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

Optimizing Treatment for Children in the Developing World

Adis

Optimizing Treatment for Children in the Developing World

Stuart MacLeod • Suzanne Hill
Gideon Koren • Anders Rane
Editors

Optimizing Treatment for Children in the Developing World

Adis

Editors
Stuart MacLeod
Department of Pediatrics
University of British Columbia
Vancouver, British Columbia
Canada

Suzanne Hill
University of Melbourne Medical School
Melbourne, VIC
Australia

Gideon Koren
Departments of Pediatrics and Pharmacology
University of Toronto
Toronto, Ontario
Canada

Anders Rane
Department of Laboratory Medicine
Division of Clinical Pharmacology
Karolinska University
Hospital Karolinska Institutet
Stockholm
Sweden

ISBN 978-3-319-15749-8 ISBN 978-3-319-15750-4 (eBook)
DOI 10.1007/978-3-319-15750-4

Library of Congress Control Number: 2015939601

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Adis is a brand of Springer
Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

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.

Melbourne, VIC, Australia — Suzanne Hill, BMed, PhD
Toronto, ON, Canada — Gideon Koren, MD, FRCPC
Vancouver, BC, Canada — Stuart MacLeod, MD, PhD, FRCPC
Stockholm, Sweden — Anders Rane, MD, PhD

References

1. McArthur J, Brookings Institution. Seven million lives saved: under-5 mortality since the launch of the Millinnium Development Goals. September 2014. Global working paper 72. http://www.brookings.edu/research/papers/2014/09/under-five-child-mortality-mcarthur. Accessed 9 Oct 2014.

2. Institute of Medicine. Safe and effective medicines for children: pediatric studies conducted under the Best Pharmaceuticals for Children Act and The Pediatric Research Equity Act. Washington, DC: The National Academies Press; 2012.
3. Council of Canadian Academies. Improving Medicines for Children in Canada: The Expert Panel on Therapeutic Products for Infants, Children and Youth. Ottawa; 2014. http://www.scienceadvice.ca/en/assessments/completed/therapeutic-products.aspx
4. Duke T, Fuller D. Randomised controlled trials in child health in developing countries over 11 years. Arch Dis Child. 2014;99:615–20.
5. Berkley JA. Randomized trials in developing countries. Arch Dis Child. 2014;99:607–8.

Contents

Contributors

Susan M. Abdel-Rahman, Pharm D Section of Therapeutic Innovation, University of Missouri-Kansas City School of Medicine, Kansas City, MO, USA

Richard Odoi Adome, MSc, PhD Department of Pharmacy, Makerere University, Kampala, Uganda

Jaime Altcheh, MD Parasitology and Chagas Service, Buenos Aires Children's Hospital "Ricardo Gutierrez", Buenos Aires, Argentina

Tariq Almuzaini, BPharm, MSc, PhD Academic Division of Child Health, University of Nottingham, Derbyshire Children's Hospital, Derby, UK

Sara Arenas-Lopez, MRPharmS, MSc Paediatric Critical Care Unit, The Evelina Children's Hospital, Guy's & St Thomas NHS Foundation Trust, London, UK

Global Research in Paediatrics, London, UK

Andrew C. Argent, MD (Paediatrics), FCPaedsSA Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa

War Memorial Children Hospital, Cape Town, South Africa

Mary Appleton, BA IWK Health Centre, Halifax, NS, Canada

Robert W. Armstrong, MD, PhD University of British Columbia, Vancouver, BC, Canada

Department of Pediatrics, Aga Khan University, Nairobi, Kenya

Zulfiqar A. Bhutta, PhD, MBBS Global Child Health, Research Institute, The Hospital for Sick Children, Toronto, ON, Canada

Nutritional Sciences and Public Health, University of Toronto, Toronto, ON, Canada

Robert Bortolussi, MD, FRCPC Department of Pediatrics, Dalhousie University, Halifax, Canada and IWK Health Centre, Halifax, NS, Canada

Imti Choonara, MRCP, MD Academic Division of Child Health, The Medical School, University of Nottingham, Nottingham, UK

Derbyshire Children's Hospital, Derby, UK

Ben Coghlan, MBBS, MPH Centre for International Health, Burnet Institute, Melbourne, VIC, Australia

Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia

Emer Cooke, BSc(Pharm), MBA International Affairs, European Medicines Agency, London, UK

