and a reduction in the proportion of deaths attributable to malaria (based on verbal autopsy) [21]. Although CCMm appears to be effective, it is noteworthy that even in communities where a CCMm program is in place, one-third of medicines needed are still obtained from drug shops [18].

To Whom Should Malaria Drug Treatment Be Targeted?

Malaria signs and symptoms are nonspecific and overlap considerably with other common self-limited infections such as viral respiratory tract infections, as well as catastrophic life-threatening infections such as bacterial pneumonia, sepsis, and

meningitis [5, 6]. The challenge in optimizing antimalarial therapy is to identify and treat cases early in the course of infection, while restricting antimalarial prescriptions to those who truly need them. In the presence of uncertainty, hospital-based clinicians, private sector drug dispensaries, and CHWs alike tend to overtreat febrile illness with antimalarials, given that withholding therapy from a febrile child who may have malaria could lead to progression to severe disease and even death [20]. On the other hand, widespread overuse of antimalarials exposes patients to potential drug toxicity, increases cost, and may drive the emergence of drug-resistant parasites.

Fever is the cardinal manifestation of malaria. In malaria hyper- or holoendemic areas, the majority of fevers are attributable to malaria. The notion has developed therefore, that fever in a young child is synonymous with malaria. This concept has roots even within local language: for example, the word "musujja" is used interchangeably for malaria and fever in Luganda, a widely spoken Bantu language in malaria-endemic southern Uganda. While fever is often due to malaria, this association may nonetheless lead to a narrow understanding of fever and its protean etiologies.

The WHO Integrated Management of Childhood Illness (IMCI) provides a clinical algorithm for the diagnosis and management of common childhood illnesses by minimally trained healthcare providers without access to laboratory testing [21]. Critical evaluation of IMCI for the diagnosis of malaria compared to a trained pediatrician with access to diagnostic imaging and laboratory support, showed sensitivity of 100%, but a specificity of 0–9% in two studies from Kenya and Gambia [22, 23]. The striking lack of specificity illustrates the difficulty in distinguishing malaria from other causes of fever on clinical grounds alone. In another study, the IMCI algorithm resulted in overdiagnosis of malaria in 30% of cases [24].

Parasitologic diagnosis using rapid diagnostic tests (RDTs), now commercially available worldwide, can be used to distinguish malaria from nonmalarial febrile illness. RDTs offer an accurate and cost-effective solution to the diagnostic dilemma of the febrile child in sub-Saharan Africa, which can be used at the village level by minimally trained practitioners. The test relies on lateral flow immunochromatography to identify from a finger-prick blood test one or more malaria antigens including histidine-rich protein 2 (HRP-2), parasite lactate dehydrogenase (pLDH), and aldolase [25]. HRP-2 is a *P. falciparum*-specific antigen; therefore, assays limited to the detection of HRP-2 cannot be used to diagnose infections with other Plasmodium species. Furthermore, HRP-2-based RDTs are inappropriate for monitoring response to therapy, as HRP-2 may persist for up to 4 weeks in peripheral blood after cure. A systematic review of RDTs for diagnosing uncomplicated *P. falciparum* in endemic settings involving 74 unique studies reported that the sensitivity and specificity of HRP-2-based assays was 95–99.5 and 91–95%, respectively [26]. Mathematical modeling suggests that such a sensitive and specific tool for malaria diagnosis requiring minimal infrastructure has the potential to avert 100,000 malaria-related deaths and approximately 400 million unnecessary treatments [27].

Given that most cases of malaria occur far from government hospitals, in communities where CHWs are an attractive human resource, can RDTs augment the quality of malaria case management at the village level? Unsupervised use of

malaria RDTs by CHWs with no formal medical/nursing training raises several questions. How should CHWs be trained? Can they safely handle testing materials and methods that involve human blood? How well are these competencies maintained over time? What are the test performance characteristics of RDTs in the hands of CHWs compared to formally trained health workers? How well do CHWs adhere to test results in their prescribing practices? How should a child with fever and a negative test for malaria be managed? Do RDTs influence outcome (morbidity and mortality) compared to presumptive diagnosis? What is the cost-effectiveness of RDTs in the community setting? We address these questions in the following section, drawing on published reports from CCMm experience in Africa.

How Should CHWs Be Trained to Use RDTs?

The WHO has freely available online resources for training CHWs in the use of RDTs, including job aids, training manuals, and evaluation tools [28]. Following an appropriate course of training (lasting no more than half a day), more than 90% of CHWs can correctly execute an RDT [29, 30]. Competence is enhanced by face-to-face training sessions and the use of a pictorial job aid. One study compared the performance of CHWs using: (1) only the manufacturer's instructions; (2) a pictorial job aid; and (3) a 3-h training session plus pictorial job aid. The mean score on a standardized checklist according to training method was 57, 80, and 90% in groups 1, 2, and 3, respectively [29]. Particular steps in the RDT execution were identified as problematic in various studies: collecting blood the right way and in the correct amount; dispensing the appropriate amount of buffer drops in the right well; waiting the correct time before interpreting the test, and recording in writing the patient result [29, 31, 32]. Skills retention by CHWs over time was evaluated in a study of CHWs in Zambia. At 3, 6, and 12 months after initial training, 40, 62, and 80 % of CHWs correctly performed critical RDT steps, respectively. The improved execution of RDTs over time was ascribed to hands-on field experience with the tests in the course of the CHWs' work [31].

What Are the Test Performance Characteristics of RDTs in the Hands of CHWs Compared to Formally Trained Health Workers?

Although RDTs are sensitive and specific under controlled study conditions in the hands of experienced lab personnel [26], CHWs without formal training may be more prone to error in their execution and interpretation of RDTs. RDTs performed by CHWs under field conditions have a sensitivity ranging between 83 and 98%, compared to microscopy as reference standard [33–38] and 62% relative to the

highly sensitive polymerase chain reaction method [37]. The specificity of RDTs in the hands of CHWs in various reports is more variable, ranging from 39% [34] to 95% [36]. Overall, test sensitivity in the hands of CHWs is acceptable, and this is arguably the most important parameter in assessing test performance. The greater cost of misdiagnosis is missing true positive cases, since this would lead to inappropriate withholding of antimalarial therapy for children with infection. The problem of test specificity may relate to inherent limitations of the HRP2-based RDTs, since the HRP2 antigen persists for up to a month after effective cure. In settings where repeated malaria infections occur, patients may have persistent circulating antigen related to recently treated, rather than acute infection (false positive RDT). Other commercially available RDTs using different parasite antigens may assist in making this distinction [39].

Can CHWs Safely Handle Test Materials Involving Human Blood?

Protection of CHWs and their patients from blood-borne pathogens (such as hepatitis B, C, and HIV) is important because RDTs involve a finger-prick blood test. CHWs in rudimentary field settings may be less likely to adhere to standard infection control practices, posing a biohazard risk. Universal precautions require the use of disposable latex gloves, which may be scarce in resource-poor areas. In one study from Senegal, stock-out of gloves prevented CHWs from taking adequate precautions [32]. When gloves are available, compliance with glove use ranges from 96 to 100% [29, 31]. Of concern, a "near-miss" was reported in one study, where an observer had to intervene when a CHW was about to reuse a lancet on a new patient [31].

Cultural fears and stigma about the manipulation of blood may also impact community acceptance of RDTs. Qualitative data from Uganda indicate that some parents worry that blood collected could be tested for HIV, the procedure could infect children with HIV, and blood collected could be used for witchcraft [13].

What Do Community Members Think of CHWs and RDTs?

Acceptability of a CCMm program by end users of the service is critical to its successful implementation and sustainability. Community attitudes toward CHWs as healthcare providers and RDT-based diagnosis, the two central elements of a CCMm program, pose potential cultural barriers to care. Obstacles reported by community members for accessing a CHW include: nonavailability of the CHW, mistrust of CHW skills, lack of drugs, fear of HIV infection, and perception that a disease is too severe for a CHW to handle [13, 18, 40]. Apart from the fear of HIV infection related to the finger-prick blood test, these barriers are not related

to the use of RDTs, but to the ambiguous role of the CHW as a healthcare provider with rudimentary training and a limited range of treatment options [41]. Relative to presumptive treatment of fevers, RDT-based treatment accentuates the limitations of CHWs, since they may have little to offer children with fever and a negative RDT.

Qualitative data suggest that patients generally welcome RDTs as aiding clinical diagnosis; however, often expectations of the RDT are unrealistic, believing the tests could identify any cause of illness, beyond malaria [42]. Improved communication between health workers and patients could help to manage patient expectations and promote patient demand for test-driven diagnoses [42]. In rural Uganda, two sequential qualitative studies assessed the views of community members on CCMm before and after introducing RDTs into the program. The first assessed perceptions in a community where a CHW program using presumptive antimalarial therapy for fevers was in place. Positive attitudes toward the CHWs were expressed, related to their voluntary services, their accessibility, and the effectiveness of the drugs they provided [13]. The second study assessed perceptions in the same community following the introduction of RDTs into the algorithm for fever management; 79% of respondents thought that care had improved, and 89% thought that CHWs should continue to use RDTs [18].

Acceptability of diagnosis and treatment by CHWs depends on the outcome of the RDT. Patients with a positive RDT result adhered to prescribed treatment in 95 and 97% of cases in two studies from Sudan and Tanzania [35, 43]. However, 20% of CHWs reported difficulties persuading patients that they did not have malaria despite the evidence of a negative RDT [43].

Are Stock-Out of RDTs and Medications a Problem in CCMm?

A reliable and continuous supply of RDTs and ACT drugs is necessary to sustain a credible CCMm program. Several studies have reported challenges with stock-outs of critical program consumable supplies, including RDTs and medicines [44, 45]. When CHWs relied on affiliated health centers to replenish stocks, 74% of villages did not have RDTs or the RDTs were expired [44], demonstrating system-wide stock management problems. Of note, even the rumor of stock-out can deter people from visiting CHWs, demonstrating the importance of responsible program and supply chain management to maintain credibility within a community [18]. In other studies, supply management was excellent with correct accounting of over 98% of RDTs and medication, demonstrating quality stock management is possible with appropriate planning [46]. Likewise, in Senegal, early widespread problems with stock-outs in CCMm largely resolved with increasing program maturity [32].

Do CHWs Follow the RDT Result in Distributing Medicines?

Overdiagnosis of malaria is rampant, not just with CHWs but also among doctors in African hospitals, who often ignore malaria diagnostic tests (RDTs or microscopy) and persist in treating malaria-negative patients with antimalarials [20]. Concordance of CHW management with the RDT result is critical if the test is to play a useful role. Studies are consistent in reporting that almost all patients with positive RDTs were provided with antimalarial drugs by CHWs [18, 32, 35, 43, 45, 46]. In most studies, CHWs appropriately withheld antimalarial therapy in >90% of RDT-negative cases [18, 33, 35, 45, 46]. However, two studies reported high rates (20% [32] and 58% [34]) of inappropriate treatment of RDT-negative patients. This propensity is similar to that observed among physicians and highlights the difficulty in withholding therapy (even inappropriate therapy) from a febrile patient to whom the diagnosis may appear uncertain.

In Cases Outside Their Expertise, Do CHWs Refer Patients for Care Appropriately?

CHWs should recognize the limitations of their management skills and therapeutic armamentarium and refer patients to the nearest health clinic or hospital for more advanced care when appropriate. Referral is incorporated into CCMm algorithms; however, less than half of patients with an absolute indication (e.g., age <2 months, severe symptoms) were appropriately referred in one report [32]. A significant patient-level barrier to referral completion was also identified, with only 40% of CHW-referred patients visiting a health center [45]. Qualitative data indicate that bad roads and difficulties in transport [44], distance to health centers, and lack of staff at the health center resulting in long waiting hours, were common reasons for not following through on referral advice [36, 44, 47]. Some studies have suggested that referral completion rates improve with experience [48], while others have found persistent low referral rates over time [32].

What Impact Does RDT-Based CCMm Have on Patient Outcomes?

CCMm using presumptive treatment of fevers increases the number of children receiving prompt effective treatment and appears to reduce mortality [17, 19, 49]. Adding RDTs to a CCMm program has the advantage of reducing inappropriate courses of ACT without affecting mortality. A Zambian study showed that

prescriptions of antimalarials were reduced by 77% with RDT diagnosis compared to a control group where CHWs used clinical diagnosis [40]. A second study in coastal Tanzania reported a 50% reduction in antimalarial use with no increase in mortality among patients of CHWs trained in RDT use versus CHWs using presumptive diagnosis [35]. The study also documented an increased referral rate among CHWs using RDTs, which may be appropriate in the context of nonmalarial febrile illness where treatment may not be available in the village. In both studies, the mortality and hospitalization rates remained very low despite the lower use of antimalarials [35, 40].

Are RDTs Cost-Effective in the Community Setting?

The cost-effectiveness of RDT-based CCMm depends on malaria endemicity. In low- to medium-transmission settings, RDT-based CCMm was shown to be cost-effective [50], while in holoendemic settings, such as rural Democratic Republic of Congo, empirically treating all fevers as malaria without recourse to testing was more cost-effective [30]. CCMm was also found to be cost-effective relative to health center-based malaria care in another Zambian study [51].

The willingness to pay for RDTs and ACT within the commercial sector has been analyzed using the bidding game technique [52]. In Uganda, health consumers were willing to pay US$0.53 for an RDT, US$1.82 for a course of ACT, and US$2.05 for a course of ACT after a positive RDT [52]. These valuations are considerably lower than prevailing prices for these commodities, indicating that market forces will not naturally promote the sale of ACT in drug shops or encourage testing with an RDT prior to self-treatment. These findings suggest that the informal private sector may not be well suited to provide quality malaria care, and support alternative models of service delivery such as subsidized ACT and RDTs in the context of CCMm [52].

Beyond Malaria: What Happens When the RDT Is Negative?

Just as RDTs illuminate the diagnosis of malaria, they also identify febrile patients without malaria. For these patients, an alternative diagnosis may not be obvious and community-based oral therapy may not be readily available. Confronted with a sick child with fever and a negative RDT, physicians [20], CHWs [32, 34], and parents themselves [43] often prefer to treat with an antimalarial rather than withhold therapy. However, mortality in this group of patients is higher than in RDT-positive patients treated with antimalarial drugs, demonstrating the importance of seeking and treating other causes of fever [20]. Furthermore, inability to effectively manage RDT-negative fevers diminishes the value of a CCMm program in the eyes of some community members, as expressed by one focus group participant: “Even if the test result is negative, they should be able to tell us what is wrong with us” [42].

While the differential diagnosis of nonmalarial febrile illness in children in sub-Saharan Africa is broad, community acquired pneumonia is one common condition that may be recognized and treated by CHWs. Lower respiratory tract infection can be suspected on the basis of tachypnea, a clinical sign that can be readily assessed by counting breaths. Oral amoxicillin will treat many of the most dangerous bacterial pathogens to prevent progression to severe pneumonia. This has led to the concept of integrated community case management (iCCM), endorsed by the WHO and UNICEF to improve access to essential treatment services for children globally [53].

Three publications from Zambia and Uganda illustrate the benefits of iCCM. In one study, iCCM (where CHWs performed RDTs, treated RDT-positive children with ACT, and treated those with tachypnea with amoxicillin) was compared to a control group (where CHWs treated all febrile children with ACT and referred those with signs of pneumonia to the health facility). While mortality remained low in both groups, the iCCM program resulted in major reductions in unnecessary antimalarial use, and increased early antimicrobial therapy for possible pneumonia [40]. In a second study, CHWs using an iCCM program correctly classified and treated malaria and/or pneumonia 94–100% of the time [46]. In a third study from Uganda, CHWs correctly diagnosed malaria with RDTs in 96% of cases, but were less competent in classifying tachypnea, leading to antibiotic treatment in only 40% of children with possible pneumonia [54]. Taken together, these studies suggest that CHWs are capable of providing integrated management of malaria and pneumonia safely and at high quality, although training in classification of tachypnea may need particular emphasis.

