PRIORITY MEDICINES FOR CHILDREN
Exploring age-appropriate medicines and antibiotic use in children

Verica Ivanovska

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Geneesmiddelen voor kinderen - kinderformuleringen en goed gebruik van antibiotica
(met een samenvatting in het Nederlands)

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GENERAL INTRODUCTION

1

BACKGROUND

Children and adolescents constitute about a third of the world's population, and their health status is important for every country and society. Children are central to sustainable development, and they are expected to contribute to the future of our planet as productive, engaged, and capable citizens.[1]

An adequate investment in children's health and wellbeing has high returns in the long run. Child health has been perceived as important not only because of its immediate consequences for the child, but also because of its long-term effects on population health. Child public health is a starting point of a life-course approach to population health; from conception until adolescence. What happens to the embryo, the foetus, the newborn baby, the infant and the child has a profound impact on health, development and wellbeing in subsequent life stages and throughout the life-course. The early years of life represent a golden opportunity to improve the health of the whole population and the development of the whole of society.[2]

The global community commitment to build a world in which all children can survive, grow and develop to their full potential has been built-in in the framework of the UN Millennium Development Goals (MDGs). Undoubtedly, the world has made a considerable progress in improving child survival and health in the past 25 years.[3,4] The global under-five mortality rate dropped from 91 to 43 deaths per 1,000 live births between 1990 and 2015. At the same time, the annual number of under-five deaths declined from 12.7 million to 5.9 million.[3] These health gains have been a result of various interventions, including better nutrition, sanitation and housing conditions, increased education levels, improved access to health care, and advances in clinical medicine, together with pharmaceutical innovations.

Although the 53 per cent drop in child mortality is substantial, it is not enough to meet the MDG 4 of a two-thirds reduction between 1990 and 2015.[3,4] Worldwide, about 16,000 children under five die every day, mostly from infectious diseases and neonatal complications.[3] As shown in Figure 1, about half of the reduction in under-5 mortality comes from better prevention and management of pneumonia, diarrhoea, measles, and malaria.[5] Many of these conditions are preventable or treatable with proven interventions, which include the use of paediatric medicines and vaccines.[6-8] But, there is still a major uncompleted agenda for child infections, because of the challenge of not having appropriate medicines as part of the treatment options.[9] Children's medical needs have been historically inadequately considered, and clinical research in children has been lagging behind.[10,11] That has led to gaps in the development of child-friendly medicines, or when they do exist, access and affordability can be problematic, especially in resource-limited settings.[12-15] So, further efforts are required to accelerate the pace of global progress in child health, and identify therapeutic priorities across the paediatric age and disease spectrums.
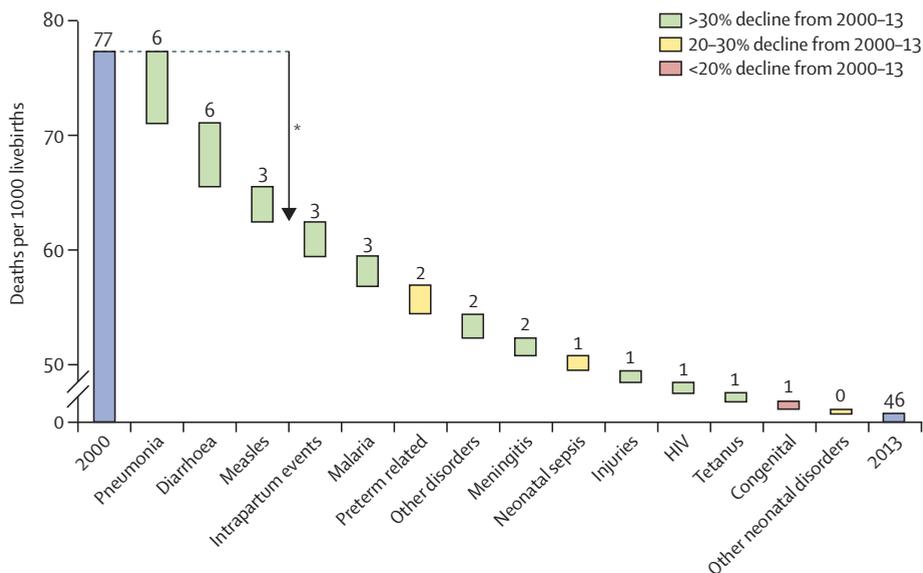
Figure 1. Global trends in cause-specific mortality rates in neonates in children aged 1-59 months, 2000-2013[5]

DISEASE BURDEN IN CHILDREN

Understanding the causes for illness and deaths in children provides important public health insights, and it is critical to inform policy makers on how to prioritise and invest in children's health. Monitoring trends in morbidity and mortality over time is also key to understanding where healthcare interventions are having an impact, and where more attention and innovative approaches in practice are needed.

The most significant global causes of death in children under 5 years of age are pneumonia, diarrhoeal diseases, measles, birth complications, and malaria.[3,5] In older children, infectious diseases (i.e. HIV/AIDS and tuberculosis), injuries, and some cancers predominate, although overall mortality is lower.[16] During adolescence, the leading causes of death are accidents, suicide, violence, pregnancy related complications, infections (i.e tuberculosis, meningitis, and HIV/AIDS), and chronic diseases (i.e. diabetes and cancer).[17] Besides, asthma and mental disorders are also common causes of ill health and disability in children and adolescents.[18-19]

Some diseases occur only in childhood, such as prematurity, congenital abnormalities, respiratory distress, certain leukaemias, or genetic conditions like phenyl ketonuria. Their diagnosis, prevention and treatment depend entirely on clinical investigations in children.[20] Moreover, certain childhood morbidities can lead to severe and chronic adult diseases (e.g., wheezing/childhood asthma and chronic respiratory diseases later in life, childhood obesity and diabetes/cardiovascular problems, paediatric mental problems and severe adult

psychiatric morbidities). Hence, their accurate diagnosis and treatment at an early age are important prevention strategies to reduce adult disease burden.[20,21] Some diseases occur in children and in adults (i.e. infectious diseases, asthma, mental disorders, certain cancers, influenza, and forms of arthritis), and all age groups are often treated with the same medicines. But disease pathophysiology, severity, course, and response to treatment may differ across the life span.[20] Thus, treatments that are safe and effective for adults may be dangerous or ineffective for paediatric use, implying that children may need different medicines, age-appropriate formulations and/or dosing schemes.[20]

UNMET MEDICAL NEEDS IN CHILDREN

Nowadays, modern medicines provide effective treatment for most infectious and chronic diseases that affect the world's population. Likewise, children are entitled to safe, efficacious, and age-appropriate medicines of assured quality. Yet, they often do not benefit from major therapeutic advances, because a large proportion of medicines used in children are not licensed for their age (unlicensed use), or are prescribed outside the terms of the drug license (off-label use).[22] These practices can place children at a risk of under- or overdosing and adverse drug effects.[23] In respect to pharmacotherapy, children are not small adults, but a heterogeneous patient group with developmental, physiological, and psychological differences from adults and between age groups.[24,25] In addition, the provision of optimal medicines for children is limited by various barriers that include insufficient research in children, delays in licensing medicines for children, inadequate development of appropriate formulations for children, and knowledge deficiencies that would enable optimal prescribing.[20] It is, however vital to ensure that children are treated with sufficiently evaluated and effective medicines.

PRIORITY MEDICINES FOR EUROPE AND THE WORLD PROJECT IN 2004

The fact that special needs for medicines in children have often been neglected by manufacturers and regulators was included in the research outline of the Priority Medicines for Europe and the World Project. Its first report was initiated by the Government of the Netherlands, in preparation for its role as the President of the European Union (EU), and the World Health Organization (WHO) in 2004.[26] The aim of this WHO Priority Medicines 2004 Report was to establish a public health-based medicines research and development (R&D) agenda and, where necessary, help bridge the gap between public health needs and the development priorities of the pharmaceutical industry. In response, WHO prepared a public health-based R&D agenda and methodology, and drew up a list of priority medicines to be proposed for research funding by the EU as part of its Seventh Framework Programme (FP7) 2007 - 2013.[26]

For the purposes of the WHO Priority Medicines 2004 Report, priority medicines have been defined as those medicines which are needed to meet the priority health care needs of the population ("essential medicines") but which have not yet been developed. A priority medicine for a priority disease is by definition also an improvement of, a replacement for, or a better formulation of already-marketed products. [26]

One chapter of the WHO Priority Medicines 2004 Report reviewed the challenges and opportunities for the development of priority paediatric medicines, and examined the availability of information on medicines use in children. The authors highlighted primarily the absence of age-appropriate formulations and doses for children. This absence has induced unlicensed and off-label medicine use in children, and has increased the risk of miscalculating doses and adverse reactions to medicines. It was suggested that new or adapted formulations for children might also improve drug administration and patient adherence to therapy (e.g. paediatric HIV therapy, methotrexate for juvenile arthritis, etc).[27]

In addition, the WHO Priority Medicines 2004 Report emphasized the need for more information on the safety, efficacy, dosage or toxicity of medication use in children. Such information cannot be linearly abstracted from adult data because of differences in diseases occurring in children and adults, or age variations in the drug metabolism. Moreover, in case of unlicensed or off-label use of medicines in children, there is no collection of clinical and pharmaceutical data on effectiveness and safety. So, the authors underlined the importance of conducting specific research on medicines in children. A number of existing obstacles to overcome were mentioned, such as financial issues (small sales market), ethical issues (potential risks, and discomfort for the child), scientific issues (heterogeneity of children) and practical issues (recruitment of a sufficient number of children, blood sampling).[27]

The report made several key recommendations for future action to improve the development of medicines for children: 1) more investment in fundamental paediatric research, 2) better participation of children in clinical trials, 3) creation of a supportive, harmonised regulatory environment for paediatric research in children in Europe, and 4) more funding for research on child specific medicine formulations.[27]

PAEDIATRIC FORMULATIONS

The first topic of interest of this thesis are (missing) paediatric drug formulations in the broader context of clinical practice, regulatory environments and global drug markets.

The WHO Priority Medicines 2004 Report has placed a high priority on addressing the scarcity of paediatric formulations.[27] Many medicines are still not available in formulations suitable for administration to the paediatric population.[28] As such, the existence of patient-friendly dosage forms in children lags far behind those of their adult counterparts, posing age-specific problems in clinical practice. For example, infants are simply unable to swallow conventionally-sized tablets, or neonates may require very small volumes of a parenteral medicine to avoid a volume overload.[29,30] The optimal design of a paediatric

formulation need to take the differences in paediatric anatomy and physiology into account, particularly for neonates and infants who differ most from adults in their development. Age-appropriate paediatric formulations need to be appropriate for the child in terms of dose, administrative route, excipients, and convenience and acceptability to ensure patient compliance with the medication.[30,31] Because of the lack of suitable formulation for children, healthcare professionals and parents or caregivers are often required to manipulate an adult medicine to obtain an appropriate dose for a child, for example, by splitting a tablet to provide a smaller dose or in more complex cases preparing a suspension from a crushed tablet.[32] Such manipulations increase the variability in the product by inaccurate measurement, and compromise drug efficacy and/or safety.[33] Then again, they may be the only option for some children to receive a certain medicine in a suitable dosage form.[33] To prevent tragedies and ensure adequate treatment of children of all ages, more work is required to promote and support paediatric drug development and the neglected area of age-appropriate formulations.

USE OF ANTIBIOTICS IN CHILDREN

The second topic of interest in this thesis is the use of antibiotics to treat infections in children. Infections are the most common cause of illness and death in paediatric patients.[3,5] The WHO Priority Medicines 2004 Report portrayed them as an even greater threat to global public health in the future due to increasing prevalence of antimicrobial resistance (AMR).[26] Resistant bacteria reduce the possibilities of treating infections effectively and increase the risk of complications and fatal outcome for patients with severe infections. Most vulnerable groups in this respect include children who are highly susceptible to infections and reduced immune response.[34]

Resistance development is a natural biological outcome of antibiotic use, and frequent use of antibiotics increases the speed of emergence and selection of resistant bacteria.[35] Previous studies have indicated an extensive overuse of antibiotic globally, e.g. use based on incorrect medical indications, as well as misuse by using the wrong agent, administration route, dose and treatment duration.[36] Moreover, it is estimated that more than 50% of antibiotics worldwide are purchased privately without a prescription, from pharmacies or street vendors in the informal sector.[34] Hence, AMR control strategies aim to improve prescribing and dispensing practices, reduce inappropriate use of antibiotics through the use of evidence-based public health interventions, and conduct high-quality surveillance of AMR and of antibiotic consumption patterns in hospitals and the community.[37] It is therefore essential to measure the antibiotics use to learn the extent of the problem and to identify areas for improvements.

The rational use of medicines in children is an area of research that has been inadequately studied. One of the few comparative studies on paediatric drug utilisation in Europe (TEDDY) illustrated that antibiotics were the most frequently used medicines in
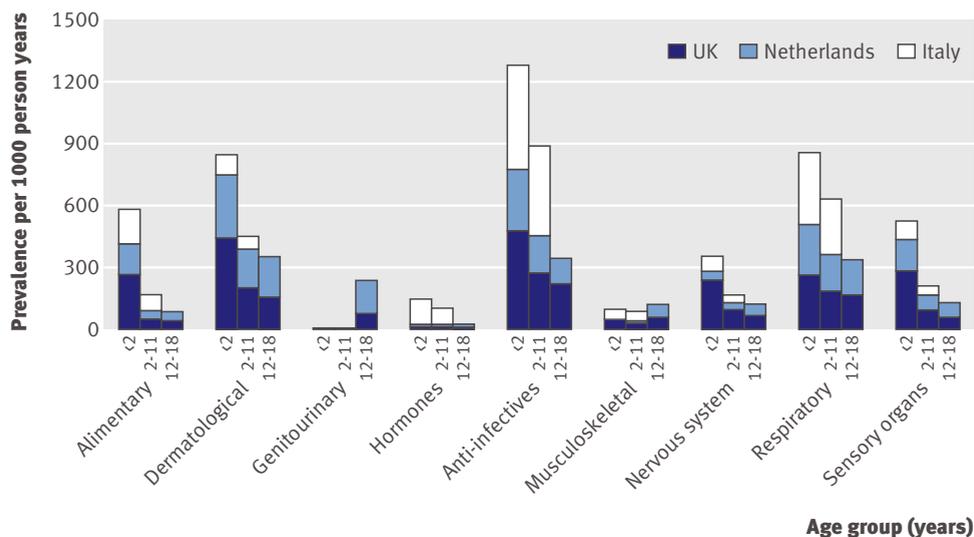
Figure 2. Year prevalence of drug use (per 1000 person years) by age (<2, 2-11, 12-18), country, and anatomical class for most prevalently used drug classes (data for Italy excluded age category 12-18).[38]

children, alongside with dermatological and respiratory drugs (Figure 2).[38] In developing countries, relatively high levels of availability and consumption have led to high incidence of inappropriate use of antibiotics in children with or without an infection.[39-41] But, in many high-income countries prescribing is often not rational either. One example is the variation in the prescribing of antibiotics between and within different countries; children in Italy are four times more likely to receive antibiotics than children in the UK, Denmark and the Netherlands.[42] Moreover, in many countries, newer broad spectrum antibiotics are used extensively, even though they are more likely to result in increased AMR.[43]

In short, major challenges still remain with respect to promoting rational use of antibiotics and measuring and monitoring their use. Additional work is needed to shed some light on the quality of antibiotic prescribing and use in children in different settings, and provide information for further actions to reduce AMR.

GOALS AND OBJECTIVES OF THIS THESIS

Despite the drop in childhood mortality and the efforts towards better medicines for children undertaken in the last decade, more work lies ahead. So, the overall aim of the present thesis is to provide an update of the current state of affairs with respect to priority medicines for children, and conduct additional research in specific areas which were highlighted in the WHO Priority Medicines 2004 Report, i.e. development of age-appropriate medicines and use of antibiotics in children in various parts of the world with different income levels.

1

THESIS OUTLINE AND PREVIEW

This thesis contains seven studies divided into three chapters, which reflect the three main research areas of interest: priority medicines for children, age-appropriate formulations and use of paediatric antibiotics. **Chapter 2** aims to provide an update on the previous WHO Priority Medicines 2004 Report. **Chapter 3** provides updated information on the development and availability of paediatric drug formulations. First, the necessity for age appropriate formulations is explored in more detail, and the challenges and progress achieved towards their development are analysed (chapter 3.1). Second, we compare the age-appropriate antibiotic formulations on relevant formularies versus the WHO List of Essential Medicines for Children (EMLc) in order to identify potential new paediatric products for inclusion on the EMLc (chapter 3.2). **Chapter 4** assesses the prescribing and patient use patterns of paediatric medicines, mainly antibiotics. We start with examining the trends in prescribing patterns for acute childhood infections over time, and analyzing the effects of interventions to improve treatment in developing and transitional countries (chapter 4.1). Thereafter, the aim is to assess antibiotic prescribing and adherence to treatment guidelines in the Netherlands, both for all children and broken down by age groups (chapters 4.2 and 4.3). And finally, in chapter 4.4 we investigate self-medication with antibiotics in children in Macedonia, and analyse the impact of a national intervention programme on parental knowledge about antibiotics and practice of antibiotic use for respiratory infections.

The thesis concludes with a general discussion in **chapter 5,** where we present key findings from our studies, discuss key lessons learned and identify future research topics. We also determine the existing gaps and provide policy recommendations to improve medicines use in children.

REFERENCES

1. United Nations Children's Fund. A Post-2015 World Fit for Children: *Sustainable Development Starts and Ends With Safe, Healthy and Well-Educated Children.* New York, UNICEF, 2013. Available at: http://www.unicef.org/agenda2030/files/SD_children_FINAL.pdf

2. Tamburrlini G, Blair M. Child Public Health in Europe. *Eurohealth* 2014;20(1):12-15.

3. United Nation Inter-agency Group for Child Mortality Estimation (IGME). *Levels and trends in child mortality - report 2015.* United Nations Children's Fund, World Health Organization, the World Bank and the United Nations Population Division. New York, 2015. Available at: http://www.childmortality.org/files_v20/download/IGME%20report%202015%20child%20mortality%20final.pdf

4. The United Nations. *Millennium Development Goals (MDGs). Goal 4: Reduce Child Mortality.* Available at: http://www.un.org/millenniumgoals/childhealth.shtml

5. Liu L, Oza S, Hogan D, *et al.* Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* 2015;385 (9966):430-440.

6. Zaidi AK, Ganatra HA, Syed S, *et al.* Effect of case management on neonatal mortality due to sepsis and pneumonia. *BMC Public Health* 2011;11(Suppl 3):S13.

7. Walker CL, Rudan I, Liu L, *et al* . Global burden of childhood pneumonia and diarrhoea. *Lancet* 2013;381:1405–1416.

8. Bhutta ZA, Das JK, Walker N, *et al.* Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost? *Lancet* 2013;381:1417–29.

9. World Health Organization. *Priority live-saving medicines for women and children 2012.* Geneva: World Health Organization, 2012 (WHO/EMP/MAR/2012.1) Available at: http://apps.who.int/iris/bitstream/10665/75154/1/WHO_EMP_MAR_2012.1_eng.pdf?ua=1

10. Nahata MC. Lack of pediatric drug formulations. *Pediatrics.* 1999;104 (3 pt 2, suppl 3):607–609.

11. Shirkey H. Therapeutic orphans. *J Pediatr* 1968;72(1):119–120.

12. Robertson J, Forte G, Trapsida JM, *et al.* What essential medicines for children are on the shelf? *Bull World Health Organ* 2009;87:231–7.

13. Chen W, Tang S, Sun J, *et al.* Availability and use of essential medicines in China: manufacturing, supply, and prescribing in Shandong and Gansu provinces. *BMC Health Serv Res* 2010;10:211.

14. Gitanjali B, Manikandan S. Availability of five essential medicines for children in public health facilities in India: a snapshot survey. *J Pharmacol Pharmacother* 2011;2:95–9.

15. Balasubramaniam R, Beneragama BV, Sri Ranganathan S. A national survey of availability of key essential medicines for children in Sri Lanka. *Ceylon Med J* 2011;56:101–7.

16. Lozano R, Naghavi M, Foreman K, *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2095–128.

17. Gore FM, Bloem PJN, Patton GC, *et al.* Global burden of disease in young people aged 10–24 years: a systematic analysis *Lancet* 2011;377:2093–2102.

18. Bousquet J, Khaltaev N , eds. *Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach.* Geneva, World

Health Organization, 2007. Available at: http://www.who.int/gard/publications/ GARD%20Book%202007.pdf

19. Suhrcke M, Pillas D, Selai C. *Economic aspects of mental health in children and adolescents.* World Health Organization, Regional Office for Europe. 2007. Available at: http://www.euro.who.int/ __data/ assets/ pdf_file/ 0003/ 76485/ Hbsc_ Forum_2007_economic_aspects.pdf. Accessed May 2, 2013.

20. Institute of Medicine (US) Committee on Clinical Research Involving Children; Field MJ, Behrman RE, editors. *Ethical Conduct of Clinical Research Involving Children.* Washington (DC): National Academies Press (US); 2004.

21. Smyth RL, Weindling AM. Research in children: ethical and scientific aspects. *Lancet* 1999;354(9180):SII21-4.

22. Conroy S, Choonara I, Impicciatore P, *et al.* Survey of unlicensed and off label drug use in paediatric wards in European countries. *BMJ.* 2000;320:79–82.

23. Choonara I Conroy S. Unlicensed and off-label drug use in children: implications for safety. *Drug Saf* 2002;25(1):1-5.

24. Moore P. Children are not small adults. *Lancet* 1998;352(9128):630.

25. Kearns GL, Abdel-Rahman SM, Alander SW, *et al.* Developmental Pharmacology – drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003;349:1157-1167.

26. *Kaplan W, Laing R,* editors. *Priority Medicines for Europe and the World. World* Health Organization. *November 2004.* Available at: http:// apps.who.int/iris/bitstream/10665/68769/1/ WHO_EDM_PAR_2004.7.pdf

27. Zuidgeest M.G.P, Willemen M.J.C, van den Anker J.N. *Chapter 7.3. Pharmaceuticals and Children.* in: *Kaplan W, Laing R,* editors. *Priority Medicines for Europe and the World. World* Health Organization. *November 2004.* Available at: http://apps. who.int/iris/bitstream/10665/68769/1/ WHO_EDM_PAR_2004.7.pdf

28. Ceci A, Felisi M, Baiardi P, *et al.* Medicines for children licensed by the European Medicines Agency (EMEA): the balance after 10 years. *Eur J Clin Pharmacol.* 2006;62(11):947–952.

29. European Medicines Agency. Committee for Medicinal products for Human use (CHMP) 2005: *Reflection Paper: Formulations of Choice for the Paediatric Population.* EMEA/CHMP/ PEG/194810/2005.

30. European Medicines Agency. *Guideline on pharmaceutical development of medicines for paediatric use.* EMA/CHMP/ QWP/805880/2012 Rev. 2.

31. World Health Organization. *Development of Paediatric Medicines: Points to Consider in Formulation.* Geneva, Switzerland: World Health Organization; 2012. WHO Technical Report Series, No. 970, Annex 5.

32. Batchelor HK, Marriott JF. Formulations for children: problems and solutions. *Br J Clin Pharmacol* 2015;79(3):405-418. doi:10.1111/bcp.12268.

33. Richey RH, Shah UU, Peak M, *et al.* Manipulation of drugs to achieve the required dose is intrinisic to paediatric practice but is not supported by guidelines or evidence. *BMC Pediatr* 2013;13:1–8.

34. Cars O, Nordberg P. Antibiotic Resistance – the Faceless Threat, *Int J Risk S af Med 2005;*17: 103–110.

35. Livermore DM. Bacterial resistance: origins, epidemiology, and impact. *Clin Infect Dis* 2003;36(Suppl 1):S11-23.

36. Goossens H, Ferech M, Vander Stichele R, *et al.* ESAC Project Group. Outpatient

37. antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; 365: 579–587.

38. World Health Organization. *The evolving threat of antimicrobial resistance – Options for action.* Geneva, 2012. Available at: http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf.

39. Sturkenboom MC, Verhamme KM, Nicolosi A, *et al*; TEDDY European Network of Excellence. Drug use in children: cohort study in three European countries. *BMJ* 2008;337:a2245.

40. Boonstra E, Lindbaek M, Ngome E. Adherence to management guidelines in acute respiratory infections and diarrhoea in children under 5 years old in primary health care in Botswana. *Int J Qual Health Care* 2005;17(3):221–227.

41. Larsson M, Kronvall G, Chuc NTK, *et al*. Antibiotic medication and bacterial resistance to antibiotics: a survey of children in a Vietnamese community. *Trop Med Int Health* 2000;5(10):711-721.

42. Togoobaatar G, Ikeda N, Ali M, *et al*. Survey of non-prescribed use of antibiotics for children in an urban community in Mongolia. *Bull World Health Organ* 2010;88(12):930-936.

43. Clavenna A, Bonati M. Differences in antibiotic prescribing in paediatric outpatients. *Arch Dis Child* 2011;96:590–595.

44. Coco AS, Horst MA, Gambler AS. Trends in broad-spectrum antibiotic prescribing for children with acute otitis media in the United States, 1998–2004. *BMC Pediatrics* 2009**;** 9:41.