Noel E. Cranswick, MBBS, LLB Clinical Pharmacology Unit, Department of Medicine, Royal Children's Hospital, Melbourne, VIC, Australia

Department of Pediatrics, University of Melbourne, Melbourne, VIC, Australia

Benson Estambale, MBChB, PhD Medical Microbiology and Infectious Diseases, Jaramogi Oginga Odinga University of Science and Technology (JOOUST), Bondo Town, Kenya

Yifat Gadot, MD The Motherisk Program, The Hospital for Sick Children, Toronto, ON, Canada

Facundo Garcia-Bournissen, MD, PhD Parasitology and Chagas Service, Buenos Aires Children's Hospital "Ricardo Gutierrez", Buenos Aires, Argentina

National Science and Technology Research Council (CONICET), Buenos Aires, Argentina

Madlen Gazarian, MBBS, MSc Faculty of Medicine, School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia

Carlo Giaquinto, MD Department of Women's and Children's Health, University of Padova, Padova, Italy

Jennifer L. Goldman, MD Adverse Drug Reaction Program, Children's Mercy Hospital, Kansas City, Kansas City, MO, USA

University of Missouri-Kansas City School of Medicine, Kansas City, MO, USA

Nicolas Gonzalez, MD Parasitology and Chagas Service, Buenos Aires Children's Hospital "Ricardo Gutierrez", Buenos Aires, Argentina

Andy Gray, BPharm, MSc(Pharm) Pharmaceutical Sciences, University of KwaZulu-Natal, Durban, South Africa

Amanda Gwee, MBBS, DTMH Clinical Pharmacology Unit, Department of General Medicine, The Royal Children's Hospital, Parville, VIC, Australia

Murdoch Children's Research Institute, Parville, VIC, Australia

Michael Hawkes, MD, PhD Department of Pediatrics, Faculty of Medicine, University of Alberta, Edmonton, AB, Canada

Lisa Hedman, BSc Department of Essential Medicines and Health Products, World Health Organization, Geneva, Switzerland

Suzanne Hill, BMed, PhD University of Melbourne Medical School, Melbourne, VIC, Australia

Shinya Ito, MD, FRCPC Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

Prakash Jeena, MBChB, FCP(Paed)SA Paediatrics, University of KwaZulu-Natal, Durban, South Africa

Jerome Kabakyenga, MBChB, PhD Maternal, Newborn and Child Health Institute, Mbarara University of Science and Technology, Mbarara, Uganda

Deborah Kennedy, ND, PhD Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, Toronto, ON, Canada

Niranjan Kissoon, MD, FRCPC Department of Pediatrics and Emergency Medicine, University of British Columbia, Vancouver, BC, Canada

Ruth Kizza Bohlin, MBChB(UG), Mmed (Psychiatry)UG ADHD Section, Northern Stockholm Psychiatry, Stockholm, Sweden

Martin Kollmann, MD, MEd Opthalmology Department of Ophthalmology, University of Nairobi, Nairobi, Kenya

Gideon Koren, MD, FRCPC The Motherisk Program, The Hospital for Sick Children and University of Toronto, Toronto, ON, Canada

Marc Lallemant, MD Paediatric HIV Programme, Drugs for Neglected Diseases Initiative, Geneva, Switzerland

Janice Soo Fern Lee, MPharm Paediatric HIV Program, Drugs for Neglected Diseases Initiative, Geneva, Switzerland

Zhiping Li, PhD Department of Pharmacy, Children's Hospital of Fudan University, Minhang, China

Michael Lutwak, BSc The Motherisk Program, Division of Clinical Pharmacology, University of Toronto, Toronto, ON, Canada

Noni E. MacDonald, MD, FRCPC Department of Pediatrics, Dalhousie University, Halifax, Canada and IWK Health Centre, Halifax, NS, Canada

Stuart MacLeod, MD, PhD, FRCPC Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada

Parvaz Madadi, PhD Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, Toronto, ON, Canada

Rhona Mijumbi, MBChB, PhD (c) College of Health Sciences Clinical Epidemiology Unit, Makerere University, Kampala, Uganda

McMaster University Center for Health Economics and Policy Analysis, Hamilton, ON, Canada

Robert M. Nelson, MD, PhD Office of Pediatric Therapeutics,
Office of the Commissioner, Food and Drug Administration,
Silver Spring, MD, USA