Conclusion

iCCM is the latest refinement in a series of public health innovations over the past several decades designed to drive rational and quality malaria care to the periphery, where it is needed most. Use of CHWs and RDTs has shown promise for distributing malaria drugs in a targeted fashion in remote areas where fiscal and human resources for health are scarce. Adding simple strategies for pneumonia management provides an integrated framework for delivery of essential medical services to the vulnerable poor. Although the cost–utility ratio of CCMm is reasonable, program costs will likely be the principal limiting factor in the scale-up of these interventions. In a context of financial hardship, the valuation of RDTs and ACTs within the informal private market tends to push individuals to choose lower-cost suboptimal therapy and empiric treatment without parasitologic confirmation. External sponsorship by local governments or foreign philanthropic agencies is likely needed to scale up iCCM. For example, in the Democratic Republic of Congo, the incremental cost of US$8.79 to avert one unnecessary treatment by using RDTs compared to presumptive treatment represents 60% of the annual healthcare spending *per capita* [30]. This cost is unlikely to be acceptable to community members, but may represent a worthwhile investment in public health from a societal perspective. Lessons learned from

published reports suggest that the numerous challenges to providing malaria care in the community can be addressed with well-designed programs through CHW training, attention to supply management, and community engagement. Models of quality iCCM exist [46] that can be emulated in order to optimize antimalarial drug treatment for children across sub-Saharan Africa. Investments in iCCM will yield dividends in lives saved through improved malaria control.

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Chapter 23
Critical Care for Children in Low- and Middle-Income Countries: Issues Barriers and Opportunities

Andrew C. Argent and Niranjan Kissoon

Introduction

In richer countries of the world, care for the critically ill has increased exponentially in complexity and sophistication over the last few years. In those countries, intensive care is a vital component of an integrated health system with a robust infrastructure and extensive transport networks that make intensive care accessible to children. In addition, the numbers of children who suffer life-threatening illness or injury in those countries are relatively small and many of the intensive care resources are directed at children undergoing major elective surgery or children with significant underlying morbidity or acute injury.

While the bulk of healthcare expenditure occurs in North America and Europe, the majority of children and in particular most sick children live in low- and middle-income countries (LMICs), particularly in Asia and Africa (Fig. 23.1). Thus, globally, the resources available for health care of the sickest of children are not distributed to those areas with the highest need. As shown in Fig. 23.2, countries with the lowest income generally have the highest under-5 mortality. However, mortality is not uniformly distributed because within countries with similar income groups there are wide ranges of under-5 mortality with some countries doing significantly better than others.

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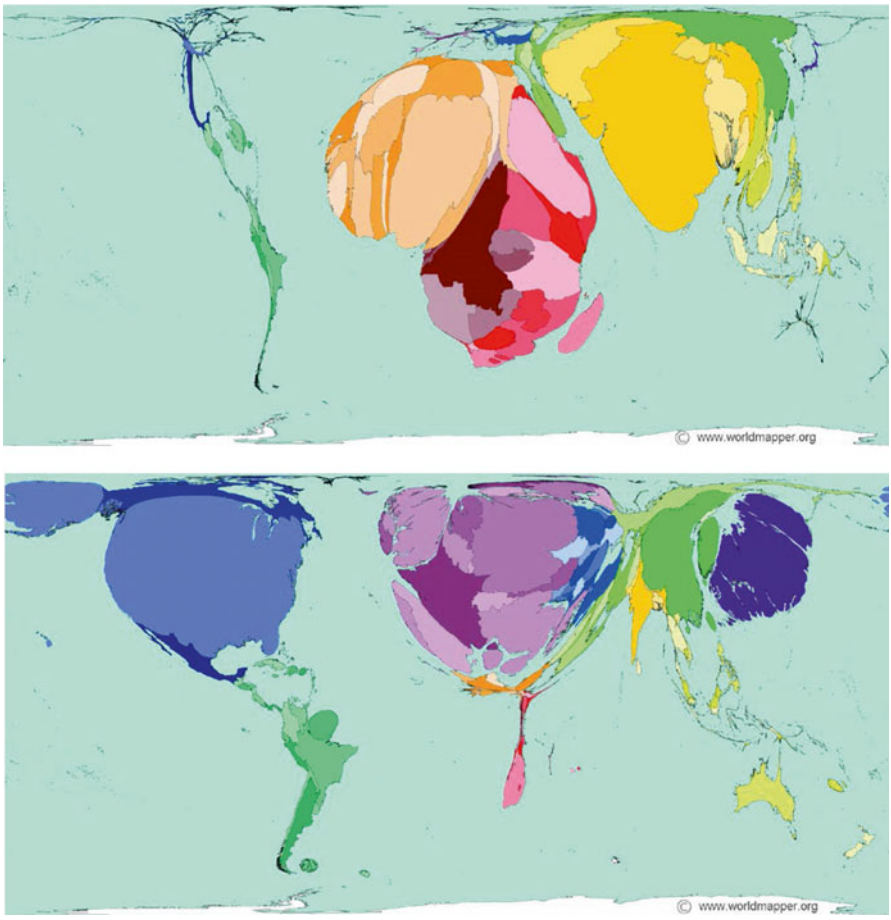

Fig. 23.1 Territory size shows the proportion of all deaths of children under 5 years of age (*top*) and the proportionate distribution of wealth (*bottom*) (Source: info.worldmapper.org © Copyright Sasi Group (University of Sheffield) and Mark Newman (University of Michigan))

Many of the factors that are related to poor health and childhood morbidity and mortality have been reviewed recently [1] and include: maternal education [2]; access to clean water and adequate sanitation [3]; access to food and nutrition [4]; urbanisation [5] and socio-economic conditions [6]; political and societal contexts [7]; appropriate immunisation and access to basic healthcare services [8]; and prevalence of infections such as HIV [9].

Recently, Soto et al. reviewed disparities in the provision of health care to critically ill patients, in the USA [10]. As shown in Fig. 23.3, they suggested that there are factors in the patient, the community, and the hospital systems that affect the care that might be provided to those requiring critical care, and indeed these factors may contribute to outcomes. In many ways this approach might also be used to consider the challenges to the delivery of critical care to children in the LMICs.

With implementation of programmes addressing preventive health management, access to health care and to some extent health behaviours, there has been a dramatic

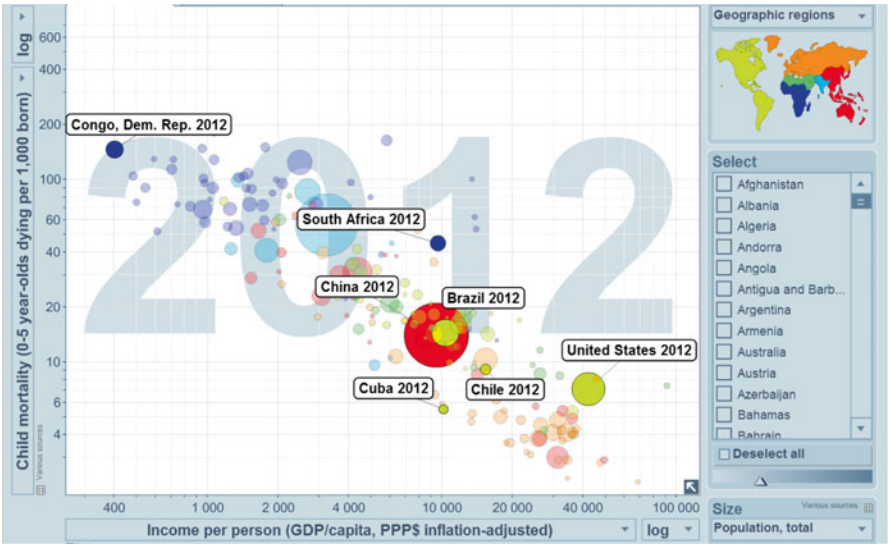

Fig. 23.2 Child mortality (0–5 years old) per 1000 born versus income per person (Source: www.gapminder.org © Copyright Gapminder Foundation, reproduced with permission)

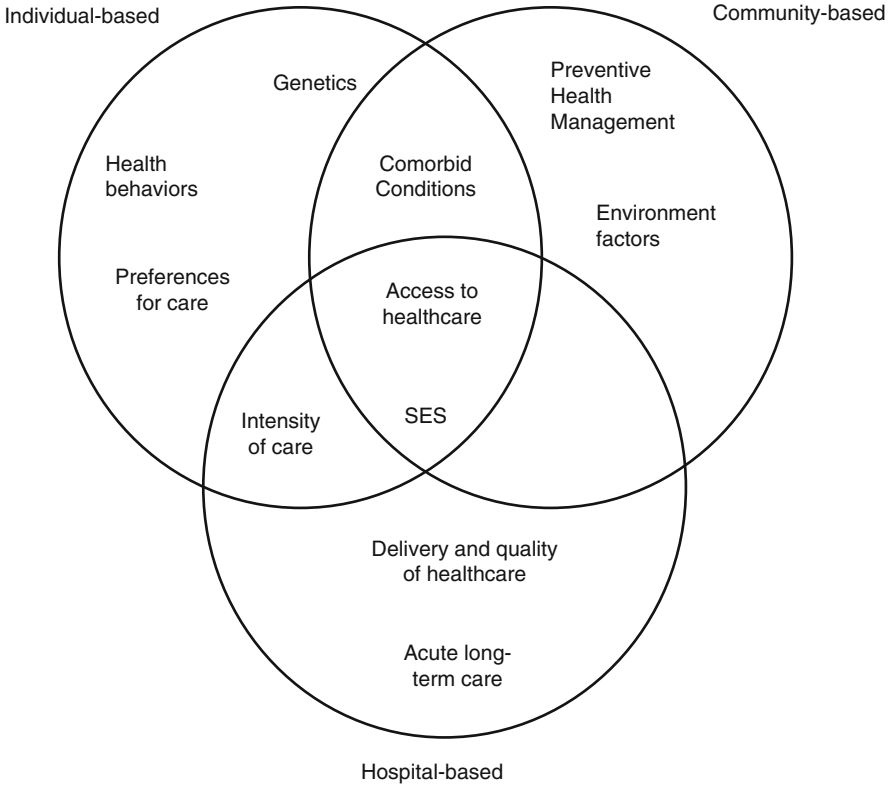

Fig. 23.3 Basis for healthcare disparities in critical illness [10]

improvement in the global under-5 mortality rate over the past decade with recent estimates showing a decline in the number of deaths from more than 12 million in 1990 to 6.9 million in 2011 [11]. Unfortunately that decline in the mortality rate has not been evenly distributed with decline interspersed with areas of increased mortality. However, as the overall health of children has improved, there is an increasing need to focus on development of healthcare systems that are able to provide appropriate care for children who are critically ill or injured or who require major surgery.

The role of critical care in resource-poor settings was recently reviewed by Riviello et al., concluding that intensive care in the broadest sense is not defined by the presence of expensive technology [12]. Substantial improvements in care can be achieved by the application of relatively simple technology (e.g. for oxygen provision) and by nursing monitoring. As reviewed by Nolan et al., a substantial proportion of children who are seen at primary care facilities require referral to a hospital (90 % with one of five common conditions that are amenable to hospital care if referral is timely) [13]. In countries such as Papua New Guinea [14], a substantial proportion of the deaths in the community actually occur in hospitals and could be averted by relatively simple interventions; failure of health systems to provide "rescue" actually undermines the credibility of the overall system [15]. In Papua New Guinea, provision of oxygen systems for childhood pneumonia produced a 35 % reduction in mortality in that group of patients at a cost of $51 per patient treated [16]. Allocation to children of even a relatively small proportion of beds in the hospital system in many countries has the potential to make a substantial difference to the mortality and morbidity of children in those countries [17].

Critical Care

An infant or child who suffers a life-threatening illness or injury requires management that provides for: easy 24/7 access to healthcare facilities that provide care for children; early recognition of life-threatening or potentially life-threatening illness or injury; appropriate and effective initial intervention and therapy; safe transport to facilities that are adequately equipped to provide advanced therapy; access to emergency care and if necessary to intensive care; access to the multiple disciplines that are required to support the care of child with a life-threatening illness or injury; access to rehabilitative facilities; and, finally, ongoing support once back in their own home.

Critical care can be defined by the severity of illness, the complexity of the care that is offered, and the training of the professionals who provide that care [18]. For the purposes of this chapter we have defined pediatric critical care as the care of children who undergo major surgery or who suffer a life-threatening injury or illness, from the time of first presentation to the point of discharge home [19]. Thus, the delivery of critical care services could occur in many settings. In the ideal world, this care should be immediately available as part of an integrated system with seamless progression from point of first presentation to appropriate levels of care.

It should be anchored by comprehensive communication at all stages and supported by rehabilitation services to discharge home and beyond. Pediatric critical care should be a component of an integrated health service and should be available throughout the health system rather than, exclusively, in intensive care units at tertiary or quaternary facilities.

Developing World

The term "developing world" or "developing country" in the medical literature may relate to a wide range of defining characteristics, including: available income; manufacturing and industrial capacity; level of education of the population; life style and standard of living of the country. The reality is that low- and middle-income countries are spread across the world with wide ranges of income (Fig. 23.2), population density, political stability, geographical environments, levels of infrastructure development and income distribution.

In the lowest-income countries, the sad reality is that health systems simply cannot provide health care beyond basic access to services such as immunisation and management of simple conditions with some unable to provide even those services. Nevertheless, there is good evidence that substantial improvements can be made with relatively low-cost interventions. However, it is unlikely that such improvements will be made unless there is attention to issues of good governance, accountability and organisation of services [7]. Reduction or elimination of corruption may be as important as investment in medical and health services.

It is clear (Fig. 23.2), in general, that under-5 mortality is related to per capita income, with a general trend towards improvement with increased income. However, this is not a simple and direct relationship with significant differences in health-related outcomes often observed between countries of similar income. Some countries of relatively low income have achieved very low under-5 mortality rates, while other countries of high income have not achieved low under-5 mortality rates.

However, there are some underlying issues are that are typical of LMICs. The resources that are almost taken for granted in richer countries are often not available (Table 23.1).

Issues

Disease Profile

The data shown in Fig. 23.4 [20] demonstrate how the burden of disease is dramatically increased in LMICs relative to low-mortality countries, and particularly within the African region. While infectious diseases such as malaria, diarrhoea and

Table 23.1 Resources and health care

		System issues	Patient issues
Access to health care	Costs	Charges for health care	Income and relationship to fees
	Geography	Geographical distribution of healthcare resources relative to population at risk	Availability of transport (particularly after hours)
	Education	Providing patients and families with information about early warning or "danger signs" for children	Lack of maternal education and expectations of care
	Transport	Both transport to the facility as well as transport for patients between facilities	
	Paediatric services	Healthcare resources	Appropriateness of the facilities for paediatric care

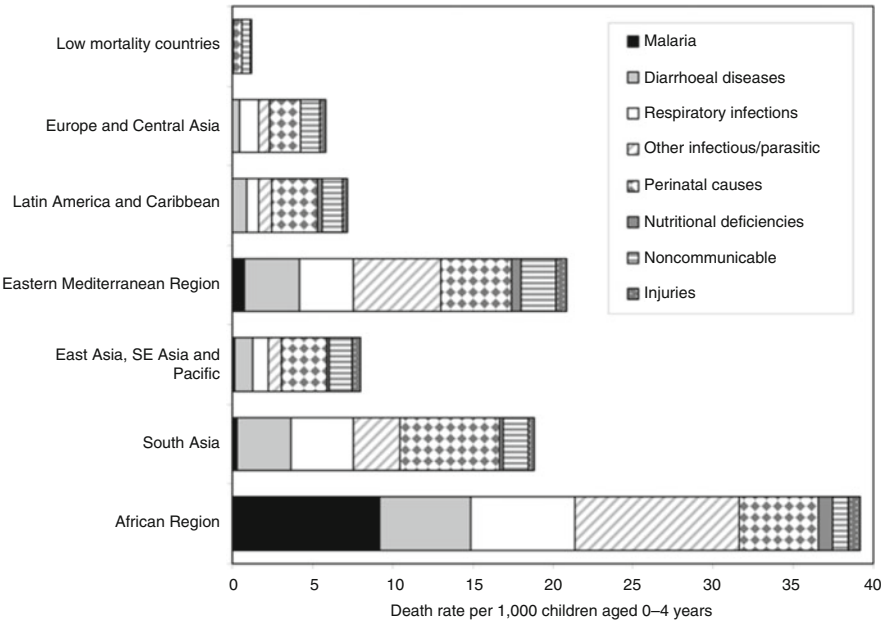

Fig. 23.4 Distribution of deaths and cause across the world (Source Mathers et al. [20])

respiratory infections are the major causes of mortality, there is a substantial burden of disease related to trauma, non-communicable disease and other infectious diseases. It is likely that incidence data on many infections in low-income countries are simply an estimate as there is very little accurate data collection in these countries.