CHAPTER 2

PRIORITY MEDICINES FOR CHILDREN

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adopted version from the Background paper on Priority Medicines for Children,
in: Priority Medicines for Europe and the World 2013 Update

INTRODUCTION

In 2003, the Government of the Netherlands established the Priority Medicines for Europe and the World Project with the World Health Organization (WHO). The aim was to prepare a public health based medicines research and development (R&D) agenda for support by the European Union (EU), and to develop a systematic methodology for this purpose that could be replicated. The following year, WHO prepared the Priority Medicines 2004 Report, which reviewed the global and European burden of diseases, assessed where pharmaceutical gaps existed, suggested areas in which pharmaceutical innovation was required, and attempted to identify future essential medicines.[1] The pharmaceutical gaps were described as pharmaceutical treatments for a disease which either did not exist, or were likely to become ineffective in the future, or were available, but the delivery mechanism or formulation was not appropriate for the target population group. The report included a preliminary list of 17 diseases for which priority medicines were needed according to *priority* of importance for research funding by the EU. In addition, the report addressed the particular needs of children, women, the elderly and those suffering from rare diseases.[1]

In 2013, the European Commission requested that the 2003 agenda would be updated to be used in planning the EU Horizon 2020 combined research program. The new report takes into account the changes in global health and pharmaceutical innovation that occurred in the last ten years (2003-2013) in order to determine present and future patient needs. The report therefore goes beyond the European setting and includes a broader global focus. It studies the progress in pharmaceutical development that was made in different disease areas, and in relation to special patients groups.[2] One of the background papers for the Priority Medicines 2013 Report specifically focused on children, and presented an update of a similar background paper in the 2004 Report.[3,4] This chapter presents the shortened version of the 2013 background paper on priority medicines in children. Its aims were:

– to identify the persistent and new pharmaceutical gaps in paediatric pharmacotherapy, and

– to make suggestions for an up-to date research agenda for developing priority medicines consistent with clinical needs in children of Europe and the world, in a supportive policy environment.

Our review on these themes focused on a number of particularly important topics: paediatric disease patterns, better medicines for children, product-related issues, regulatory aspects, and the paediatric usage environment.

CHILD MORTALITY AND MORBIDITY

The disease burden in children and trends over time shed light on areas that need more attention. Therefore, more detailed information on causes of child mortality and morbidity

is an essential input into policy decision making on resource allocation to disease prevention and treatment programs.

Infectious diseases are the most common cause of illness in children in the developing world and a predominant cause of childhood mortality in these countries. As shown by recent statistics, pneumonia, diarrhoea and neonatal conditions are major contributors to the global burden of disease in children below five years of age.[5,6] In addition, malaria and tuberculosis represent major threats, especially in low- and middle-income countries, and tuberculosis is also an important disease in some European countries.[5-7] Antibacterial resistance remains an important challenge for the public health care sector, as the worldwide increase in resistant bacteria has been coupled with a downward trend in the development of new antibiotics. Even though the overall prevalence and burden of infectious diseases is much lower in Europe compared to the developing world, their public health effects extend beyond direct disability and death. Increased global mobility can lead to an increased risk of epidemics, while the emergence of antimicrobial and multidrug resistance can complicate the management of subsequent infections.

Moreover, many chronic non-communicable diseases (NCDs) contribute substantially to the paediatric disease burden (disability and mortality) globally.[8] Asthma is the most common chronic childhood disease in Europe, affecting up to one fifth of the school-aged children.[9] The childhood type 1 diabetes annual incidence rate continues to rise across Europe over time, and the risk of type 2 diabetes in adolescents is increasing due to overweight and obesity.[10,11] Mental disorders are increasingly important causes of ill health and disability in children and adolescents, but the recent broadening of age ranges and the scope of diseases has led to debates on the medicalisation of certain conditions.[12,13] Chronic NDCs no longer only occur in high income settings. The vast majority of these diseases are increasingly prevalent in the developing world or will be in the not-too-distant future.[14] Perhaps even to a greater extent than in 2004, the health needs of Europe and the rest of the world are converging, and the so-called commonality of interest identified in the Priority Medicines 2004 Report continues to be relevant.[2]

BETTER MEDICINES FOR CHILDREN

To ensure optimal treatment of diseases, any medicine should be designed to meet patient needs and to consistently deliver the intended product performance. Before a medicine is placed on the market, it generally has to have undergone extensive studies, including preclinical tests and clinical trials, to confirm that it is safe, of high quality and effective for use in the target population.[15]

Children are not small adults, but distinct and heterogeneous entities with dynamic processes inherent to growth from birth into adulthood and the distinct scope of diseases in childhood.[16,17] Accordingly, safe and effective paediatric pharmacotherapy requires medicines adjusted to the needs, acceptability and preferences (of each subpopulation)

of children. Yet, children have been commonly considered "therapeutic orphans" because the majority of medicines on the market have not been studied or authorised for use in the paediatric (sub)population.[18] It has created gaps in the availability of *medicines* for children, that are adapted to children's body development, child related toxicity and children's preference. Thus, it is important to facilitate the development and accessibility of paediatric medicines that are subject to research of high quality, with an authorisation for paediatric use, and age-appropriate labeling.[19]

Development of age appropriate medicines for children requires not only a knowledge of the physical and biochemical differences between children and adults, but also an understanding of their preferences for different formulations, flavours and textures of products.[19] Overall, the design of an ideal paediatric formulation needs to consider the following factors: 1) producing minimal impact on the lifestyle of the child, manifesting as the lowest dosage frequency and a palatable product, 2) provision of individualized dosing or dose banding appropriate for effective therapy, 3) sufficient bioavailability, 4) non-toxic excipients in the formulation, 5) convenient and reliable administration and 6) robust production process at minimal cost.[20]

The Priority Medicines 2004 Report made several recommendations for future action, including suggestions to promote and support paediatric drug development, especially in the neglected area of age-appropriate formulations.[3] It is encouraging to note that in recent years, the culture and practice of developing medicines for children has evolved, evidenced by increased research activities, product label changes and more child-friendly medicines.

Product-related issues in children

Since 2004, the progress in paediatric drug development mostly concerns oral formulations. Formulation research has been directed towards novel solids with dose flexibility, such as mini-tablets, chewable and orodispersible tablets for younger children, and dosage forms dispersible into liquids or mixed with food. This development is in line with the global shift towards the use of solid oral dosage forms for children, as proposed by a WHO expert forum in 2008.[21] According to recent studies on orally disintegrating mini-tablets, the age at which young children can safely swallow orally administered solid forms is decreasing, with promising results for infants younger than two years of age.[22,23] Table 1 presents a number of novel oral, solid dosage forms for paediatric use that have recently become commercially available or are under development.[24,25]

In addition, the WHO Prequalification Programme has been evaluating the quality, safety and efficacy of prioritised essential medicines for HIV/AIDS, malaria and tuberculosis since 2001 to make them available for the benefit of those in need, including children. The list of prequalified medicines, compliant with unified international standards, has been used as a procurement tool by the United Nations agencies, countries and other organizations. Paediatric formulations have been considered a high priority, so the current list of prequalified products comprise a number of novel oral dosage forms (Table 2).[26]

Table 1. Examples of novel drug formulations for children, which have become commercially available[24, 25]

Dosage form	Generic name - Brand product (Manufacturer)
Multiparticulates	
Granules / Sprinkles / Pellets	terbinafine granules - Lamisil® (Novartis)
	montelukast granules – Singulair® (MSD)
	artesunate + mefloquine granules - Artequin® Pediatric (Mepha)
	methylphenidate granules – Medikinet® (Medice)
	pancreatin micropellets - Creon® (Solvay)
	ethylphenidate controlled release micropellets – Ritalin® pellets (Sandoz)
Minitablets	pancreatin minitablets - Pankreatan® (Novartis)
	pancreatin minitablets - Cholspasminase® (Merck)
	pancreatin minitablets - Enzym-Lefax® (Bayer)
	pancreatin minitablets - Cotazym® (UCB)
	methylphenidate extended-release minitablets - Concerta® trilayer (J&JPRD)
Flexible dispersible formulations	
Dispersible tablets	artemisinin-based combination therapy dispersible tablets - Coartem® Dispersible (Novartis, MMV)
	herbal supplement - Sinupret® Liquitabs® (Bionorica)
Oral lyophilisates	cetirizine oral liophilisate - Zyrtec® (Duncan)
Orally disintegrating tablets (ODT)- lozenges	loratadine ODT - Redi-Tab® (Bayer)
	prednisolone ODT - Orapred® ODT (Concordia Pharmaceuticals)
	lansoprazole - Prevacid® SoluTab (TAP Pharmaceutical)
	fexofenadine - Allegra® ODT (Chattem)
	sodium fluoride lozenges - Fluoretten® (Sanofi-Aventis)
Oral strips / Buccal wafers	dextromethorphan + acetaminophen oral strips- Triaminic® Thin Strips (Novartis)
	ondansetron orodispersible films - Setofilm® (Applied Pharma Research & Labtec & Monosol Rx)
Chewable tablets	magnesium hydroxide gummy bears-Pedia Lax® (Fleet)
	montelukast sodium chewable tablets – Singulair® (MSD)
Chewing gums	dimenhydrinate chewing gums - Superpep® (Hermes)
Medicated lollipop	fentanyl citrate lollipop- Actiq® (Cephalon)

Despite the research on novel paediatric products, the literature suggests very limited clinical evidence to support ongoing technological advances in children. A recent systematic review on oral medicines for paediatric use analysed the effects of a number of pharmaceutical technologic aspects on patient-related outcomes.[27] Table 3 shows that side effects, tolerability and administration errors received limited attention, resulting in no evidence being available to substantiate that improved formulations lead to fewer side

Table 2. Examples of WHO prequalified paediatric formulations for HIV/AIDS, TB and malaria[26]

Dosage form	WHO prequalified paediatric products
Dispersible tablets	Abacavir (as sulfate) 60 mg
Dispersible tablets	Lamivudine/Nevirapine/Stavudine 60 mg/100 mg/12 mg
Dispersible tablets	Lamivudine/Nevirapine/Stavudine 30 mg/50 mg/6 mg
Dispersible tablets	Lamivudine/Nevirapine/Zidovudine 30 mg/50 mg/60 mg
Dispersible tablets	Isoniazid/Pyrazinamide/Rifampicin 30 mg/150 mg/60 mg
Dispersible tablets	Artemether/Lumefantrine 20 mg/120 mg
Dispersible tablets	Lamivudine 30 mg
Dispersible tablets	Isoniazid/Rifampicin 60 mg/60 mg
Tablets	Lamivudine 30 mg
Tablets	Zidovudine 100 mg
Tablets	Abacavir (as sulfate)/Lamivudine 60 mg/30 mg
Tablets	Lopinavir/Ritonavir 100 mg/25 mg
Tablets	Abacavir (as sulfate)/Lamivudine/Zidovudine 60 mg/30 mg/60 mg
Tablets	Lamivudine/Zidovudine 30 mg/60 mg
Oral suspension	Nevirapine 50 mg/5 ml

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effects. The majority of studies were conducted in children aged 2 to 12 years, revealing the lack of clinical trials in neonates and infants. Most of the studies were considered to be of poor methodological quality, suggesting that paediatric pharmaceutical development studies may need more suitable instruments, as randomized controlled and double blind trials might not always be appropriate.[27] Instead, practice-based evidence on the impact of novel formulations, generated by health care professionals and caregivers, may provide further support for the development of pediatric medicines with clear clinical advantages.[27]

As future steps, it is also important that innovations are accompanied by adequate studies on price implications and access to innovative products, children's preferences and adherence to different dosage forms, safe excipients and their levels in children, and possibilities for new administrative routes (mainly for neonates). The newly acquired knowledge on suitable paediatric formulations need to be absorbed by the industry and translated into new paediatric products.

Regulatory aspects related to children

Another key recommendation of the Priority Medicines 2004 Report was the need to include more children in clinical trials.[3] Progress since then includes the adoption of the Paediatric Regulation in the EU in 2007, which combines requirements for paediatric drug development (Paediatric Investigation Plans – PIPs) with incentives for the pharmaceutical industry to, at least partly, cover the additional investment for testing medicines in children.[15]

During 2007-2011, the number of EU clinical trials with paediatric populations was stable with an average of 350 trials a year, while the proportion of paediatric trials among all trials increased from 7.4% to 9.9%. Of these paediatric trials, 109 were part of an agreed

Table 3. Impact of pharmaceutical technologic aspects on patient-related outcomes parameters.[27]

Patient-related outcomes parameter	Pharmaceutical technological aspects			
	Formulation and Dosage Form (n=85)	Route and Frequency of Administration (n=77)	Packaging, Administration Device, and User Instruction (n=14)	All Assessments (n=176)*
Patient acceptance	38 (45%)	5 (6%)	1 (7%)	44 (25%)
Patient preference	19 (22%)	4 (5%)	0 (0%)	23 (13%)
Adherence	11 (13%)	15 (19%)	6 (43%)	32 (18%)
Clinical efficacy	8 (9%)	31 (40%)	2 (14%)	41 (23%)
Side effects and tolerability	8 (9%)	22 (29%)	0 (0%)	30 (17%)
Administration errors	1 (1%)	0 (0%)	5 (36%)	6 (3%)

* Two investigations assessed >1 pharmaceutical technologic aspect.

PIP.[28] One effect was the inclusion of younger children in clinical trials for cholesterol-lowering and anti-hypertensive medicines, juvenile idiopathic arthritis, diabetes mellitus and haemophilia A and B. The new regulation may also aid in preventing unnecessary trials since protocol-related information is made publicly available through the EU clinical trials database (EudraCT).[28]

Since 2007, approximately 70% of all PIPs proposed or required the development of indications for the whole or subsets of the paediatric population. This indicates an increase in the development of medicines for children, as only approximately 30% of medicines applied for and obtained a paediatric indication before the regulation came into force.[28] Between 2007 and 2012, 29 PIPs were completed in compliance with the new regulation, which led to the approval of 24 new paediatric indications and seven new pharmaceutical forms appropriate for children. Centralized authorisations for paediatric use were obtained for 34 new medicines, and 38 new paediatric indications, as variations of 33 already authorized medicines. In addition, 14 centrally authorized products had either a new pharmaceutical form, a new route of administration, or a new strength authorized for paediatric use.[28] Rewards were obtained for 12 medicines; supplementary protection certificate (SPC) extensions for 11 medicines, and Paediatric Use Marketing Authorisation (PUMA) exclusivity for one off-patent paediatric medicine (midazolam paediatric oromucosal solution Buccolam®).[28]

Overall, the Paediatric Regulation has put a framework and structure in place to encourage a systematic evaluation of each new compound to identify paediatric needs and potential value for children, and this system has produced initial results. Yet, the question as to whether its implementation has delivered what was expected needs to be critically answered, pointing out the challenges and alternative solutions. Paediatric therapeutic areas addressed by the industry since 2007 seem more aligned with adult drug development than with the indicated high priority and unmet therapeutic paediatric needs, including rare diseases or diseases that occur only in children (e.g. paediatric oncology, pain, neonatal morbidity).[28] To indicate the medicines with the highest need in children, the European Medical Agency (EMA) has published a range of lists covering potentially all therapeutic areas (cardiology, psychiatry, endocrinology, gastroenterology, haematology, immunology, infections, intensive care, metabolism, neonatology, nephrology, neurology, oncology, pain, pneumology and rheumatology) and age groups where off label use in children is significant and data and studies were lacking.[29] On the other hand, alternative methodological approaches to classical clinical trials should also be encouraged to facilitate clinical trials in children or reduce the need for investigation in this vulnerable and limited population. That includes modeling and simulation approaches, as well as extrapolations, which depend on basic knowledge on specific diseases in children, such as pathophysiology, biomarkers and pharmacodynamic end-points.

As far as incentives are concerned, the reward of a six-month SPC extension may delay generic entries and have cost implications for public payers. A recent example

showed that a deficient market approval of a new paediatric product at national level may result in higher healthcare spending than if a generic had been used, and an unsafe drug use due to inadequate packaging and labeling (see Table 4).[30] It is therefore, essential that the introduction of new paediatric products on the market resulting from this regulation is accompanied by adequate national regulatory, political and financial decisions. The cost implication of access to improved medicines is to be put in the context of the drug development expenditures and the costs related to off label use and lack of available medicines.

The fact that only one PUMA (with limited therapeutic benefit) has been granted between 2007 and 2012 indicates that it may not be an adequate incentive to the industry for the development of off-patent drugs. Hence, the EMA has produced a priority list to serve as a basis for the EU Seventh Framework Programme (FP7) community funding for research into off-patent medicines. The following areas have been considered of high priority: development of age-appropriate formulations and strengths, data in neonates for all conditions (except oncology), and data in infants for oncological conditions and for refractory paediatric epilepsy syndromes.[31]

Table 4. Undesirable outcomes of the introduction of a new paediatric product on the national market, an example of Cozaar® oral suspension[30]

Name of the Medicine	Cozaar® oral suspension, paediatric form of the antihypertensive drug losartan
Paediatric Regulation reward	Six-months extension to its market exclusivity in France, including non-paediatric indications
Therapeutic use	Hypertension, but not standard treatment for hypertension in children
Packaging and labeling	Suspension not ready to use Not labeled properly Poor quality packaging prone to dosing mistakes (diluting)
Availability	Difficult to obtain from retail pharmacies via wholesalers
Price implications	Company did not ask for inclusion in the French reimbursement list Expensive, out-of-pocket expenditure High profitability for the company*

According to figures from the French National Health Insurance Fund for salaried workers (Cnamts) on reimbursement requests in France during 2009, reimbursements for losartan (excluding the losartan + hydrochlorothiazide combination) over a 6-month period totaled 27 million Euros.

The paediatric usage environment

Over the period 1995-2005, only a third of all authorised medicines approved by EMA were licensed for use in paediatric patients.[32] This leaves no alternative for prescribers other than to use adult medicines for children as off-label (medicines prescribed outside their authorised indications with respect to age, dosage, indication or route) or unlicensed medicines (modified formulations, extemporaneous preparations, imported medicines before the authorisation license is granted). A survey published in 2010 estimated that 45-60% of all medicines given to children in the EU were used outside their marketing authorisation, especially in neonates, patients with serious conditions and those in intensive care units.[33] The most frequently used off-label and unlicensed paediatric medicines were anti-arrhythmics, anti-hypertensives, proton pump inhibitors, H2-receptor antagonists, anti-asthmatics, and antidepressants.[33] The collection of data on the indications and the extent of off-label and unlicensed medicine use helps to identify unmet needs in children, and it has been suitably used to establish priority lists for real improvements in paediatric pharmacotherapy.

One implication of the frequent off-label use of paediatric medicines is the lack of adequate information about their possible indications, dosing regimens, dose adjustments, and administration. This information is neither included in the Summary of Product Characteristics (SmPC) for health-care professionals, nor in the patient information leaflets for patients and their caregivers. In order to obtain better information on the use of medicines in children, the Paediatric Regulation has included an instrument for collecting data from existing paediatric studies. The Regulation has obliged companies holding data on the safety or efficacy of authorized medicines in children, as well as newly generated paediatric data, to submit those studies to the competent authorities, so that data can be assessed and authorized product information can be amended.[15] Since 2007, more than 18,000 study reports on 2,200 medicinal products have been submitted to the competent authorities, revealing the large amount of existing paediatric information available at company level. These study reports are being assessed by the authorities, resulting in the publishing of assessment reports on 140 active substances, and recommending changes to the SmPC for authorized products. However, marketing authorisation holders have not progressed much in updating the SmPCs, so little of those new data have been systematically included in SmPCs.[28] Alternatively, it can be argued that since off-label use of medicines in children is such a common practice, it already relies on sufficient data. It may be possible for healthcare professionals to systematically monitor the use of off-label medicines in paediatric clinical practice and share patient records to produce robust safety and efficacy data. The expanded availability and use of electronic medical records will hopefully soon allow practitioners and researchers to link clinical treatments and outcomes with off-label medication prescribing trends in order to elucidate the implications of off-label use of medicines in children. It is also expected that the new EU Pharmacovigilance Regulation

will support the evidence-based use of off-label medicines in children, as it includes both marketed and unlicensed/off label medicines.

Other recent initiatives to improve information dissemination on medicines use in children include the new websites 'Dutch Pediatric Drug Formulary', 'Medicines for children' in the United Kingdom, the British National Formulary for Children and the WHO Model Formulary for Children.[34-37] Nonetheless, more should be invested in evaluating the impact of existing information on medicine use in children on improving daily clinical practice and the adherence to treatments. Various studies on medicine use trends and patterns in children indicate that more efforts are needed to guarantee the rational use of medicines, especially of antibiotics, psychotropic medicines, medicines for neonates, and medicines used in hospitals. Given the growing burden of antimicrobial resistance, it is particularly worrisome to see that inappropriate antibiotic prescribing for children is common in many parts of the world. The majority of antibiotics are used in outpatient settings, often to treat infections with predominantly viral aetiologies (e.g. most upper respiratory infections, diarrhoea).[38-40] Antimicrobials were also among the most commonly prescribed drugs in hospitals. The targets for inpatient quality improvement included the excessive use of antimicrobial combinations, high proportion of parenteral antimicrobials, and long surgical prophylaxis times.[41] Equally, the irrational use of medications has been a frequent pattern for most common childhood diseases (pneumonia, diarrhoea, and malaria) in resource poor settings. A recent WHO review of interventions to improve use of medicines suggested that the most effective interventions were multifaceted and took place at the system level, as opposed to the individual prescriber level.[42]

Importantly, there have been considerable variations in antibiotic use not only between different regions and countries, but also between practices within one single country.[43-44] So, systematically collected and evaluated evidence enables to measure medicine use within health systems, carry out inter- and intra-countries comparisons, and evaluate progress over time. Better performing settings may help set up attainable standards for benchmarking purposes, and progress may be achieved by targeting settings with irrational prescribing patterns. But, the lack of systematic and continuous monitoring of the use of medicines in most of the countries and the heterogeneity between studies make comparative evaluations difficult or incomplete. To counter this, the methodological quality of data collection should be improved, and more multinational collaborative studies should be performed with the EU and WHO support.

IDENTIFIED GAPS AND RECOMMENDATIONS FOR RESEARCH AND POLICY

Since the Priority Medicines 2004 Report, numerous activities have been undertaken to support the development and administration of appropriate paediatric medicines and to improve the information available on their use. Despite the rapid technological advances

and emerging networks for collaborations and expertise, we identified the following knowledge gaps and areas that still need strengthening and/or future research in the area of medicine use in children.

Further research into development of age-appropriate medicines

In recent years, much progress has been made in the development of age-appropriate novel, oral formulations with dose flexibility and medical devices for easier administration of paediatric medicines. In addition, new routes of administration, such as oral-transmusosal (buccal strips), intra-nasal and transdermal routes (for neonates mainly), are ripe for future development and research. In neonates, particular caution is needed for these forms in terms of optimal use and dosing.

Given the safety and toxicity concerns of some excipients in paediatric formulations, more research is needed into safe alternatives for children. It is also important to incorporate the available knowledge on excipients into a single, public repository to avoid a duplication of efforts and to encourage further discovery and innovation.

Irrespective of all technological developments, there is limited evidence on the impact of pharmaceutical formulations, routes, and dosage forms on patient-related outcomes (e.g. clinical efficacy, side effects and tolerability, and patient preference, acceptance, and adherence). This research should be central to the support of the pharmaceutical development of paediatric medicines with clear clinical advantages.

In addition, although many novel formulations and paediatric drug delivery devices have been developed, very few appear to be available on the market. This is most likely due to the high costs of patent protection and the (un)willingness of health insurance bodies to reimburse for these new items. Therefore, current formulation research should also be accompanied by studies on price implications and access to innovative products that have tangible therapeutic benefit.

Increase efficiency of the Paediatric Regulation with a focus on real paediatric needs

The Paediatric Regulation aims to achieve an integrated approach to the development of paediatric medicines in the overall medicine development area. However, current PIPS and their therapeutic areas covered by the industry seem to be more in alignment with adult drug development than with unmet public health needs in children. As a response, the EMA has been producing lists on unmet therapeutic needs in children to identify priority research areas. This activity should be complemented by proactive demands for clinical trials on priority medicines with significant therapeutic benefits in children.

In addition, alternative methodological approaches to classical clinical trials should be encouraged to facilitate and optimize clinical trials in children, and potentially also reduce the need for (or size of) clinical trials in this vulnerable and limited population. Research in this field should be stimulated.

Moreover, some paediatric medicines awarded six-month Supplementary Protection Certificate (SPC) extensions have cost implications and may increase public health expenditures. It is therefore essential that regulatory authorities have active systems in place to detect and act upon such unintended effects, resulting from the introduction of new paediatric products on the market.

Improve (information on) rational use of paediatric medicines

Due to the lack of clinical trials using children, the available evidence on safety, quality, and efficacy and the knowledge of the potential risks of adverse drug reactions with off-label medicines used in children is limited. It is essential to systematically collect and use the real life data on off-label or unlicensed medicine use in children to produce such evidence. Hopefully, the expanded availability and use of electronic medical records will soon allow researchers to link clinical treatments and outcomes with off-label medication prescribing trends and elucidate the implications of their use in children. The new EU Pharmacovigilance Regulation may have potential added value in providing safety and efficacy data on off-label-medicine use in children, which should be evaluated.

Various studies on medicine use trends and patterns in children indicate that more efforts are needed to guarantee the rational use of medicines, especially of antibiotics, psychotropic medicines, medicines for neonates, and medicines used in hospitals. Previous reviews suggested that effective interventions to improve the use of medicines have been multifaceted and have taken place at the system level. Furthermore, data should be systematically collected and evaluated to measure and test the effectiveness of interventions in improving medicine use. The collection of data use of medicines in children at a country level would allow analysis of trends over time and inter-country comparisons. The main challenges are the lack of systematic and continuous monitoring in many countries and the disparity between studies. Therefore, the methodological quality of data collection should be improved and more multinational collaborative studies should be performed with EU and WHO support.

Recent improvements in information dissemination on medicine use in children for both healthcare workers and the public include the creation of websites in the Netherlands, the UK and by WHO. Complementary research should follow up on this to evaluate how healthcare professionals obtain information to treat children in daily practice and to evaluate what impact new information resources have on the use of medicines and adherence to treatment in children.

In summary, to further improve the development and use of medicines in children, investments are needed to:

– stimulate additional research into the development of age-appropriate medicines,

– study the impact of formulation development and paediatric regulations on patient related and public health outcomes,

– increase the efficiency of the EU Paediatric Regulation with a focus on genuine paediatric needs,

– facilitate the collection, linkage and use of data on medicines use in children,

– improve (information on) the rational use of medicines in children.