Irena Nulman, MD, PhD The Motherisk Program,
Division of Clinical Pharmacology, University of Toronto, Toronto, ON, Canada

Isaac Odame, MBChB Division of Hematology/Oncology,
The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

Martin Offringa, MD, PhD Child Health Evaluative Sciences,
Research Institute, The Hospital for Sick Children, Toronto, ON, Canada

Department of Pediatrics, University of Toronto, Toronto, ON, Canada

Atieno Ojoo, BPharm, MPH Kenyatta National Hospital, Nairobi, Kenya

Gertrude's Children's Hospital Nairobi, Nairobi, Kenya

Clive Ondari, PhD, MBA Department of Essential Medicines
and Health Products, World Health Organization, Geneva, Switzerland

Maya Pearlston, BSc The Motherisk Program,
Division of Clinical Pharmacology, The Hospital for Sick Children,
University of Toronto, Toronto, ON, Canada

Senga Pemba, MEd, PhD Tanzanian Training Centre for International Health,
Ifakara, Tanzania

Martina Penazzato, MD, PhD HIV Department, World Health Organization,
Geneva, Switzerland

MRC-CTU University College London, London, UK

Anders Rane, MD, PhD Division of Clinical Pharmacology/Lab Medicine,
Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

Michael J. Rieder, MD, PhD Clinical Investigation Program,
Paediatrics, Physiology and Pharmacology and Medicine,
Western University and Robarts Research Institute,
Western University, London, ON, Canada

Susan Reynolds Whyte, PhD Department of Anthropology,
University of Copenhagen, Copenhagen, Denmark

Child Health and Development Centre, Makerere University, Kampala, Uganda

Jane Robertson, PhD, BPharm Department of Essential Medicines
and Health Products, World Health Organization, Geneva, Switzerland

Daniela Rocco, PhD Parasitology and Chagas Service, Buenos Aires Children's
Hospital "Ricardo Gutierrez", Buenos Aires, Argentina

Michelle Roth-Cline, MD, PhD Office of Pediatric Therapeutics, Office of the Commissioner, Food and Drug Administration, Silver Spring, MD, USA

Agnes Saint-Raymond, MD Programme Design Board, European Medicines Agency, London, UK

Klaus Rose, MD, MS Pediatric Drug Development, Riehen, Switzerland

Helen Sammons, MRCPCH, MD Academic Division of Child Health, The Medical School, University of Nottingham, Nottingham, UK

Derbyshire Children's Hospital, Derby, UK

Lena Serghides, PhD Toronto General Research Institute; Sandra Rotman Centre for Global Health, University Health Network, Toronto, ON, Canada

Shalini Sri Ranganathan, MD, PhD Faculty of Medicine, University of Colombo, Colombo, Sri Lanka

Paul Nathan Terrana, BSc, MD Candidate The Motherisk Program, Division of Clinical Pharmacology, University of Toronto, Toronto, ON, Canada

School of Medicine, Queen's University, Kingston, ON, Canada

Stephen Tomlin, BPharm, FRPharmS Pharmacy Department, Evelina London Children's Hospital. St Thomas' Hospital, London, UK

Children's Services, London, UK

Kings College London University, London, UK

Wendy J. Ungar, MSc, PhD Program of Child Health Evaluative Sciences, Peter Gilgan Centre for Research and Learning, The Hospital for Sick Children, Toronto, ON, Canada

Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, ON, Canada

Richard M. Zur, PhD Program of Child Health Evaluative Sciences, Peter Gilgan Centre for Research and Learning, The Hospital for Sick Children, Toronto, ON, Canada

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-

C. Ondari, PhD, MBA (✉) • L. Hedman, BSc • J. Robertson, PhD, BPharm
Department of Essential Medicines and Health Products, World Health Organization, Geneva, Switzerland
e-mail: ondaric@who.int

S. MacLeod et al. (eds.), *Optimizing Treatment for Children in the Developing World*,
DOI 10.1007/978-3-319-15750-4_1

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.