Infectious Diseases

The infectious disease burden of LMICs is generally far higher than that in richer countries. In some cases that may be related to the physical environment (tropical countries have a range of endemic pathogens that are not present in most of the richer countries of the world), but it is also related to factors such as overcrowding, poverty and malnutrition. In Africa, the burden of HIV, with tuberculosis being closely related, has had a huge impact on paediatric mortality. Even children of HIV-positive parents who are not infected by mother to child transmission appear to have a higher burden of infectious diseases, possibly related to poor health in their parents.

Nosocomial Infections

Not only is there a high burden of infectious disease in the community in many LMICs, there is evidence that the rates of nosocomial infections in hospitals and in paediatric critical care units in these countries are very high and may be related to overcrowding and lack of facilities that permit adherence to hand hygiene precautions.

Trauma

As can be seen in Fig. 23.4, there is a substantial burden of trauma for children in LMICs. This burden is probably underestimated as many children with trauma and burns are seen in adult units and these patients may not be included in paediatric statistics. The burden of trauma relates not only to day-to-day injuries (including burns, pedestrian motor vehicle accidents, trauma from the environment), but also to mass casualty events that occur with much higher frequency in LMICs. Regrettably, in many cases, the needs of children are poorly met under the organisational structure fostered by national and local and through development assistance.

Support Services for the Treatment of the Acutely Ill

There are many services that may be regarded as essential components of a system to care for the acutely ill or injured child. Many of these services are extremely limited in their availability throughout the developing world.

Transfusion Services

Blood transfusion services are a critical element in the care of sick children, particularly in areas with a high incidence of conditions such as malaria, dengue fever and trauma. Implementing a blood transfusion protocol based on simple clinical features

in Malawi (one of the world's poorest countries with endemic malaria) was feasible and resulted in a significant reduction in transfusions [18]. However blood transfusion services are extremely limited in those areas with potentially high need [19, 20]. Some factors for non-availability of transfusion therapy in developing countries include lack of effective services, limited donor base, lack of quality-assured blood screening for transmissible infections, lack of expertise and standards to direct clinical use [21]. In addition, blood-transfusion-related HIV infection, in some high-risk settings, may be as high as 25 % [22]. Indeed, approximately 80 % of the world's population has access to only 20 % of the world's safe, screened blood supply [20, 21].

Clinical and Diagnostic Imaging Laboratories

There are major deficiencies in the availability and safety of clinical laboratory services [23, 24], and these problems provide significant challenges to the development of clinical services [25]. Lewis [26] has provided an overview of WHO recommendations for the development of basic haematology services at clinics, health centres and hospitals with recommendations on training programmes and facilities available at each level.

Two reviews of children who had suffered blunt abdominal injury highlighted the fact that imaging facilities could have substantially reduced the need for operative intervention [27, 28]. Recently, workers from Malawi have commented on the usefulness of portable ultrasonography in this setting [29]. Given that ultrasound equipment is increasingly mobile, user friendly, and can be operated without a substantial infrastructure, this may represent an important opportunity for improvement. Another study from Rwanda reported on the use of ultrasound assessment for severe dehydration in children with diarrhoea and vomiting [30].

Drugs

Access to medication is severely limited by financial, political and socio-cultural constraints; while an additional problem has been the sale of counterfeit drugs [31] (see Chap. 9). It is estimated that 50 % of medicines prescribed for children do not exist in appropriate dosage forms leading to inaccurate dosing with resulting reduced efficacy due to underdosing or adverse events due to overdose. Information on how best to prepare and administer paediatric drug formulations are lacking across all cultural and geographical settings. In 2007, the World Health Assembly identified improved access to essential medication for children as an essential component in achieving the MDGs.

Evidence Base for Therapy

Unfortunately, the vast majority of health-related research has been done in richer countries and thus many of the currently agreed protocols and approaches may not be either appropriate or correct in countries with very different health-related problems. For instance, a cautious approach to fluid administration in children with

febrile illnesses may need to be adopted because of the lack of availability of ventilator support if respiratory insufficiency secondary to fluid overload occurs.

Late presentation in the disease process is also a characteristic in resource-poor areas and hence therapy may need to be tailored differently [21]. Many factors including the inability to recognise serious illness such as malaria and pneumonia may contribute to late presentation of sick or injured children to healthcare services [21, 23]. Even when a potentially life-threatening illness/injury is recognised, financial considerations, cultural beliefs and previous experience with the health services may affect the decision by families or community health workers to seek help [21]. Clearly, the role of primary care facilities in providing access to the healthcare system is crucial, but English et al. [23–25] have highlighted the importance of well-functioning district and regional hospital services if patients are to be referred from primary healthcare facilities.

Transport and Emergency Transport Facilities

The provision of transport and emergency services in any country is profoundly affected by the geography, population density and distribution of that country. Processes for provision of critical care in Macao (population density 19,885 people/km^2 [32] will be completely different to those required in Rwanda (population density 464 people/km^2 [32] with most people distributed widely throughout a very hilly country (with dense vegetation and relatively poor road system outside the main roads) or in Namibia (population density 3 people/km^2 [32], with most people widely distributed across a very arid countryside). Difficulty in access to care is compounded by the condition of roadways with high income having up to 100 % of their main roads paved, while, in Nicaragua, only 13 % of roads are paved [33]. Planning of emergency services can make a substantial difference to patient care and outcome, even in countries with low income [28].

Healthcare Personnel

LMIC often have limited access to healthcare workers. Table 23.2 shows some selected data on the resources available for health care, and particularly the number of physicians and nurses in selected countries. Shortage of healthcare personnel is a major impediment to provision of care. In addition, this deficiency implies that systems of care from the resource-rich world cannot be transposed to the LMIC countries and hence other models of care delivery must be explored.

Opportunities for Provision of Critical Care

It is obvious that models that are relevant to resource-poor areas need to be home grown. However, this is not an all or none proposition because there are resources that can be brought to bear to build capacity and improve services for critical care.

Table 23.2 Data on resources available for health care in selected countries

Country	Income per capita (GDP per capita in US$) in 2010[a]	Total health expenditure per person per annum in 2010 (US$)[b]	Government health expenditure per person per annum in 2010 (US$)[b]	Physicians per 1,000 population[c]	Nurses and midwives per 1,000 population[c]
USA	48,358	8,233	3,967	2.42	9.82
South Africa	7,176	631	294	0.76	2.10
Malaysia	8,754	368	204	1.2	3.28
Brazil	10,978	990	466	1.76	6.42
India	1,417	51	14	0.65	1.0
Nigeria	2,311	67	21	0.4	1.61

[a]Data from World bank (http://data.worldbank.org/indicator/NY.GDP.PCAP.CD, accessed 14 October 2014)
[b]Data from World Health Statistics 2013 (published by the World Health Organisation, Geneva, Switzerland) at average exchange rate
[c]Data from World Health Statistics 2013 (published by the World Health Organisation, Geneva, Switzerland)

However, advances in care should move incrementally without compromising primary care resources [34]. Using personnel, materials and health-system infrastructure creatively can cost-effectively optimise the provision of emergency care in resource-poor settings [35, 36]. Researchers and decision-makers should promote the case for universal access to emergency care and research agendas to fill the gaps in knowledge. Obstacles to developing effective emergency medical care include a lack of structural models, inappropriate training foci, and concerns about cost and sustainability in the face of a high demand for services [15, 34].

The intellectual siphoning of critical care providers from resource-poor to resource-rich countries exacerbates the healthcare worker crisis in many countries. Critical care professionals in developed nations have a duty, wherever possible, to avoid damaging the healthcare systems of resource-poor countries by advocating against such diversion of essential of healthcare professionals [37].

Leveraging Education Resources

Education clearly has a role to play in developing a sufficiently large pool of healthcare professionals to meet demand. However, education should be context specific. Since there is little prospect of enhanced return or retention of physicians, WHO has placed increasing emphasis on task sharing (shifting) and training of non-specialist physicians, nurses, and non-physician clinicians to perform surgery or other skill sets. Simulation training provides an opportunity to engage learners regardless of language and cultural barriers and has been found especially useful in introducing

primary triage and culturally sensitive treatments [38]. Simulation training [39], telemedicine [40], and Internet courses [41] are useful adjuncts for training and evaluating humanitarian health workers, but they have not yet been fully explored as an educational tool for everyday critical care [39].

Development of Innovative Approaches to Support the Critically Ill Child

Non-invasive ventilation provides a degree of respiratory support without airway invasion and hence minimises nosocomial infections such as ventilator-associated pneumonia and sinusitis. Moreover, it has the advantage of a greater degree of autonomy, control and comfort, in that they can talk, eat and drink while receiving support. With this control there is a trend towards less need for sedation. High-flow nasal cannula delivery of supplemental oxygen as well as continuous positive airway pressure (CPAP) has been used with great success to support children with respiratory insufficiency and has, indeed, in many cases averted the need for mechanical ventilation in resource-poor areas where mechanical ventilators are not available. Moreover, rather than relying on physicians, bubble CPAP as a mode of respiratory support can be applied safely and successfully by nurses [42].

There are many examples of innovative care for the critically ill child in resource-limited settings. As examples, the Preventing Intensive Care Admissions for Sepsis in Tropical Africa project in Malawi has improved sepsis care by the following: preventing elective operations and invasive procedures in malnourished children, improving referral timing and patterns of referral and contributing to the training of a cadre or workers to administer emergency care. In addition, the training of villagers in basic first aid and resuscitation [43], provision of low-cost antibiotics to village healthcare workers [44]. modification of IMCI protocols, development of district hospital services [45], reorganisation of emergency services at referral hospitals [46], and provision of oxygen therapy for hypoxaemic children in district clinics [47] and home-based treatment can be applied in a variety of settings [48]. Additionally, the use of rapid diagnostic tests and drugs by community health workers to manage pneumonia and malaria [49] has proven to be effective and beneficial to critically ill children (see Chap. 22).

Kangaroo Care for Neonates

Kangaroo care provides closeness of the newborn with mother or father by placing the infant in direct skin-to-skin contact with one of them. This ensures physiological and psychological warmth and bonding. The kangaroo position provides

ready access to nourishment. The parent's stable body temperature helps to regulate the neonate's temperature more smoothly than an incubator, and allows for readily accessible *breastfeeding*. While this model of infant care is substantially different from that expected in a typical Western *NICU*, it is a low cost-effective method for care of the neonate where expensive incubators are not available.

Global Healthcare Partnerships

Another resource that is available to build capacity in resource-poor areas is global health partnering between like-minded institutions with the resources and the willingness to form mutually beneficial relationships to improve capacity and delivery of child health care.

Conclusions

Critically ill children in LMICs face great obstacles in accessing critical care services. However, with innovative approaches setting-appropriate critical care can be afforded in many cases. A new level of partnership between resourceful caregivers and policy makers is needed.

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Chapter 24
Child and Adolescent Mental Health Disorders: Organization and Delivery of Care

Ruth Kizza Bohlin and Rhona Mijumbi

Children (5–14 years) make up 19.8 %, and youth (15–24 years) make up 18 % of the world's population. In the least-developed nations, 32 % of the population is between the ages of 10 and 19 years [1].

The rates of mental illness are similar among children and youth to those of adults. In their work, Fayyad et al. [2] concluded that the range and rates of psychiatric symptomatology in children and youth in developing countries were similar to those in the developing world. There is, however, a well recognised gap in identification and treatment of mental health disorders in low- and middle-income countries and this gap is especially large in child and adolescent populations.

There is an ongoing debate about the appropriateness of use of medication in the treatment of child mental health disorders; however, the benefit of rational medication use in treatment of some serious mental disorders is undeniable. Medication use data from high-income countries indicate ongoing substantial growth in prescribing of CNS active drugs, especially for treatment of mental health conditions among older children and youth. Even children under 5 years of age are receiving more prescriptions for drugs in this class. Psychotherapeutic or psychological interventions, which are often the first line of treatment in the developed world, require specialised personnel that are frequently unavailable in low- and middle-income countries. Practitioners, therefore, almost always rely on drug treatment alone for child and adolescent mental health issues. Consequently, therapy must be optimised

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in order to bring an acceptable level of care to the patient. This chapter examines the issues surrounding drug treatment of children and youth with mental health problems in the developing world.

Clinical Issues

Centred on the Child

Children and youth in developing countries are most often entirely dependent on parents and other responsible adults for support in finding health services and treatment. The difficulties discussed in this chapter consequently affect the primary care givers as well as the children. There is a lack of child autonomy in most developing countries. Unfortunately, the systems currently in place do not protect the rights of children to health. This results in primary caregivers' attitudes and circumstances having a direct effect on their health and treatment of children in a more concrete and direct way than in societies where children's right to health care is more consistently enforced.

Centred on the Patient and Family

Residence in a developing country and earlier age of onset of mental disorder have been associated with delay and failure in treatment seeking. Children are especially vulnerable [3]. There is a widespread failure to recognise and treat mental health disorders in children in developing countries, in part, because children are often considered not to be susceptible to mental illness. Unfortunately, there is, in addition, a common attribution of mental health issues to spiritual or moral origins. Prevention and treatment is therefore often sought, without direct benefit, from spiritual or moral/ethical leaders.

Traditional healers still see a large proportion of the population that seeks treatment for all conditions in low-income countries. However, for mental health this pattern it is even more prominent because these populations tend to associate the cause of mental illness and therefore its treatment and ultimate cure with the supernatural. This inevitably lays fertile ground for the use of traditional healers as the first, or even only, port of call for many that seek treatment for mental illness. Usually, when compared to their regulation counterparts in the medical field these traditional healers are not trained or equipped to handle mental illness, and especially child and adolescent mental health.

In a study in Uganda, 80 % of the patients seeking medical treatment for mental illness also attended a traditional healer and 80 % of patients seeking traditional healers for psychotic illness also had treatment from a "Western" medical practitioner [4]. These deep-rooted beliefs in traditional medicine as the only true cure for

mental illness often lead to delay by caregivers in seeking treatment and later complicates drug adherence. Delay in accessing care has ramifications in the choice of drugs for treatment. It also may lead to presentation of more severe and more difficult-to-treat forms of disease later, resulting in complex and sometimes more hazardous therapy.

Centred on the Clinician

Once the child comes into the clinic, there are hurdles remaining. There is a shortage of health workers with competence in child mental health [5]. At the health unit, the child is often seen by clinicians with limited knowledge in child mental health and mental disorders. This may lead to incorrect diagnoses and prescription of inappropriate and sometimes unsafe medicines for children. Even among licensed physicians, there are often gaps in knowledge and competence to identify, prevent and treat mental health issues in children. Prescription is usually patterned on adult drug choices with little regard to the differing pharmacodynamics and pharmacokinetics in children.

Additionally, clinicians in rural settings are often isolated with no peers to consult and little access to continuing medical education. This leads to rigid and sometimes outdated prescribing patterns that do not reflect changes in the current evidence base.