REFERENCES

1. *Kaplan W, Laing R,* editors. *Priority Medicines for Europe and the World.* *World* Health Organization. *November 2004.* Available at: http://apps.who.int/iris/bitstream/10665/68769/1/WHO_EDM_PAR_2004.7.pdf

2. Kaplan W, Wirtz VJ, Mantel-Teeuwisse A, Stolk P, Duthey B, Laing R. *Priority Medicines for Europe and the World 2013 Update*. Geneva: World Health Organization in collaboration with Utrecht University and Boston University; 2013.

3. Zuidgeest M.G.P, Willemen M.J.C, van den Anker J.N. *Chapter 7.3. Pharmaceuticals and Children*. in: *Kaplan W, Laing R,* editors. *Priority Medicines for Europe and the World.* *World* Health Organization. *November 2004*. Available at: http://apps.who.int/iris/bitstream/10665/68769/1/WHO_EDM_PAR_2004.7.pdf

4. Ivanovska V, Mantel-Teeuwisse AK, Van Dijk L. *Background Paper 7.1. Priority Medicines for Children*. in: Kaplan W, Wirtz VJ, Mantel-Teeuwisse A, Stolk P, Duthey B, Laing R. *Priority Medicines for Europe and the World 2013 Update*. Geneva: World Health Organization in collaboration with Utrecht University and Boston University; 2013.

5. Liu L, Johnson HL, Cousens S, *et al*, for the Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet* 2012; 379: 2151–61.

6. United Nations Inter-agency Group for Child Mortality Estimation (IGME). *Levels & Trends in Child Mortality – Report 2012*. UNICEF, WHO, WB, UNDP. New York, 2012. Available at: http://www.childmortality.org/files_v11/download/Levels%20and%20Trends%20in%20Child%20Mortality%20Report%202012.pdf.

7. Walls T, Shingadia D. The epidemiology of tuberculosis in Europe. *Arch Dis Child* 2007; 92(8): 726–729.

8. Torpy JM, Campbell A, Glass RM. Chronic Diseases of Children. *JAMA*. 2010;303(7):682.

9. Bousquet J, Khaltaev N , eds. *Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach*. Geneva, World Health Organization, 2007. Available at: http://www.who.int/gard/publications/GARD%20Book%202007.pdf

10. Patterson CC, Dahlquist GG, *et al*, and the EURODIAB Study Group. Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005–20: a multicentre prospective registration study. *Lancet* 2009; 373: 2027–33.

11. Aanstoot HJ, Anderson BJ, Daneman D. Diabetes in children: epidemiology. *Pediatric Diabetes* 2007: 8 (Suppl. 8): 10–18.

12. Suhrcke M, Pillas D, Selai C. *Economic aspects of mental health in children and adolescents*. World Health Organization, Regional Office for Europe. 2007. Available at: http://www.euro.who.int/__data/assets/pdf_file/0003/76485/ Hbsc_Forum_2007_economic_aspects.pdf

13. Hodgman CH. The "medicalization" of pediatric mental illness. *Pediatr Ann*. 2001;30(3):126-128.

14. World Health Organization. *World Health Statistics 2012*. World Health Organization, 2012. Available at:http://who.int/entity/gho/publications/world_health_statistics/2012/en/index.html

15. The European Parliament and the Council of the European Union. Regulation EC No. 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use. 2006; Available at: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf

2

16. Kearns GL, Abdel-Rahman SM, Alander SW, *et al.* Developmental Pharmacology – drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003;349:1157-1167.

17. Institute of Medicine (US) Committee on Clinical Research Involving Children; Field MJ, Behrman RE, editors. *Ethical Conduct of Clinical Research Involving Children.* Washington (DC): National Academies Press (US); 2004.

18. Shirkey H. Therapeutic orphans. J Pediatr 1968;72:119-20.

19. European Medicines Agency. *Guideline on pharmaceutical development of medicines for paediatric use.* EMA/CHMP/QWP/805880/2012 Rev. 2.

20. Breitkreutz J, Boos J. Paediatric and geriatric drug delivery. *Exp Opin Drug Deliv* 2007; 4:37–45.

21. World Health Organization. *Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children.* World Health Organization, 2008. Available at http://www.who.int/selection_medicines/committees/expert/17/application/ paediatric/Dosage_form_reportDEC2008.pdf

22. Thomson SA, Tuleu C, Wong IC, *et al.* Minitablets: new modality to deliver medicines to preschool-aged children. *Pediatrics*, 2009, 123(2):e235-8.

23. Spomer N, Klingmann V, Stoltenberg I, *et al.* Acceptance of uncoated mini-tablets in young children: results from a prospective exploratory cross-over study. *Arch Dis Child*, 2012, 97(3):283-6.

24. Stoltenberg I, Winzerburg G, Breitkreutz J. Solid oral forms for children – formulations, excipients and acceptance issues. *J Appl Ther Res* 2010; 7(4): 141-146.

25. Breitkreutz J. Nach der EU-Reform. Arzneiformen für Kinder. *Pharm Unserer Zeit* 2009;38: 30-37.

26. World Health Organization. Prequalification Programme, A United Nations Programme managed by WHO. 2011; Available at: http://apps.who.int/prequal/. Accessed May 2, 2013.

27. van Riet-Nales DA, Schobben AF, Egberts TC, *et al.* Effects of the pharmaceutical technologic aspects of oral pediatric drugs on patient-related outcomes. *Clin Ther* 2010;32(5):924-938.

28. European Medicines Agency with its Paediatric Committee. 5-year Report to the European Commission. General report on the experience acquired as a result of the application of the Paediatric Regulation. EMA/428172/2012 2012. Available at: http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf

29. European Medicines Agency. Paediatric needs. Available at: www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000096.jsp&mid=WC0b01ac05800260a1

30. Prescrire. Who Benefits from the European Paediatric Regulation? Response to the European Commission's public consultation on the lessons learnt from the first 5 years of application of the Paediatric Regulation. Paris, 2012.71.

31. European Medicines Agency. Revised priority list for studies into off-patent paediatric medicinal products. EMA/98717/2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004017.pdf

32. Ceci A, Felisi M, Baiardi P, *et al.* Medicines for children licensed by the European Medicines Agency (EMEA): the balance after 10 years. *Eur J Clin Pharmacol* 2006;62(11):947-952.

33. European Medicines Agency. *Report on the survey of all paediatric uses of medicinal products in Europe.* EMA/794083/2009. Available at: http://www.ema.europa.

eu/docs/en_GB/document_library/ Report/2011/01/WC500101006.pdf

34. Nederlands Kenniscentrum voor Farmacotherapie bij Kinderen (Dutch Knowledge for Pharmacotherapy in Children). Kinderformularium. - in Dutch. Available at: https://www.kinderformularium.nl/

35. Royal College of Paediatrics and Child Health (RCPCH), Neonatal and Paediatric Pharmacists (NPPG) and WellChild, the UK. Medicines for Children. Available at: http://www.medicinesforchildren.org.uk/

36. Royal Pharmaceutical Society, the UK. British National Formulary. Available at: http://www.bnf.org/bnf/index.htm

37. World Health Organization, WHO model formulary for children 2010. World Health Organization, Geneva 2010. Available at: www.who.int/selection_medicines/list/WMFc_2010.pdf

38. Peterson I, Hayward AC. Antibacterial prescribing in primary care. *J Antimicrob Chemother* 2007;60:i43-47.

39. Hersh AL, Shapiro DJ, Andrew T, *et al.* Antibiotic prescribing in ambulatory paediatrics in the United States. *Paediatrics* 2011;128:1053.

40. Akkerman AE, van der Wouden JC, Kuyvenhoven MM, *et al.* Antibiotic prescribing for respiratory tract infections in Dutch primary care in relation to patient age and clinical entities. *J Antimicrob Chemother* 2004;54:1116-1121.

41. Amadeo B, Zarb P, Muller A, *et al.* European Surveillance of Antibiotic Consumption (ESAC) point prevalence survey 2008: paediatric antimicrobial prescribing in 32 hospitals of 21 European countries. *J Antimicrob Chemother* 2010;65(10):2247-2252.

42. World Health Organization. *Medicines use in primary care in developing and transitional countries: Fact book summarizing results from studies reported between 1990 and 2006.* WHO/EMP/MAR/2009.3. WHO Geneva, 2009. Available at: http://www.who.int/medicines/publications/primary_care_8April09.pdf

43. Grigoryan L, Burgerhof JG, Degener JE, *et al.* Determinants of self-medication with antibiotics in Europe: the impact of beliefs, country wealth and the healthcare system. *J Antimicrob Chemother* 2008;61(5):1172-1179.

44. Liem TBY, Krediet TG, Fleer A, *et al.* Variation in antibiotic use in neonatal intensive care units in the Netherlands. *J Antimicrob Chemother* 2010;65:1270-75.

CHAPTER 3

AGE-APPROPRIATE MEDICINES FOR CHILDREN

CHAPTER 3.1

PEDIATRIC DRUG FORMULATIONS:
A REVIEW OF CHALLENGES AND PROGRESS

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ABSTRACT

Children differ from adults in many aspects of pharmacotherapy, including capabilities for drug administration, medicine-related toxicity and taste preferences. It is essential that pediatric medicines are formulated to best suit a child's age, size, physiological condition and treatment requirements. To ensure adequate treatment of all children, different routes of administration, dosage forms and strengths may be required. Many existing formulations are not suitable for children, which often leads to off-label and unlicensed use of adult medicines. New regulations, additional funding opportunities and innovative collaborative research initiatives have resulted in some recent progress in the development of pediatric formulations. These advances include a paradigm shift towards oral solid formulations and a focus on novel preparations, including flexible, dispersible and multiparticulate oral solid dosage forms. Such developments have enabled greater dose flexibility, easier administration and better acceptance of drug formulations in children. However, new pediatric formulations address only a small part of all therapeutic needs in children; moreover, they are not always available. Five key issues need to be addressed to stimulate the further development of better medicines for children: (1) the continued prioritization of unmet formulation needs, particularly drug delivery in neonates and treatment gaps in pediatric cancers and childhood diseases in developing countries, (2) a better use of existing data to facilitate pediatric formulation development, (3) innovative technologies in adults that can be used to develop new pediatric formulations, (4) clinical feedback and practice-based evidence on the impact of novel formulations, and (5) improved access to new pediatric formulations.

INTRODUCTION

Drug formulations used in pediatric pharmacotherapy should be adapted to children's needs to suit their age, size, physiological condition and treatment requirements.[1,2] Such pediatric medicines are key to achieving safe and accurate dose administration, reducing the risk of medication errors, enhancing medication adherence and improving therapeutic outcomes in children.[3,4]

3.1

The use of inadequate drug formulations in children may pose problems not seen in adults, such as difficulty in swallowing conventionally sized tablets, safety issues with certain excipients that are acceptable in adult formulations, and adherence problems with unpalatable medicines.[1,5] These issues have led to serious tragedies in the past, and they exist partly because only a small fraction of all marketed drugs are available in formulations which are age appropriate.[6-12] As a result, many adult medicines are used off-label in children, a practice which carries additional health and environmental risks.[13-15]

To strengthen the development of pediatric drug formulations, new legislation was introduced in the United States and Europe, and efforts for global collaboration were made by the World Health Organization (WHO).[16-20] A number of innovative pediatric formulations have followed, but their actual effect on pediatric drug approvals remains to be seen, as clinical trials and marketing authorization take a substantial amount of time.[21-24]

To optimize pharmacotherapy in children, it is important for clinicians to understand the background of the aforementioned problems as well as to gain insight into the challenges, developments and potential solutions. The aim of the present review was to describe why there is a specific need for pediatric drug formulations and to illustrate the clinical consequences of the absence of suitable medicines for children. We will discuss the progress achieved so far and determine additional steps required to improve the development and availability of pediatric drug formulations.

THE NECESSITY OF PEDIATRIC DRUG FORMULATIONS
Diversity in children

It has been well established that children are not small adults, but rather a distinct and heterogeneous patient group with regard to pharmacotherapy.[25] They often exhibit a different response to both active substance and excipients.[26] Children present a continuum of growth and developmental phases as a result of their rapid growth, maturation of the body composition, and physiological and cognitive changes during childhood.[26]

Children differ from adults in many aspects of pharmacokinetics and pharmacodynamics, potential routes of administration, medicine-related toxicity and taste preferences.[3,25] Important pharmacokinetic differences between children and adults include the rate of gastric emptying and pH, gastrointestinal permeability, and the surface area available for drug absorption. Dissimilarities have also been reported in drug metabolism, transporter expression, biliary function, and renal clearance, resulting in differences in

drug disposition and elimination.[27,28] The largest deviation from adult pharmacokinetics is observed in the first 12–18 months, when organ functions are developing.[29,30] In older children and adolescents, the pharmacokinetic parameters approach adult values and are thus easier to predict.[26,31-33] The effect of age on pharmacokinetics leads to different dosing requirements for different age groups. [26,31-33] From birth to adulthood, the body size and weight of an average child increases up to 20-fold, and the magnitude of dose variation administered throughout childhood may be a 100-fold.[5] More dramatically, premature neonates admitted to the hospital can weigh as little as 500 g, further highlighting the need for dose variability.[29,30] Maturation processes in children are not linear, and therefore doses in certain age subsets may be lower, identical to, or higher than in adults, depending on a drug's metabolic pathway [32,34-35]

Due to this extensive variability in children, there is an obvious need for drug formulations tailored to children in all the target age groups. The International Conference of Harmonization divides childhood into 5 age groups related to the developmental stages, derived from the physiological and pharmacokinetic differences mentioned earlier.[28] These groups (with age ranges) are: preterm newborn infants, term newborn infants (0-27 days), infants and toddlers (1-23 months), children (2-11 years), and adolescents (12-16 years in the United States or 12-18 years in the European Union).[5,36]

The European Committee for Medicinal Products for Human Use further subdivides the age group 'children' (2-11 years) into 'preschool children' (2-5 years) and 'school children' (6-11 years), to more precisely reflect the children's ability to accept and use different dosage forms.[5] However, the classification of the pediatric population into age categories is to some extent arbitrary, because children of the same chronological age may still develop at different rates.[28]

Age-Related Adherence to Pediatric Drug Formulations

Formulation acceptability and preferences facilitate medication adherence in children, and they are important factors in achieving the intended treatment outcomes. Formulation acceptability differs across age groups as children gradually develop their cognitive and motor skills, and improve their ability to swallow medications. At certain ages, the dependence on caregivers also plays a role in the administration of pediatric dosage forms.[1] Pain, discomfort and an unnecessary burden on children and/or caregivers during drug administration should be minimized to assure adequate medication adherence. In older children and adolescents, lifestyle and peer pressure may also influence medication adherence and possible preferences for particular formulations.[1]

Taste attributes may be critical to ensure acceptable adherence to pediatric oral formulations. Because children have a low tolerance for disagreeable taste, the use of tasteless or palatable medicines can minimize the loss of medication from spillage and/or spitting.[14,37,38] Taste preferences may differ between children and adults, as children prefer

sweet and salty flavors, and dislike bitter and peppermint taste. These findings suggest that taste assessment should involve children early in the drug formulation development.[35,38,39] Children's communication about taste perceptions can be facilitated by using age-appropriate methods, scales, and measures.[40] Alternative taste screening methods may include adult taste panels with validated design for data transferability, or predictive electrochemical sensor systems (so called "electronic tongues").[41,42]

3.1

CLINICAL CONSEQUENCES OF THE ABSENCE OF SUITABLE PEDIATRIC DRUG FORMULATIONS

Potential Limitations of Pediatric Drug Formulations

Historically, the failure to appreciate the developmental changes in children has led to many adverse outcomes in clinical practice. Examples include infant deaths from choking on albendazole tablets, the lethal use of benzyl alcohol or diethylen glycol in sulfanilamide elixirs, and electrolyte imbalances caused by high contents of sodium or potassium in parenteral formulations.[6-9]

To prevent such tragedies and ensure adequate treatment of children of all ages, different routes of administration, dosage forms and strengths are often needed for the same active substance.[1] Table 1 illustrates the specific purposes, potential strengths, and weaknesses of various routes of administration and dosage forms for pediatric use.[1,2,5,43-47] As in adults, the oral route is the predominant route of administration in children.[1,2,43] Alternative nonoral routes of administration include rectal, dermal, nasal, pulmonary, and ocular routes.[1,2]

The selection for clinical use is influenced by the limitations of each dosage form. Oral solids are associated with the risk of choking or chewing and with limited dose flexibility, whereas palatability and dose uniformity may be challenging for liquid preparations.[1,2,43,44] In addition, liquid forms raise issues regarding stability (chemical, physical or microbiological) and the requirement for clean water; moreover, they can be bulky, impractical, and expensive to ship and store, particularly in lower income countries with hot and humid climates.[48,49]

The use of nonoral routes of drug administration may be hampered by difficult application, local irritation, fluid overload, electrolyte imbalance, or poor drug acceptability (Table 1).[1,2,5,43-47] In neonates, intravenous administration may lead to volume overload. Moreover, measuring small dose volumes may cause large dosage variations and errors.[47] Similarly, age-appropriate dosing volumes are important to ensure full dose ingestion for oral liquids.[5]

Another important concern in pediatric drug formulations are the excipients, frequently used as preservatives, sweeteners, fillers, solvents, and coating and colouring agents. Their selection for pediatric medicines is challenging because neither the inactive

Table 1. Potential clinical advantages and disadvantages of different formulations and routes of administration in children[1,2,5,43-47]

Administration and dosage forms	Potential advantages	Potential disadvantages
ORAL[1, 2, 5,43]	- main route for (long-term) treatments in children	- first pass effect
Liquid preparations	- acceptability from full term birth	- instability of multidose preparations
suspensions solutions, syrup, drops powders and granules for reconstitution	- maximum dose flexibility	- age-appropriate dosing volume for full dose ingestion - (less than 5 ml in younger and less than 10 ml in older age groups) - dose measuring device critical - shaking for dose accuracy (suspensions) - incorrect dosing for oral drops (criticality of dose) - risks of administration without prior dispersion/dissolution
Solid dosage forms tablets capsules	- stability, portability, good dosage uniformity - options for different doses and modified release	- ability to swallow intact dosage forms - risks of chocking and chewing - limited dose flexibility
powders, granules, sprinkles, multi-particulates, mini-tablets	- better acceptability (with liquid/semi-solid food) - dose flexibility	- dose measuring device needed - compatibility with food/drinks - limited control over dose intake
orodispersible/chewable preparations	- ease of administration	- taste masking requirements - less stable than standard tablets - risk of direct swallowing - intellectual properties costs
Administration through nasogastric tubes	- can be used in neonates and seriously ill infants	- ease of administration and dosing accuracy (volume, density, viscosity, particle size) - potential compatibility with feeding tube material - doses and rinse volume relevant to target age group - relevant size of feeding tubes

Table 1. (continued)

Administration and dosage forms	Potential advantages	Potential disadvantages
PARENTERAL[1,2,5,43-47] intravenous injections subcutaneous injections intramuscular injections pump systems	- main route for neonates and emergency cases - quick/high/constant blood and tissue drug concentration - sustained release preparations	- infections, phlebitis, embolism - fluid overload, electrolyte imbalance - inappropriate diluents - measurement of dose volumes - lag-volume effects in IV line - small veins, punctuation pain, needle phobia - incompatibilities with IV co-administered medicines - drug migration into plastic tubes (plasticizer desorption of phthalates from circuits)
RECTAL[1,2,5,43] suppositories rectal liquids	- can be used in severely ill children or unable to swallow	- size considerations - limited bioavailability (minor absorption area, lack of active - drug transporters, small fluid volume for dissolution) - frequent stooling in breast-fed infants, uncontrolled - defecation in infants - lower compliance and concordance - cultural and regional acceptance barriers
TOPICAL, TRANSDERMAL[1,2,5] transdermal patches medicated plasters ointments/creams/gels/ liquids	- provision of constant blood levels - painless and easy administration of bolus - sustained drug delivery	- unintended systemic absorption/toxicity risk in neonates - (large skin surface area, thickness, hydratation, perfusion) - natural barrier for penetration of many drugs - safety of excipients - local skin irritation - deliberate removal of patches/plasters
NASAL[1,2,5] solutions, drops semisolid dosage forms	- good nasal transmucosal bioavailability - needle-free access to systemic circulation	- unwanted systemic effect - irritation of the mucosa - ineffective in abundant secretion
PULMONARY[1,2,5] metered dose inhaler with spacer/facemask nebulisers (older children) dry powder inhalers (older children)	- avoidance of hepatic first-pass metabolism - painless application	- increased deposition in upper/central airways (small airway diameter) - decreased total lung deposition (reduced motor abilities/low inspiration volume) - device use critical to improve inhaled doses

ingredients guide list of the US Food and Drug Administration, nor the "generally regarded as safe" status has been validated for pediatric use.[3,29,30,50] Little is known about the safety of excipients in children, and accepted daily and cumulative intakes of excipients have not been established. Anecdotal evidence suggests an association between some excipients commonly used in adult medicines and elevated toxicity and safety issues in children, especially neonates (Table 2).[3,6-9,26,50-60] A recent example is the administration of lopinavir/ritonavir (Kaletra® [Abbott Laboratories, Abbott Park, IL]) oral solution in premature newborns who were exposed to the risk of ethanol and/or propylene glycol toxicity. This situation resulted in a Food and Drug Administration drug safety communication and a change in the drug label in 2011.[61] A number of recent studies in NICUs revealed systemic concentrations of excipients that were intolerable even in older age groups.[54,62,63]

The urgent need to understand these safety concerns has led to a collaborative effort by the United States and the European Union to create a STEP (Safety and Toxicity of Excipients for Paediatrics) database. Its aim is to improve systematic data collection on excipient toxicity and tolerance in children.[64-66] A similar initiative, ESNEE (European Study for Neonatal Exposure to Excipients), has developed a platform for the systematic assessment of excipients in neonates.[67]

Concerns Over Off-label and Unlicensed Use of Medicines in Children

Pediatric drug development is associated with numerous challenges, including methodological and ethical requirements for pediatric trials, high developmental costs, and a small and fragmented market.[3,4,50,68-71] As a result of these challenges, there have only been limited research efforts to adapt medicines according to pediatric needs. Thus, only one third of all medicines approved by the European Medicines Agency over the period of 1995 to 2005 were licensed for use in children.[11,23,72] Higher but still unsatisfactory rates were reported in New Zealand (35%), Australia (38%) and the United States (54%).[23,73,74] The pediatric market has focused mostly on only a limited number of therapeutic areas, such as antiinfectives, hormones, and medicines for the respiratory and central nervous system.[75] Meanwhile, there are hardly any dermal preparations and medicines specifically aimed at younger age groups for the cardiovascular system, sensory organs and cancers.[23]

Table 2. Examples of excipients with elevated toxicity and safety risks for (pre-term and term) newborns and infants less than 6 months of age[7,8,53-60]

Excipient	Adverse reaction
Benzyl alcohol[7,8,53,54]	Neurotoxicity, metabolic acidosis
Ethanol[55]	Neurotoxicity, cardiovascular problems
Propylene glycol[54,56-59]	Neurotoxicity, seizures, hyperosmolarity
Polysorbate 20 and 80[60]	Liver and kidney failure

Moreover, especially in younger children and neonates, even authorized pediatric medicines may not always be age appropriate with respect to dosing, suitability of dosage forms and excipients.[23]

This lack of pediatric formulations often leaves health care professionals no alternative but to use adult medicines in an off-label or unlicensed manner. The trend is widespread: in the European Union 45-60% of all medicines are given to children off-label. This trend is also true for 90% of medicines administered to neonates and infants, particularly in PICUs.[76] Not surprisingly, off-label use is common for antiarrhythmics, antihypertensives, proton pump inhibitors, H2-receptor antagonists, antiasthmatic agents, and some antidepressants.[76] In the United States, two-thirds of medicines used in pediatrics were off-label; worldwide this proportion is up to three-quarters.[77]

Risk Management of Compounding and Manipulation of Medicines for Children

Alternative treatment options are often used to make unavailable drugs accessible for children and/or to adjust drug doses according to individual patient needs. These options include the modification of administration routes (eg, oral use of parenteral formulations), manipulation of adult dosage forms (eg, diluting liquid formulations), segmenting tablets and suppositories, cutting patches, and dispersing open capsules or crushed tablets in water, liquid or food, or extemporaneous dispensing (ie, compounding medicines from ingredients within pharmacies).[5,78]

Administering medicines in this way is difficult and unsafe because limited data are available to validate stability, bioavailability, pharmacokinetics, pharmacodynamics, dosing accuracy, tolerability and reproducibility.[79-84] A documented example is the crushing of Kaletra tablets for pediatric administration, which resulted in reduced bioavailability and drug exposure in children.[85] All these manipulations may compromise drug efficacy and/or safety, as well as create risks for the environment and individuals handling the dosage forms, particularly in the case of mutagen and cytotoxic compounds.[79-84]

Producing a medicine by extemporaneous dispensing may be the only option for some children to receive a certain medicine in a suitable dosage form. In such situations, the risks can be reduced by applying sound quality assurance systems. Pharmacists should ensure that good manufacturing principles are implemented, adequate raw materials and formulae are used, and stability studies are validated and conducted by certified laboratories. Moreover, because practices and guidelines for extemporaneous formulations differ greatly among practitioners, there is an urgent need for a standardization of commonly applied compounding practices.[78,86] Existing networks, resources, and guidelines should be stimulated to provide appropriate information on the standards of practice for extemporaneous formulations.[78,84] However, the available information may not always be easily transferable to a local situation, or may not be exclusively focused on children.[87]

3.1

PROGRESS IN DEVELOPING PEDIATRIC DRUG FORMULATIONS

New Frameworks for the Development of Pediatric Drug Formulations

In order to overcome the aforementioned challenges, a new pediatric regulatory environment has been created to stimulate the development and availability of age-appropriate medicines for children.[16-19] The intended long-term aim is to integrate pediatric needs into overall drug development, so that each new component is systematically evaluated for its potential use in children.[16-19] Initial progress has been made by combining legal requirements with incentives for companies to test, authorize, and formulate medicines for use in children. Over the past decade, the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act in the United States, and the Paediatric Regulation in the European Union have fueled an increasing number of pediatric clinical trials and innovations in pediatric drug formulations.[22,24]

Nonetheless, therapeutic areas addressed by the industry seem to be more aligned with adult drug development than with unmet public health needs in children.[22,68,88,89] To guide the efforts towards significant therapeutic benefits for children, the US and European Union government agencies have produced priority medicines lists, highlighting areas with substantial off-label use in children and gaps in pediatric data.[90,91]

Simultaneously, a WHO initiative ("Make medicines child size") has drawn attention to the fact that the lack of medicines most acutely affects children living in developing countries.[20,92] A focus on the development of suitable dosage forms to treat diseases of high burden in childhood in low-resource settings could greatly reduce childhood morbidity and mortality.[92]. There have been comprehensive WHO activities to improve access to and use of safe and appropriate pediatric medicines. These activities include establishing a model list of essential medicines for children and a list of priority life-saving medicines for women and children, developing model formularies for children, updating childhood treatment recommendations, and including pediatric medicines in the prequalification process.[93-97]

Furthermore, the present reward system has not proved to be an adequate incentive for investment in off-patent drug research.[69,89] This tendency may be linked to prescription reimbursement rules that attach little value to old medicines, even if they include new child-friendly formulations.[69] To generate more interest in off-patent medicines, new public funding opportunities in academia and small and medium sized enterprises have been provided by both the US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Pediatrics Formulation Initiative and the EU's Seventh Framework Program for Research.[98-100] However, new technologies developed from these initiatives must be adopted by the industry and marketed so they can realize their full potential.

