PhD Thesis

PRIORITY MEDICINES FOR CHILDREN

Exploring age-appropriate medicines and antibiotic use in children

Verica Ivanovska

Utrecht University, 2017

Summary

Children are not small adults, but rather a distinct and heterogeneous patient group with specific therapeutic needs. Child development entails dynamic processes inherent to growth from birth into adulthood, and children face a scope of diseases different than those of adults. Accordingly, safe and effective paediatric pharmacotherapy requires medicines adjusted to the needs, acceptability and preferences (of each subpopulation) of children.

In the introduction (**chapter 1**) we refer to the global progress made in improving child survival and health between 1990 and 2015. Although the 53 per cent drop in child under-five mortality is substantial, it is not enough to meet the UN Millennium Development Goal (MDG) 4 of a two-thirds reduction. About half of the reduction in child under-five deaths comes from better prevention and management of pneumonia, diarrhoea, measles, and malaria. Many of these conditions are preventable or treatable with proven interventions, which include the use of paediatric medicines and vaccines. But, there is still a major challenge because appropriate medicines as part of the treatment options are not available.

The failure to meet the special needs for medicines in children was outlined in the Priority Medicines for Europe and the World Report in 2004. This report emphasized the importance of conducting specific research on medicines in children, and made recommendations to support paediatric drug development, including the neglected area of age-appropriate formulations.

Beyond the development of child-specific medicines, it is equally important that these medicines are made accessible, and that they are used rationally within healthcare systems. In chapter 1 we highlight the optimization of antibiotic use as an important aspect of rational use of medicines, given the emergence and spread of antibiotic resistance, and the extensive misuse of antibiotics globally. While antibiotics remain the most widely prescribed medicines in children, systematic data on use of antibiotics in children is very sparse, especially for resource-restricted countries.

Fortunately, all stakeholders have become progressively aware of the relevance of more evidence-based paediatric pharmacotherapy and drug development, although much remains to be done. In this landscape where further action is required to address public health needs in children, the aim of the present thesis was to document recent advancements with respect to priority medicines for children, and conduct additional research on age-appropriate formulations and use of antibiotics in children across different settings.

Chapter 2 presents the update of the 2004 Background paper on Priority medicines in children for Europe and the world. The unmet needs for medicines in children continue to exist due to children's particular needs in terms of drug delivery mechanism and/or formulations, mostly at younger age. Some of the priority diseases for which child-specific medicines are lacking as a treatment option, include: HIV/AIDS, tuberculosis, cancers, rare diseases, malaria, pneumonia, cardiovascular diseases, infections due to antibacterial resistance, and many neglected tropical diseases. In addition, some unmet needs for medicines in children are also related to the fact that more research is required to develop new therapies for diseases and conditions restricted to children, such as preterm births, neonatal sepsis, and birth asphyxia.

In response to the lack of paediatric medicines, the European Union implemented the Paediatric Regulation in 2007, combining legal requirements with incentives for companies to test, authorize, and formulate medicines for use in children. It has created a new structured framework to screen every new adult product for its potential paediatric value, and promote capacity building and closer cooperation in the area of paediatric medicines research. The initial progress includes increasing numbers of paediatric clinical trials, and intensified development of medicines for children. Nonetheless, therapeutic areas addressed by the industry seem to be more aligned with adult drug development than with unmet public health needs in children. To guide the efforts towards significant benefits for children, the European Medicines Agency has produced priority medicines lists to highlight areas with substantial off-label use in children and gaps in paediatric data. These lists need to be accompanied by appropriate reward systems for investment in paediatric drug. The commercial viability of paediatric medicines might be improved by an increased market size (e.g. global scale, inclusion of geriatric patients and adults with swallowing difficulties), new incentives schemes (e.g. for off-patent drugs), and public-private partnerships that support the development of orphan drugs and other less profitable niches.