Even if there are some qualified physicians in most developing countries, there are very few countries with a register of prescribers that is available to pharmacies or drug shops. There is, therefore, inadequate control over who can prescribe medicine and this can result in frequent misprescribing or inappropriate dispensing.

Stigma of Mental Health Disorders

Stigma is an actual and inferred attribute that damages the bearer's reputation and degrades the person to socially discredited status [6]. Critical dimensions of stigma include negative attitudes and behavioural dispositions such as discrimination and devaluation behaviour. The stigma attached to mental disorders is prevalent in all settings, but it is especially problematic in the developing world.

Stigma attached to mental health conditions is a major barrier to the utilisation and therefore scale-up of mental health treatment and management [7]. A big proportion of the burden of mental illness experienced by patients results from the attitudes and discrimination they experience, and this is worse in low-income countries. A study in Nigeria found that stigma and discrimination against the mentally ill was prevalent even in a population that was expected to be enlightened. The authors noted that the "respondents held strongly negative views about the mentally ill, mostly being authoritarian and restrictive in their attitudes and placing emphasis

on custodial care" [8]. Regrettably, health workers who are meant to deliver treatment and take responsibility for scaling-up of interventions have also been reported to be a part of such discrimination.

Health Systems Barriers

Leadership and Governance

Health system leadership and governance involves a series of activities that ensure guidance for the system. This guidance, which may take the form of policy frameworks and strategic plans, builds a crucial framework on which the system operates. It provides system designs, regulation and accountability, effective oversight and team and partnership building [9]. It is, therefore, clear that the leadership and governance of a health system is essential for its functioning and sustainability. It is, therefore, not surprising that health systems in low-income countries are sometimes almost non-functional, or absent in some areas because of recurring leadership and governance problems.

These problems arise from several factors:

1. Guidance in terms of policies and guidelines is frequently lacking. Data from the World Health Organization's Mental Health Atlas Project 2011 [10] showed that out of 184 countries surveyed, only 60 % had a dedicated mental health policy, just over 70 % had a mental health plan and only 59 % had dedicated mental health legislation [10].
2. Of low-income countries, only 24 of 39 were reported to have national mental health plans. Such plans were in place in 37 of 51 lower-middle income countries and in 28 of 43 upper-middle income countries. Mental health legislation was in force in 38.5 % of lower-income countries and 60.6 % of middle-income countries. Mental health plans cover only 72.1 % of the population in low-income countries as compared to almost total coverage in lower-middle income countries and high-income countries and over 95 % in upper-middle-income countries.

   For those countries with guidance provided through policies and plans, it is noteworthy that much of the guidance has been available only in the past decade. For example, in the African region, 81 % of the current dedicated policies have been enacted since the year 2000 (74 % after the year 2005) [10]. Therefore, many of these countries do not have experience with their guidelines and have not monitored or evaluated them long enough to determine what works and what does not to be able to revise them accordingly. In addition, because this problem is widespread, there are few regions from which lessons can be drawn or models derived for sound policies and guidelines.

   The implications are that missing guidance creates an environment where different parties work as they deem right or convenient. It leads to duplication, inequitable distribution and suboptimal coverage of services. Vulnerable

populations such as the poor and children who are already more prone to having mental health disorders [11] are likely to suffer disproportionately in such circumstances. They bear the greatest burden of illness because they are not in an empowered position in several ways, for example, by virtue of their age, income and social power.

3. Where policy, legislation and mental health plans are present, it is not uncommon to find their content lacking, rarely updated, and often poorly enforced or regulated. For example, earlier mental health legislation was often drafted in such ways as to protect the public from "dangerous" individuals (i.e. mentally ill persons). This legislation, in many cases, has not been updated to reflect the need for special care and respect for the mentally ill from their caregivers, medical personnel and the public, as is now informed by our increasing understanding of causes and implications of mental illness. This failure to update legislation is a direct consequence of the poor leadership and governance, characterised by, among other things, laissez faire management, poor accountability and lack of appropriate legislation to enforce change.

   Although 61.5 % of low-income countries had mental health plans, only half (38.5 %) are reported as having legislation to enact the plans. The goal of mental health legislation, like all legislation, is aimed at protecting and promoting the mental well-being of citizens [12]. More importantly, mental health legislation is crucial because people with mental disorders are particularly prone to abuse and violation of their rights. The development of guidelines and mental health plans without appropriate legislation may be futile. The policies and guidelines address issues and details of care such as access to quality mental health care and services, integration of persons with mental disorders into the community, and promotion of mental health in society. The legislation then provides a legal framework for implementation, regulation and enforcement of the issues covered in the policy and plans. The two are complementary; however, almost half of the low-income countries with guidance in terms of mental health plans have no legislation to enforce these plans and their mental health stakeholders are left in vulnerable positions. The scenario is worse when considering legislation and plans drawn especially for children and youth. Mental health policy and legislation for children and adolescents is deficient worldwide [13].

Financing

Even with the best policy and plans in place, and with the best intentions in legislation, without financing for implementation, the outcomes of mental health treatment and management will at best remain poor. Financial resources are needed to translate policies into action, they are needed to hire and train personnel, set up well-equipped facilities and purchase necessary drugs and services. In many low-income countries, financial resources for mental health are meagre. Most low-income countries spend less than 1 % of their total public healthcare budgets on mental health [14].

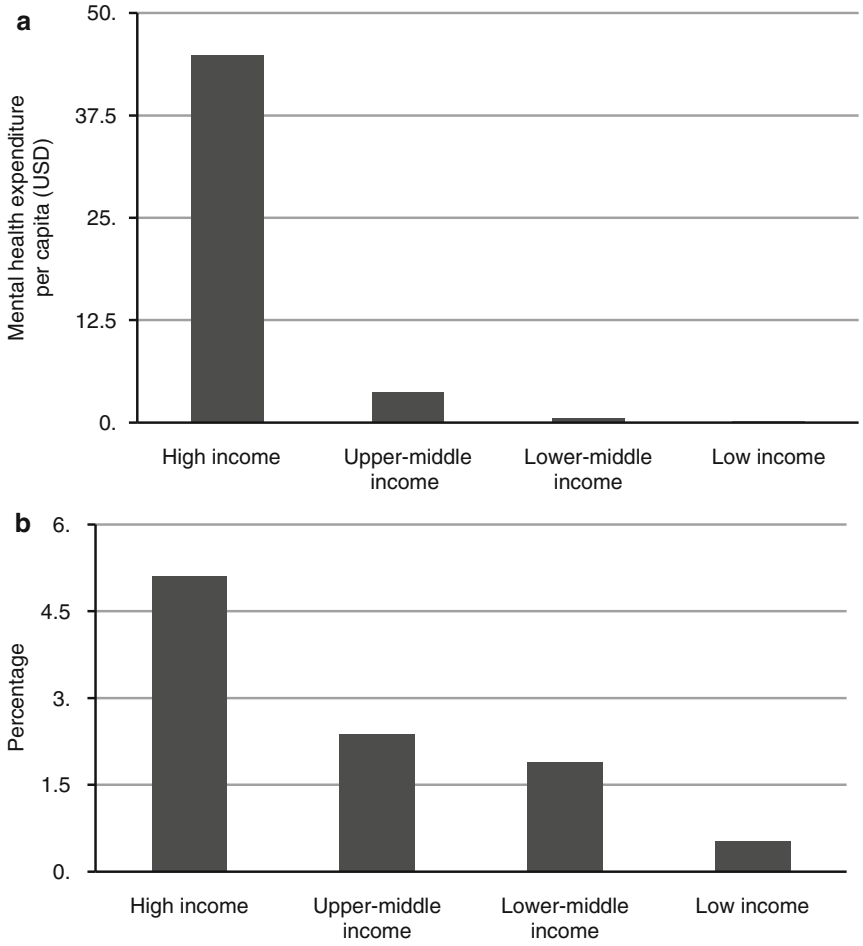

Fig. 24.1 (**a**) Median mental health expenditures per capita (USD) by World Bank income group (Source: Mental Health Atlas 2011 [10]). (**b**) Median percentage of health budget allocated to mental health by World Bank income group (Source: Mental Health Atlas 2011 [10])

Funding in low-income countries comes from three sources: government, development partners (directly or through government) and private or out-of-pocket funding. When considering public funds dispersed through the government, mental health has generally been of low priority on the agenda of many stakeholders, including policymakers, governments, and development partners, at both the national and international levels.

Figure 24.1, b shows expenditures by countries in different World Bank income groups on mental health broadly defined. On average, low-income countries spent 0.5 % of their health budgets and about USD 0.2 per capita. In 2011, the year for which expenditures are shown, low-income countries had a GNI per capita of US$1,026 or less [15].

However, even where there is commitment and will from policymakers and governments to provide finances and other resources for mental health, the level of such funding in low-income countries is generally inadequate. This is because general government revenue is low to start with and problems such as late disbursement of funds and diverted funds usually result in the population having to pay directly for their services at the point of use. The proportion of services covered by out-of-pocket expenditure is therefore large. Out-of-pocket funding is the primary method of financing mental health care in about 40 % of low-income countries [16].

Coupled with this is the fact that there is very little pooling of health resources through social insurance in low-income countries. In a more ideal policy environment, such pooling of resources would mean that the poor are subsidised by the rich, the young by the elderly and the sick by those healthier.

These circumstances should be viewed from the perspective of the average patient developing mental illness. Mental illness in low-income countries is closely linked with impoverishment. When poor people have to pay in order to access mental health services, it becomes a major hurdle in accessing health services and drugs. Aside from the fact that this hurdle is skewed towards disadvantaging the poor and causes inequitable provision of services, it may result in catastrophic payments that leave the already poor family in a worse financial situation.

Purchasing of services, if they are readily accessed, as already highlighted, is especially difficult if payment is expected at the point of care. In many low- and middle-income countries, where patients meet the larger proportion or all of their drug costs through out-of-pocket fees and without subsidy, the high cost of psychiatric treatment, often due to high consultation and medication prices, is a significant barrier to care. Scaling-up of interventions is also impeded. Where social or private insurance is available, most mental health care and management is not covered by the policies.

The financing of child and adolescent mental health, and mental health in general, is a daunting barrier to scaling-up of interventions and until a change is made in the process by which resources are mobilised, pooled and used to purchase services, it will remain an insurmountable hurdle.

Health Work Force

There is a general lack of capacity in terms of human resources for health in low- and middle-income countries. This is evident not only in the numbers of practitioners but also in their qualifications and skill. Although this problem is not unique to any particular discipline in the health sector, it is felt more by some than others. Mental health is one of those disciplines that appears to be especially vulnerable. There is an average deficit of 22.3 mental health professionals per 100,000 population in low-income countries and most of those available are located in large cities with close to none at all in the rural areas [17]. In a survey of 58 low- and middle-income countries, investigators found a shortage of psychiatrists, nurses and

psychosocial care providers of 67, 95 and 79 %, respectively [18]. The shortage of personnel is even more severe for children and youth services, with an almost complete absence of mental health specialists equipped to manage this group. Child psychiatrists are a rarity in low-income countries, for example, the state of California in the USA has more child psychiatrists than the whole of Africa [18]. The World Health Organization reports that most low- and middle-income countries have only one child psychiatrist for every one to four million people. In Africa, the exceptions to this are Algeria, South Africa and Tunisia, with more than one psychiatrist per 100,000 population (none of these better-served jurisdictions are low income) [19]. By 2005, in Africa, with the exception of South Africa, there were no more than ten psychiatrists that could be identified as trained to work with children and youth. Close to a decade later, the situation in these low-income countries does not show signs of significant improvement.

The shortage of mental health professionals is a glaring gap that is further made worse by large within-region and within-country variations or disproportionate distributions. Mental health resources are inequitably distributed the world over: on the international scene, more than 95 % of specialised mental health personnel are in high-income countries [18]. The gap between low- and high-income countries is enormous; psychiatrists are 200 times fewer in low-income countries than high, and there is a 350-fold difference for clinical psychologists and clinical social workers [20].

The absence of personnel is compounded by the absence of other related resources that are needed, such as facilities, equipment, programmes and training specifically for the care of children and youth. No low-income country has paediatric beds for mental health, and only 40 % of countries in Africa have reported having special programmes in mental health for children [19]. There are few formal training programs for developmental and behavioural paediatrics, child psychiatry, speech and language therapy or other major disciplines concerned with child mental health in low- and middle-income countries [18]. Of those reporting special paediatric programmes, very few have formal training programmes, let alone provide access to formally trained child psychiatrists. In fact, only South Africa in the African region has a training program that awards a tertiary qualification in child and adolescent psychiatry [21].

A survey that aimed to gather information on youth services and resources in all regions of the world, which involved about 66 countries, reported that, of these, 37 countries identified their paediatricians as providers of mental health care, yet only ten countries reported that more than 25 % of their paediatricians receive mental health training [19]. This reflects the absence of deliberate plans to equip child mental health providers with the skills needed to manage patients or even improve management.

Because of the lack of trained psychiatrists, nurses and psychologists, education or special needs professionals and specialists such as speech and language pathologists are greatly involved in child and adolescent mental health care in developing countries. However, as for their medical counterparts, these individuals have generally not been equipped with the training and skills needed to adequately provide the services required. In the survey reported above, only 31 countries of the

66 reported that speech therapists received mental health training. Aside from the specialists, there is also a lack of multi-disciplinary teams and community and public health resources that are essential for the comprehensive management of childhood mental health disorders.

There are also limited efforts to update practitioners on the latest treatment trends through further training or continuing professional development. Information on continuing professional development or continuing medical education (CPD/CME) in child and youth mental health in low-income countries is generally absent or at most inconsistent.

Remaining Knowledge Gaps

Reliable, consistent and systematic data are a great facilitator of planning, monitoring and evaluation efforts in any given health system, yet almost a quarter of the world's low- and middle-income countries have no arrangement for reporting basic mental health information [22]. This deficiency significantly hampers efforts to improve service delivery. There are several reasons these systems are lacking, including the fact that there are too frequently deficits or defects in the mental health systems to be monitored. Only 1 in 16 low-income countries reported in the Atlas survey of 2005 had epidemiological survey data associated with child and adolescent mental disorders and that country was in Europe. Furthermore, only 3 of 16 low-income countries had child and adolescent mental health disorders reported in the country's annual health survey [19].

With the advent of modern information technology, health services data monitoring systems are improving in several countries, including low- and middle-income countries. However, reports on availability of mental health services and related issues are still mostly inadequate. Such information is needed to enable an accurate estimation of needs, without which there are likely to be continuing service shortfalls on the one hand or a waste of resources through duplication on the other.

Conclusion

Of the common mental health disorders affecting children and adolescents, only learning disorders are commonly treated without resort to pharmacotherapy. Drugs are an important part of the therapeutic armamentarium for depression, psychoses and attention deficit disorder. They play a less critical but sometimes important role in the treatment of autism and a variety of behavioural disorders. Rapidly increasing knowledge of pharmacogenomics is providing hope that many rare disorders characterised by clinical presentation with developmental delay, neurodegenerative change or mental health anomalies may, in future, become pharmacologically treatable. It is unrealistic to think that outcomes in mental health treatment or prevention

will improve dramatically until sufficient attention is paid to the conduct of stronger basic and clinical pharmacology studies. There is a critical need for exemplary clinical trials of psychopharmcologic drug actions, both safety and efficacy, among the child/adolescent population of LMICs. Since, as described in this chapter, the need for dramatic progress is greatest in LMICs, it is vitally important that we address the relevant research and training gaps as a matter of global priority.