There is also increased recognition that the selection of appropriate pediatric formulations requires a risk/benefit analysis on a case-by-case basis.[1,2] Taking into consideration the heterogeneity of children and specific characteristics of each dosage form (Table 1), the industry has recently proposed a composite assessment tool to guide

optimal formulation choices for individual patients.[44] This structured framework is based on 3 predetermined criteria for each drug formulation: product efficacy and ease of use (eg, dose flexibility, drug acceptability, convenient handling, correct use), patient safety (eg, bioavailability of active substances, safety of excipients, medication stability, risk of medication errors) and patient access (eg, product manufacturability, affordability, development, production speed).[41] The choice between alternatives is based on a quantitative scoring system for each pharmaceutical formulation option.[44] This individualized approach to optimal formulations can also be replicated in clinical settings if the selection criteria include relevant aspects of patient care.

Novel oral pediatric formulations

Recent progress in pediatric drug development mostly concerns oral formulations.[22,101] Until recently, liquid formulations were preferred for younger children because of their easy and simple dosing across age subgroups.[5,10,102] In 2008, a WHO expert forum proposed a paradigm shift towards pediatric oral solids in view of stability problems and the high transportation and storage costs involved in liquid formulations.[92] From then on, flexible oral solid dosage forms, such as orodispersible tablets, and/or tablets used to prepare oral liquid preparation suitable for younger children, have become the recommended pediatric dosage forms worldwide.[94] In 2009, Coartem Dispersible (Novartis International AG, Basel, Switzerland, and Medicines for Malaria) was launched to offer flexible artemisinin-combination therapy for children (5-35 kg) with a cure rate comparable to that of the Coartem tablet.[103,104]

For oral medicines requiring precise dose measurement, a new flexible platform technology was proposed to produce solid multiparticulate dosage forms (eg, mini-tablets, pellets) and dosage forms dispersible in liquids or sprinkled on food.[92] This platform technology has the potential flexibility to construct fixed-dose combination products, especially for chronic diseases such as HIV or tuberculosis.[105-107] Table 3 illustrates some of the quality-certified, innovative oral pediatric dosage forms brought to market, including much needed heat-stable formulations and fixed-dose combination products for low-resource settings.[97,104,108-116]

Current surveys reveal that novel oral solids may be used in children at an earlier age than previously anticipated.[5,117,118] Initially, in 2009 Thomson et al.[119] demonstrated that 46% of 2-year-old children and 86% of 5-year-old children could swallow innovative 3 mm mini-tablets without choking or aspiration. The age limit was further decreased in an exploratory study that demonstrated that children aged 6–12 months were capable of swallowing uncoated, drug-free, 2-mm mini-tablets and accepted them better than sweet liquid formulations.[120,121] For infants aged <2 years, a new promising development is the orally disintegrating mini-tablet, which combines mini-tablets and fast-dissolving dosage forms.[111]

Table 3. Examples of recently marketed/prequalified novel oral drug formulations for children[97,104,108-116]

Dosage form	International Non-proprietary Name	Regulatory agency authorization / WHO Prequalification year
Multi-particulates[97,108-110]		
Sprinkles, granules and pellets	Para-aminosalicylate granules	WHO PQ 2009
	TFV granules	FDA 2012, EMA 2012
	Rabeprazole sprinkles	FDA 2013
Flexible dispersible formulations[97,104,111-114]		
Dispersible and orodispersible tablets	Artemether/Lumefatrine dispersible tablets	Swissmedic 2008 / WHO PQ 2009
	3TC/NVP/d4T	WHO PQ 2008
	Izoniazid/Pyrazinamide/ Rifampicin	WHO PQ 2009
	Izoniazid/Rifampicin	WHO PQ 2009
	3TC/NVP/AZT (Mylan Laboratories)	WHO PQ 2009
	ABC	WHO PQ 2010
	3TC/d4T	WHO PQ 2011
	3TC/AZT	WHO PQ 2011
	EFV	WHO PQ 2012
	3TC	WHO PQ 2012
	Artemether/Lumefatrine	WHO PQ 2012
	Izoniazid/Pyrazinamide/ Rifampicin	WHO PQ 2012
	Izoniazid/Rifampicin	WHO PQ 2012
	Benznidazole	WHO PQ 2012
	Lamotrigine orodispersible tablets	FDA 2012
	AZT	WHO PQ 2013
Orodispersible films (wafer)	Ondasetron	FDA 2010
Chewable dispersible tablets	Lamotrigine	FDA 2012
Orally disintegrating mini-tablets	Hydrochlorothiazide	Model drug under investigation
Other novel oral formulations[115-116]		
Chewable tablets	Atorvastatin	EMA 2011
	Raltegravir	FDA 2012

3TC –Lamivudine, ABC – Abacavir, AZT – Zidovudine, d4T- Stavudine, EFV – Efavirenz, ODT - Orodispersible tablet, PQ – Prequalification, NVP – Nevirapine, TFV – Tenofovir

A complementary research area is the development of pediatric dosing devices, which facilitate the accurate and consistent administration of oral pediatric formulations.[1,122]

New devices generally assist the oral delivery of liquids to small children by using modified feeding bottles and pacifiers with medicines placed in a reservoir, help improve the palatability of oral solutions by using a dose-sipping technology, or help increase product stability by using a pulp-spoon with a single dry dose of medicine (see Table 4 for more detailed examples).[3,116,122]

Table 4. Examples of novel drug devices that facilitate oral administration of medicines in children[3, 116, 122]

Novel drug devices	Examples of medicines administered with drug devices (brand name, manufacturer)	Purpose of use
Modified teat /pacifier with drug-loaded reservoir	Nystatin (Mykundex°, Bioglan)	Constant delivery of medicine (in oral cavity) in neonates/infants
Dosing spoon filled with liquid medicine	Diphenhydramin (Benadril°, Pfizer)	Exact measurement of single doses, low risk of spillage
Coated particles on dosage spoon (pulp-spoon)	Azythromycin powder for oral pulp (Pre-dosed azithromycin spoon, Sandoz)	Exact measurement of single doses, low risk of spillage improves stability of medicines
Dropper tube	Codeine drops (Paracodin°, Stella/Abbott)	Ensures dose uniformity
Dose sipping technology – straw with medicine and beverage	Clarithromycin micropellets (Clarosip°, Grünenthal)	Improves palatability and adherence
Solid dosing pen	Carvedilol/Metoprolol tartrate (model drugs)	Exact measurement of doses

FUTURE STEPS

The ideal pediatric formulation should have flexible dosage increments and minimal excipients, be palatable, safe and easy to administer, and be stable with regard to light, humidity, and heat. Nevertheless, a significant number of drug formulations are unsuitable for children, which leads to unsafe off-label and unlicensed use of adult medicines. Recent initiatives promoting pediatric drug development have made some initial progress in the neglected area of pediatric formulations. Most efforts have focused on age-appropriate oral solid preparations, which enable dose flexibility, easier administration, and better acceptance in children. Despite these advances, the new pediatric formulations are still only a small part of the full therapeutic arsenal needed to serve all pediatric patients.

The following 5 priorities have been identified as critical for the further development of appropriate pediatric formulations. The first key issue is the continuous prioritization process that focuses on unmet public health issues and ensures that drug development aligns with the true clinical needs in children. Special attention should be paid to innovations that improve drug delivery in neonates, fill treatment gaps in pediatric cancers, and treat diseases of high burden in developing countries. [49,90,91,94,123]

Second, better use of existing data is required to facilitate pediatric drug development. Some innovative scenarios under investigation include preliminary 'enabling' formulations that bridge existing adult formulations and potential pediatric market formulations, adjustments of adult in vitro gastrointestinal models to study drug bioavailability in children, and refined criteria for the extrapolation of adult efficacy data to the pediatric population. [124-126]

Third, future research on pediatric formulations could potentially benefit from existing or innovative technologies under development in adults. [127] Novel experimental treatments of adult cancers, infections and asthma have used nanoparticle targeted therapy, novel smart polymer-based drug delivery systems, new chemical entities (e.g. dendrimers) and remote triggering devices. These may have significant applications in children, and the identification of appropriate animal models for pediatric preclinical studies should be a research priority. [128-130]

Fourth, ongoing technological advances need to be accompanied by relevant patient outcome studies and clinical feedback on efficacy, safety, patient acceptability, preferences, and adherence regarding new formulations; currently, such studies and feedback are lacking. [131] Practice-based evidence on the impact of novel formulations, generated by healthcare professionals and caregivers, could provide further support for the development of pediatric medicines with clear clinical advantages.

The fifth priority concerns finance. Because innovative technologies are costly, the ultimate challenge is to make these new pediatric formulations available on the market and in daily practice. [22,89,132] Their commercial viability might be improved by an increased market size (eg, global scale, inclusion of geriatric patients and adults with swallowing difficulties), new incentives schemes (particularly for off-patent drugs), such as limited exclusivity and premiums, funding, and tax breaks; and public-private partnerships that support the development of orphan drugs and other less profitable niches. [69,98-100]

In sum, to reach these goals, it is essential that there is a committed collaboration between stakeholders that extends across disciplines and geographic regions. Moreover, this collaboration should have the innovative potential to further shape the pediatric drug development agenda and thus to close the adult-child medicine gap.

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REFERENCES

1. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP)

2. Paediatric Committee (PDCO). *Guideline on pharmaceutical development of medicines for paediatric use.* 1 August 2013. EMA/CHMP/QWP/805880/2012 Rev. 2.

3. World Health Organization. *Development of Paediatric Medicines: Points to Consider in Formulation.* WHO Technical Report Series, No. 970, 2012, Annex 5.

4. Breitkreutz J, Boos J. Paediatric and geriatric drug delivery. *Exp Opin Drug Deliv* 2007;4:37-45.

5. Ernest TB et al. Developing pediatric medicines: identifying the needs and recognizing the challenges. *J. Pharm. Pharmacol.* 2007,59:1043-1055.

6. European Medicines Agency. Committee for Medicinal products for Human use (CHMP) 2005: *Reflection paper: formulations of choice for the paediatric population.* EMEA/CHMP/PEG/194810/2005.

7. Geling EMK, Cannon PR. Pathological effects of elixir of sulfanilamide poisoning. *JAMA* 1938;111:919-926.

8. Hiller JL, Benda GI, Rahatzad M et al. Benzyl alcohol toxicity: impact on mortality and intraventricular hemorrhage among very low birth weight infants. *Pediatrics* 1986; 77: 500–506.

9. Brown WJ, Buist NRM, Gipson HTC, Huston RK, Kennaway NG. Fatal benzyl alcohol poisoning in a neonatal intensive care unit. *Lancet.* 1982;1:1250.

10. World Health Organization. *Promoting safety of medicines for children.* Geneva, Switzarland, World Health Organization, 2007.

11. Nahata MC. Lack of pediatric drug formulations. *Pediatrics* 1999;104(3 pt 2, suppl 3):607-609.

12. Ceci A, Felisi M, Baiardi P, et al. Medicines for children licensed by the European Medicines Agency (EMEA): the balance after 10 years. *Eur J Clin Pharmacol.* 2006 Nov;62(11):947-952

13. Shirkey H. Therapeutic orphans. *J Pediatr.* 1968;72:119-20.

14. European Medicines Agency. *Report on the survey of all paediatric uses of medicinal products in Europe.* EMA/794083/2009.

15. Bazzano A, Mangione-Smith R, Schonlau M, et al. Off-label prescribing to children in the United States outpatient setting. *Ambul Pediatr.* 2009; 9: 81–88.

16. Mason J, Pirmohamed M, Nunn T. Off label and unlicensed medicine use and adverse drug reaction in children; a narrative review of the literature. *Eur J Clin Pharmacol* 2011, 68:21-27.

17. Best Pharmaceuticals for Children Act. In *proceedings of 107th Congress of the United States of America,* Washington D.C., USA, 3 January 2002.

18. Pediatric Research Equity Act of 2003. In proceedings of 108th Congress of the United States of America, Washington D.C., USA, 7 January 2003.

19. US Food and Drug Administration Amendments Act of 2007. In proceedings of 110th Congress of the United States of America, Washington D.C., USA, 4 January 2007.

20. The European Parliament and the Council of the European Union. Regulation EC No. 1901/2006 of the European Parlament and of the Council on Medicinal Products for Paediatric Use.

21. World Health Organization. *Make medicines child size.* Geneva, 2007. Available at: http://www.who.int/childmedicines/en/ Accessed August 15, 2013

22. BPCA Collaborative Efforts, Inter-Agency Initiatives. *Pediatric Formulations Platform.* Inter-Agency Agreement between the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the U.S. Food and Drug Administration (FDA). Available at: http://bpca.nichd.nih.gov/collaborativeefforts/initiatives/index.cfm, Accessed August 15, 2013

23. European Medicines Agency. Draft *5-year Report to the European Commission: General report on the experience acquired as a result of the application of the Paediatric Regulation.* 8 July 2012 EMA/428172/2012.

24. van Riet-Nales DA, de Jager KE, Schobben AFAM, et al. The availability and age-appropriateness of medicines authorized for children in the Netherlands. *Br. J. Clin. Pharmacol.* 2011;72(3):465-473.

25. Balakrishnan K, Grieve J, Tordoff J, et al. Pediatric licensing status and the availability of suitable formulations for new medical entities approved in the United States between 1998 and 2002. *J Clin Pharmacol.* 2006;46:1038–1043.

26. Moore P. Children are not small adults. *Lancet* 1998;352(9128):630.

27. Kearns GL, Abdel_Rahman SM, Alander SW, et al. Developmental pharmacology-drug disposition, action, and therapy in infants and children. *New Engl. J. Med.* 2003;349:1157-1167.

28. Fernandez E, Perez R, Hernandez A, et al. Factors and mechanisms for pharmacokinetic differences between pediatric population and adults. *Pharmaceutics* 2011,3:53-72.

29. European Medicines Agency (EMEA) 2000: ICH Topic E 11. Clinical Investigations of Medicinal Products in the Paediatric Population, EMEA/CHMP/ICH/2711/99.

30. Allegaert K. Neonates need tailored drug formulations. *World J Clin Pediatr* 2013; 2(1): 1-5

31. Noel GJ, Van Den Anker JN, Lombardi D, et al. Improving Drug Formulations for Neonates: Making a Big Difference in Our Smallest Patients. *J Pediatr* 2012;161(5):947-948.

32. Bartelink IH, Rademaker CMA, Schobben AFAM, et al. Guidelines on pediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. *Clin Pharmacokinet* 2006; 45 (11):1077-1097.

33. Strolin Benedetti M, Whomsley R, Baltes, EL. Differences in absorption, distribution,

34. metabolism and excretion of xenobiotics between the paediatric and adult populations. *Expert Opin. Drug Metab. Toxicol.* 2005, 1, 447-471.

35. Strolin Benedetti M, Baltes, EL. Drug metabolism and disposition in children. *Fundam. Clin. Pharmacol.* 2003, 17, 281-299.

36. Meissner HC, Smith AL. The current status of chloramphenicol. *Pediatrics* 1979, *64*, 348-356.

37. Albani M, Wernicke I. Oral phenitoin in infancy: dose requirement, absorption and elimination. *Pediatr Pharmacol* (New York) 1983;3(3-4):229-236.

38. Food and Drug Administration. Specific requirements on content and format of labeling for human prescription drugs: revision of "Pediatric Use" subsection in the labeling; final rule. 21 CFR Part 201 (Docket No 92N-0165). Federal Register: December 13, 1994. Available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3778b1_Tab6_7-21CFR%20Part%20201.pdf Accessed August 15, 2013.

39. Matsui D. Assessing the palatability of medications in children. *Paediatr Perinat Drug Ther* 2007; 8 (2):55-60.

40. Cram A, Breitkreutz J, Desset-Brèthes S, et al. European Paediatric Formulation Initiative (EuPFI). Challenges of developing palatable oral paediatric formulations. *Int J Pharm* 2009; 365(1-2):1–3.

41. Mennella JA, Beauchamp GK. Optimizing oral medications for children. *Clin Ther* 2008;30(11):2120-2132.

42. Davies EH, Tuleu C. Medicines for chidren: a matter of taste. *J Pediatr* 2008;153;599-604.

43. Tuleu C, Breitkreutz J. Educational paper: Formulation-related issues in pediatric clinical phamacology. *Eur J Pediatr* 2013;172(6):717-20.

44. Clapham D, Kirsanov D, Legin A, et al. Assessing taste without using humans: rat brief access aversion model and electronic tongue. *Int J Pharm* 2012;435:137-139.

45. Breitkreutz J, Wessel T, Boos J. Dosage forms for peroral administration to children. *Paediatr. Perinat. Drug Ther* 1999;3:25–33.

46. Sam T, Ernest TB, Walsh J, et al. European Paediatric Formulation Initiative (EuPFI). Abenefit/risk approach towards selecting appropriate pharmaceutical dosage forms – An application for paediatric dosage form selection. *Int J Pharm* 2012;435:115-123.

47. Shea KM; American Academy of Pediatrics Committee on Environmental Health: Pediatric exposure and potential toxicity of phthalate plasticizers. *Pediatrics* 2003; 111:1467-1474.

48. Haishima Y, Matsuda R, Hayashi Y, et al. Risk assessment of di(2-ethylhexyl) phthalate released from PVC blood circuits during hemodialysis and pump-oxygenation therapy. *Int J Pharm* 2004; 274:119-129.

49. Allegaert K, Anderson BJ, Vrancken M et al. Impact of a paediatric vial on the magnitude of systematic medication errors in neonates. *Paediatr Perinat Drug Ther* 2006; 7:59–63.

50. Mulberg A, Silber S, van den Anker J, eds., *Pediatric Drug Development, Concepts and Applications,* Hoboken NJ, J. Wiley & Sons, 2009.

51. UNICEF/WHO. *Priority Essential Medicines for Child Survival Report.* Copenhagen, Denmark. September 2010. Available at: http://www.who.int/childmedicines/progress/Unicef_prioriry_meds_child_survival.pdf Accessed August 15, 2013

52. Fabiano V, Mameli C, Zuccotti GV. Paediatric pharmacology: remember the excipients. *Pharmacol Res* 2011 May;63(5):362-5.

53. Nahata MC. Safety of "inert" additives or excipients in paediatric medicines. *Arch Dis Child Fetal Neonatal Ed* 2009;94:F392-393.

54. American Academy of Pediatrics Committee on Drugs. Inactive" ingredients in pharmaceutical products: update (subject review). *Pediatrics* 1997;99:268-278.

55. Hiller JL. Benda GI, Reynolds JW. Benzyl alcohol toxicity: Impact on mortality and intraventricular hemorrhage among very low birth weight infants. *Pediatrics* 1986;77(4):500-506.

56. Shehab N, Lewis CL, Streetman DD, et al. Exposure to the pharmaceutical excipients benzyl alcohol and propylene glycol among critically ill neonates. *Pediatr Crit Care Med.* 2009;10:256-259.

57. American Academy of Pediatrics. Committee on Drugs. Ethanol in Liquid Preparations Intended for Children. *Pediatrics* 1984;73(3):405-407.

58. Arulanantham K, Genel M. Central nervous system toxicity associated with ingestion of propylene glycol. *J Pediatr* 1978;93:515–16.

59. Martin G, Finberg L. Propylene glycol: a potentially toxic vehicle in liquid dosage form. *J Pediatr* 1970;77:877–8.

60. Macdonalds MG, Getson PR, Glasgow AM, et al. Propylene glycol: increased incidence of seisures in low birth weight infants. *Pediatrics* 1987;79:622-625.

61. Glasgow AM, Boeckx RL, Miller MK, et al. Hyperosmolarity in small infants due to propylene glycol. *Pediatrics* 1983;72:353-355.

3.1

62. Balistreri WF, Farrell MK, Bove KE. Lessons from the E-ferol tragedy. *Pediatrics.* 1986;78(3):503–506

63. US Food and Drug Administration, 2011. *Drug Safety Communication: Serious Health Problems Seen in Premature Babies Given Kaletra (Lopinavir/Ritonavir) Oral Solution.* Available at: http://www.fda. gov/Drugs/DrugSafety/ucm246002.htm. Accessed August 15, 2013

64. Whittaker A, Currie A E, et al. (2009) Toxic additives in medication for preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2009; 94(4):F236-40.

65. Lass J, Naelapää K, Shah U, Käär R, Varendi H, Turner MA, Lutsar I. Hospitalised neonates in Estonia commonly receive potentially harmful excipients. *BMC Pediatr.* 2012;12:136.

66. Salunke S, Giacoia GP, Tuleu C. The STEP (Safety and Toxicity of Excipients for Paediatrics) Part 1: A Need assessment Study. *Int J Pharm* 2012;435:101-111.

67. Salunke S, Branys B, Giacoia GP, Tuleu C. The STEP (Safety and Toxicity of Excipients for Paediatrics) Part 2 - The pilot version. *Int J Pharm* 2013;457:310-322.

68. Paediatric Formulation Initiative. STEP database: Database of Safety and Toxicity of Excipients for Paediatrics. Available at: http://www.eupfi.org/gpage11.html. Accessed August 15, 2013

69. Turner MA, Storme T. European Study for Neonatal Excipient Exposure (ESNEE). *Eur J Hosp Pharm* 2012;19(2):67.

70. Schirm E, Tobi H, de Vries TW, et al. Lack of appropriate formulations of medicines for children in the community. *Acta Paediatr* 2003;92:1486-1489.

71. Milne CP, Bruss JB. The economics of pediatric formulation development for off- patent drugs. *Clin Ther* 2008;30(11):2133-2145.

72. Institute of Medicine (US) Committee on Clinical Research Involving Children. *The Necessity and Challenges of Clinical Research Involving Children.* In: Field M, Behrman R, eds. *Ethical Conduct of Clinical Research Involving Children.* Washington (DC): National Academies Press; 2004.

73. Institute of Medicine (US) Addressing the Barriers to Pediatric Drug Development: Workshop Summary. Forum on Drug Discovery, Development, and Translation. Washington (DC): National Academies Press; 2008.

74. Balakrishnan K, Tordoff J, Norris P, Reith D. Establishing a baseline for the monitoring of medicines availability for children in the UK: 1998–2002. *Br J Clin Pharmacol* 2007; 63:85–91.

75. Chui J, Tordoff J, Kennedy J, Reith D. Trends in accessibility to medicines for children in New Zealand: 1998–2002. *Br J Clin Pharmacol* 2004; 57: 322–7.

76. Chui J, Tordoff J, Reith D. Changes in availability of paediatric medicines in Australia between 1998 and 2002. *Br J Clin Pharmacol* 2005; 59: 736–42.

77. Osterberg RE. *4. FDA Approach to Pediatric Testing.* In: Hoberman AM, Lewis EM, eds. *Pediatric Nonclinical Drug Testing: Principles, Requirements, and Practices.* Hoboken, NJ: John Wiley & Sons, Inc;2012:59-78.

78. European Medicines Agency. *Report on the survey of all paediatric uses of medicinal products in Europe.* December 10, 2010, EMA/794083/2009.

79. Tobias LD, Harkness J. *IAPO Briefing Paper on Paediatric Medicines and Clinical Research (*November 2006). International Alliance of Patients' Organizations (IAPO). Available at: www.patientsorganizations. org/paediatrics. Accessed May 23, 2014.

80. Nahata MC, Allen LV Jr. Extemporaneous Drug Formulations. *Clin Ther* 2008;30(11):2112-2120.

81. Choonara I Conroy S. Unlicensed and off-label drug use in children: implications for safety. *Drug Saf*. 2002;25(1):1-5.

82. European Medicines Agency. *Evidence of harm from off-label or unlicensed medicines in children*. EMEA/126327/2004. EMEA, 2004.

83. Shah SS, Hall M, Goodman DM, et al. Off Label Drug Use in Hospitalized Children, *Arch Pediatr Adolesc Med* 2007,161(3):282-290.

84. Cuzzolin L Atzei A, Fanos V. Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. *Expert Opin. Drug Saf*. 2006; 5(5):703-718.

85. Pandolfini C, Bonati M. A literature review on off-label drug use in children *Eur J Pediatr* 2005; 164:552–558.

86. Lowey A, Jackson M. *Handbook of Extemporaneous Formulation - A Guide to Pharmaceutical Compounding*. London; Pharmaceutical Press, 2010.

87. Best BM, Capparelli EV, Diep H, et al. Pharmacokinetics of Lopinavir/ Ritonavir Crushed versus Whole Tablets in Children. *J Acquir Immune Defic Syndr*. 2011; 58(4): 385–391.