In **chapter 3** we focus on age-appropriate formulations for children. In **chapter 3.1** the progress in this area is illustrated by the shifting trends towards novel age-appropriate oral formulations with dose flexibility: mini-tablets, chewable and orodispersible tablets for younger children, and dosage forms dispersible into liquids or mixed with food. This is in line with the consensus reached at the WHO expert forum in 2008 that flexible solid oral dosage forms have advantages over traditional liquid preparations, particularly for children of younger age and those living in

4

developing countries. Nevertheless, despite the research on novel paediatric products, there are limited patient outcome studies with clinical feedback (e.g. impact on side effects, tolerability and administration errors) to support ongoing technological advances for children. Moreover, there have been examples of low-uptake levels of novel solid formulations, due to their high cost implications, or common unfamiliarity with new formulations. Thus, patient and health care professionals' education about novel formulations, and evidence-based research on added value for children (i.e. efficacy, safety, patient acceptability, preferences and adherence) are needed to link their development to the acceptance in clinical practice.

Since the lack of medicines most acutely affects children living in low-resource settings, there has been a global action focusing on appropriate medicines to treat diseases of high burden in childhood. Consequently, the WHO Essential Medicines List for Children (EMLc) was released in 2007 to stress the special needs for medicines in children, and promote the inclusion of paediatric medicines in national procurement programs. In **chapter 3.2** we compare the age-appropriate antibiotic formulations on relevant formularies from the United Kingdom, Australia and the Netherlands versus the WHO EMLc in order to identify potential new paediatric products for inclusion on the EMLc. All the formulations on comparator lists that differed from the EMLc formulations in relation to administration routes, dosage forms and/or drug strengths were evaluated for their added clinical values as well as costs. The analysis identified seven oral and two parenteral formulations on comparator lists that may offer clinical benefits for low-resource settings, including simplified administration and increased dosing accuracy. On the other hand, the complexity of both procuring and managing multiple strengths and formulations also needs to be considered. Similarly, the barriers for the implementation of new formulations at the field level should be considered, as listing in the WHO EML does not always translate into demand for the medicines.

There are equal challenges to ensure not only that medicines for children are developed and made available, but also that they are used in a rational manner. So, understanding the extent of medicines consumption is an essential starting point to monitor and improve prescribing and use patterns. The focus in **chapter 4** is mostly on challenges of measuring and improving the use of antibiotics, due to their wide use in children, and the impact of infections on child morbidity and mortality. In **chapter 4.1** we assess the trends in prescribing patterns for acute childhood infections in primary care in developing and transitional countries between 1990 and 2009, and

analyze the effects of interventions to improve their treatment. Data were extracted from the WHO Medicines Use Database, and consisted of 344 paediatric studies conducted in 78 countries. The results showed a mixed progress, with most of the treatment aspects of infections remaining sub-optimal over time. There was an improvement in the treatment of diarrhoea, reflecting an increased use of oral rehydration salts, although the trend was not statistically significant (from 14% pre-1990 to 60% in 2006–2009, p=0.57). However, the rates of treating pneumonia with appropriate antibiotics remained below 80% over time. Also, there was a non-significant trend towards increased inappropriate use of antibiotics to treat viral upper respiratory tract infections (URTI), from 42% pre-1990 to 72% in 2006–2009 (p=0.07). Of the 226 intervention groups included to improve use of medicines, only 44 (19%) were in studies with a methodologically appropriate design. Multi-component interventions resulted in larger improvements than single-component ones. The median effect size indicated a 28% improvement with community case-management, an 18% improvement with provider education combined with consumer education, but only 9% improvement with provider education alone. The solutions to improve antibiotic use need to adopt the cross-cutting approach, and restructure health systems to "institutionalize" the promotion of the rational use of medicines. Sound standard systems to monitor medicines and antibiotic use are also essential, as they are currently lacking in many low- and middle-income countries.

In **chapter 4.2** we examined general practitioners' adherence to treatment guidelines for paediatric fever, acute respiratory and ear infections in relation to antibiotic prescribing in the Netherlands during 2010-2012, and explored potential variations across practices. The data on diagnoses and prescriptions for children were derived from the electronic health records-based NIVEL Primary Care Database. Half of the episodes with respiratory and ear infections with restrictive prescribing policy (acute otitis media - AOM, strep throat, sinusitis and tonsillitis) and 65% of episodes with pneumonia were treated with antibiotics. This shows a relatively conservative use of antibiotics in the Netherlands for these infections. The figures could be used as indicators of attainable prescribing rates by other EU countries with higher antibiotic consumption. One potential aspect of concern is that 40% of children with acute bronchitis were prescribed antibiotics, opposite to the guidelines. The second challenge is that between 15% and 50% of cases with any of the diagnoses were not prescribed their first-choice antibiotics, with adherence being particularly low for narrow-spectrum penicillins. Moreover, we found marked

variations in antibiotic prescribing by practices, especially for first-choice antibiotics. This suggests that progress may be achieved by targeting practices with lower adherence rates to guidelines for antibiotic prescribing.