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Chapter 25
Psychotropic Medications in Pregnancy

Irena Nulman, Paul Nathan Terrana, Michael Lutwak, and Maya Pearlston

Introduction

The World Bank reports that there are approximately 849 million people living in low-income countries and 4.97 billion people living in middle-income countries; with corresponding high birth rates of 32 per 1,000 and 19 per 1,000, respectively, one can infer that the majority of pregnancies and deliveries worldwide will occur in low-and middle- income countries (LMICs) [1]. Considering that the first onset of mental illness coincides with childbearing age [2] and over 80 % of the global prevalence of mental illnesses occur in LMICs [3], the burden caused by reproductive psychiatry in these countries will be costly and potentially devastating. Fourteen to thirty percent of pregnant women are affected by psychiatric disorders [4, 5] and if uncontrolled, these represent a risk for both the mother and fetus.

Effective psychopharmacology and pharmacotherapy have allowed patients to function productively in society. However, pregnancy may represent a conflict between optimal control of maternal mental health and potential drug teratogenicity. It is essential to study the reproductive safety of psychotropic medications in order to prevent costly adverse effects on child health, neurodevelopmental impairments, and future child psychopathology.

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Teratogenicity

A teratogen is a substance (e.g., medications), environmental hazard (e.g., radiation), or a maternal disorder (e.g., infections, mental health) that adversely affects fetal development when acting during pregnancy. Outcomes from exposure to teratogens vary from death (miscarriage and stillbirth), impaired organ formation (major malformations, minor anomalies), growth impairments (intrauterine growth restriction, macrosomia), to organ dysfunction (adrenal insufficiency), as well as long-term consequences such as adverse neurocognitive and behavioral outcomes (low IQ, increased risk for psychopathology), increased mutagenicity (higher risk for pediatric malignancies) and impaired fertility.

The extent of teratogenic effects depends on many factors including the placental transfer of the drug, the dose and duration of exposure, the maternal and fetal genetic variability in drug handling, and the time of exposure during pregnancy. There are recognized critical windows of exposure; the "all-or-none" period is 8–14 days post conception. If the implantation is successful during this period, despite teratogenic action, then the fetus is expected to develop normally [6]. The gastrulation period is 3–5 weeks post conception and is a period of major cell differentiation. It is of particular importance to teratology, as exposure during this time can adversely affect every system. In the first trimester (organogenesis), the fetus is susceptible to congenital malformations. In the second and third trimesters, exposures mainly affect fetal growth, organ maturation, and the development of the CNS [6].

When assessing teratogenic risk, it is important to understand that even pregnancies in healthy, unexposed women are at 1–3 % risk for major malformations. The baseline incidence of miscarriage in the general population is up to 15 % [7] and 0.5 % for stillbirths [8]. Intrauterine growth restrictions (IUGRs) occur in approximately 4–8 % of pregnancies [7, 8].

Antipsychotic Medications

Antipsychotics are a class of psychotropic medications initially indicated for the treatment of schizophrenia but also used to treat other psychiatric disorders such as bipolar disorder, depression, and anxiety disorders [9]. First-generation antipsychotics (FGAs), also known as typical antipsychotics, were first developed in the 1950s and shown to be effective; however, they are associated with serious side effects. These serious side effects resulted in the need to develop new and safer drugs, which led to second-generation antipsychotics (SGAs or atypical antipsychotics).

Stability in prolactin levels in patients taking SGAs, as well as the improved understanding of psychiatric disorders and the decreased stigma toward patients with mental illness has increased the incidence of pregnancy among these patients. Given that antipsychotics have been shown to cross the placenta [10], the reproductive safety of these drugs must be considered.

First-Generation Antipsychotics (FGAs)

One of the earliest and largest prospective cohort studies analyzing the safety of FGAs [11] reported on over 1,300 children who were exposed to phenothiazines (a subclass of FGAs) during the first trimester of pregnancy. The study found that, although the overall rates of malformations were similar between the exposed and unexposed control groups, there were significantly more cardiac malformations in the FGA-exposed group. An increase in cardiovascular malformations following FGA exposure has been confirmed [12]; however, it has been suggested that the increased risk might be due to confounding factors. A recent study examined 284 pregnancies exposed to FGAs in the first trimester and found no increased risk for major malformations in the exposed cohort [13]. These results corroborate earlier findings [14].

In utero FGA exposure may be associated with a higher rate of preterm births as well as a lower median birth weight [12–14]. Furthermore, Habermann found that prenatal exposure to FGAs increases the risk for poor neonatal adaptation syndrome (PNAS), which commonly affects the fetal CNS and may cause jitteriness, somnolence, and seizures [12]. The authors suggested that these pregnancies be considered high risk and deliveries should be scheduled in hospitals with neonatal monitoring.

The long-term outcomes of children exposed to FGAs in utero are underrepresented in research. In the 1970s Slone measured intelligent quotient scores of children at 4 years of age and found no significant difference between the exposed and unexposed children. Further studies are needed to support these findings [11].

Second-Generation Antipsychotics

An analysis of 561 pregnant women exposed to SGAs in their first trimester found a significant twofold increased risk for major malformations compared to healthy controls [12]. Specifically, an increase in cardiac defects such as atrial and ventricular septal defects was described; however, it was suggested that the increased risk be

attributable to ascertainment bias. Sadowski et al. [15] reported that 72 % of exposed women received SGAs in polytherapy (combined with other psychotropics). In utero exposure to SGA monotherapy appears to be associated with less risk to the fetus, while prenatal exposure to polytherapy was associated with prematurity, higher rates of PNAS, admissions to the NICU, and higher rates of inborn defects. It was concluded that polytherapy is common and that reproductive safety of this drug group should be studied in the reality of polytherapy.

There have been conflicting results regarding additional pregnancy outcomes studied. Some authors found an increased risk of small for gestational age neonates following in utero SGA exposure [16, 17]; however, others found an increased risk of large for gestations age neonates [15, 18]. A significant risk of preterm births has been described in pregnancies that were exposed to SGAs [19] and it has been suggested that prenatal exposure to SGAs increases the risk for PNAS [12].

To address contradictory findings in the current research regarding SGAs, a meta-analysis was performed by our laboratory to determine the reproductive safety of SGAs. The authors found a twofold increased risk for major malformations after analyzing 1,042 SGA pregnancies (OR = 2.03 (1.41–2.93)), and a nearly twofold increased risk for preterm births analyzing 645 SGA pregnancies (OR = 1.85 (1.20–2.86)). However, the included studies did not stratify monotherapy and polytherapy results. Also, no specific pattern of malformations was found and there was no significant increased risk for miscarriages, still births small for gestational age neonates, large for gestational age neonates, or differences in mean birth weight and mean gestational age.

The information on long-term neurocognitive effects of in utero SGA exposure is scarce. A recent study of 6-month-old infants prenatally exposed to antipsychotics (both FGAs and SGAs) using INFANIB scores (measures infant posture, muscle tone, reflexes, and motor abilities) found that exposed infants had significantly lower scores than unexposed infants [20]. A prospective follow-up study was conducted with 76 children of schizophrenic mothers exposed to a single SGA and 76 matched healthy controls. They found that children exposed to SGAs scored significantly lower on the Bayley Scale of Infant and Toddler development (3rd edition) compared to healthy infants at 2 months [21]. No differences were seen in the children at 12 months using the same scale, which may suggest there is potential for development to "catch-up." These results need to be replicated in older children when definitive cognitive tests can be applied, in order to provide appropriate management and guidance.

In summary, presently, there are no clear associations between antipsychotics and adverse pregnancy outcomes in monotherapy; however, their use in polytherapy needs further research.

Antidepressant Medications

Depression is the most common psychiatric disorder affecting up to 25 % of women [22] and as many as 51 % in specific [23]. Rates of depression are even higher in women of childbearing age, resulting in 13–16 % of pregnant women requiring

pharmacotherapy [24]. If left untreated in pregnancy, there are increased risks for the mother as well as for the fetus and for the child's future development. Depression in pregnancy has been associated with poor self-care, late pregnancy diagnosis, inadequate nutrition and weight gain, associated comorbidities, sleep disturbances, emotional deterioration, substance abuse, suicide attempts, and risk for devastating postpartum depression. In addition, there is increased risk for prematurity, obstetric complications, and future psychopathology [25]. Furthermore, fetal exposure to stress-induced maternal behavior and depression was found to be associated with impaired fetoplacental function, increased rates of malformations, intrauterine growth restriction, stillbirth, and perinatal complications [26].

Although depression poses a risk for both mother and fetus, it is also one of the most treatable mental health disorders. Effective options include tricylic antidepressants and selective reuptake inhibitors. When taken during pregnancy, these medications greatly reduce debilitating depressive symptoms and minimize the risks associated with untreated depression during pregnancy. Despite general agreement that maternal depression should be controlled during pregnancy, the condition remains undiagnosed in patients that often discontinue their medication because of fear of teratogenicity [27]. Furthermore, up to 80 % of depressed mothers who do not receive adequate treatment during pregnancy experience devastating postpartum depression [25, 28], which exacerbates the risks for the mother as well as poor immediate and long-term outcomes for the child.

Tricyclic antidepressants (TCAs) have been used to treat depression for over 50 years. While very effective, TCAs have a narrow therapeutic index, are nonselective to serotonin and norepinephrine inhibitions, and have a high affinity for blocking histaminic, cholinergic, and alpha 1-adrenergic receptor sites, resulting in significant side effects, including cardiac, and may therefore be lethal in overdoses. The severe anticholinergic effect can result in poor compliance, undertreatment, and premature discontinuation of therapy.

The adverse effects of TCAs necessitated the development of a new generation of antidepressant medications, selective reuptake inhibitors (SRIs). Unlike TCAs, SRIs are highly specific for inhibiting neurotransmitter reuptake and are equally effective thus rendering them the most current prescribed group of antidepressants [29].

Reproductive Safety of TCAs

TCA medications have not been found to be associated with an increased rate or any specific pattern of major malformations. Both prospective and retrospective studies on thousands of women have failed to confirm an association of the drugs with impaired organogenesis or long-term neurodevelopment [30–32].

Transient neonatal toxicity (i.e., urinary retention and functional bowel obstruction) and withdrawal symptoms (e.g., irritability, jitteriness, seizures, etc.) were observed in newborns when TCAs were used in late pregnancy and near term [30, 33].

Reproductive Safety of SRI Antidepressants

No significant increase in major malformation rate above that seen in the general population has been identified over at least two decades of research. A recent meta-analysis of 23 studies showed that there is no association between SRI exposure during pregnancy and spontaneous abortions; however, slight reductions in gestational age and Apgar scores were associated with SRI exposure when compared to normal pregnancies or to pregnancies of mothers with untreated depression [34]. These risks were deemed small and unlikely to be of clinical significance.

An accumulated body of research has reported that the use of SRIs during the third trimester or prior to delivery is associated with nonspecific and self-limited PNAS findings within about a week after delivery. Symptoms include irritability, crying, shivering, increased muscle tone, eating and sleeping difficulties, convulsions, and increased risk of neonatal intensive care unit stay occurring in approximately 8–30 % of the neonatal population exposed to SRIs in late gestation [35, 36]. PNAS may also be associated with drug toxicity, withdrawal, toxicity followed by withdrawal, or may even result from maternal–fetal pathology unrelated to pharmacotherapy. Some regulators have nonetheless adopted product labeling that suggests tapering SRIs in late pregnancy in order to reduce the likelihood of PNAS [37, 38]. Since such a policy may increase the risk for postpartum depression and can detrimentally impact the mother and the child's well-being, and given that the neonatal symptoms are transient and self-limited, tapering the drug may not always be the preferred clinical alternative.

Several studies link SRI exposure in late pregnancy to persistent pulmonary hypertension of the newborn (PPHN) [39, 40]; however, some of these studies did not control for common known risk factors in depressed women. Other studies have not supported this association [41]; however, a recent meta-analysis found an increased risk for persistent pulmonary hypertension in infants exposed to SRIs in late pregnancy [42]. It is speculated that the pulmonary accumulation of the drug may be a contributing factor since serotonin has the potential to induce vasoconstriction and mediate pulmonary arterial smooth muscle cell proliferation through the serotonin transporter [43]. It is estimated that PPHN may occur in less than 1 % of the pregnant women treated with SRIs, which represents a very small absolute risk, and no mortality has been reported in infants who developed PPHN [44]. Given that this pathology is rare and that the chance of a full recovery of PPHN associated with prenatal SRI exposure is high, the benefit of depressive treatment far outweighs this potentially very small risk.

Some investigators have reported a relatively weak association of prenatal paroxetine with cardiac defects [45, 46], but this finding was not supported by others [47, 48].

Long-Term Neurodevelopment of Children Exposed to SRIs

Cognitive and behavioral development presents concerns surrounding prenatal psychotropic medication exposure. Although there have been two studies [49, 50] suggesting motor impairments in a small number of children exposed in utero to SRIs, one [49] did

not control for sedatives, hypnotics, and alcohol, and the other [50] did not separate the effects of antidepressants from other psychotropic medications. A significant number of studies, using more robust methodology and a variety of test batteries to assess >1,000 children exposed to SRIs during pregnancy, exhibited no differences in neurodevelopment when compared with controls [31, 32, 51]. These studies were not designed to assess neurocognitive development as a primary outcome and did not separate the effect of maternal depression from the effect of the antidepressant drug. In another study, this limitation was overcome by assessing the cognitive and behavioral development of children prenatally exposed to SRIs in relation to the intelligence of children of mothers with untreated depression and children of nondepressed mothers [25]. The results of this study did not find SRIs to be neurotoxic, supporting previous findings; the drug dose and duration of exposure during pregnancy did not predict any cognitive outcomes.

Other studies have revealed that child internalizing and externalizing behaviors are associated with maternal stress, mood, anxiety, and depressive episodes following delivery (and potentially during the third trimester), but not with antidepressant exposure during pregnancy [51, 52].

Recent research has suggested an association between SRI exposure during the first trimester of pregnancy and an increased risk of autism spectrum disorders (ASD) [53, 54]. The etiology of ASD is not clear; however, both blood and brain serotonin levels are known to be different in autistic compared to normal individuals [55], and brain serotonergic function is influenced by sex hormones. Therefore, it is conceivable that a link exists between prenatal exposure to medications that affect serotonin levels (such as SRIs) and ASD. More research is needed to confirm these findings and determine absolute risks.

In summary, the potential fetal risks should be weighed against the benefits of optimal treatment of maternal depression. Untreated prenatal depression is associated with numerous adverse outcomes for both mother and child, including high risk for postpartum depression. Effective pharmacotherapy is available and the overall risks for adverse pregnancy outcome are small. Disease control is essential for favorable outcomes and prevention of future child psychopathology.

Antiepileptic Drugs and Lithium

The multiple mechanisms of action of the antiepileptic drugs (AEDs) has made them pertinent in psychiatry for bipolar disorder, schizophrenia, mood swings, aggression, and post-traumatic stress disorder control [56]. Evidence of clinical effectiveness in mental illnesses has been reported on a number of AEDs (valproate, carbamazepine, lamotrigine, topiramate, and levetiracetam). Encouraging clinical results have been observed following pharmacotherapy with AED for acute mania and bipolar disorder [57] causing many to believe that there are shared biological mechanisms between epilepsy and psychiatric disorders [57]. However, knowledge of the mechanism of action remains obscure and evidence-based information concerning AEDs' reproductive safety comes mostly from epilepsy research.

Reproductive Safety of AEDs

Valproate and carbamazepine are established teratogens associated with an increase in rates of malformations with specific pattern of neural tube defects in 1–5 % and 0.5–1 %, respectively [58]. Prenatal exposure to topiramate, lamotrigine, and levetiracetam has not shown substantial evidence of increased teratogenic risk, showing major malformation rates within the 1–3 % of the general population. At present, prenatal exposure to levetiracetam has not revealed any associated malformations and it is considered to be drug of choice (if clinically indicated) in the treatment of epilepsy and psychiatric disorders in pregnancy [59].

Prenatal use of valproate has also been associated with an increased incidence of autism spectrum disorder; however, a recent study did not support such association after controlling for maternal epilepsy [60]. Further research is needed to support these findings.