88. Kairuz TE, Gargiulo D, Bunt C, et al. Quality, Safety and Efficacy in the 'Off-Label' Use of Medicines. *Current Drug Safety*, 2007, 2, 89-95.

89. PharmInfoTech. eMixt database: database of oral liquid formulations. Available at: http://www.pharminfotech.co.nz/ manual/Formulation/mixtures/ Accessed August 15, 2013

90. Boots I, Sukhai RN, Klein RH et al. Stimulation programs for pediatric drug research – do children really benefit? *Eur J Pediatr* 2007; 166:849–855.

91. European Medicines Agency. General report on the experience acquired as a result of the application of the Paediatric Regulation. Summary of the replies to the public consultation. SANCO/ D5/FS/ci D(2013) 27105 Available at: http://ec.europa.eu/health/files/ paediatrics/2013_pc_paediatrics/2013_ paediatric_report_summary.pdf. Accessed August 15, 2013

92. Best Pharmaceuticals for Children Act (BPCA). *Priority List of Needs in Pediatric Therapeutics, 2012. Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). Best Pharmaceuticals for Children Act. Available at: http://bpca.nichd.nih.gov/ prioritization/upload/2012_Priority_List_ FINAL.pdf. Accessed August 15, 2013

93. European Medicines Agency. *Revised priority list for studies into off-patent paediatric medicinal products*. EMA/98717/2012, August 2013. Available at: http://www. ema.europa.eu/docs/en_GB/document_ library/Other/2009/10/WC500004017.pdf Accessed August 15, 2013

94. World Health Organization. *Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children*. WHO Headquarters, Geneva, Switzerland, 2008. Available at: http://www.who. int/selection_medicines/committees/ expert/17/application/paediatric/Dosage_ form_reportDEC2008.pdf. Accessed August 15, 2013

95. World Health Organization. *WHO Model List of Essential Medicines for Children, 4th list*. WHO, Geneva, April 2013. Available at http://www.who.int/ medicines/ publications/essentialmedicines/ 4th_ EMLc_FINAL_web_ 8Jul13.pdf. Accessed August 15, 2013

96. World Health Organization. *Priority life-saving medicines for women and children*. Geneva WHO/EMP/MAR/2012.1. Available at http:// apps.who.int/iris/bitstream/10665/75154/1/ WHO_EMP_MAR_2012.1_eng.pdf Accessed August 15, 2013

3.1

97. World Health Organization. *WHO Model Formulary for Children*. WHO, Geneva, 2010. Available at http://www.who.int/selection_medicines/list/WMFc_2010.pdf Accessed August 15, 2013

98. World Health Organization. *Maternal, newborn, child and adolescent health. Documents on child health.* Available at http://www.who.int/maternal_child_adolescent/documents/child/en/ Accessed August 15, 2013

99. World Health Organization. *WHO List of Prequalified Medicinal Products*. Available at http://apps.who.int/prequal/97. Accessed August 15, 2013

100. National Institutes of Health (NICHD) Funding Opportunities: Development of Appropriate Pediatric Formulations and Pediatric Drug Delivery Systems (R01, R03, R21, R41/R43). Available at http://grants.nih.gov/grants/guide Accessed August 15, 2013

101. Zajicek A. The National Institutes of Health and the Best Pharmaceuticals for Children Act. *Pediatric Drugs* 2009;11:45-47.

102. European Commission. *EU Research Projects FP7 Health.* CORDIS (Community Research and Development Information Centre). Available at: http://cordis.europa.eu/projects/home_en.html Accessed August 15 2013

103. Pediatric Formulations Platform - BPCA - National Institutes of Health**.** Inter-Agency Agreement between the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the U.S. Food and Drug Administration (FDA). Oral Formulations Platform-Report 1. Available at: http://bpca.nichd.nih.gov/collaborativeefforts/initiatives/upload/Formulations_Table_for_Web_11-02-11.pdf Accessed August 15, 2013

104. Nunn T, Williams J. Formulation of medicines for children. *Br J Clin Pharmacol* 2005;6:674-676.

105. Stoltenberg I, Winzerburg G, Breitkreutz J. Solid oral forms for children – formulations, excipients and acceptance issues. *J App Ther Res*, 2010; 7(4):141-146.

106. Abdulla S, Sagara L, Borrmann S, et al. Efficacy and safety of artemether-lumefantrine dispersible tablets compared with crushed commercial tablets in African infants and children with uncomplicated malaria: a randomised, investigator-blinded, multi-centre comparison with the crushed commercial tablet. *Lancet* 2008; 372(9652):1819-1827.

107. Kayitare E, Vervaet C, Ntawukulilyayo JD, et al. Development of fixed dose combination tablets containing zidovudine and lamivudine for paediatric applications *Int J Pharm*. 2009;370(1-2):41-46.

108. Vanprapar N, Cressey TR, Chokephaibulkit K, et al. IMPAACT P1056 Team. A chewable pediatric fixed-dose combination tablet of stavudine, lamivudine, and nevirapine: pharmacokinetics and safety compared with the individual liquid formulations in human immunodeficiency virus-infected children in Thailand. *Pediatr Infect Dis J*. 2010;29(10):940-944.

109. Chokephaibulkit K, Cressey TR, Capparelli E, et al. IMPAACT P1056 Team. Pharmacokinetics and safety of a new paediatric fixed-dose combination of zidovudine/lamivudine/nevirapine in HIV-infected children. *Antivir Ther* 2011;16(8):1287-1295.

110. Larka. *Press Release 2012: Aptalis announces European Commission approval for new formulation of Viread.* Available at: http://www.pharmaceutical-technology.com/contractors/drug_delivery/eurand/pressaptalis-ec-approval-new-formulation-of-viread.html Accessed August 15, 2013

111. Eisai Inc. Press Release 2013: *FDA Approves ACIPHEX Sprinkle(Rabeprazole Sodium) For Use in Children Ages 1 to 11.* Available at: http://us.eisai.com/wps/wcm/connect/Eisai/Home/Press+Room/Press+Releases/2013/

FDA approves aciphex sprinkle.html Accessed August 15, 2013

112. World Health Organization. Benznidazole: child-adapted dosage form approved. *WHO Drug Information* 2012;26(1):21—22.

113. Food and Drug Administration: *Lamictal medication guide.* Available at: http://www. fda.gov/downloads/Drugs/DrugSafety/ UCM152835.pdf Accessed August 15, 2013

114. Drug Information online. *Press Release 2012: FDA Approves Zuplenz.* Available at: http://www.drugs.com/newdrugs/ fda-approves-strativa-pharmaceuticals-zuplenz-ondansetron-oral-soluble-film-2208.html Accessed August 15, 2013

115. Stoltenberg I, Breitkreutz J. Orally disintegrating mini-tablets (ODMTs) – A novel solid oral dosage form for paediatric use. *Eur J Pharm Biopharm* 2011;78:462–469.

116. Pfizer Medic and News 2009. *Pfizer announces European Union approval of a new form of Lipitor (atorvastatin) for use in children.* Available at: http://press.pfizer. com/press-release/pfizer-announces-european-union-approval-new-form-lipitor-atorvastatin-use-children. Accessed August 15, 2013

117. Merck News Room, 2012: *FDA approves Merck's ISENTRESS (raltegravir) for use in children ages two years and older as part of HIV-1 combination therapy.* Available at: http://www.mercknewsroom.com/press-release/prescription-medicine-news/fda-approves-mercks-isentress-raltegravir-use-children-ages. Accessed August 15, 2013

118. Breitkreutz J. Nach der EU-Reform. Arzneiformen für Kinder. *Pharm Unserer Zeit* 2009;38(1):30-37.

119. Yeung VW, Wong ICK. When do children convert from liquid antiretroviral to solid formulations? *Pharm World Sci.* 2005;27(5):399–402.

120. Garvie PA, Lensing R, Rai SN, et al. Efficacy of a Pill-Swallowing Training Intervention to Improve Antiretroviral Medication Adherence in Pediatric Patients With HIV/ AIDS. *Pediatrics* 2007;119(4). Available at: www.pediatrics.org/cgi/content/ full/119/4/e893 Accessed August 15, 2013

121. Thomson SA, Tuleu C, Wong ICK, et al. Minitablets: new modality to deliver medicines to preschool-aged children, *Pediatrics* 2009;123(2). Available at: www. pediatrics.org/cgi/content/full/123/2/e235 Accessed August 15, 2013

122. Spomer N, Klingmann , Stoltenberg I, et al. Acceptance of uncoated mini-tablets in young children: results from a prospective exploratory cross-over study. *Arch Dis Child* 2012;97:283–286.

123. Klingmann V, Spomer N, Lerch C, et al. Favorable Acceptance of Mini-Tablets Compared with Syrup: A Randomyzed Controlled Trials in Infants and Preschool Children. *J Pediatr* 2013;163(6):1728-1732.e1.

124. Walsh J, Bickmann D, Breitkreutz J, Chariot-Goulet M, on behalf of the European Paediatric Formulation Initiative (EuPFI). Delivery devices for the administration of paediatric formulations: Overview of current practice, challenges and recent developments. *Int J Pharm* 2011;415:221– 231.

125. World Health Organization. Priority Medicines for Europe and the World Update Report, 2013. WHO Geneva, 2013. http:// www.who.int/medicines/areas/priority_ medicines/en/ Accessed August 15, 2013

126. Ricci BM. Bridging studies in support of oral pediatric formulation development. *Int J Pharm* 2013;457(1):323-326.

127. Havenaar R, Anneveld B, Hanff L, et al. In vitro gastrointestinal model (TIM) with predictive power, even for infants and children? *Int J Pharm* 2013;457:327-332.

128. Dunne J, Rodriguez WJ, Murphy MD, et al. Extrapolation of Adult Data and Other

3.1

Data in Pediatric Drug-Development Programs. *Pediatr* 2011;128(5) Available at: www.pediatrics.org/cgi/content/full/128/5/e1242 Accessed August 15, 2013

129. Giacoia GP, Taylor-Zapata P, Zajicek A. Eunice Kennedy Shriver National Institute of Child Health and Human Development Pediatric Formulation Initiative: Proceedings from the Second Workshop on Pediatric Formulations. *Clin Ther* 2012;34 (11):S1-S10.

130. Menjoge AR, Kannan RM, Tomalia DA. Dendrimed-based drug and imaging conjugates: design considerations for nanomedical applications. *Drug Discovery Today* 2010;15:171-185. 129. Timko BP, Kohane DS. Materials to Clinical Devices: Technologies for Remotely Triggered Drug Delivery. *Clin Ther* 2012;34(11) S25-S35.

131. Krishnan V, Xu X, Barwe SP, et al. Dexamethasone-loaded block copolymer nanoparticles induce leukemia cell death and enhance therapeutic efficacy: a novel application in pediatric nanomedicine. *Mol Pharm*. 2013 Jun 3;10(6):2199-210.

132. van Riet-Nales DA, Schobben AF, Egberts TC, Rademaker CM. Effects of the pharmaceutical technologic aspects of oral pediatric drugs on patient-related outcomes. *Clin Ther* 2010;32(5):924-938.

133. United States Government Accountability Office. Pediatric Medical Devices. Provisions Support Development, but Better Data Needed for Required Reporting. Report to Congressional Committees. December 2011 (GAO-12-225) Available at: http://www.gao.gov/assets/590/587164.pdf Accessed August 15, 2013

CHAPTER 3.2

ARE AGE-APPROPRIATE ANTIBIOTIC FORMULATIONS MISSING FROM THE WHO LIST OF ESSENTIAL MEDICINES FOR CHILDREN? A COMPARISON STUDY

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ABSTRACT

Objective

There is a global call for formulations, which are better suited for children of different age categories and in a variety of settings. One key public health area of interest are age-appropriate paediatric antibiotics. We aimed to identify clinically relevant paediatric formulations of antibiotics listed on pertinent formularies that were not on the WHO Essential Medicines List for Children (EMLc).

Methods

We compared four medicines lists versus the EMLc and contrasted paediatric antibiotic formulations in relation to administration routes, dosage forms and/or drug strengths. The additional formulations on comparator lists that differed from the EMLc formulations were evaluated for their added clinical values and costs.

Results

The analysis was based on 26 EMLc antibiotics. Seven oral and two parenteral formulations were considered clinically relevant for paediatric use. Frequently quoted benefits of oral formulations included: filling the gap of unmet therapeutic needs in certain age/weight groups (phenoxymethylpenicillin and metronidazole oral liquids, and nitrofurantoin capsules), and simplified administration and supply advantages (amoxicillin dispersible tablets, clyndamycin capsules, cloxacillin tablets, and sulfamethoxazole + trimethoprim tablets). Lower doses of ampicillin and cefazolin powder for injection could simplify the dosing in newborns and infants, reduce the risk of medical errors, and decrease the waste of medicines, but may target only narrow age/weight groups.

Conclusions

The identified additional formulations of paediatric antibiotics on comparator lists may offer clinical benefits for low-resource settings, including simplified administration and increased dosing accuracy. The complexity of both procuring and managing multiple strengths and formulations also needs to be considered.

INTRODUCTION

Millions of children die every year from preventable or treatable infections, such as pneumonia, diarrhoea, malaria, tuberculosis, HIV/AIDS and neonatal complications.[1,2] Many of these deaths could be avoided with the use of safe and affordable age-appropriate medicines.[3,4] The response to medications in children is different from that of adults, and it may also vary across age groups due to their development phases.[5,6] That implies that strengths and dosing regimens, tablet sizes, and volume of parenteral medicines need to be well adapted to children's age.[7-10]

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As a global action to improve access to child-specific medicines, the WHO Essential Medicines List for Children (EMLc) was released on the 30th anniversary of the general EML in 2007.[11] Essential medicines are those that satisfy the priority health care needs of the population. They are selected based on public health relevance, evidence on clinical efficacy and safety, and comparative cost-effectiveness.[12] 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 the community can afford.[12] So, the aim of the EMLc is to recognise special needs for medicines in children, and to promote the inclusion of paediatric medicines in national procurement programmes.[11]

Even with these systematic efforts to respond to paediatric therapeutic needs, more work lies ahead.[13] One key public health area of interest in the field of infectious diseases are child-specific antibiotics, due to their potential to fight bacterial infections, including pneumonia and neonatal sepsis that are among leading causes of death in early life.[3,14-16]

A first step in improving the availability of age-appropriate formulations of paediatric antibiotics is to obtain up-to-date information if more formulations exist globally, but are not on the EMLc. Therefore, the aim of this study was to compare the antibiotic formulations on relevant medicines lists versus the EMLc, and identify potential new clinically relevant products for paediatric use in low-resource settings.

METHODS

Four medicines lists were compared with the EMLc in respect to their paediatric formulations, focusing on the EMLc antibiotics: (1) the British National Formulary for Children (BNFc) 2014/2015, (2) the Dutch Kinderformularium (Formulary for Children) 2015, (3) the Australian Pharmaceutical Benefits Scheme (APBS), and (4) the Management Sciences for Health (MSH)/WHO International Drug Price Indicator Guide 2014.[17-20] The first three medicines lists originate from high-income countries, which are known for their comprehensive, high quality healthcare systems and good availability of paediatric medicines. The MSH/WHO guide corresponds to a global burden of diseases in children. The fifth edition of the EMLc from 2015 was used as a standard reference list for our

comparison.[13] The analysis focused on EMLc antibiotics in section 6: Anti-infectives, subsection 6.2: Antibacterials (6.2.1: β-lactam medicines and 6.2.2: Other antibacterials).[13,21]

For the purpose of our comparison, three parameters were used to define the formulations: (1) administration routes, (2) dosage forms and (3) drug strengths. We assessed whether the formulations on the comparator lists differed from the EMLc formulations in any of the parameters. Our findings were arranged to indicate how many EMLc formulations per antibiotic were missing on each of the lists, and how many formulations were an addition to the EMLc.

Importantly, EMLc employs the main terms for oral solid dosage forms, such as tablets, capsules, and so on. Thus, the comparison was made at the EMLc level of detail, although comparator lists are more specific (ie, scored, crushable, chewable, dispersible tablets). Besides, our interest was on the lower paediatric age bands, as the EMLc corresponds to clinical needs of children up to 12 years of age, and comparator lists mostly refer to children up to 18 years.

The additional formulations on the comparator lists that differed from the EMLc formulations were extracted for further analysis. They were checked for their compliance with WHO rules on age and weight restrictions - which are established on the basis of drug efficiency and safety data within the age/weight ranges, suitable administration routes, and/or drug content, as described in the WHO model formulary for children.[21]

Ultimately, formulations that countered WHO rules, and/or had been excluded on similar grounds from previous EMLc (2007 - 2013) were disqualified. The remaining formulations were evaluated for their relevance in paediatric care according to: (1) formulations' added value in clinical practice (ie, unmet needs in certain age/weight group, easier dosing or drug administration, and disease importance), and (2) logistical, supply chain and financial advantages (ie, no need for refrigeration/cold chain, and less drug wastage). Three authors (CR, EZ, MWP) independently appraised all potential new formulations for their relevance, and documented each opinion in a narrative form. Inter-rater agreements were calculated.

The relevance of each formulation was categorised into 4 groups by author VI: (1) major relevance (unmet needs in certain age/weight group), (2) medium relevance (easier dosing or drug administration, no need for refrigeration/cold chain, less drug wastage), (3) little relevance (narrow age range, few therapeutic indications), and (4) no relevance (unreliable drug administration, uncommon formulation use). A randomly selected subset of six formulations was scored independently by author AKM-T to validate the scoring.

Finally, all EMLc antibiotics were classified into five categories: (1) Antibiotics with additional formulations on comparator lists, compliant WHO clinical decisions, with clinical relevance, (2) Antibiotics with additional formulations on comparator lists, compliant WHO clinical decisions, with little or no clinical relevance, (3) Antibiotics with additional formulations on comparator lists, but not compliant with WHO clinical

decisions, (4) Antibiotics with no additional formulations on comparator lists, and (5) Antibiotics absent on comparator lists

The costs of the additional formulations with clinical value and their corresponding formulations on the EMLc (ie, same dosage forms, different drug strengths, or different dosage forms, same drug strengths) were compared, using the prices from the MSH/WHO International Drug Price Indicator Guide 2014.[20]

3.2

RESULTS

Table 1 presents the quantitative summary of paediatric formulations listed on the comparator lists and the EMLc for all 26 EMLc antibiotics. All antibiotics existed on at least one of the comparator lists, but numerous discrepancies existed between the EMLc and the four individual lists including many missing or additional formulations (see online supplementary table S1). Subsequently, 16 antibiotics with 40 additional formulations were selected for further analysis. Of those, 22 formulations were excluded, because 21 of them had potential contradictions with WHO rules, and one formulation was removed from the EMLc in 2008.

The remaining 13 antibiotics with 18 new potential WHO-compatible formulations were selected for the clinical evaluation. Seven antibiotics had formulations with an oral, seven with a parenteral, and one with a rectal route. The clinical evaluation of these potential new formulations is summarised in table 2. The inter-rater agreement in the assessment of formulations' relevance was around 83% (82% for oral and other formulations, and 85% for injectables). The scoring of formulations by author AKM-T showed no discrepancies in categorisation between the two authors.

All seven oral formulations were considered to have major or medium added value for improved use of antibiotics in children. Frequently quoted reasons for clinical benefits included: filling the gap of unmet therapeutic needs in certain age/weight groups (phenoxymethylpenicillin oral liquid, metronidazole oral liquid, and nitrofurantoin capsules), and simplified administration and logistical and supply chain advantages (amoxicillin dispersible tablets, clindamycin capsules, cloxacillin tablets, and sulfamethoxazole + trimethoprim tablets).

The judged value of parenteral formulations for the EMLc ranged from no to medium value. The existing doses of injections on the EMLc were generally seen as sufficient for all ages. For ampicillin and cefazolin powder for injection, lower doses were expected to simplify the dosing in younger children, reduce the risk of medical errors, and decrease the waste of medicines. The drawbacks included: narrow target age/weight groups for the new strengths, and impractical supply system burdened with non-availability, high prices and non-reimbursement. The formulations with new administration routes (doxycycline injections, gentamycin intrathecal injections and intravenous infusion, metronidazole

suppositories) were not recommended for clinical practice due to their uncommon use, age restrictions, or unreliable drug absorption routes (table 2).

Table 1. Quantitative summary of antibiotic formulations on comparator lists and the Essential Medicines List for Children (EMLc)

Name of EMLc antibiotic	EMLc number of formulations	Summary 4 lists number of additional formulations
6.2.1 β - LACTAM MEDICINES		
Core list		
Amoxicillin	4	5
Amoxicillin + clavulanic acid	3	9
Ampicillin	2	5
Benzathine benzylpenicillin	2	0
Benzylpenicillin	2	0
Cefalexin	3	0
Cefazolin	1	1
Ceftriaxone	2	1
Cloxacillin	2	2
Phenoxymethylpenicillin	2	1
Procaine benzylpenicillin	2	0
6.2.1 β - LACTAM MEDICINES		
Complementary list		
Cefotaxime	1	0
Ceftazidime	2	1
Imipenem and cilastatin	2	0
6.2.2 OTHER ANTIBACTERIALS		
Core list		
Azythromycin	3	0
Chloramphenicol	4	0
Ciprofloxacin	3	0
Doxycycline	4	1
Erythromycin	2	3
Gentamycin	2	4
Metronidazole	6	2
Nitrofurantoin	2	1
Sulfamethoxazole + trimethoprim	4	1
Trimethoprim	3	0
6.2.2 OTHER ANTIBACTERIALS		
Complementary list		
Clindamycin	3	1
Vancomycin	1	2

Table 2. Summary of clinically added value of potential new formulations of antibiotics

Name of product/dosage form/strength	Clinically added value	Reason for classification
ORAL FORMULATIONS		
Phenoxymethylpenicillin powder 125mg/5ml	Major	New low strength formulation can fill the gap of unmet therapeutic needs in young children and neonates
Metronidazole oral liquid 125mg/5ml	Major	
Nitrofurantoin capsules 50mg	Major	New intermediate strength formulation can fill the gap between lower strength syrup, and higher dose capsule/tablet.
Cloxacillin tab/capsule 250mg	Medium	
Sulfamethoxazole + trimethoprim tablet 200mg+40mg	Medium	It offers simplified administration and supply/stock, by replacing same-strength syrup in young children without swallowing difficulties.
Clindamycin capsule 75mg	Medium	
Amoxicillin dispersible tab 125mg	Medium	It offers simplified administration and supply/stock, by replacing same-strength syrup in young children with swallowing difficulties.
PARENTERAL FORMULATIONS		
Ampicillin powder for injection 250mg	Medium	Lower strength injection would be appropriate for younger children.
Cefazolin powder for injection 500mg	Medium	
Cloxacillin powder for injection 250mg	Little	Lower strength injection would be appropriate for younger children, but it has minor clinical relevance.
Ceftriaxone powder for injection 500mg	Little	New intermediate dose allows easy dosing with less spill of antibiotics, but it has minor clinical relevance.
Ceftazidime powder for injection 500mg	Little	
Doxycycline injection 20mg/ml	No value	It is a proposed new route, but oral forms are sufficient. It has few indications for use in children, and it is age restricted.
Gentamycin intrathecal injection 5mg/mL, and intravenous infusion 800μg/mL, 1mg/mL, 3mg/mL	No value	No added value of infusion bags/ intrathecal formulation, the available injection strengths suffice for all children,
OTHER FORMULATIONS		
Metronidazole suppository 500mg	No value	It is a proposed new route in case of vomiting or refusal of oral liquids. It is unsuitable for initiating treatment of serious conditions, due to slow absorption and low plasma concentrations.

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The final classification of additional antibiotic formulations according to their clinical relevance is presented in table 3. Nine antibiotic formulations were considered to be clinically relevant for paediatric use, while seven formulations were classified to have little or no clinical relevance.

Table 3. Classification of antibiotics regarding discrepancy formulations and their clinical relevance

Categories	Antibiotics
Antibiotics with additional formulations on comparator lists, compliant with WHO clinical decisions, with clinical relevance	Amoxicillin dispersible tablets, ampicillin powder for injection, cefazoline powder for injection, cloxacilline tablets, phenoxymethyl penicillin oral liquid, metronidazole oral liquid, nitrofurantoin capsules, sulfamethoxazole + trimetoprim tablets, clindamycin capsules
Antibiotics with additional formulations on comparator lists, compliant with WHO clinical decisions, with little or no clinical relevance	Cloxacilline powder for injection, ceftriaxone powder for injection, ceftazidime powder for injection, doxycycline injection, gentamycin intrathecal injection and infusion, metronidazole suppository
Antibiotics with additional formulations on comparator lists, but not compliant with WHO clinical decisions	Amoxicillin injection, amoxicillin + clavulanic acid powder for suspension and powder for injection, ampicillin suspension and capsules, erythromycin injections and infusion, vancomycin capsules
Antibiotics with no discrepancy formulations on comparator lists	Benzathine benzylpenicillin, benzylpenicillin, cefalexin, procaine benzylpenicillin, cefotaxime, chloramphenicol, imipenem and cilastatin, azytromycin, ciprofloxacin, trimetoprim
Antibiotics absent in comparator lists	/

Regarding prices, the identified lower strengths injections on the comparator lists cost the same (ampicillin), or twice less (cefazolin) compared with the twice higher strengths phials on the EMLc. The prices of all six oral formulations from the comparator lists were available, except for clindamycin capsules. They show that two formulations (metronidazole, sulfamethoxazole + trimethoprim) have costs similar to the twice higher strength formulations on the EMLc, three formulations (phenoxymethylpenicillin, amoxicillin, cloxacillin) cost twice as less as the higher strength formulations, and one formulation (nitrofurantoin) costs twice as much. (table 4).

DISCUSSION AND CONCLUSIONS

This study provides an overview of the differences in age-appropriate formulations of paediatric antibiotics between four comparator lists and the EMLc.