References

1. Knibbe CA, Krekels EH, van den Anker JN, deJongh J, Santen GW, van Dijk M, et al. Morphine glucuronidation in preterm neonates, infants and children younger than 3 years. Clin Pharmacokinet. 2009;48:371–85. doi:10.2165/00003088-200948060-00003.
2. Cella M, Knibbe C, Danhof M, Della Pasqua O. What is the right dose for children? Br J Clin Pharmacol. 2010;70:597–603. doi:10.1111/j.1365-2125.2009.03591.x.
3. Tayman C, Rayyan M, Allegaert K. Neonatal pharmacology: extensive inter-individual variability despite limited size. J Pediatr Pharmacol Ther. 2011;16:170–84. doi:10.5863/1551-6776-16.3.170.
4. World Health Organization. Antiretroviral therapy for HIV infection in infants and children: towards universal access: recommendations for a public health approach: 2010 revision. Annex E: prescribing information and weight-based dosing of available ARV formulations for infants and children. http://www.who.int/hiv/pub/paediatric/infants2010/en/. Accessed 10 Oct 2014.
5. Swaminathan S, Rekha B. Pediatric tuberculosis: global overview and challenges. Clin Infect Dis. 2010;50 Suppl 3:S184–94. doi:10.1086/651490.
6. World Health Organization. Rapid advice: treatment of tuberculosis in children. Geneva: World Health Organization. 2010. http://apps.who.int/iris/bitstream/10665/44444/1/9789241500449_eng.pdf?ua=1. Accessed 10 Oct 2014.
7. World Health Organization. Global tuberculosis report 2013. http://www.who.int/tb/publications/global_report/en/. Accessed 6 Sept 2014.
8. UNITAID. Tuberculosis – innovative approaches for an ancient disease: Speeding treatments to end paediatric tuberculosis (STEP-TB). http://www.unitaid.eu/en/what/tb. Accessed 8 Oct 2014.
9. World Health Organization. Make medicines child size. http://www.who.int/childmedicines/en/. Accessed 10 Oct 2014.
10. European Medicines Agency. Paediatric regulation. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000068.jsp. Accessed 10 Sept 2014.
11. US Food and Drug Administration. Should your child be in a clinical trial? http://www.fda.gov/forconsumers/consumerupdates/ucm048699.htm. Accessed 10 Sept 2014.
12. European Medicines Agency. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population. http://ec.europa.eu/health/files/eudralex/vol-10/ethical_considerations_en.pdf. Accessed 10 Oct 2014.
13. European Medicines Agency. Medicines for children. http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000302.jsp. Accessed 10 Oct 2014.
14. Boots I, Sukhai RM, Klein RH, Holl RA, Wit JM, Cohen AF, et al. Stimulation programmes for pediatric drug research – do children really benefit? Eur J Pediatr. 2007;166:849–55. doi:10.1007/s00431-0016-0381-z.
15. World Health Organization. Essential medicines for children. Paediatric medicines Regulators' Network (PmRN). http://www.who.int/childmedicines/paediatric_regulators/en/. Accessed 10 Oct 2014.
16. United Nations 2012. Every woman every child. UN Commission on life-saving commodities for women and children. Commissioners' report, Sept 2012. http://everywomaneverychild.org/images/UN_Commission_Report_September_2012_Final.pdf. Accessed 8 Oct 2014.

17. International Union Against Tuberculosis and Lung Disease. Global asthma report 2011. http://www.globalasthmanetwork.org/publications/Global_Asthma_Report_2011.pdf. Accessed 6 Sept 2014.
18. World Health Organization. WHO essential medicines and health products information portal. http://apps.who.int/medicinedocs/en/. Accessed 10 Oct 2014.
19. Oxman AD, Glenton C, Lewin S, Olsen K, Rosenbaum SE, Austvoll-Dahlgren A. Supporting informed health choices in low income countries. http://www.kunnskapssenteret.no/prosjekter/sihclic?language=english. Accessed 6 Sept 2014.
20. World Health Organization. Service availability and readiness assessment. http://www.who.int/healthinfo/systems/sara_introduction/en/. Accessed 6 Sept 2014.

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

S. MacLeod, MD, PhD, FRCPC (✉)
Department of Pediatrics, University of British Columbia,
Vancouver, BC, Canada
e-mail: smacleod@cfri.ca

Z. Li, PhD
Department of Pharmacy, Children's Hospital of Fudan University, Shanghai, China

A. Ojoo, BPharm, MPH
Kenyatta National Hospital, Nairobi, Kenya

Gertrude's Children's Hospital Nairobi, Nairobi, Kenya

S. MacLeod et al. (eds.), *Optimizing Treatment for Children in the Developing World*,
DOI 10.1007/978-3-319-15750-4_2

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.