The possible long-term neurocognitive effects of AEDs are being increasingly studied. Prenatal use of valproate in mono- or polytherapy has been associated with an increased risk for abnormal child neurodevelopment [61, 62]. The observed results have culminated in FDA issuance of safety alerts regarding the risk for birth defects and impaired cognitive development associated with in utero exposure to valproate [63]. Exposure to carbamazepine, lamotrigine, or levotiracetam monotherapy was not found to be associated with impaired children's long-term neurodevelopment [62].

Adequate disease management, including prenatal care, folic acid supplementation, level II ultrasound, and patient education, will lead to 95 % of successful pregnancy outcomes.

Lithium

Lithium is indicated for the treatment of affective disorders. Despite its clinical cost-effectiveness, lithium is associated with a specific pattern of cardiovascular malformations: Ebstein's anomalies [64]. More recent epidemiological research indicates that the risk of malformation ranges from 0.05 % to 0.1–2.4 % above the population baseline [65, 66]. Level II ultrasound and fetal echocardiogram can be performed to rule out cardiac anomalies. The maternal and fetal toxicity of lithium can be minimized by monitoring serum lithium levels and maintaining minimally effective plasma levels throughout gestation and monitoring neonatal symptoms.

Conclusion

Mental disorders are a significant cause of morbidity in pregnant women. Although not thoroughly studied in LMIC settings, the use of pharmacotherapy in pregnancy poses a major public health challenge that is certain to be prominent in populations

skewed to reproductive age. Control of perinatal mental disorder is the standard of care and is essential for favorable pregnancy outcomes for both mother and neonate. Psychotropic medications have been shown effective in disease control and presently are not associated with evidence of significant teratogenic risk, with the exception of some antiepileptic drugs. In all cases, the benefits of maternal, fetal, and neonatal well-being should be weighed individually against the potential teratogenic risk. Thoughtful preconceptional, antenatal, and postpartum management of pregnant patients and prescription of monotherapy, if clinically suitable, will increase the odds of favorable maternal and neonatal outcomes, which will improve child well-being later in life.

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Chapter 26
Child Development, Disability and Global Health: Opportunity and Responsibility

Robert W. Armstrong

The world over, children with disabilities face an uphill battle to achieve the potential they are born with. Parents are often left with limited options in finding the support their children need. If the child is disadvantaged by being born in a low- or middle-income country (LMIC), the challenges can appear overwhelming. Cultural beliefs and norms and the challenge of limited resources drive a level of neglect and sense of helplessness that leaves families struggling to simply cope with the daily care of their children.

People with disabilities represent a significant proportion of the world's population. According to the World Health Organization, there are one billion people in the world with a disability, disproportionately distributed to low- and middle-income countries [1]. In addition to the sheer number of individuals with a disability, there are significant challenges in many countries to address societal barriers that prevent persons with disabilities to access services, receive an education, and achieve employment and personal success as adults.

Unfortunately, the available statistics are shocking! The UN Development Programme has published some "facts" about disability: "80 % of persons with disabilities live in developing countries [2]. UNESCO estimates that 90 % of children with a disability will not attend school and literacy rates for adults are as low as 3 %. Mortality for children with disabilities is as high as 80 % in countries where under-5 mortality has decreased by more than 20 %. According to UNICEF 30 % of street youth are disabled. Women and girls with disabilities are particularly vulnerable".

Heymann and McNeill from the UCLA World Policy Analysis Centre point out that "by any estimate, disabled girls and boys make up one of the world's largest minority communities [3]. These children are among the last in most countries – and on the world stage – to have rights recognized. It was treated as inevitable that

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children with disabilities had fewer opportunities and worse outcomes. Over the past decade, it has been increasingly recognized that the limitations faced by children with disabilities are often primarily the result of the social context in which they find themselves".

By any measure, there is a long and challenging road ahead for people with disabilities if they are to achieve a valued and respected position in the societies within which they live. However, there are important new opportunities and resources that with concerted effort can lead to advances in the lives of disabled children [3, 4].

This chapter frames these opportunities in the context of the focus of this book, that is, access to appropriate and timely therapeutics for children living in low- and middle-income countries. The chapter explores the challenges that parents face in getting the care they need for their child and how as professionals with an interest in therapeutics we can better understand and support this effort.

Recognising Rights: The Tools to Impact Society

Parents, practitioners and policy makers can achieve more if they have a framework that recognises the rights of children who have a disability. We are fortunate that the United Nations Convention on the Rights of the Child (CRC) serves this purpose and has been ratified by virtually all of the countries of the world [5]. Four general principles of the CRC define the foundation for the realisation of all of the other rights: non-discrimination, the best interests of the child, survival and development, and respect for the views of the child. The child who is disabled can expect to have rights the same as those of any other child.

The CRC can then be linked to the other major global achievement; the United Nations Convention on the Rights of Persons with Disabilities. This Convention requires state parties to protect and safeguard all human rights and fundamental freedoms of persons with disabilities. The Convention defines people with disabilities to include those who have long-term physical, mental, intellectual or sensory impairments that in interaction with various barriers may hinder their full and effective participation in society on an equal basis [6].

What this means for children is that, no matter where they live in the world or what their socio-economic circumstances might be, their parents, parent organisations and disability professionals have an obligation to uphold a framework that their government has endorsed. While reality may be far from the endorsement by government, without this framework in place advancing the rights of children who have a disability would be much more difficult.

There is now global attention being directed to the issues of disability as highlighted by the recent high-level meeting of the UN General Assembly that focused on the Millennium Development Goals and other internationally agreed upon development goals as they influence and provide opportunity to individuals who have a disability [7]. As therapeutic services are defined and developed for children, it will

be important for advocates to utilise the Conventions and to remind governments of their obligations to children who have disabilities.

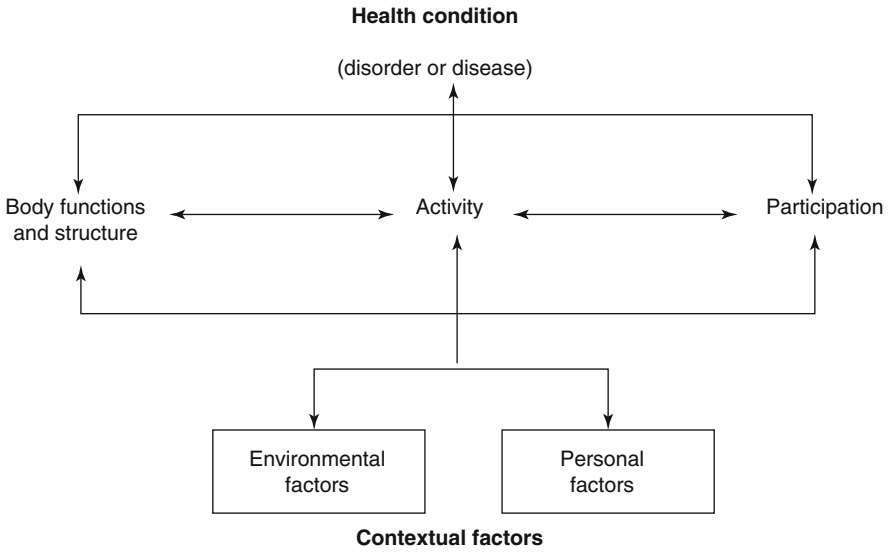
Child Development as a Global Priority

Over the last 20 years, there has been a growing body of knowledge about the interaction between biology and environment on child development with the period of prenatal development and of development in the first 3 years being of particular importance. These early interactions, termed "experience-based brain and biological development", which influence health, impairments, function and diseases, have enormous implications for the health and economic development of societies and has gained global attention [8]. As a result, significant investments will be made to maximise support in these early years of child development, including strategies to integrate early development support into programmes that up to now have simply focused on child survival [9, 10].

What has been largely missed in this discussion is how these early influences on development impact the child with an established disability. While the focus on improving outcomes of the population as a whole is extremely important, it is also important to not leave behind those children who have an established disability. Indeed, early diagnosis, focused therapeutic interventions, for example, related to communication, access to anti-epileptic medication for children with seizures, and behavioural or physical therapies may have important long-term impact on outcomes for these children. Government public policy that focuses on early child development must be inclusive of children who have established disabilities. Governments also need to support evidence-based decisions on effective therapeutics such that public investment has greatest impact for these children. The important message for policy makers is that children with established disabilities also have important developmental potential and required special attention in the early years.

Framing Disability

One of the most significant advances that have occurred in our understanding of disability has been the reconceptualisation of disability not simply as a disease or disorder but an interaction between biology, activity, environment or context and barriers. The International Classification of Function (ICF) developed by the World Health Organization has fundamentally changed the way we think about disability [11]. The ICF is structured around two dimensions: body functions and structure and activities and participation with contextual factors of environment and personal factors influencing function.



An adaptation of the ICF for children has been published [12] and work is ongoing to develop a core set of descriptors for specific disabilities that can be utilised by the global community [13–15]. The utilisation of this framework as a language of description and as a mechanism for refocusing attention to not only the underlying biology of the disability but most importantly the opportunity to focus on activities and participation of the child as he develops and ensuring that the individual characteristics and environmental barriers are a focus of attention.

An Irrational Commitment!

Parents are the drivers of opportunity for their disabled children. In the words of Urie Bronfenbrenner, parents have an irrational attachment to their children [16]. This irrational attachment is most often independent of whether or not their child has a disability. Within their personal and financial capacity, parents will do all they can to support the development of their children. Parents are of course an enormous resource that surprisingly we, as professionals, are still learning to respect and value.

Over the last 10–15 years professionals have increasingly incorporated parents as partners in the habilitation/rehabilitation plans for their children [17, 18]. A number of studies have defined parental needs and roles in relation to their children, leading to restructuring service systems to better meet the goals for their child [19, 20] and to more efficient use of scarce resources, better outcomes for the child and greater emotional support for families. Equally important has been the growth of parent-based advocacy and support organisations that provide a powerful collective force to influence institutions and governments.

In the LMIC setting, the role of parents becomes even more critical given the often significant limitations in available resources. In fact, where progress has been made in these settings it has often been driven by parent-based collectives and by non-government or overseas organisations that recognise and tap into the capacity of families to deliver the required services.

Essential Therapeutics for Children with Disabilities

Therapeutic interventions, whether these are pharmaceutical, technological, behavioural, or physical therapies are essential tools that support a child's development. Evidence-based and culturally and community adapted to the life of the individual child must be considered "essential" support to children with disabilities and of equal importance to the "essential medicines", which define those pharmaceuticals for children that are most important to survival.

There are challenges in building the evidence base that can be used with confidence by policy makers and this presents barriers to effective advocacy. This field in particular is prone to therapeutic interventions that have less to do with evidence and more to do with the promotional capacity of their advocates and the position of vulnerability parents feel in their search for the best approach for their child. Professionals have a responsibility to both develop the evidence for therapeutics and to ensure that this evidence can be used both by parents and by policy makers.

Defining the Strategies for Achieving Progress

While the challenges are significant, the opportunity does exist to move forward, to have a common vision of where we need to be, which is framed by the Conventions and the International Classification of Function and our understanding of child development and the unique developmental pathways that children with a range of disabilities will follow.

How do we achieve impact on the health and well-being of children who have a disability and who are living in low- and middle-income countries? Five interrelated strategies are proposed to answer this most important question.

First, participate in organised advocacy. Bring the Conventions to life and do this as a collaborative effort with parents, parent organisations, professionals and professional organisations. Make sure we frame this advocacy within our understanding of human development, particularly early child development and within the framework of the ICF.

Health professionals have a special relationship of trust with their clients and are in a position to help address complex rights issues. In particular, their attitudes and behaviours towards the child with a disability can significantly impact parent perceptions and decision-making. Health professionals are also connected to their community and can have significant impact on policy issues.

Institutions can also be influential both in creating an internal environment of acceptance and support but also as advocates in the community and to government. Organisations that advocate for early child development must also be inclusive of children with disabilities.

Advocacy needs to be organised, strategic and persistent. If this is achieved, then governments and the institutions of civil society will listen. There are many examples of situations in which this strategy has proven effective.

Second, it is important to think and design for population solutions. The best evidence in the world will not help a child if it is not accessible or if it does not lead to tangible improvement. While our therapeutics focus on the individual child, our reach must be to all children. This demands the development of local leadership and expertise and this must drive innovation in delivery systems for therapeutics. The principle of "no child left behind" should apply to children with disabilities and our challenge is to be able to reach them as a population, a very big challenge in low- and middle-income countries where poverty, transportation and rural distribution of the population defines the challenge.

Third, we must drive innovation in child disability. Innovation not only in better prevention, promotion and therapeutic interventions but also innovation in systems of delivery and economics such that low- and middle-income countries can achieve important outcomes for their children even within a socio-economic environment that will present barriers for many years to come. The opportunity to harness e-health technologies to reach children and their families has enormous promise. Of equal importance, supply chain innovations, technology adaptations, and innovations in education and training can significantly advance service to children while still ensuring a strong evidence base and quality delivery. Indeed, innovation in low- and middle-income countries may well, in the future, drive change in more developed and established services in developed countries.

Fourth, build sustainable partnerships between institutions that have a focus on children with disabilities. Resource-limited countries will benefit from structured support over time that builds capacity within these countries while taking advantage of the resources that developed countries have to offer. The major gaps in evidence that exist in LMICs present enormous challenges to achievement of positive change in practice and policy [21]. At a recent meeting of three major academic organisations who have a focus on child disability (American Academy of Cerebral Palsy and Developmental Medicine, European Academy of Childhood Disability, and the Australasian Academy of Cerebral Palsy and Developmental Medicine), there was agreement to create an International Alliance of Academies for Child Disability, which will now assist the development of regional or country academies that will align with the international body and be supported to develop local capacity. In the past, these academies invited participation of professionals from resource-poor countries to their individual meetings but now the focus is on building capacity within the low-resource countries while at the same time providing rich opportunities for global collaborative engagement. These strategies sustained over time will have major benefits in advancing access and innovation.

Finally, whatever we do we must set achievable goals, measure progress against milestones over time and adjust as we move forward. Child disability is complex and developing common conceptual models for understanding disability provides the framework for developing standard indicators of inputs, processes, outputs, outcomes and impact with clear and measurable plans [22]. Furthermore, such an approach allows for design of interventions that can be compared. An iterative process for service improvement can be highly effective if the right information is available for analysis.

Summary

Children with disabilities have the same rights as all children. They have developmental potential that is important to recognise and support. Therapeutic interventions play a critically important role in supporting the early development of children and children living in resource-poor countries are at particular disadvantage. However, utilising advocacy tools, focusing on innovative solutions, and building sustained collaborative relationships can have a very important impact on the developmental potential of children no matter where they live or what resources are available to them. Building strong professional alliances and working with parents to organise services and advocate for children eventually provides them with the best opportunity.

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Chapter 27
Hydroxyurea Therapy for Sickle Cell Disease in Low-Income Countries

Isaac Odame

Introduction

Sickle cell disease (SCD) is a group of genetic blood disorders in which the red blood cells have a predominance of sickle hemoglobin (Hb S) produced due to an inheritance of a β-globin mutation (β^S) resulting from a single amino acid substitution (HBB Glu6Val) in the β-globin chain. Affected individuals are either homozygous for the β^S mutation (SS) or compound heterozygous with other β-globin mutations (e.g., SC, Sβ-thalassemia, SO^{Arab}, SD^{Punjab}). Hemoglobin S is poorly soluble and polymerizes in the deoxygenated state, resulting in damage to the red cell membrane, hemolysis, vaso-occlusion, and vascular endothelial damage.