In summary, seven oral formulations from the comparator lists were regarded as potential solutions for better tolerated and more efficient therapy, since they simplify drug administration and enhance dosing accuracy in children. Two lower strength oral

Table 4. Price comparison of additional formulations and corresponding formulations on the Essential Medicines List for Children (EMLc)

Drug name	Price of additional formulations with clinical value	Price of corresponding formulations on EMLc
ORAL FORMULATIONS		
Phenoxymethylpenicillin	Powder 125mg/5mL 0.47$ /bottle	Powder 250mg/5mL 0.71$/bottle
Metronidazole	Oral liquid 125mg/5mL 0.77$/bottle	Oral liquid 200mg/5mL 0.8$/bottle
Nitrofurantoin	Capsules 50mg 0.03$/capsule	Capsules 100mg 0.01$/capsule
Cloxacillin	Tab/capsule 250mg 0.02$/tablet	Tab/capsule 500mg 0.04$/tablet
Sulfamethoxazole + trimethoprim	Tablet 200mg+40mg 0.013$/tablet	Syrup 200mg+40mg 0.29$/bottle Tablet 400mg+80mg 0.012$/tablet
Amoxicillin	Dispersible tab 125mg 0.02$/tablet	Powder for syrup 125mg/5mL 0.39$/bottle Dispersible tab 250mg 0.03$/tablet
PARENTERAL FORMULATIONS		
Ampicillin	Powder for injection 250mg 0.12$/phial	Powder for injection 500mg 0.12$/phial
Cefazolin	Powder for injection 500mg 0.27$/phial	Powder for injection 1g 0.4$/phial

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liquids could be used in children below 4 years of age, who currently have unmet needs for suitable EMLc formulations. Five solid oral forms were seen as alternatives for the oral liquids on the EMLc in children with no swallowing difficulties. Their advantages include accurate dosing, stability, taste masking, easy transport and no need for manipulation before use.[22,23] Dispersible tablets (DTs) may add to the treatment possibilities as they are palatable and easy to administer in younger children with swallowing difficulties. This is in line with the WHO statement in 2008 that flexible oral solid formulations are most optimal formulations for use in children, particularly in low-income, middle-income

countries.[24, 25] Amoxicillin DT 250mg is the United Nations new recommended treatment for pneumonia in children under the age of 5 years, and the lower strength DT may further expand paediatric options.[3]

Parenteral antibiotics are important for paediatric, and especially neonatal care, but our clinical assessments put less value on their clinical benefits.[26,27] As indicated, while lower doses of injections may simplify the dosing in neonates and infants, and reduce the waste of medicines, the target age/weight groups for the new strengths may be too narrow.

It is also important to consider the financial implications that these new formulations may have for low-income countries. Our cost comparisons between corresponding antibiotic formulations showed that half of all new oral and parenteral formulations could decrease the cost of treatment, and have a favourable budget impact.

The strength of our study is the use of diverse lists to depict existing therapeutic options globally. The main limitations are the small sample of evaluators and the narrative description of formulations' clinical relevance, although a high inter-rater agreement was reached. Our evaluation criteria and the proposed categorisation represent an early attempt to translate relevant clinical principles into measurable operational components. Further development of a user-friendly instrument, and its validation and testing are needed to verify our tool's consistency and reliability.

Besides the aforementioned benefits, introducing more formulations on the lists may lead to a complex procurement of multiple strengths and formulations, and less efficient drug management, including prescribing.[12] The EMLc is not envisaged as a comprehensive list of all marketed formulations and strengths for children. Nonetheless, it is important to find a suitable platform to share up-to-date information about available age-appropriate paediatric formulations and their advantages and shortcomings, and advocate for their rational use in line with relevant formularies and treatment guidelines. Besides, it is vital to consider the barriers for the implementation of new formulations at the field level, as listing in the WHO EML does not always translate into demand for the medicines at country level.[28-30]

Concluding, the present study identified relevant age-appropriate formulations of paediatric antibiotics that exist. The progress made in developing new formulations needs to be extended for the benefit of children globally.

REFERENCES

1. United Nations Inter-agency Group for Child Mortality Estimation (UN IGME). *Levels and trends in child mortality 2015.* UNICEF, WHO, World Bank, UN-DESA Population Division, 2015. Available at: http://www.childmortality.org/files_v20/download/IGME%20Report%202015_9_3%20LR%20Web.pdf

2. Liu L, Oza S, Hogan D, *et al.* Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* 2015;385 (9966):430-440.

3. World Health Organization. *Priority live-saving medicines for women and children 2012.* Geneva: World Health Organization, 2012 (WHO/EMP/MAR/2012.1). Available at: http://apps.who.int/iris/bitstream/10665/75154/1/WHO_EMP_MAR_2012.1_eng.pdf?ua=1

4. Bhutta ZA, Das JK, Walker N, *et al.* Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost? *Lancet* 2013;381:1417–29.

5. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med.*2003;349(12):1157–1167.

6. Fernandez E, Perez R, Hernandez A, Tejada P, Arteta M, Ramos JT. Factors and mechanisms for pharmacokinetic differences between pediatric population and adults. *Pharmaceutics* 2011;3(1):53–72.

7. European Medicines Agency. Guideline on pharmaceutical development of medicines for paediatric use. EMA/CHMP/QWP/805880/2012 Rev. 2. 1 August 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf

8. Breitkreutz J, Boos J. Paediatric and geriatric drug delivery. *Expert Opin Drug Deliv* 2007;4(1):37–45.

9. World Health Organization. *Development of Paediatric Medicines: Points to Consider in Formulation.* Geneva, Switzerland: World Health Organization; 2012. WHO Technical Report Series, No. 970, Annex 5.

10. Tuleu C, Breitkreutz J. Educational paper: formulation-related issues in pediatric clinical pharmacology. *Eur J Pediatr.* 2013;172(6):717–720.

11. World Health Organization. The selection and use of essential medicines. Report of the WHO Expert Committee, October 2007 (including the Model List of Essential Medicines for Children). Technical Report Series 950. Geneva: WHO, 2008. Available at: http://apps.who.int/iris/bitstream/10665/43887/1/WHO_TRS_950_eng.pdf

12. World Health Organization. Essential medicines. available: http://www.who.int/medicines/services/essmedicines_def/en/

13. World Health Organization. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 5th Model List of Essential Medicines for Children). Technical Report Series 994. Geneva: WHO, 2015. Available at: http:// apps.who.int/ iris/ bitstream/10665 /189763/1/9789241209946_eng.pdf?ua=14

14. Nair H, Simoes EAF, Rudan I, et al. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. *Lancet* 2013;381(9875):1380–1390.

15. Zaidi AK, Ganatra HA, Syed S, *et al.* Effect of case management on neonatal mortality due to sepsis and pneumonia. *BMC Public Health* 2011;11(Suppl 3):S13.

16. European Medicines Agency. Inventory of paediatric therapeutic needs, infectious diseases. EMA/PDCO/287222/2012.

3.2

Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/05/WC500166168.pdf

17. National Institute for Health and Care Excellence (NICE). British National Formulary for Children (BNFc) 2014/2015. Available at: http://www.evidence.nhs.uk/formulary/bnfc/current

18. Nederlands Kenniscentrum voor Farmacotherapie bij Kinderen (Dutch Knowledge for Pharmacotherapy in Children). Kinderformularium. - in Dutch. Available at: https://www.kinderformularium.nl/

19. Australian Government Department of Health. The Pharmaceutical Benefits Scheme. Available at: http://www.pbs.gov.au/pbs

20. Management Sciences for Health. Drug Price Indicator Guide 2014. Available at: http://erc.msh.org/ mainpage.cfm? file= 1.0.htm& module= DMP&language= English

21. World Health Organization. WHO Model Formulary for Children 2010. Geneva: WHO; 2010. Available at: http://www.who.int/selection_medicines/list/WMFc_2010.pdf

22. Ivanovska V, Rademaker CM, van Dijk L, et al. Pediatric drug formulations: a review of challenges and progress. *Pediatrics*. 2014;134(2):361-72.

23. van Riet-Nales DA, de Jager KE, Schobben AF, *et al*. Safe and effective pharmacotherapy in infants and preschool children: importance of formulation aspects. *Arch Dis Child* 2016;101:662-669.

24. World Health Organization. 17th meeting of the Expert Committee on Selection and Use of Essential Medicines. Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children. December 2008. Available at: http://www.who.int/selection_medicines/committees/expert/17/application/paediatric/ Dosage_form_reportDEC2008.pdf

25. World Health Organization. Development of pediatric medicines: points to consider in formulation. WHO Technical Report Series, No. 970, 2012, Annex 5.

26. Coffey P, Kelly K, Baqui A, *et al*. Case study: injectable antibiotics for treatment of newborn sepsis. 1–24 p. United Nations Commission on Commodities for Women's and Children's Health, 2012 Available at: http://pdf.usaid.gov/pdf_docs/pnady703.pdf

27. Darmstadt GL, Batra M, Zaidi AK. Parenteral antibiotics for the treatment of serious neonatal bacterial infections in developing country settings. *Pediatr Infect Dis J* 2009;28:S37-42.

28. Robertson J, Forte G, Trapsida J, *et al*. What essential medicines for children are on the shelf? *Bull World Health Organization* 2009;87:231-237.

29. Gitanjali B, Manikandan S. Availability of five essential medicines for children in public health facilities in India: A snapshot survey. *J Pharmacol Pharmacother* 2011;2:95-99.

30. Balasubramaniam R, Beneragama BV, Sri Ranganathan S. A national survey of availability of key essential medicines for children in Sri Lanka. *Ceylon Med J* 2011;56:101-107.

SUPPLEMENTARY FILE

3.2

Supplementary table 1. Detailed list on formulations on the EMLc and comparison lists

WHO EMLc	UK BNFc	ABPS	Kinderformularium	MSH/WHO Guide
6.2.1 BETA - LACTAM MEDICINES				
Amoxicillin J01CA04				
Powder for oral liquid 125mg/5mL, 250mg/5mL **Solid oral dosage form** 250mg, 500 mg	**Pediatric suspension** 125mg/1.25mL 125mg/5mL **Capsules** 250mg, 500mg **Injection** 250mg, 500mg, 1g, 2g phial	**Powder for oral liquid** 125 mg/5 mL (100 mL), 250 mg/5 mL (100 mL), **Capsules** 250mg, 500mg	**Powder for suspension** 25 mg/mL, 50 mg/mL **Capsule/ tablet dispersible** 250 mg, 500 mg **Powder for injestion** 250 mg, 500 mg, 1g	**Powder for oral liquid** 125mg/5mL, 250mg/5mL **Solid oral dosage form** 250mg, 500 mg **Tablet dispersible** 125 mg
Amoxicillin + Clavulanic acid J01CR02				
Oral liquid 125mg +31.25mg/5mL 250mg+62.5mg/mL **Tablet** 500mg +125mg	**Tablet** 250mg+125mg 500mg+125mg **Oral suspension** 125mg+31.25mg/5mL 250mg+62.5mg/5mL **Powder for injection** 500mg+100mg, 1000g+200mg **Powder suspension** 400mg+57mg/5mL	**Powder for oral liquid** 125 mg+31.25mg/5mL **Tablets** 500mg+125mg	**Powder for suspension** 100mg+12.5mg/ml (8:1) **Powder for injection** 250mg+25mg, 500mg+50mg, 1000mg+100mg, 2000mg+200mg (10:1) 500mg+100mg, 1000mg+200mg (5:1) **Tablets** 500mg+125mg (4:1)	**Oral liquid** 125mg +31.25mg 250mg+62.5mg **Tablets** 250mg+125mg 500mg+125mg

Supplementary table 1. (continued)

WHO EMLc	UK BNFc	ABPS	Kinderformularium	MSH/WHO Guide
Ampicillin J01				
Powder for injection 500mg, 1g in phial	**Oral suspension** 125mg/5mL, 250mg/5mL **Capsules** 250mg, 500mg Injection 500mg	**Powder for injection** 500mg, 1g	No	**Capsules** 250mg, 500mg **Injection** 250mg, 500mg
Benzathine benzylpenicillin J01				
Powder for injection 900mg benzylpenicillin (=1.2 milion IU)/ 5mL 1.44g benzylpenicillin (=2.4 milion IU)/5mL	No	**Pre-filled syringe, single use** 900mg in 2.3mL	**Powder for injection** 1.2 milion IU/5mL phial	**Powder for injection** 1.2 milion IU/5mL phial, 2.4 milion IU/5mL phial
Benzylpenicillin J01CE01				
Powder for injection 600mg, 3g in phial	**Powder for injection** 600mg, 3g	**Injection** 600mg, 3g	**Powder for injection** 600mg	**Injection** 600mg, 3g
Cefalexin J01DB01				
Powder reconstitution with water: 125mg/5mL, 250mg/5mL **Solid oral dosage form** 250mg	**Powder for oral liquid** 125mg/5mL, 250mg/5mL **Capsule/tablet** 250mg	**Powder for oral liquid** 125mg/5mL, 250mg/5mL **Capsule** 250mg	No	**Powder for oral liquid** 125mg/5mL, 250mg/5mL **Capsule** 250mg

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Supplementary table 1. (continued)

WHO EMLc	UK BNFc	ABPS	Kinderformularium	MSH/WHO Guide
Cefazolin J01DB04				
Powder for injection	No	Injection	Powder for injection	Powder for injection
1g in phial		500mg, 1g	500mg, 1g	500mg, 1g
Ceftriaxone J01DD04				
Powder for injection	Powder for injection	Powder for injection	Powder for injection	Powder for injection
250mg, 1g in phial	250mg, 1g	500mg, 1g	500mg, 1g	500mg, 1g
Cloxacillin J01				
Powder for injection	No	No	No	Powder for injection
500mg in phial				250mg, 500mg in phial
Powder for oral liquid				Powder for oral liquid
125mg/5mL				125mg/5mL
Capsule 500mg, 1g				Capsule 250mg, 500mg
Phenoxymethylpenicillin J01				
Powder for oral liquid	Powder for oral liquid	Powder for oral liquid	No	Powder for oral liquid
250 mg/5mL	125/5mL, 250 mg/5mL	125 mg/5mL, 250mg/5mL		125/5mL, 250 mg/5mL
Tablet 250mg	Tablet 250mg	Capsule/Tab 250mg		Cap/Tab 250mg
Procaine benzylpenicillin J01				
Powder for injection	No	Injection (syringes)	No	Powder for injection
1g (=1 million IU), 3g (=3 million IU) in phial		1g		1g (=1 million IU), 3g (=3 million IU) in phial

Supplementary table 1. (continued)

WHO EMLc	UK BNFc	ABPS	Kinderformularium	MSH/WHO Guide
Cefotaxime J01DD01				
Powder for injection 250mg per phial	No	No	Powder for injection 250mg	No
Ceftazidime J01DD02				
Powder for injection 250mg, 1g in phial	Powder for injection 500mg, 1g	No	Powder for injection 500mg, 1g	Powder for injection 250mg, 1g in vial
Imipenem and cilastatin J01DH51				
Powder for injection 250mg + 250mg in phial 500mg + 500mg, in phial	Powder for infusion 500mg + 500mg	No	Powder for infusion 500mg + 500mg	Powder for injection 500mg + 500mg
6.2.2 OTHER ANTIBACTERIALS				
Azythromycin J01DH51				
Capsules 250mg, 500mg Oral liquid 200mg/5mL	Capsules/tablets 250mg, 500mg Oral liquid 200mg/5mL	Tablets 500mg Powder for oral liquid 200mg/5mL	Tablets 250mg, 500mg Oral liquid 40mg/mL	Tab/cap 250mg, 500mg Oral liquid 200mg/5mL
Chloramphenicol J01				
Capsules 250mg Oral liquid 150mg/5mL Oily suspension for injection 1g 0.5g/mL in 2mL Powder for injection 1g	Capsules 250mg Powder for injection	No	No	Tab/Cap 250mg Oral liquid 150mg/5mL Powder for injection 1g

Supplementary table 1. (continued)

WHO EMLc	UK BNFc	ABPS	Kinderformularium	MSH/WHO Guide
Ciprofloxacin J01MA02				
Tablet 250mg	**Tablet 250mg**	No	**Tablet 250mg**	**Tablet 250mg**
Oral liquid 250mg/5mL	Oral liquid 250mg/5mL		**Oral liquid**	Oral liquid 250mg/5mL
Solution for IV infusion	**Solution for IV infusion**		250mg/5mL	Solution for IV infusion
2mg/mL	2mg/mL		**Solution for IV infusion**	2mg/mL
			2mg/mL	
Doxycycline J01AA02				
Solid oral dosage form	**Capsules**	No	**Tablet/Dispersible tablets**	Tab/Cap 100mg
50mg, 100mg	50mg, 100mg		100mg	
Oral liquid			**Injection 20mg/mL**	
25mg/5mL, 50mg/5mL				
Erythromycin J01FA01				
Solid oral dosage form	**Cap/ Tab 250mg**	**Tablet enteric 250mg**	**Tab/Tablet enterosolubile**	**Cap/ Tab 250mg**
250mg	**Powder for oral liquid**	**Injection 1g**	250mg	**Powder for oral liquid**
Powder for oral liquid	125mg/5mL,		**Granules for oral**	125mg/5mL
125mg/5mL	**IV infusion 1g**		**suspension**	**IV infusion 0,5g**
			25mg/mL	
			Powder for infusion 1g	
Gentamycin J01FA01				
Injection	**Injection 10mg/ml, 40mg/mL**	**Injection 80mg/2mL**	**Injection 10mg/mL, 40mg/**	**Injection 10mg/mL, 40mg/**
10mg, 40mg/mL	**Intrathecal injection**		mL	mL
	5mg/mL			
	IV infusion 800mcg/mL, 1mg/			
	mL, 3mg/mL			

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Supplementary table 1. (continued)

	WHO EMLc	UK BNFc	ABPS	Kinderformularium	MSH/WHO Guide
Metronidazole P01AB01	Injection 500mg/100mL; Oral liquid 200mg/5mL; Tablet 200mg to 500mg	No	Injection 500mg/100mL; Oral liquid 200mg/5mL; Tablet 200mg, 400mg Suppository 500mg	Infusion 5mg/mL; Oral liquid 40mg/mL; Tablet 250mg to 500mg	Injection 5mg/mL; Oral liquid 125mg/5mL, 200mg/5mL; Tablet 200mg to 500mg; Suppository 500mg
Nitrofurantoin J01XE01	Oral liquid 25mg/5mL; Tablet 100mg	Oral liquid 25mg/5mL; Tablet/cap 100mg; Capsules 50mg	Capsules 50mg, 100mg	Capsules with regulated release /Cap100mg; Capsules 50mg; Suspension 5mg/mL	Cap/ Tab 50mg, 100mg; Oral liquid 25mg/5mL
Sulfamethoxazole + trimethoprim J01	Oral liquid 200mg+40mg/5mL; Tablet 100mg+20mg, 400mg+80mg; Injections 80mg+16mg/mL	No	Oral liquid 200mg+40mg/5mL	No	Oral liquid 200mg+40mg/5mL; Tablet 100mg+20mg, 200mg+40mg, 400mg+80mg; Injections 80mg+16mg/mL
Trimethoprim J01EA01	Oral liquid 50mg/5mL; Tablet 100mg, 200mg	Oral liquid 50mg/5mL; Tablet 100mg, 200mg	No	Tablet 100mg, 300mg	No

Supplementary table 1. (continued)

WHO EMLc	UK BNFc	ABPS	Kinderformularium	MSH/WHO Guide
Clindamycin J01FF01				
Oral liquid 75mg/5mL	**Liquid** 75mg/5mL	No	**Powder for oral suspension** 15mg/mL	Tab/cap 150mg
Capsule 150mg	**Capsule** 75mg, 150mg		**Capsule** 150mg	Injection 150mg/mL
Injection 150mg/mL	**Injection** 150mg/mL		**Injection** 150mg/mL	
Vancomycin J01XA01				
Powder for injection 250mg in vial	**Capsule** 125mg, 250mg	**Capsule** 125mg, 250mg	**Capsule** 250mg	No

CHAPTER 4

ANTIBIOTIC USE IN CHILDREN

CHAPTER 4.1

PRESCRIBING FOR ACUTE CHILDHOOD INFECTIONS IN DEVELOPING AND TRANSITIONAL COUNTRIES, 1990–2009

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ABSTRACT

Background

Evidence of global progress in treating acute paediatric infections is lacking. We assessed progress over two decades in prescribing for childhood infections and interventions to improve treatment by reviewing empirical evidence in developing and transitional countries.

Methods

Data were systematically extracted on the use of medicines for diarrhoea, respiratory infections and malaria from published and unpublished studies (1990–2009) in children under 5 years of age. Medians of each indicator were calculated across studies by study year, geographic region, sector, country income level and prescriber type. To estimate intervention effects from studies meeting methodologically accepted design criteria [randomised controlled trials (RCTs), pre-post with control, and time series studies], the medians of the median effect sizes (median MES) were calculated across outcome measures.

Results

Data were extracted from 344 studies conducted in 78 countries with 394 distinct study groups in public (64%), private (22%) and other facilities to estimate trends over time. Of 226 intervention studies, only the 44 (19%) with an adequate study design were used to estimate intervention effects. Over time, use of anti-diarrhoeals for acute diarrhoea decreased significantly ($P<0.01$). However, treatment of malaria and acute respiratory infection remained largely sub-optimal. Multi-component interventions resulted in larger improvements than single-component ones. The median MES 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.

Conclusions

While diarrhoea treatment has improved over the last 20 years, treatment of other childhood illnesses remains sub-optimal. Multi-component interventions demonstrated some success in improving management of acute childhood illness.

INTRODUCTION

The global burden of childhood mortality from acute infectious diseases is enormous.[1,2] WHO has long advocated the implementation of integrated management of childhood illness (IMCI) programmes to improve case management in the primary care of childhood infections, including pneumonia, malaria and diarrhoea.[3] While many studies have reviewed the effectiveness of interventions to improve medicines use,[4–6] only one review[7] has previously focused on children.

In the 1990s, WHO developed the IMCI approach and (in collaboration with the International Network of the Rational Use of Drugs, INRUD) a method to investigate use of medicines in primary health-care facilities in resource-poor settings.[8] Since then, many studies of medicines use in children in developing and transitional countries have been conducted, most in the context of public sector IMCI programmes or national control programmes for acute respiratory infection (ARI), diarrhoea or malaria. To date, there has not been a systematic review of available data on the treatment of acute childhood illness.

WHO has developed a database of studies of medicines use and interventions to improve primary care in developing and transitional countries. Summary results of 1990–2006 data have been published.[9] This article presents a further analysis of 1990–2009 data not previously published, from the updated WHO Medicines Database, focusing on the use of medicines for acute childhood illnesses.

OBJECTIVES

The objective of the study was to assess progress over two decades in the treatment of acute childhood illness by reviewing studies from developing and transitional countries between 1990 and 2009 which investigated the treatment of acute illnesses in children under 5 years of age, including the subset of studies which evaluated the effects of interventions to improve treatment.

METHODS

Creation of the WHO Medicines Use Database has been described previously.[9] Briefly, the database contains systematically extracted information on studies of medicines use from developing and transitional countries published or reported between 1990 and 2009. Developing and transitional countries were defined as all countries except those in North America, Western Europe, Australia, New Zealand and Japan. In addition to quantitative data on medicines use in the form of standard IMCI[3] and WHO-INRUD indicators,[8] the database contains information on study setting, methodology and the nature of interventions (if any).

4.1

Search strategy

Studies in the database were identified from the INRUD bibliography[10] (containing 8717 references as of 2 June 2010, identified from systematic searches in PubMed, EMBASE and over 50 hand-searched journals), PubMed and Embase searches, and the WHO Department of Child and Adolescent Health and Development. Search terms included 'drug use', 'drug utilization', 'drug therapies', 'prescriptions', 'prescribing', 'antibiotics', 'diarrhoea', 'acute respiratory infections', 'malaria', 'integrated management of childhood illness', 'interventions', 'evaluation studies', 'education', 'developing countries', 'Africa', 'Asia', and 'Central America and South/Latin America'. Using standard fields recorded in the database, information was extracted for the subset of studies that focused on medicines use and interventions in children under 5 years.

Variables

Since authors frequently fail to differentiate between primary and secondary outcomes, the WHO Medicines Use Database includes all outcome measures reported in studies that meet inclusion criteria.[9] Descriptive data are presented for seven indicators commonly used in studies of acute illness in children under 5 years: percentage of diarrhoea cases receiving oral rehydration solution (ORS); percentage of diarrhoea cases receiving an anti-diarrhoeal; percentage of diarrhoea cases receiving an antibiotic; percentage of pneumonia cases receiving an appropriate antibiotic; percentage of cases of upper respiratory tract infection receiving an antibiotic; percentage of patients not needing antibiotics who received an antibiotic; and percentage of malaria patients who received appropriate anti-malarial medication. For intervention studies, effects were assessed for 39 standard treatment indicators recorded in the WHO Medicines Use Database,[9] including commonly used INRUD/WHO indicators.[8]

The database also contains 102 fields to describe key features of the study population: these include sector (public/private); setting [primary health care centre (PHC), hospital, pharmacy, household]; prescriber type (doctor, nurse, paramedic, community health worker, other); and year of data collection. For articles reporting treatment by more than one prescriber type or health facility type, the database contains only one category reflecting either the mix (e.g. hospitals + PHC) or the dominant (if over 80%) type. Studies were grouped according to study survey year (in 4-year groups from the date of the earliest study in 1987 until 2009), geographic region (Africa, South Asia, East Asia, Pacific, Eastern Europe, Eastern Mediterranean, Central Asia, Latin America) and World Bank country income category (low, lower-middle, upper-middle or high).

Analysis

Descriptive analyses included data from non-intervention studies, baseline data from intervention studies, control group data for post-only intervention studies, and repeated measures from national surveys that reported no discrete intervention. To estimate

patterns of use and trends over time, medians and 25th and 75th percentiles of indicators were calculated across subgroups classified by survey year, region, sector, country income level and prescriber type. Studies were included only if treatment was investigated in more than two health facilities and/or included more than 599 patient encounters. Owing to the heterogeneity of the studies, formal meta-analysis could not be undertaken.