In **chapter 4.3** we further explore age-specific antibiotic prescribing patterns, in terms of degree of prescribing per diagnosis and choice of antibiotics, by stratifying children from previous study in three age groups (0-4/5-11/12-17 years). The results show that for bronchitis more antibiotic prescriptions were found in episodes of adolescents compared to children aged 0-4 and 5-11 years (52.0% vs. 42.4% and 42.7%). Likewise, more adolescents were prescribed antibiotics for diagnoses that require antibiotics (i.e. strep throat, pneumonia, and tonsillitis) except for AOM. In contrast, underuse of narrow-spectrum penicillins was mostly seen in the 0-4 years age group than in age groups 5-11 years and adolescents (strep throat: 60.9% vs. 63.6% and 72.0%, and tonsillitis: 33.1% vs. 45.9% and 67.9%). These two studies indicate the areas in which there is a room for improvement in antibiotic prescribing, even in the Netherlands. Future efforts to improve the disease-specific antibiotic use may consider prescribers' training in communication skills to better manage patient pressure, and use of rapid diagnostic tests that differentiate viral from bacterial lower tract infections. More research should focus on the barriers to use first-choice antibiotics, particularly in younger children.

The aim of the study presented in **chapter 4.4** was to investigate the aspect of self-medication with antibiotics for children in Macedonia, and analyse the impact of national interventions on parental knowledge on antibiotic use, and self-medication. The interventions had a multifaceted approach and consisted of: mass media (TV) campaign on appropriate antibiotic use, discussions with parents at kindergarten on respiratory infections and antibiotic use, and seminars for health workers on the management of respiratory infections and appropriate antibiotic prescribing. Data were collected through a structured questionnaire applied to 1203 parents over the three years period (2014 - 2016). We found that the parental knowledge of antibiotics in Macedonia was similar to average knowledge levels in adults across the EU. More than 80% of parents knew that inappropriate use of antibiotics could lead to their inefficacy or side effects, and that antibiotics could kill bacteria. Around 40% of parents wrongly believed that antibiotics were effective against viruses and common URTIs. The results showed that parental knowledge on antibiotics did not change significantly after the interventions. In terms of self-medication, 20% of the parents and 10% of the children who received antibiotics in previous year used over-the-counter

or left-over antibiotics at baseline. The parental self-medication rates did not change during or after the interventions, while children's rates dropped to 5% during the intervention, but increased again to 9% in 2016. This implies a need for continuous health education, or at least repetitive actions to improve public knowledge and actions on appropriate antibiotic use. This should be followed by restrictive measures for prescription-only medicines, and a cooperation with pharmacists to attain sustainable changes in antibiotic use across the health system.

In the general discussion in **chapter 5** we present key findings of our studies and discuss these in regards to challenges and progress for the development of age-appropriate paediatric medicines, as well as antibiotic use in children across different regions and income levels.

This thesis documents how the practice of developing, selecting and using paediatric medicines has evolved within recent paediatric regulatory frameworks and global initiatives to provide better medicines for children. Progress and concerted efforts have been made to improve the therapies available for children, and novel age-appopriate formulations have become available on the market. However, unmet therapeutic needs continue to exist, and further steps in paediatric drug research, based on continual prioritisation process, better use of novel technologies for adults, and clinical feedback, are needed.

On equal importance, this thesis evaluates antibiotic use in children across different healthcare and income settings. Our results are expected to lead to better understanding of both appropriate prescribing patterns and areas for concerns, and the range of interventions implemented to improve antibiotic use in children. The studies have shown that, to identify areas for improvements, more emphasis is needed on measuring antibiotic use in resource-restricted settings, and self-medication practices, where data are scarce. Much work remains to be done, and solutions need to focus on multifaceted and multilevel interventions that define local barriers, and integrate the promotion of the rational use of antibiotics for children within health systems.