SCD is one of the most common genetic diseases worldwide. As a result of selection pressure from malaria infection, the disease occurs widely in sub-Saharan Africa, parts of the Middle East and some areas of the Indian subcontinent. Migrations of populations from these sites of origin to North America, Brazil, Caribbean, Central America, Europe, and Asia account for the variable frequencies of SCD across the world. It is estimated that annually in Africa, more than 300,000 babies with SCD are born, with an incidence of up to 2 % of babies born in some regions of sub-Saharan Africa. SCD is characterized by life-long hemolytic anemia and acute and chronic damage to body tissues and organs. Acute complications include unpredictable severe pain episodes, acute severe anemia (commonly malaria-related), acute chest syndrome, stroke, and priapism. Chronic organ damage has its onset in infancy with loss of splenic function and increased susceptibility to infection from encapsulated bacteria. With age and ongoing hemolytic anemia, vaso-occlusion, and vascular endothelial dysfunction, other organs such as the brain, kidneys, lungs, major joints, and eyes become damaged.

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In high- and middle-income countries, survival of children with SCD (estimates of more than 90 % by age 20 years) has improved due to the implementation of public health interventions directed at early diagnosis through newborn screening followed by antipneumococcal prophylaxis with penicillin and pneumococcal vaccination. By contrast, in low-income countries (sub-Saharan Africa in particular), home to nearly 90 % of the world's children born with SCD, these interventions are not commonplace, accounting for the high under-5 mortality rates estimated at 50–90 % within this patient population. In sub-Saharan Africa, SCD-related mortality accounts for about 10 % (range 5–16 %) of all under-5 mortality.

The only curative treatment for SCD is hematopoietic stem cell transplantation (HSCT), a procedure not widely available or affordable in most healthcare systems. In place of curative therapy, the increasing delivery of disease-modifying therapies such as hydroxyurea therapy and chronic blood transfusions is helping to improve survival as well as alleviating SCD-related morbidity. Delivery of chronic blood transfusions remains a challenge in many low-income countries because of limited access to blood supplies, cultural barriers, and lack of resources to prevent or treat transfusion-related complications such as iron overload. Hydroxyurea therapy, orally administered and relatively more affordable, appears to be the most feasible or viable disease-modifying option for the management of SCD in resource-poor settings. Furthermore, there is evidence of an epidemiologic transition occurring in low-income countries, whereby children born with SCD who previously did not survive, are now surviving beyond 5 years through widespread implementation of primary immunization, nutritional programs and better use of antimicrobial therapy. As a consequence, with time, the numbers of surviving children needing care would most likely increase and pose considerable strains on the already overstretched healthcare systems. The successful implementation of a safe, efficacious and affordable disease-modifying therapy for SCD is crucial not only in improving patients' survival, but also reducing morbidity and improving their quality of life.

This chapter reviews the potential benefits of hydroxyurea therapy for SCD in low-income countries based on what we know about such benefits among patients treated in high- and middle-income countries. The unique advantages of hydroxyurea therapy in low-income settings, where other disease-modifying therapies such as chronic blood transfusion and HSCT are largely unavailable, are highlighted. Finally, the challenges and opportunities for conducting clinical trials to provide evidence of the safety and effectiveness of hydroxyurea therapy are addressed. The study of hydroxyurea therapy for SCD highlights many of the challenges faced in studying new therapies in poor resource settings.

Key Messages

- SCD is associated with high morbidity and mortality, particularly in sub-Saharan Africa with the heaviest disease burden.
- Hydroxyurea therapy has proven clinical efficacy in patients with SCD in high-income settings.

- Considerable barriers exist in undertaking studies in poor resource settings where hydroxyurea therapy could have the most impact.
- Through collaborative north–south research partnerships, studies of hydroxyurea therapy have begun in sub-Saharan Africa.

Hematological and Clinical Effects of Hydoxyurea Therapy

While individuals with SCD all have a common genetic basis for their disease, there is wide phenotypic diversity in disease expression. Fetal hemoglobin (Hb F) expression is known to be one of the factors protective against clinical severity. Thus, pharmacologic induction of Hb F has been a focus of laboratory and clinical research to find effective treatments for SCD.

Hydroxyurea has emerged as a leading drug for Hb F induction because of the ease of administration, safety profile, predictable hematological effects, and proven clinical efficacy. First synthesized in 1869, and demonstrated to have antileukemic activity in the 1960s, hydroxyurea inhibits ribonucleotide reductase, a rate-limiting enzyme in DNA synthesis, but does not affect RNA or protein synthesis. While the exact mechanism by which hydroxyurea induces Hb F production is not completely understood, it has been proposed that it transiently suppresses erythropoiesis followed by a recovery period during which immature progenitors that retain ability to synthesize Hb F are recruited. In addition to Hb F induction, the potential benefits of hydroxyurea is thought to include decrease in neutrophil count, increased erythrocyte volume and hydration, increased deformability of sickle erythrocytes, and reduced adhesion of sickle erythrocytes to the vascular endothelium. From earlier proof-of-principle experiments in humans, through phase 1/II trials, double-blind placebo-controlled, randomized trials in adults in the 1990s and more recent placebo-controlled trials in infants and toddlers, substantial evidence for the laboratory efficacy of hydroxyurea has been provided.

The laboratory outcomes include increases in Hb F, hemoglobin, and MCV with decreases in WBC, reticulocytes, and LDH. These laboratory effects have been demonstrated in American studies in which doses were escalated to maximum tolerated dose (MTD) as well as European studies using lower, fixed dosing regimens. Hydroxyurea has shown clinical efficacy in reducing acute pain episodes, acute chest syndrome, hospitalizations, and need for blood transfusions. Recent reports from USA, Brazil, and Greece have demonstrated improved survival of adults on long-term treatment with hydroxyurea. In 1998, hydroxyurea was approved by the US Food and Drug Administration for the treatment of adult patients to prevent recurrent pain episodes and need for blood transfusion. The European Medicines Agency granted its approval of hydroxyurea for the treatment of children and adults with SCD in 2007. While some concerns remain about the long-term risk of malignancy and effects on pregnancy and fertility, the tens of thousands of exposure years that have now accumulated confirm that the clinical benefits of hydroxyurea therapy far outweigh these potential risks.

Barriers to Implementing Hydroxyurea Therapy in Low-Income Countries

Evidence for the efficacy and safety of hydroxyurea therapy in low-income countries is very limited as most of the available evidence is based on studies conducted in high-income countries. Being a cytostatic agent, hydroxyurea has predictable myelosuppressive effects requiring hematological monitoring when administered to patients. Such monitoring will be challenging in low-income settings with limited laboratory and clinical resources. Further, treatment-induced neutropenia could impact on prevailing comorbidities such as infections (e.g., malaria, tuberculosis, and other bacterial infections) and malnutrition. Other potential barriers to widespread implementation of hydroxyurea therapy include acceptability of the treatment to patients, families and care providers, as well as medication costs to patients and healthcare systems. Given the robust evidence for the efficacy of hydroxyurea therapy for SCD already available from in high-income countries, current considerations for placebo-controlled trials in low-income countries raise important ethical and logistical questions. What is paramount is the need for effectiveness research that examines the safety and clinical effectiveness of hydroxyurea therapy in well-designed open-label trials. Cost-effectiveness studies and studies to demonstrate improvement in patient/family quality of life would subsequently be critical in strengthening the case for governments and development agencies to fund programs for widespread implementation of hydroxyurea therapy. This is particularly important, considering the increasing burden imposed by SCD on health systems in low-income countries, where limited funding resources creates perpetual and challenging situations of competing priorities for healthcare financing. A well-coordinated stepwise approach beginning with safety and effectiveness studies of hydroxyurea therapy, to cost-effectiveness and quality improvement studies, education of patients/families and care providers, and then to coordinated evidence-based advocacy for public and private funding to support hydroxyurea treatment programs is needed in low-income countries.

Addressing the Problem

Safety Concerns

Hydroxyurea therapy is associated with predictable dose-dependent myelosuppression that commonly manifests as neutropenia, but occasionally as reticulocytopenia and more rarely as thrombocytopenia. The myelosuppression is usually transient and mild, and typically resolves within a week of drug withdrawal or dose reduction. Clinical trials conducted in high-income countries have demonstrated that hydroxyurea therapy does not contribute to an increased risk of bacterial infections. However, in low-income settings with a high prevalence of infections such as

malaria, helminthic disorders, tuberculosis, and other bacterial infections (e.g., pneumococcal and salmonella), the possibility of increased risk of infection requires that safety of hydroxyurea therapy be tested in appropriately designed clinical trials. The safety and appropriate dosing of hydroxyurea therapy in the context of other comorbidities such as anemia and malnutrition also need to be studied. Initial clinical trials should consider interventions to minimize the potential treatment-related risks, including pneumococcal vaccinations, early diagnosis and treatment of malaria and other bacterial infections, nutritional support programs, and regular monitoring of blood counts. But, ultimately, the safety of hydroxyurea therapy within real-life situations of health systems in which these interventions are not easily accessible will need to be tested, given the possibility that hydroxyurea therapy may reduce rather than increase the risk of these comorbidities.

Feasibility of Clinical Trials in Low-Income Settings

To conduct appropriately designed prospective clinical trials, sites in low-income countries with the prerequisite clinical and laboratory infrastructure need to be identified. Laboratory capabilities to monitor blood counts including hemoglobin, total white count, and differential and platelet count should be the barest minimum. Other necessary infrastructure elements needed include research pharmacy and access to computers for data entry. Recent collaborative efforts between clinicians and researchers in high-income countries and their counterparts in low-income countries are yielding fruit in helping to identify suitable sites for the conduct of critical safety trials of hydroxyurea therapy. A notable example is the comprehensive survey of SCD centers in sub-Saharan Africa conducted by the Global Sickle Cell Disease Network, which gathered information about existing clinical and laboratory infrastructure in these centers. Such valuable information is being helpful in planning feasibility studies that have a high chance of success. The importance of creating human resource capacity in low-income countries cannot be understated. The training of local healthcare providers in the ethics and rigor of research design and execution requires considerable efforts and resources but is crucial if appropriate clinical trials that determine the feasibility, safety, and effectiveness of hydroxyurea therapy in low-income settings are to be conducted leading to conclusive proof.

Dosing Regimens and Endpoints to Be Tested

Given the strong evidence for the efficacy of hydroxyurea therapy for SCD in high-income countries, many clinicians in low-income countries would view the conduct of placebo-controlled trials in those settings as ethically problematic. Most clinician experts in low-income countries favor open-label trials designed to evaluate safety and effectiveness of hydroxyurea therapy. Several dosing regimens

have been studied, including fixed-dose (low: <15 mg/kg; medium: 15–20 mg/kg) and maximum tolerated dose (MTD) regimens (typically 25–30 mg/kg). Lower dosing regimens would be advantageous in not requiring rigorous monitoring within these low-resource settings. However, higher dosing regimens might prove to be more effective in achieving the desired clinical endpoints. Monthly blood counts are typically performed in high-income countries for children on hydroxyurea therapy for management of SCD. It is very possible that less intensive regimens could be safely monitored at 2–3 monthly intervals, best suited for low-income settings.

As discussed previously, safety endpoints, including laboratory toxicities and infectious comorbidities should be a primary goal of the early clinical trials in low-income settings. Laboratory and clinical efficacy data can be linked to safety studies as a prelude to conducting definitive larger-scale effectiveness trials.

Inclusion criteria for safety and feasibility trials of hydoxyurea therapy could be limited to subjects with severe disease (e.g., previous stroke with a goal to prevent recurrent stroke, acute chest syndrome, recurrent severe pain episodes or primary stroke prevention for children with high transcranial Doppler (TCD) velocities) or open to all comers with SCD. However, given the challenges with implementing widespread hydroxyurea therapy in the context of limited resources, the practical reality suggests that low-income countries might best target limited hydroxyurea supplies to treat patients with severe disease.

Costs and Sustainability Concerns

While the costs of hydroxyurea therapy are largely affordable in high-income countries, the same cannot be said of low-income countries with the heaviest disease burden. For many patients in low-income settings, their only access to hydroxyurea therapy may be through enrollment in clinical trials. This creates long-term ethical implications as to how continued therapy can be maintained after the trials are completed. Strategies to address these challenges need to be considered during the design of prospective clinical trials in low-income countries. Broad partnerships with pharmaceutical industry partners (particularly manufacturers of hydroxyurea), international donor agencies, and governments would be helpful in sourcing the necessary funding to support evidence-based implementation of hydroxyurea therapy once its safety and effectiveness have been proven. In this regard, it is noteworthy that the World Health Organization has placed hydroxyurea on its list of essential drugs for the specific indication of treating SCD. This should serve as a major boost to advocacy efforts to place SCD high on the agenda of global health funders who aim to support evidence-based solutions for major health problems in low-income countries. Prospects exist for pursuing strategies to manufacture hydroxyurea within regions like sub-Saharan Africa with the heaviest burden of SCD. This could result in substantial cost reduction and increased access to hydroxyurea in African health systems for the treatment of SCD.

Current Studies of Hydroxyurea Therapy for SCD in Africa

A number of clinical trials of hydroxyurea therapy for SCD have recently been initiated in sub-Saharan Africa. The SCD Stroke Prevention Trial in Nigeria (SPIN), funded by the US National Institute of Neurological Disorders and Stroke of the National Institutes of Health, is a single-arm feasibility study at the Aminu Kanu Teaching Hospital, Kano, Nigeria in which children with SCD aged 5–12 years with high TCD velocities are administered low-dose (20 mg/kg) hydroxyurea. The trial aims to test the acceptability of hydroxyurea therapy for primary prevention of stroke in children with SCD with a primary endpoint of measured daily adherence to hydroxyurea therapy. Secondary aims are to establish a safety protocol for using hydroxyurea for primary prevention of strokes in a low-income country and to evaluate adverse events including hydroxyurea-related morbidity and mortality in those settings.

Another study, Realizing Effectiveness Across Continents with Hydroxyurea (REACH), sponsored by the Cincinnati Children's Hospital and Research Center, is a multicenter prospective phase I/II open-label dose-escalation of oral hydroxyurea for children with SCD. This study aims to access feasibility of conducting prospective research study with hydroxyurea in sub-Saharan Africa. It will also monitor the safety of hydroxyurea therapy in children with SCD aged 1–10 years. Secondary objectives include evaluating the efficacy of hydroxyurea therapy and investigating the effects of hydroxyurea dose-escalation. Upon completion, the REACH trial could achieve the largest enrollment of children in sub-Saharan Africa on hydroxyurea therapy for SCD.

A randomized placebo-controlled trial, Novel use Of Hydroxyurea in an African Region with Malaria (NOHARM), sponsored by the University of Minnesota, has a goal to investigate the safety and efficacy of hydroxyurea for children with SCD in a malaria endemic region within sub-Saharan Africa. This Kampala (Uganda)-based study will determine the incidence of malaria as well as hematological toxicities and adverse events in children with SCD treated with hydroxyurea compared to placebo.

These and other studies of safety and efficacy of hydroxyurea therapy for children with SCD in sub-Saharan Africa will help to provide the needed evidence for larger effectiveness studies. Lessons learned about safe and effective dosing and monitoring regimens for hydroxyurea therapy will be helpful in developing innovative treatment strategies that are affordable and sustainable in countries with limited clinical and laboratory resources for the management of children with SCD.

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Part V
Concluding Comments

Chapter 28
Challenges in Drug Therapy of Children in Africa

Anders Rane and Parvaz Madadi

"When women and children die prematurely the future of a nation is doomed" (Dr E Bai Koroma, President of the Republic of Sierra Leone) is just one among many reflections on the high global maternal death rate and high mortality in children under 5 years [1]. However, these consequences are secondary to the immense suffering of all those humans affected by malnutrition, starvation, poor sanitation, and infections.

About six million children under 5 years of age die every year, a number almost equal to the total population of countries like Hungary, Switzerland, or Israel. Furthermore, there are more than 300,000 maternal deaths annually in the world, and more than half of all these deaths occur in the African continent.

Although one-third of the deaths in children may be ascribed to or worsened by malnutrition, it is estimated that some 70 % of the relevant children's diseases are amenable to treatment with drugs, preferentially antibiotics for pneumonia, diarrheal diseases, malaria, and HIV/AIDS.