In accordance with recommendations for systematic reviews of interventions by the Cochrane Collaboration's Effective Practice and Organization of Care (EPOC) review group,[11,12] intervention analyses included only studies meeting criteria for adequate study design, i.e. randomised controlled trials (RCT), pre-post with control, and time series studies. Studies using other study designs were excluded. In studies reporting multiple post-intervention assessments, only the last post-intervention data-point was used to calculate intervention effects. Interventions were classified into 11 types by dominant component, as described elsewhere.[9] Interventions were also classified according to the different intervention components used in the IMCI approach.

Data were analysed using Microsoft Excel 2010™ and Stata12.0. Medians, 25th and 75th percentiles of the outcome measures were calculated by 4-year periods; Cuzick's non-parametric test for trend across ordered groups, which is an extension of the Wilcoxon rank-sum test, was calculated for each measure. Medians for each measure were also calculated by region, sector, country income level and prescriber type; non-parametric equality-of-medians tests were undertaken to determine whether the medians were statistically different across sub-groups.To adjust for multiple comparisons between groups, results are not considered statistically significant unless $P<0.01$.

Sensitivity analyses were conducted to determine the impact of including only specific categories of data in the descriptive analyses. One sensitivity analysis excluded data from post-only studies without a control group, while a second included only data from control groups of studies with multiple intervention groups. Sensitivity analyses did not substantially change the results so all data were included in the results presented.

Effect sizes of interventions for each indicator were estimated as follows:[13–15]

For percentage outcome measures (e.g. % patients receiving antibiotics)

$$\text{Effect size} = (\%Post-\%Pre)_{Intervention} - (\%Post-\%Pre)_{Control}$$

For numeric outcome measures (e.g. average number of medicines per patient)

$$\text{Effect size} = ([Post-Pre]/Pre)_{Intervention} - ([Post-Pre]/Pre)_{Control}$$

All outcome measures were first converted to a scale where positive changes toward recommended practice were indicated by positive numbers. As has been done elsewhere

to evaluate the effect of interventions in heterogeneous studies using different outcome measures,[14,15] the median change across all indicators reported was calculated as the median effect size (MES) for each intervention study; the MES across studies was then calculated overall and within intervention types. For each intervention type with four or more studies, non-parametric equality-of-medians tests were undertaken to determine whether pairs of medians were statistically different. Owing to multiple comparisons, $P<0.01$ was again used as the criterion for statistical significance.

RESULTS

Overall, 344 studies conducted in 78 countries were identified and data were extracted for 394 study groups. Of these, 325 study groups (94%) contained data from more than two health facilities and/or included more than 599 patient encounters; only these studies were included in the descriptive analyses.

The proportion of studies conducted in public sector facilities was 64% (209), in private-for-profit facilities was 22% (70), a single study was conducted in a private-not-for-profit facility, and the remaining 14% (45) of studies were undertaken in households or unknown types of facility. The proportion of studies undertaken in primary health care facilities was 39% (128), in hospitals was 7% (22), in mixed hospital and primary health-care settings was 29% (93), in pharmacies 13% (42), in non-licensed shops 3% (9), in households 6% (21), and the remaining 3% (10) were conducted in unknown facilities. Doctors were the prescribers of interest in 22% (73) of studies, nurses or paramedics in 48% (156), community health workers in 9% (28), pharmacy personnel in 3% (9), and laypersons in 4% (13) of studies, with the prescriber being unknown in 14% (46) of studies.

Figure 1 shows patterns of practice for six indicators of acute childhood illness treatment from 1990 to 2009. These data largely reflect treatment patterns in the public sector since few studies were conducted in the private sector. There is some evidence of improvement in the treatment of acute diarrhoea, reflected by a trend towards increased use of ORS (from 14% pre-1990 to 60% in 2006–9 (*P*-value for trend in medians over time = 0.57) and a significant decrease in the use of anti-diarrhoeals (from 45% pre-1990 to 7% in 2002–5, $P<0.01$). However, other aspects of the treatment of acute childhood infections have remained sub-optimal over the last 20 years. Rates of treating pneumonia with an appropriate antibiotic have remained below 80% over time; there has been 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 2006–9 (*P*=0.07). Appropriate antimalarial treatment has declined from 81% in 1994–7 to 65% in 2006–9(*P*=0.48). Relatively few studies have measured treatment of childhood illnesses from 2006 onwards, thus providing little information on current practices.
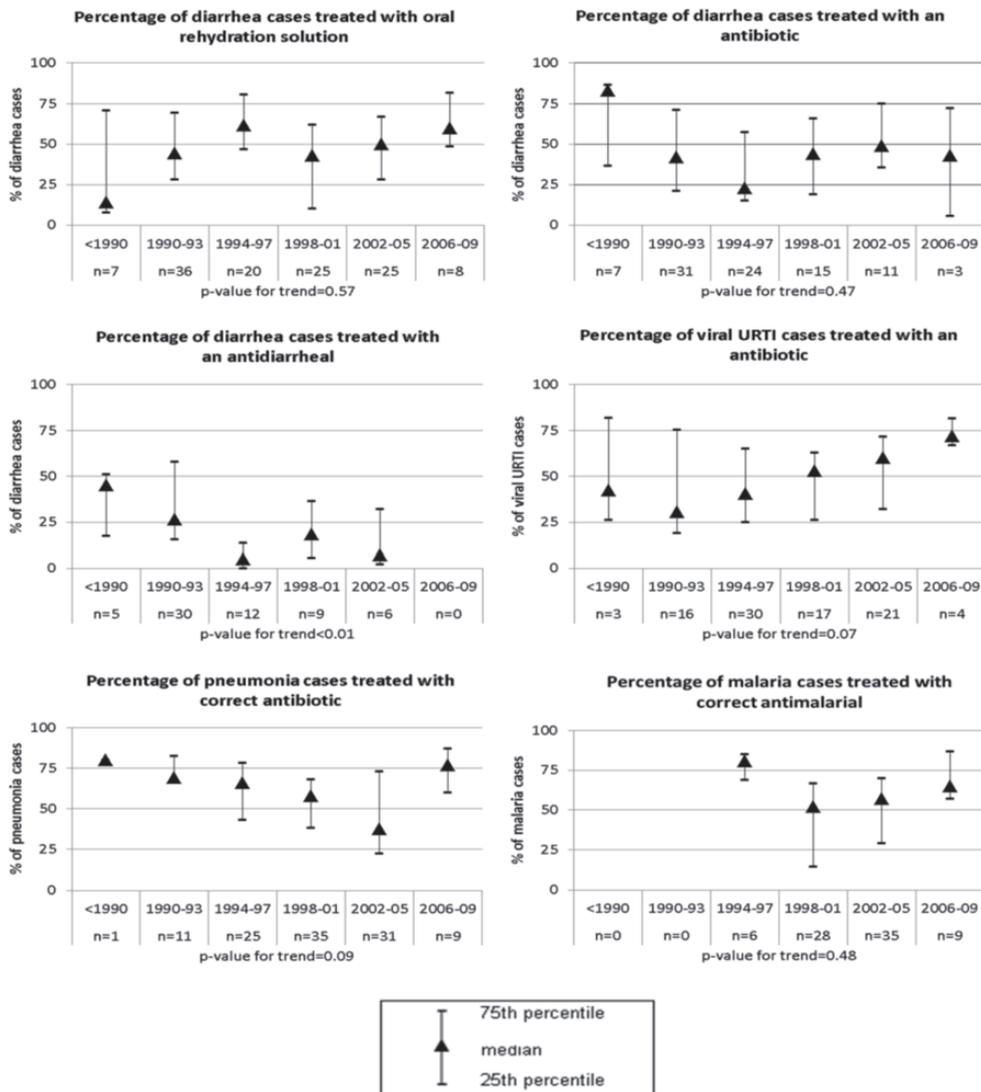
Figure 1. Median, 25th and 75th percentile values of prescribing indicators for acute childhood infections by time period (n, number of studies contributing to estimates; URTI, upper respiratory infection)

Table 1 shows variations in seven indicators of child illness treatments across key contextual factors – region, sector, country income level and prescriber type. Data were insufficient to analyse trends in these key contextual factors over time.

Treatment of acute childhood illnesses has differed across regions, with little consistency in recommended practices across illnesses. Inappropriate antibiotic use remains a concern in all regions. Median percentages of diarrhoea cases receiving antibiotics contrary

Table 1. Median values of indicators of use of standard medicines for childhood illnesses by region, sector, country income level and prescriber type

	Acute diarrhoea			Acute respiratory illness		All illnesses	Malaria
	Cases receiving ORS n* (%)	Cases receiving anti-diarrhoeal n* (%)	Cases receiving antibiotic n* (%)	Pneumonia cases receiving appropriate antibiotic n* (%)	URTI cases receiving inappropriate antibiotic n* (%)	Cases receiving inappropriate antibiotic n* (%)	Cases receiving appropriate antimalarial n* (%)
Geographic region							
Africa	55[50.0]	23[10.0]	33[34.0]	53[56.0]	26[62.5]	26[33.5]	74[58.4]
S. Asia, E. Asia, Pacific	40[53.9]	26[26.4]	35[64.9]	24[58.1]	28[36.2]	10[56.9]	2 [NA]
E. Europe &E. Medit., C. Asia	6[55.5]	2[NA]	4[26.5]	14[68.9]	17[61.9]	7[16.0]	0[NA]
Latin America	20[47.0]	11[17.3]	19[36.6]	21[65.0]	20[25.8]	14[19.0]	2[NA]
Median difference test *P*-value	0.97	0.13	0.03	0.33	<0.01	**0.01**	NA
Sector							
Private-for-profit	35[33.0]	25[47.6]	25[44.0]	9[52.6]	18[54.0]	1[NA]	17[40]
Public	70[61.0]	31[10.0]	59[41.7]	91[63.0]	66[49.0]	52[25.0]	42[66.5]
Median difference test *P*-value	**<0.01**	**<0.01**	0.81	0.36	1.00	NA	0.05
World Bank country income level							
Low	63[56.0]	23[9.5]	42[41.5]	55[53.1]	30[57.5]	23[43.0]	70[58.4]
Lower middle	42[48.0]	30[31.3]	34[47.0]	35[68.8]	36[47.1]	17[31.0]	6[25.6]
Upper middle & high	16[50.6]	9[15.4]	15[31.0]	22[68.0]	25[42.4]	17[18.0]	2[NA]
Median difference test *P*-value	0.95	**0.01**	0.70	**0.02**	0.61	0.14	NA
Prescriber type							
Doctor	27[60.7]	16[17.8]	24[60.0]	17[72.0]	26[55.9]	16[22.3]	2[NA]
Nurse & paramedic	59[60.0]	24[5.5]	44[25.5]	85[58.2]	48[54.0]	41[28]	51[68.0]
Community health worker	16[39.1]	8[60.0]	9[40.0]	4[44.5]	3[40.0]	0[NA]	12[40.5]
Median difference test *P*-value	0.08	**<0.01**	0.30	**0.03**	0.76	0.61	**<0.01**

* No. of surveys contributing to the estimate; results not reported if there were fewer than three surveys in a group. Note: Results in bold indicate P<0.01.ORS, oral rehydration solution; URTI, upper respiratory tract infection

to recommendations were higher in South Asia, East Asia and the Pacific (64.9%) and lower in Eastern Europe, the Eastern Mediterranean and Central Asia (26.5%) compared with Africa (34.0%) and Latin America (36.6%) (*P*-value for difference across regions = 0.03). By contrast, inappropriate antibiotic use for upper respiratory tract infections was significantly lower in Latin America (25.8%) and in South Asia, East Asia and the Pacific (36.2%) compared with Africa (62.5%) and Eastern Europe, the Eastern Mediterranean and Central Asia (61.9%, *P*<0.01).

Results suggest better practices in the public than in the private sector, reflected by significantly higher median ORS use across studies(61.0% *vs.* 33.0%, *P*-value<0.01 for difference across sector) and significantly lower median use of anti-diarrhoeals for acute diarrhoea (10.0% *vs.* 47.6%, *P*<0.01); appropriate use of antimalarials for malaria was marginally higher in the public versus the private sector (66.5% *vs.* 40.0%, *P*=0.05). Restricting the analysis to doctors, nurses and paramedical workers does not change these results (data not shown).

The median rates of anti-diarrhoeal use for children were significantly lower in lower-income (9.5%) and upper-middle and higher-income (15.4%) countries compared with lower–middle-income countries (31.3%, *P*=0.01), whereas median rates of appropriate use of antibiotics to treat pneumonia were marginally better in upper-middle and higher-income (68.0%) and lower–middle-income (68.8%) countries compared with lower-income ones (53.1%, *P*=0.02).

In general across studies, nurses and paramedics (5.5%) are significantly less likely than doctors (17.8%) or community health workers (60.0%) to use anti-diarrhoeals to treat diarrhoea (*P*=0.001). Doctors rank highest (72.0%) across studies for correct treatment of pneumonia with antibiotics, with nurses and paramedics (58.2%) and community health workers (44.5%) lagging behind, although differences are not significant. Community health workers (40.5%) have also performed significantly more poorly across studies than nurses and paramedics (68.0%, *P*=0.01) in treating malaria with appropriate antimalarials.

Of the 226 intervention groups included in interventions to improve use of medicines, only 44 (19%) were in studies with a methodologically appropriate design. Most interventions targeting improved treatment of acute child illnesses involved a mix of components. Provider education (10 studies, 23%) usually included printed material. Provider supervision (five studies,11.4%) generally involved printed educational material and face-to-face training. Provider group process quality improvement strategies (two studies, 4.5%) generally involved peer review or self-monitoring of prescriptions. Community case management (CCM) approaches (eight studies, 18.2%) consisted of community members being trained to treat common childhood illnesses, provided with medicines, and supervised in their care delivery. Essential drug programmes (EDP) (one study, 2.2%) consisted of supervised provider education and an improved drug supply system. One study evaluated the abolition

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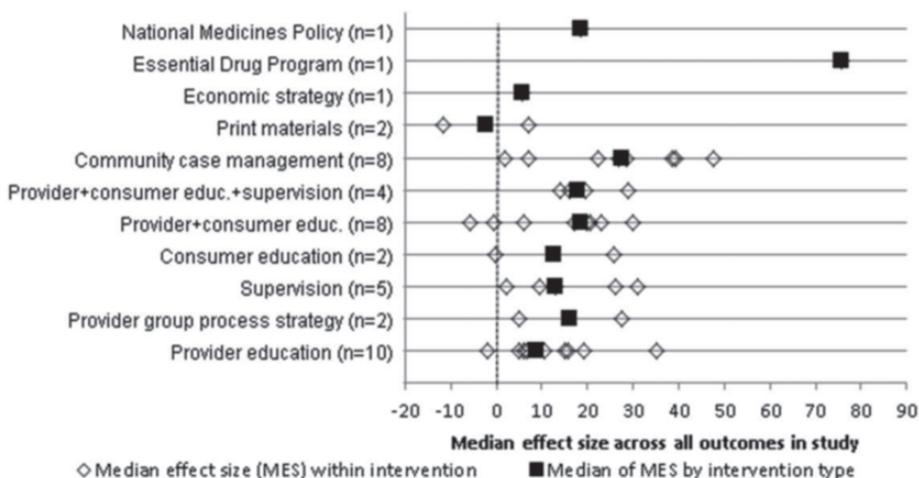
Figure 2. Median effect sizes in interventions to improve prescribing for acute childhood infections

of user fees (economic strategy) and one evaluated the introduction of a new first-line antimalarial drug (national drug policy).

Figure 2 shows the median effect size (MES) across all indicators reported in each intervention study with methodologically appropriate designs, as well as the MES across interventions for each intervention type.

Overall, the MES across all intervention studies was 15.8% (25th,75th percentiles = [5.8%,26.4%]), indicating that the majority of interventions achieve moderate-to-large improvements in prescribing outcomes. Most interventions were structured around provider education, provider supervision, consumer education, or combinations of the three; community case-management of paediatric illness was also studied as an approach in eight studies. Very few other intervention types have been evaluated in studies with methodologically appropriate designs.

When delivered as sole interventions, provider education [MES 8.7% (5.3, 15.5)] and improvements in supervisory systems [MES 13.0% (9.6, 26.3)] resulted in small-to-modest improvements in prescribing. However, provider education combined with consumer education [MES 18.5% (4.3, 21.1)] or with consumer education and improved supervision [MES 17.8% (15.5, 21.8)] tended to show more promising effects. However, because of the relatively small numbers of interventions tested in each category and the largely overlapping distributions of median effects, none of these differences was statistically significant.

Community case management appears to be an effective multi-component strategy to manage paediatric illness in community settings, resulting in consistently positive improvements in prescribing [MES 27.7% (18.6, 38.8)]. With only one or two interventions in each of the other intervention categories, it is impossible to reliably judge their impact.

Seven intervention studies involved implementation of the WHO-recommended IMCI approach to case management, which was associated with moderate-to-large improvements in prescribing [MES 16% (14.5, 25.1)]. This approach had been implemented in a variety of ways: provider education (two studies); provider education with supervision (one study); provider and consumer education together with supervision (two studies); provider group process quality improvement (one study) and EDP (one study).

DISCUSSION

4.1

Our results indicate that treatment of acute childhood illnesses has remained sub-optimal in all developing and transitional countries over the past 20 years. While there appears to have been improvement in the treatment of acute diarrhoea, as reflected by increased ORS use and reduced use of anti-diarrhoeals, other indicators of appropriate use of medicine changed little or got worse. Improvements in acute diarrhoea treatment in developing countries, particularly Africa, may be a result of donor emphasis; much of the data on diarrhoea treatment in this review comes from donor-sponsored projects. Inappropriate use of antibiotics to treat paediatric infections remains common in all regions and appears to be increasing.

Most studies have been conducted in the public sector. Nevertheless, the data are sufficient to indicate poorer private sector prescribing patterns, which may be owing to a lack of qualified prescribing personnel. However, the difference between sectors remains when studies measuring treatment by unqualified prescribers are excluded from the analysis. Poorer prescribing in the private-for-profit sector has also been described in Zimbabwe and Korea.[16–18] Since a large proportion of paediatric health care is provided by the private and informal sectors in developing countries, poor and infrequently monitored prescribing in this sector is of serious concern.

Nurses and paramedics appear to treat acute diarrhoea more appropriately than doctors, while doctors tend to treat pneumonia better than nurses. Direct comparisons of prescribing patterns by different prescriber types in the same study are rare, but nurses have been reported to prescribe as well as doctors.[19–21] Prescribing for diarrhoea, pneumonia and malaria was consistently worse by community health workers (CHWs) than by nurses or doctors, although not with regard to antibiotics for upper respiratory tract infection. Many community case management programmes have used CHWs to good effect.[22–27] However, such programmes have generally involved training and close supervision of the CHWs with a narrow focus on one type of childhood illness and the provision of very limited medicines for its treatment. Most CHW studies included in this review did not have the benefit of such a supportive infrastructure, which may explain the apparent difference in findings between our review and previous studies. Our findings have serious implications for policy development in many poor countries with limited access to health

services and more frequent task-shifting to lower levels of health personnel or training of community members to treat children.

The number of well designed studies evaluating interventions to improve the treatment of childhood illness is small for a 20-year period, and only 19% of all studies were of methodologically adequate design. Other reviewers have noted the absence of adequate study designs to evaluate intervention effectiveness in low- and middle-income countries.[28] The 15.8% MES improvement in prescribing was moderate but nevertheless slightly higher than that reported in most other reviews.[5] These larger improvements may reflect poorer baseline practices in these settings.

As reported from industrialised countries,[4] most interventions were educational in nature. Single-component interventions, such as dissemination of printed educational material or provider education alone, had an only small-to-modest impact, which has been a consistent finding in other reviews.[5,29–31] Our finding that multi-component interventions were more effective than single-component ones – unlike in some other reviews[32]–might reflect poorer baseline adherence to desired medicines use behaviour and poorer health infrastructure in developing than in developed countries.[33] It is to be expected that the way in which interventions are implemented influences their effectiveness. However, differences in the intensity or effectiveness of the implementation cannot be assessed since these aspects are not well described in published reports.

This is the first review to examine trends over time in the treatment of acute childhood illnesses and the effects of interventions in developing and transitional countries. The relative stability of results over time suggests that the descriptive data have reasonable validity. The lack of improvement in key prescribing indicators suggests that current quality improvement approaches are insufficient. This type of review can also provide some information on global progress in both the public and private sectors, although evidence about the latter is sparse. Such information is not available in demographic and health surveys. Despite the heterogeneity of studies and methods, results suggest that treatment of diarrhoea and malaria according to guidelines is significantly better in the public sector; treatment of respiratory infections remains far from recommended practice in both settings.

It is likely that our search strategy was unable to identify many unpublished reports, especially at country level, since much related work is often done as a part of operational programmes and results are not widely disseminated. The studies identified were often poorly described, which may have resulted in misclassification of study setting or intervention type. No attempt was made to adjust for large differences in the numbers of studies undertaken in different countries or quite substantial differences in sample sizes across studies. Each study was treated equivalently in the analyses with equal weight, regardless of the sample size or within-study variance. Nevertheless, results did not substantially change with sensitivity analyses which included and excluded various types of studies.

Progress in the treatment of acute childhood illnesses in primary care in developing and transitional countries has been mixed, with some improvements over time in the treatment of diarrhoea, but without improvement in malaria treatment or the use of antibiotics for various conditions. Furthermore, there have been few well designed interventions to improve treatment of acute childhood illnesses. There is a clear need for more work to test strategies to reduce continuing high levels of mortality and morbidity from childhood infections.

4.1

REFERENCES

1. Bryce J, Boschi-Pinto C, Shibuya K, *et al.* WHO Child Health Epidemiology Reference Group. WHO estimates of the causes of death in children. *Lancet* 2005;365:1147–52.

2. Black RE, Cousens S, Johnson HL, *et al.* Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet* 2010;375:1969–87.

3. Gove S for the WHO Working Group on Guidelines for Integrated Management of the sick child. Integrated management of childhood illness by outpatient health workers: technical basis and overview. *Bull WHO* 1997;75 (suppl 1):7–24.

4. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. *Lancet* 2003;362:1225–30.

5. Sketris IS, Ingram EML, Lummis HL. Strategic opportunities for effective optimal prescribing and medication management. *Can J Clin Pharmacol* 2009;16:e103–25.

6. Holloway KA. Combating inappropriate use of medicines. *Expert Rev Clin Pharmacol* 2011;4:335–48.

7. Cabana MD, Coffman JM, Bekmezian A, Cho CS, Hersh A, Okumura M, *et al.* Analysis of Published Trials Examining Methods to Change Provider Prescribing Behaviour and Child Health Outcomes. Philip R Lees Institute of Health Policy Studies, Department of Paediatrics, Department of Community Medicine, University of California, San Francisco. Report to the Better Medicines for Children Project, Department of Essential Medicines and Health Products, World Health Organisation, Geneva, Switzerland, 2009. Available at: http://www.who.int/childmedicines/progress/Published_trials.pdf

8. World Health Organization. How to Investigate Drug Use in Health Facilities: Selected Drug Use Indicators. Geneva: WHO, 1993.

9. World Health Organization. Medicines Use in Primary Care in Developing and Transitional Countries: Factbook Summarizing Results from Studies Reported Between 1990 and 2006. Geneva: WHO, 2009; WHO/EMP/MAR/2009.3.

10. International Network for Rational Use of Drugs. INRUD Bibliography. Available at: http://www.inrud.org/Bibliographies/INRUD-Bibliography.cfm

11. Cochrane Effective Practice Practice and Organisation of Care Group. What study designs should be included in an EPOC review and what should they be called? Available at: http://epoc.cochrane.org/epoc-author-resources, 2013

12. Rockers PC, Feigl AB, Røttingen JA, *et al.* Study-design selection criteria in systematic reviews of effectiveness of health systems interventions and reforms: a meta-review. *Health Policy* 2012;104:206–14.

13. Ross-Degnan D, Laing R, Santoso B, *et al.* Improving pharmaceutical use in primary care in developing countries: a critical review of experience and lack of experience. Paper presented at the 1st International Conference on Improving the Use of Medicines, Chiang Mai, Thailand, 1–4 April 1997.

14. Rowe AK, Rowe SR, Holloway KA, *et al.* Does shortening the training on integrated management of childhood illness guidelines reduce effectiveness? Results of a systematic review. *Health Policy Plan* 2012;27:179–93.

15. Holloway KA, Ivanovska V, Wagner AK, *et al.* Have we improved the use of medicines in developing and transitional countries and do we know how to? Two decades of evidence. *Trop Med Int Health* 2013;18:656–64.

16. Trap B, Hansen EH, Hogerzeil HV. Prescription habits of dispensing and non-

dispensing doctors in Zimbabwe. *Health Policy Plan* 2002;17:288–95.

17. Trap B, Hansen EH. Treatment of upper respiratory tract infections– a comparative study of dispensing and non-dispensing doctors. *J Clin Pharm Ther* 2002;27:289–99.

18. Park S, Soumerai SB, Adams AS, *et al*. Antibiotic use following a Korean national policy to prohibit medication dispensing by physicians. *Health Policy Plan* 2005;20:302–9.

19. Ministry of Health, Ethiopia. Assessment of the Pharmaceutical Sector in Ethiopia. Ministry of Health, Federal Democratic Republic of Ethiopia and the World Health Organisation, Addis Ababa, October 2003. Available at: http://collections.infocollections.org/whocountry/en/d/Js6891e/

20. Massele AY, Mwaluko GM. A study of prescribing patterns at different health care facilities in Dar es Salaam, Tanzania. *East Afr Med J* 1994;71:314–16.

21. Ali ASA, Jaffer SB. Assessing quality of patient care in health centres. *Pharmaco Logical Oman* 2005;1:11.

22. Arifeen SE, Hoque DME, Akter T, *et al*. Effect of the integrated management of childhood illness strategy on childhood mortality and nutrition in a rural area in Bangladesh: a cluster randomised trial, *Lancet* 2009;374:393–403.