Given this lamentable situation, the UN set up the Millenium Development Goals (MDG) with the aims among others for the year 2015 to reduce child mortality by two-thirds (goal 4), to improve maternal health (goal 5), and to combat HIV/AIDS, malaria, and other major diseases (goal 6).

These goals have had different degrees of success in different countries, All regions except sub-Saharan Africa and Oceania have reduced the mortality rate in children under 5 (U5MR) by more than 50 %. The relatively poor achievements in Africa have been highlighted and discussed by the African Union [1]. Launching

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of the "Better Medicines for Children" Resolution of the World Health Assembly in 2007 [2] is recognized as an important international measure to help developing countries to establish a sound, effective, and evidence-based drug policy. The key point of the WHA60:20 resolution is to urge member states to promote the development of appropriate pediatric drug formulations, to promote research in drugs for children, to implement essential drug lists, and to stimulate the use of drugs identified in this process. Not the least important objective is improved accessability to drugs for children through a variety of strategies, including equitable reimbursement schemes and price monitoring.

The real situation with children's access to evidence-based drug therapy is far below acceptable standards in developing countries throughout Africa, although the situation has improved since 2000 thanks to the MDG and WHA initiatives.

The achievements of MDG4 and MDG5 are easy to monitor and measure if the basic information is provided by the member states. In contrast, various indicators of pharmacotherapy such as *quality* of the treatment, or *quantitative* information about extent of treatment in the pediatric population are more difficult to obtain. The major reasons for this include insufficient amount and poor quality of sources of information, and the multifactorial determinants of quality and efficiency in drug provision and transport, and in establishment and maintenance of contact with the target children. The final outcome is also dependent on diagnostic and therapeutic knowledge on the part of the drug providers and drug prescribers. It is also dependent on accessability, affordability, and an unbroken chain of drug delivery all the way from the manufacturer to the patient. We know very little about the radius of influence of healthcare providers, or the routes by which drugs reach the children, if ever. Information about treatments and outcomes is difficult to track and must be based on interviews of people in direct contact with the population affected.

A recent study on the perceptions among African scientific investigators of different parameters related to quality of drug prescription, choice of drugs, accessability, and affordability of drugs for children in African countries has revealed considerable problems regarding therapeutics in African children (2015, *in manuscript*). This kind of information is not obtainable through registries or medical records since they often are nonexistent in low- and middle-income countries. The informants received a questionnaire by e-mail and were asked to answer ten semi-quantitative or open-ended questions. These individuals across all of Africa were identified by means of a PubMed literature search using the keywords "drugs/medicine + child/children + a specific African country". Additional informants were also identified by referrals.

The responses received suggest that only about half of all prescribed drug orders were written by licensed primary care physicians and specialists. Moreover, a significant portion of the children were perceived not to receive needed medicines because they could not afford them. Approximately half of respondents perceived that an Essential Medicine List for Children did not exist in their country, and even fewer children were considered to have access to the drugs on the list.

This situation is deleterious to health among children in African countries and contributes to the severe disease burden in the population. It is obvious that decisive

measures on a national level need to be taken to implement the key recommendations of the WHA60:20 (2007) programme in order to make needed medicines affordable and accessible to children. Evidence-based drug therapy in children is crucial to successful achievement of the MDG4 as treatable diseases play such a large causative role in the high mortality.

The major themes identified for further study based on the survey described relate to the *quality* and *extent* of drug treatment of African children in need of drugs. *Quality* of prescribing is highly dependent on level of education of nonphysician prescribers or providers. It is important that a correct choice of drug and dosing strategy is made, that the chemical–pharmaceutical formulation of the substance be of high quality, and that treatment results be followed up adequately. The source of the medicines and the means by which they are transported and stored may be crucial elements determining satisfactory product quality. Many of these controlling tasks may be performed by the medical community, by various community-based organizations and institutions, as well as by governments.

As discussed in the concluding commentary that follows, future studies will also have to investigate the implementation of the Essential Medicines List for Children in the member states, while exploring the affordability of essential drugs for children. Teaching and education in pharmacotherapeutic principles are crucial in almost all of the professional categories mentioned above.

Given this situation, it is obvious that nothing will change to the better if the interest in drugs for children and the incentives and impetus to investigate such medicines continue to be as weak as they are today in those parts of the world where the MDG are struggling to be achieved. It is hoped that the current volume will serve as a compelling signal and exhort caregivers, organizations, authorities, and local and national governments responsible for health of the world's children, to react and act!

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Chapter 29
Training Clinicians in Developing Countries on Rational Use of Medications in Children and Pregnant Women

Gideon Koren

This volume has offered a rather detailed blueprint, highlighting a variety of elements that must take place if we are to ensure that children and pregnant women in developing countries are to benefit from the advantages of medications existing in the developing world. However, even if all the stars are lined up in a way that will make this possible, not much will happen without a maximal effort made to educate physicians, nurses, pharmacists, and parents on rational use of medications during development.

Training in rational therapeutics is a challenge even in the most developed areas in the world, due to the complexity of the knowledge and skills the clinician needs to obtain, and because medical learning is still very Oslerian in its focus on diagnosis.

All too often, studying therapeutics still translates mostly to memorizing drugs, indications, and dosages. Yet, many of these schedules will become obsolete in years to come, leaving clinicians without appropriate tools to understand and adopt new medicines.

The Pillars of Training

Any training must address the needs in three different pillars: knowledge, skills, and attitudes. While knowledge is the most commonly touched upon, skills, such as understanding pharmacokinetic principles and critical appraisal of data, are essential. Attitudes are equally important, as they reflect the sustained "wisdom" of making the right choices, of being advocates for our patients, and being able to work in teams and learn from each other.

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Core Training Areas

After training health professionals in pediatric and developmental pharmacology for most of my professional life, I believe that the key elements needed for training them in rational drug use in children and pregnancy should include:

1. Knowledge in the essentials of pharmacology and toxicology. This must include pharmacokinetics and pharmacodynamics, treatment effects, adverse effects, therapeutic drug monitoring, and overdose.
2. Basic understanding of how children differ from adults in the ways their bodies handle drugs and respond to them.
3. Safety of drugs in pregnancy.
4. Pharmacovigilance –how to evaluate adverse events and establish or disprove causality.
5. Critical appraisal. One cannot overestimate the importance of developing abilities to read data relating to a medication and be able to appraise its value, quality and clinical significance. Without these abilities the health professional is almost totally dependent on instructions given by drug company representatives.

The international academic community of experts in developmental therapeutics is small, and many members of this community, being physicians or pharmacists, have, throughout their careers, been training physicians, pharmacists, and other health professionals in developing countries. In most cases, the training takes place in the developing country itself, although in the minority of cases learners join existing courses in Western countries (e.g., the Summer Institute in Developmental Pharmacology jointly organized by the American NIH and Canadian CIHR) [1].

While the models of such training are as variable as the individuals delivering them, it may be useful to discuss some key principles that can increase the effectiveness of such modules.

1. Problem-based learning: Rather than absorbing didactic lectures, most learners react more favorably and retain data optimally when the material is discussed in the context of carefully selected cases that are presented first and then discussed in parallel with provision of the knowledge needed to diagnose and treat the case [2]. In the same vein, using multimedia to convey therapeutic principles more vividly proves very effective, as we have shown over the last two decades with the use of the movie *Awakening* [3].
2. Learners should come to the learning experience after being prepared by tasks and learning materials sent to them in advance. In our courses this element was ranked very highly by participants [1]. For example, training in critical appraisal of published data on therapeutics necessitates learners to invest time before the course. Coming prepared makes the input by the trainer, as well as by other participants, much more effective [4].
3. Understanding of the difference between adverse events and adverse drug reaction should emphasize the need to evaluate the probability of causation, using one of several existing methods [5, 6].

4. One of the major sources of medication-related morbidity and mortality of children is deficient parental knowledge concerning the drug, its dose, its effects and adverse effects. This aspect must be emphasized during training, because even experienced physicians, pharmacists or nurses who do not communicate such information effectively with a parent caring for children, are not likely to decrease the risk of therapeutic mishaps [7]. Although there are only limited studies from developing countries, it is reasonable to assume that the issue in low-income countries is much more severe than in developing countries [8].
5. Among infants and young children, tenfold errors in drug dosing due to calculation errors of stock solutions is another major life-threatening risk from drugs. Making learners aware of this issue is critical. It has been shown that overcoming this issue is not achieved simply by short tutorials. Probably longer retraining processes targeting erring physicians are needed [9].

While presently the efforts to train health professionals in the field of developmental therapeutics are based on local initiatives through bilateral connections of academic institutions, it would be beneficial to plan this important activity on a global scale, through existing organizations such as the World Health Organization, the International Union of Pharmacology, or the International Pediatric Association. In addition to solidifying a standard international curriculum, such an effort should also include the financial support needed to ensure the viability of effective training.

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Chapter 30
Taking Medicines for Children Forward

Suzanne Hill

There has been progress over the last 10 years in getting medicines for children on the shelf, but there is still much to do. A major challenge is getting a medicine from the shelf to the child, for the right purpose and at the right dose. So we consider that there are four main strategies that need to be promoted to continue to improve access to medicines for children:

1. Continuing advocacy and increasing demand
2. Ensuring financing and reducing out of pocket payments, through universal health coverage or health insurance
3. Strengthening the supply chain for medicines for children, as part of strengthening health systems
4. Improving prescribing of medicines for children by all health professionals

Advocacy and Increasing Demand

It can be argued that one of the impediments to getting medicines for children on the shelf is the lack of demand from pediatricians, other clinicians, and caregivers. There has been a long history of "making do" – with adult formulations, estimated doses, and lack of evidence to guide practice. That is now changing, with the regulatory requirements in the USA and the EU as one example, but there is still a long way to go. Other countries have not had the same success in prodding industry to develop and register formulations for children. Although there are arguments about

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market size and costs of development, it is clear that if demand is inconsistent there will be no progress in supply.

A related issue is promoting appropriate, good-quality clinical trials in children. The ethical position that children are too vulnerable to be included in clinical trials has now been rightly reversed. If we do not perform clinical trials in children, the alternative is continuing to guess the right dose and duration of treatment as well as tolerating uncertainty about efficacy and safety. This approach is no longer acceptable in the context of standards for evidence-based practice. But good-quality clinical trials are demanding of resources and skills and, in resource-limited settings, these capacities will need to be developed with careful foresight. Sharing data from these trials, transparently and systematically, will also promote integrity and trust in settings where there is still concern about including children in clinical research.

So there is a need for continuing advocacy for better evidence, better formulations, and better use of medicines in children. Pharmacists need to be less ready to provide extemporaneous preparations if there is no formally marketed suitable product available. Parents must demand better options for treatment, at affordable prices. And notwithstanding the attractions of some of the new technologies available, such as micro-tablets, "better" does not necessarily mean greater complexity or cost. As has been seen in malaria, oral dispersible solid tablets are an ideal answer to meet needs in resource-poor environments.

Ensuring Financing and Affordability

The UN resolution on Child's Right to Health, 2013, clause 45 acknowledges that

> …universal health coverage implies that all children have access, without discrimination, to nationally determined sets of the needed promotive, preventive, curative and rehabilitative basic health services and essential, safe, affordable, effective and quality medicines, while ensuring that the use of these services does not expose the users to financial hardship, with special emphasis on the poor, vulnerable and marginalized segments of the population…

Yet in the recent series published in PLoS Medicine on progress on universal health coverage (UHC) [1], the indicators for access to medicines for children were limited to vaccination, availability of antibiotics for pneumonia, ORS for diarrhea, and where appropriate, use of antimalarials. While these are undoubtedly essential interventions, they are limited and do not adequately take into account either future developments or some current needs that would enhance child health. What about access to appropriate analgesic and palliative care medicines for children? Or ensuring coverage of cheap, off-patent cytotoxics that are curative for some of the most common children's tumors? Paying out of pocket for these medicines can have a catastrophic impact on family finances and well-being.

Case studies of the implementation of UHC in countries such as Thailand and Ghana are accumulating. Without appropriate attention to the selection of cost-effective medicines, Jonathan Quick describes UHC as a "Trojan Horse" that can increase expenditure [2]. In health systems that have significant budget constraints, "special" populations and "special" products may be understandably lowest in the

priority list for inclusion in coverage. So implementing UHC successfully, while at the same time trying to make sure that children are adequately covered, will require that medicines for children are carefully considered from the beginning. As the evidence consistently shows that copayments reduce access to medicines [3], options such as no-copayments for children under 5 years, or no copayments for products that are "essential" will need to be included in the assessment of finances required for sustainable coverage. Otherwise, out-of-pocket expenses will remain a major barrier to access to medicines.

Strengthening the Supply Chain

Medicines for children are a challenge to pharmaceutical supply chains. If the medicines are liquid, there are problems of weight, mass, and stability and appropriate storage conditions. In addition, if there are different dosage forms or multiple different strengths of products, tracking product inventory and ensuring that there is no wastage but at the same time, adequate supply, can be a real problem even in high- and middle-income countries.

So the resources and capacity to manage a supply chain are essential if access to medicines is to be guaranteed. These resources include human skills – management, administration, logistics, inventory, accounting, IT – as well as infrastructure such as warehouses (public or private) and transport. The assumption often seems to be that if you ensure the presence of a pharmacist on staff, then all will be managed – but pharmacists also need training to make sure that the skill set they need is acquired. Countries such as Indonesia have to overcome geographic distance, transport and infrastructure challenges, as well as human capacity limitations in order to ensure supply of medicines, including medicines for children to all districts. In small island countries such as those in the Pacific, the entire national pharmaceutical supply chain may be under the control of a single individual, who may be there temporarily or part time, and who may or may not have appropriate training.

So partnerships such as People That Deliver [4] have a significant role to play in promoting the skills that are required for supply chain security. Educational institutions, including those providing tertiary training for pharmacy, need to take account of the requirements for management skills as part of the curriculum. Additional cadres of trained pharmacy assistants and technicians, prepared with appropriate training, may also be an option in places where there are limited numbers of pharmacists. Planning for this workforce in any analysis of a national pharmaceutical sector is essential in promoting access to medicines for children.

Improving Prescribing

Prescribing accurately for children is a demanding skill. Once the diagnosis is clear, doses of appropriate medicines have to be adjusted for age and weight. The form to be administered has to be matched to the child's developmental capacity to ingest it,

as well as to the ability of parents/carers to administer the medicine reliably and correctly. If the route of administration is via injection, then appropriate skills are needed.

Yet even in high-income countries, medical education about prescribing is variable and at times poor, in relation to the adult population – let alone for special populations such as pediatrics. This becomes evident, for example, in the overuse of stimulants and antibiotics as well as inappropriate use of cough syrups and sedatives. The adverse outcomes of this inappropriate use of medicines can be both individual- and system-wide, particularly with respect to wasting of limited resources.

Tackling poor-quality prescribing is an enormous challenge. Medical educators must work with pediatricians and academics to ensure that university curricula provide for teaching of prescribing skills. These need to be assessed, but then there also needs to be consideration of how to manage postgraduation influences on prescribing, such as pharmaceutical promotion. Strategies such as standard treatment guidelines (if appropriately developed without commercial influence and based on clinical evidence), quality of care processes, and formularies may help in hospital settings. But practitioners also need point-of-care decision aids in private practice as well as incentives to remain up-to-date. Some countries have introduced national programs to promote good prescribing, but ongoing funding and interest in these must be sustained for full effect.

So how to bring this complex set of system changes into being? While it is tempting to insist on special pediatric medicine programs and projects, this approach risks the establishment of medicines for children as a special "silo" – and sometimes silos are the first targets in any reallocation of resources or restructure. So we need to keep the balance between the special and the routine and promote the development of health systems that deliver for the "child" as part of patient-centered care. Achieving that balance will deliver on medicines for children and health outcomes.

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