23. Kouyaté B, Somé F, Jahn A, *et al*. Process and effects of a community intervention on malaria in rural Burkina Faso: randomized controlled trial. *Malar J* 2008;7:50.

24. Nsungwa-Sabiiti J, Peterson S, Pariyo G, *et al*. Home-based management of fever and malaria treatment practices in Uganda. *Trans R Soc Trop Med Hyg* 2007;101:1199–1207.

25. Bang AT, Bang RA, Baitule SB, *et al*. Effect of home-based neonatal care and management of sepsis on neonatal mortality: field trial in rural India. *Lancet* 1999;354:1955–61.

26. Pandey MR, Daulaire NMP, Starbuck ES, *et al*. Reduction in total under-five mortality in western Nepal through community-based antimicrobial treatment of pneumonia. *Lancet* 1991;338:993–7.

27. Fauveau V, Stewart MK, Chakraborty J, *et al*. Impact on mortality of a community-based programme to control acute lower respiratory tract infections: *Bull WHO* 1992;70:109–16.

28. Rowe AK, de Savigny D, Lanata CF, *et al*. How can we achieve and maintain high-quality performance of health workers in low resource settings? *Lancet* 2005;366:1026–35.

29. Wensing M, van der Weijden T, Grol R. Implementing guidelines and innovations in practice: which interventions are effective? *Br J Gen Pract* 1998;48:991–7.

30. Francke AL, Smit MC, De Veer AJE, *et al.*. Factors influencing the implementation of clinical guidelines for health care professionals: a meta-review. *BMC Med Inform Dec Mak* 2008;8:38.

31. Siddiqi K, Newell J, Robinson M. Getting evidence into practice: what works in developing countries? *Int J Qual Health Care* 2005;17:447–54.

32. Grimshaw JM, Thomas RE, MacLennan G, *et al*. Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess* 2004;8:1–72.

33. Jamtvedt G, Young JM, Kristoffersen DT, *et al.*. Audit and feedback: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev* 2006;19:CD000259.

CHAPTER 4.2

ANTIBIOTIC PRESCRIBING FOR CHILDREN IN PRIMARY CARE AND ADHERENCE TO TREATMENT GUIDELINES

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ABSTRACT

Objectives

Antibiotic use is unnecessarily high for paediatric respiratory tract infections (RTIs) in primary care, and implementation of treatment guidelines is difficult in practice. This study aims to assess guideline adherence to antibiotic prescribing for RTIs in children and examine potential variations across Dutch general practices.

Methods

We conducted a retrospective observational study, deriving data on diagnoses and prescriptions from the electronic health records-based NIVEL Primary Care Database. Patients < 18 years of age with a diagnosis of fever, ear and respiratory infections (International Classification of Primary Care codes A03, H71, R72, R75, R76, R78 and R81) during 2010–12 were included. Antibiotics were linked to episodes of illness. Two types of disease-specific outcomes were used to assess adherence to national guidelines regarding antibiotic prescribing choices. Inter-practice variability in adherence was assessed with multilevel analysis.

Results

Half of the episodes with RTIs with restrictive prescribing policy and 65% of episodes with pneumonia were treated with antibiotics. General practitioners prescribed antibiotics for 40% of episodes with bronchitis, even though guidelines discourage antibiotic prescribing. First-choice antibiotics were prescribed in 50%–85% of episodes with selected diseases, with lowest values for narrow-spectrum penicillins. Levels of adherence to guidelines varied widely between diagnoses and between practices.

Conclusions

Most paediatric RTIs in the Netherlands continue to be treated with antibiotics conservatively. Potential aspects of concern are the inappropriate antibiotic prescribing for acute bronchitis and the underuse of some first-choice antibiotics. Continuing progress may be achieved by targeting practices with lower adherence rates to guidelines.

INTRODUCTION

Over 80%of antibiotics in developed countries are prescribed in primary care, mainly for respiratory tract infections (RTIs).[1,2] Antibiotic treatments are often unnecessary, as a majority of RTIs are viral and self-limiting.[3–6] Antibiotic use is especially high among children, and up to a third of their consultations for RTIs in primary care result in an antibiotic prescription.[7,8] This high prescription rate is probably based on concerns about children's susceptibility to bacterial infections and development of secondary complications, even though only a small number of them are at such risk.[9,10]

In response, numerous efforts to optimize antibiotic prescribing have been ongoing with mixed success.[11-13] Since the late 1990s, an overall decrease in antibiotic prescription rates for children has been reported in Europe and the USA, but prescription rates seem to have stabilized now.[14-17]

Clinical practice guidelines have increasingly been used to support physicians in their decision whether or not to prescribe antibiotics and which antibiotics to prescribe.[18] However, the implementation of treatment guidelines for antibiotic prescribing has proved to be difficult in practice.[19,20] Moreover, available evidence has shown marked differences in adherence rates to guidelines across paediatric respiratory and ear infections and substantial variations by practice.[21,22]

A country that has maintained a comparatively low and stable antibiotic use in primary care over the years, with antimicrobial resistance rates that are among the lowest in Europe, is the Netherlands.[23,24] The Dutch College of General Practitioners (NHG) produces and updates evidence-based guidelines.[25–29] To facilitate the decision-making process in daily practice, NHG prescribing advice is included in the physicians' software as electronic prescription decision support.

Guidelines are generally accepted and used by Dutch general practitioners (GPs), but recent research on antibiotic use in the adult population has revealed two potential aspects of concern. Firstly, most antibiotics have been prescribed for uncomplicated RTIs. Secondly, 20%–30% of antibiotic prescriptions have not been for the recommended first-choice antibiotics.[30,31] Similar issues were highlighted in children during earlier evaluations of adherence to RTI guidelines between 1998 and 2008.[32,33]

However, recent studies that measure GPs' adherence to guidelines for antibiotic prescribing in Dutch children and its variation across practices are not available. Our study objectives were to assess guideline adherence to antibiotic prescribing in paediatric fever and ear and respiratory infections in the Netherlands, in terms of both the degree of prescribing per diagnosis and the choice of antibiotics. In addition, we intended to examine potential variations in guideline adherence across different general practices.

Guidelines are generally accepted and used by Dutch general practitioners (GP), but recent research on antibiotic use in adult population has revealed two potential aspects of concern. Firstly, most antibiotics have been prescribed for uncomplicated RTIs.

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Secondly, 20-30% of antibiotic prescriptions have not been the recommended first-choice antibiotics.[30, 31] Similar issues were highlighted in children during earlier evaluations of adherence with RTI guidelines between 1998 and 2008.[32, 33]

METHODS

Datasets and study population

Our data were derived from the NIVEL Primary Care Database (NPCD), which collects data from routine electronic health records of a large and dynamic pool of general practices across the Netherlands.[34]

The participating practices are representative of the Dutch GP population regarding type of practice (single-handed/group), urbanization level and region. The population covered has similar demographic characteristics to the national Dutch population. The database includes information on patient gender, year of birth, dates of consultation and clinical diagnoses, which are coded using the International Classification of Primary Care version 1 (ICPC-1) scheme.[35] In addition, information on prescriptions by physicians is available, coded according to the Anatomical Therapeutic Chemical (ATC) Classification Index.[36]

Practices were included in the study on a per-year basis if at least 70% of consultations included a registered diagnosis, and prescription and morbidity data were registered for at least 46 weeks of the year. Our study population consisted of all patients from these practices, 18 years of age who were diagnosed by their GP with fever or ear or respiratory infection, and had a database history of at least one quartile of a year in 2010, 2011 or 2012. The study was carried out according to Dutch legislation on privacy.[37] The privacy regulation of the NPCD was approved by the Dutch Data Protection Authority. According to Dutch legislation, obtaining informed consent and/or approval by medical ethics committee is not obligatory for observational studies.

Study definitions

First, we matched the ICPC codes used in the database to clinical conditions as specified in the NHG guidelines.[25–29] Seven ICPC codes were sufficiently specific to the diseases described in the guidelines to be included in our analysis: fever (A03); acute otitis media (AOM; H71); strep throat/scarlet fever (R72); sinusitis acute/chronic (R75); acute tonsillitis (R76); acute bronchitis/bronchiolitis (R78); and pneumonia (R81). The wider group of upper RTIs (R74) was not included in our study as there are no specific Dutch guidelines for children on these health conditions. Acute cough (R05) was also excluded, since children's cough may in general be associated with a broader array of conditions other than acute RTIs.

Our analysis was based on constructed episodes of illness that included all the consultations concerning the same health problem within a pre-set time frame. The algorithm used is described elsewhere.[38]

The antibiotics in the study were defined as antibacterials for systemic use (ATC code J01). They were linked to the episodes of illness using prescription date and episode start and stop date. This enabled us to determine whether and which antibiotics were prescribed for a specified diagnosis. In case more than one antibiotic was prescribed during an episode, we used the first prescription for analysis.

We used two types of disease-specific outcomes to examine discrepancies between clinical practice and national recommendations for antibiotic prescribing in children during 2010, 2011 and 2012.[39,40] The first type of outcome measured guideline adherence on whether or not to prescribe antibiotics for the diagnosis. The second type of outcome evaluated the kind of antibiotic prescribed, and was used for the five diagnoses that require antibiotic use according to guidelines (H71, R72, R75, R76 and R81).

Table 1 summarizes the recommendations of the NHG guidelines. Lower values (closer to the minimum score) for the percentages of episodes of fever and bronchitis treated with antibiotics probably represent greater adherence to guidelines. In contrast, higher values (closer to the maximum score) for the percentages of episodes of pneumonia treated with antibiotics may show greater adherence to guidelines. Appropriate values for the percentages of episodes with restrictive antibiotic use (AOM, strep throat, sinusitis and tonsillitis) might vary according to patient age and case mix. The ideal level of appropriate prescribing is therefore not known. However, lower scores probably represent greater adherence to guidelines. Higher values for first-choice antibiotics represent greater adherence to guidelines.

Analysis

We first calculated the annual incidence rates for each diagnosis per 1000 person-years in order to see the extent of the problem and to calculate numerators.

The first group of indicators was computed by dividing the number of ICPC episodes with an antibiotic prescription by the total number of episodes for that ICPC during that year. The second set of indicators was calculated by dividing the number of ICPC episodes prescribed an antibiotic with a specific ATC code by the total number of the ICPC episodes treated with any antibiotic.

To assess inter-practice variability in guideline adherence to antibiotic prescribing, multilevel logistic regression analysis (MLA) was performed for both sets of indicators in 2012. We included only the first consultation for illness for each ICPC and corrected the results for patient age and gender. The size of variation between practices was illustrated by their 95% practice range, within which 95% of practices' adherence falls. Values between 2.5% and 97.5% were used to exclude the bottom and top 2.5% of practices with extreme values, and thereby drop the outliers.

Data on disease episodes treated with antibiotics were analysed with SPSS version 20.0 (SPSS Inc., Chicago, IL, USA), while the variability was analysed using STATA version 13.1 (StataCorp LP, College Station, TX, USA).

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Table 1. Recommended antibiotic prescribing per diagnosis by the Dutch College of General Practitioners[25-29]

National guidelines	Diagnosis and ICPC	Indication for antibiotic prescription	Recommended antibiotics
Fever	Fever - A03	No antibiotics in general	None
Acute otitis media (AOM)	Acute otitis media (AOM) - H71	Restrictive antibiotic use	1st choice: Amoxicillin (J01CA04) 2nd choice: Azithromycin (J01FA10) or Cotrimoxazole (J01EE01)
Acute sore throat	Strep throat/ scarlet fever - R72	Restrictive antibiotic use	1st choice: Phenethicillin (J01CE05) or Phenoxymethylpenicillin (J01CE02) 2nd choice: Azithromycin (J01FA10) if persists: Amoxicillin - clavulanate (J01CR02) or Clindamycin (J01FF01)
Rhinosinusitis	Sinusitis acute/ chronic - R75	Restrictive antibiotic use	1st choice: Amoxicillin (J01CA04) or Doxycycline (J01AA02) 2nd choice: Azithromycin (J01FA10) or Erythromycin (J01FA01)
Acute sore throat	Acute Tonsillitis - R76	Restrictive antibiotic use	1st choice: Phenethicillin (J01CE05) or Phenoxymethylpenicillin (J01CE02) 2nd choice: Azithromycin (J01FA10) if persists: Amoxicillin - clavulanate (J01CR02) or Clindamycin (J01FF01)
Acute cough	Acute Bronchitis/ Bronchiolitis - R78	No antibiotics in general	None
Acute cough	Pneumonia - R81	Antibiotic use	1st choice: Amoxicillin (J01CA04) 2nd choice: Azithromycin (J01FA10)

RESULTS

Overall, 68 general practices in 2010, 133 in 2011 and 101 in 2012 were included in this study. The total number of children being diagnosed with the diagnoses of interest was 10717 in 2010, 22508 in 2011 and 13755 in 2012. Their gender and age distribution did not change substantially over the years: 51% of the patients were boys and their mean age was around 6.8 years during the study period. All incidence rates remained stable over time, ranging from 3 per 1000 person-years for strep throat to around 75 per 1000 person-years for AOM (Table 2).

Figure 1 illustrates GPs' adherence to recommendations on whether or not to prescribe antibiotics for the selected diagnoses during the period 2010-12. Among clinical conditions that require antibiotics, highest antibiotic prescribing rates were seen in pneumonia cases (>65%), followed by strep throat and tonsillitis episodes (50% - 60%) and AOM and sinusitis cases (<50%). For those diagnoses where antibiotics are generally not recommended, 11% of fever cases and >40% of cases with acute bronchitis were prescribed an antibiotic.

Table 3 provides an overview of guideline adherence to first choice antibiotics for diagnoses that require antibiotics. During the period 2010-12, around 85% of AOM cases

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Table 2. Number of episodes and incidence rates (cases/1000 person-years) of fever, ear and respiratory infections during 2010 - 2012

| Clinical condition (ICPC)	ICPC frequency	2010	2011	2012
Fever (A03)	Number of episodes (% of all cases)	2511 (23.4%)	5552 (25.3%)	3425 (24.9%)
	Incidence rates	39.8	44.7	41.9
AOM (H71)	Number of episodes (% of all cases)	4239 (39.5%)	8365 (38.1%)	5547 (40.3%)
	Incidence rates	75.1	73.5	76.8
Strep throat (R72)	Number of episodes (% of all cases)	192 (1.8%)	347 (1.6%)	187 (1.4%)
	Incidence rates	3.3	3.1	3.4
Sinusitis (R75)	Number of episodes (% of all cases)	437 (4.1%)	795 (3.6%)	510 (3.7%)
	Incidence rates	8.1	7.3	7.1
Tonsillitis (R76)	Number of episodes (% of all cases)	1206 (11.3%)	2461(11.2%)	1543 (11.2%)
	Incidence rates	21.3	22.1	22.1
Bronchitis (R78)	Number of episodes (% of all cases)	1510 (14.1%)	2913 (13.3%)	1716 (12.5%)
	Incidence rates	27.2	26.8	24.9
Pneumonia (R81)	Number of episodes (% of all cases)	622 (5.8%)	1551 (7.1%)	827 (6%)
	Incidence rates	10.8	13.7	11.7
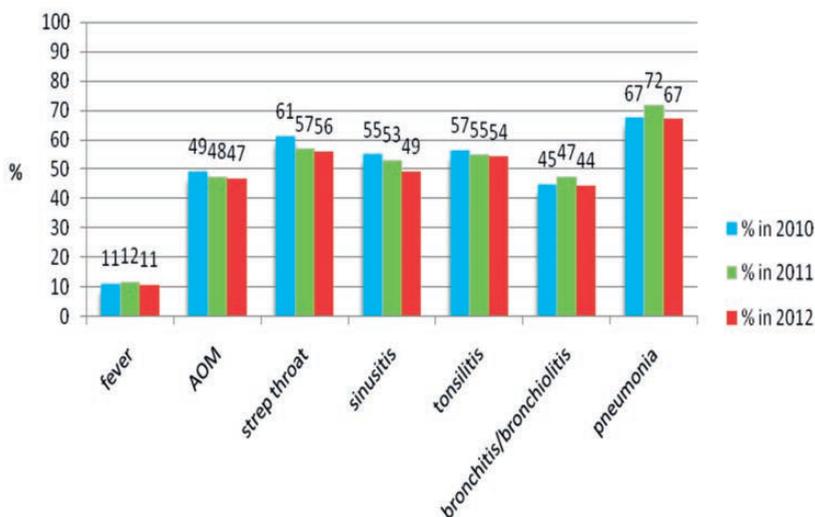
Figure 1. Percentages of infection episodes treated with antibiotics during the period 2010-2012

were treated with first choice amoxicillin and 75% of sinusitis cases with doxycycline or amoxicillin in accordance with guidelines. The recommended antibiotic (amoxicillin) was prescribed in > 60% of pneumonia episodes, while 20% received the non-recommended antibiotics (amoxicillin/clavulanate or clarithromycin). Only 55% - 65% and 50% - 55% of strep throat and tonsillitis cases, respectively, were prescribed first-choice narrow-spectrum penicillins, while 15% - 31% of cases used the non-recommended amoxicillin.

Table 4 illustrates the variance in antibiotic prescribing according to diagnosis between general practices for both restrictive prescribing and choice of antibiotics. Among clinical conditions that require antibiotics, the widest 95% practice range for antibiotic prescribing rates were seen in children with strep throat (16.8% - 88.7%) and sinusitis (19.4% - 77.2%), followed by tonsillitis (30.7% - 6.8%), pneumonia (40% - 84%) and AOM episodes (27.3 - 70%). Large variation in antibiotic prescribing was also found in bronchitis (23.2% - 70.1%), where antibiotics are generally not recommended. Inter-practice variations in adherence to first-choice antibiotics were larger compared with variations in adherence to restrictive prescribing for most diagnoses. The practice variation in the use of first-choice antibiotics was particularly marked in cases of tonsillitis (9.2% - 83.3%), sinusitis (29.5% - 95.9%) and pneumonia (28% - 90.5%).

DISCUSSION

Summary

We found that about two-thirds of patients with pneumonia and about half of the cases with AOM, strep throat, tonsillitis and sinusitis were treated with antibiotics. GPs prescribed antibiotics to >40% of children with acute bronchitis, which is not in accordance with

Table 3. Choice of antibiotics for episodes of ear and respiratory tract infections recommended to be treated with antibiotics 2010-2012

Diagnosis (ICPC)	Antibiotic use	2010 (%)	2011 (%)	2012 (%)
AOM (H71)	in line with 1st choice	84.4	85.7	86
	in line with 2nd choice	4.5	5.8	5.9
	in line with 1st or 2nd choice	88.9	91.5	91.9
	Amoxicillin - clavulanate (J01CR02)	7.1	4.8	5.1
	Clarithromycin (J01FA09)	2.8	2.8	2
Strep throat (R72)	in line with 1st choice	54.5	64.5	64.4
	in line with 2nd choice	9.8	13.2	7.7
	in line with 3rd choice	4.9	3.6	5.8
	in line with 1st or 2nd or 3rd choice	69.1	81.2	77.9
	Amoxicillin (J01CA04)	22.8	14.7	16.4
Sinusitis (R75)	in line with 1st choice	77.9	79	74.8
	in line with 2nd choice	7.1	8.8	12.8
	in line with 1st or 2nd choice	85	87.7	87.6
	Clarithromycin (J01FA09)	7.1	5.7	4
	Amoxicillin - clavulanate (J01CR02)	6.3	4.7	6.8
Tonsillitis (R76)	in line with 1st choice	54.6	53.9	49.9
	in line with 2nd choice	6.8	6.6	7.2
	in line with 3rd choice	6.3	6.3	6.7
	in line with 1st or 2nd or 3rd choice	67.7	66.8	63.9
	Amoxicillin (J01CA04)	25.8	27.6	31.4
Pneumonia (R81)	in line with 1st choice	60.4	66.9	63
	in line with 2nd choice	9.8	8.5	13.3
	in line with 1st or 2nd choice	70.2	73.4	76.3
	Amoxicillin – clavulanate (J01CR02)	14.1	12.8	12
	Clarithromycin (J01FA09)	8.6	6.6	7.3

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guidelines. Between 15% and 50% of cases with any of the diagnoseswere not prescribed their first-choice antibiotics, with adherence being particularly low for narrow-spectrum penicillins. The large inter-practice variations in antibiotic use indicate there is room for improvement with regard to choice of type and indication of antibiotics.

Strengths and limitations

The main strength of our study is that the data come from a large nationwide database, using individual patient records. We were able to link the information on antibiotics to the diagnosis, which helps identify inappropriately treated infections. We report episode-based antibiotic prescription rates, which may affect comparability with studies that applied different definitions, such as contact-based rates, or used a distinct episode construction.

Table 4. Inter-practice variations in paediatric antibiotic prescribing per diagnosis in 2012

Diagnosis - ICPC	Mean %	95% practice range	Number of practices
1. Acute otitis media (AOM) - H71			
1a. Percentage of H71 disease episodes prescribed antibiotics	48.4	27.3 - 70	101
1b. Percentage of H71 disease episodes prescribed antibiotics receiving 1st choice antibiotic	88.3	62.9 - 97.1	101
1c. Percentage of H71 disease episodes prescribed antibiotics receiving 1st choice or 2nd choice antibiotics	93.7	70.7 - 98.9	101
2. Strep throat - R72			
2a. Percentage of R72 disease episodes prescribed antibiotics	55.7	16.8 - 88.7	71
2b. Percentage of R72 disease episodes prescribed antibiotics receiving 1st choice antibiotics*	62.1	62.1 - 62.1	55
2b. Percentage of R72 disease episodes prescribed antibiotics receiving 1st or 2nd or 3rd choice antibiotics*	76.3	76.3 - 76.3	55
3. Sinusitis acute/chronic - R75			
3a. Percentage of R75 disease episodes prescribed antibiotics	47.5	19.4 - 77.2	88
3b. Percentage of R75 disease episodes prescribed antibiotics receiving 1st choice antibiotics	75.8	29.5 - 95.9	80
3b. Percentage of R75 disease episodes prescribed antibiotics receiving 1st or 2nd choice antibiotics	85.2	68.1 - 94	80
4. Acute Tonsillitis - R76			
4a. Percentage of R76 disease episodes prescribed antibiotics	54.8	30.7 - 76.8	100
4b. Percentage of R76 disease episodes prescribed antibiotics receiving 1st choice antibiotics	41.5	9.2 - 83.3	100
4b. Percentage of R76 disease episodes prescribed antibiotics receiving 1st or 2nd or 3rd choice antibiotics	59	14.2 - 92.6	100
5. Acute Bronchitis/Bronchiolitis - R78			
5a. Percentage of R78 disease episodes prescribed antibiotics	45.7	23.2-70.1	99
6. Pneumonia - R81			
6a. Percentage of R81 disease episodes prescribed antibiotics	65.2	40 - 84	94
6b. Percentage of R81 disease episodes prescribed antibiotics receiving 1st choice antibiotics	65.8	28 - 90.5	87
6c. Percentage of R81 disease episodes prescribed antibiotics receiving 1st or 2nd choice antibiotics	78.6	40.9 - 95.2	87

- Low patient numbers per practice (<10 patients per practice).

Nevertheless, RTIs are often acute, short-term diseases for which patients contact the GP only once (as was the case in 74% of our episodes in 2012), so the results are expected to be comparable to contact-based outcomes.

This study was set in GP practices, and it assessed antibiotic prescribing during office hours. Further research on guideline adherence in Dutch out-of-hours (OOH) primary care service is highly relevant to the provision of an overview of national prescription patterns for RTIs.

Our study has several limitations, which are inherent to the use of electronic patient records. Firstly, earlier Dutch studies showed that GPs that participated in NPCD had lower antibiotic prescribing rates than other GPs in their region.[1,41] The network has expanded since then, and we expect that these differences have become smaller.

The second potential bias might be related to GPs' incomplete or incorrect registration of diagnostic codes. The completeness of GP diagnostic coding has greatly improved in recent years, as much attention has been paid to improving routine registration at the national level (such as use of the Electronic Patient Dossier scan to measure the quality of registration, and reimbursement for good registration).[42] However, it is possible that coding differences could have contributed to the wide variation by practice that we observed. If this is the case, a combination of diagnostic codes and available clinical information at the patient level will be an important next step to improve prescribing quality assessment.

In this study no information was retrieved on patients' disease severity, risk factors for complications or inappropriateness of first-choice antibiotics. Moreover, we did not investigate patients' referral or hospitalization rates or GPs' utilization of (rapid) diagnostic tests. These missing details may restrict our ability to determine to what extent observed prescribing practices are justified according to NHG guidelines. It is particularly difficult to set the standards for restrictive prescribing in children. On the one hand, Cochrane reviews suggest that most cases may resolve without antibiotic treatment (82% of sore throats, 80% of acute sinusitis and 78% of AOM).[3-5] On the other hand, antibiotics can be clinically indicated for many of these episodes on the basis of illness severity, bacterial aetiology or a child's age. Thus, other studies from primary healthcare settings with a comparable patient case mix may be useful to better interpret the measured outcomes.

Comparison with existing literature

Our results show lower antibiotic use for paediatric tonsillitis and sinusitis in the Netherlands compared with the period 2002–08, when antibiotics were prescribed in 60% of such cases, while prescribing rates of 50% for AOM stayed the same over time.[33] A recent analysis in the UK displayed a downtrend in the percentage of sore throat episodes treated with antibiotics from 77% to 62% during the 1990s and a tendency to stabilization afterwards, though these levels are still higher than our results.[19] UK percentages of AOM cases linked with an antibiotic were broadly unchanged over the period 1995–2011, with a mean of 83%, which is far above our rates.[20] International research illustrates that antibiotic use for AOM

ranged from 40% to 80% in Norway and the USA, respectively, considering differences in national recommendations and GP practices.[43,44]

In terms of acute bronchitis, we show that a comparable number or fewer cases were treated with antibiotics than before in the Netherlands (52%) and in comparison with other Western countries: Norway (40%); the UK (48%); and the USA (60% - 80%).[30,43,45,46] Such universally high rates of unnecessary prescribing for bronchitis across all ages may imply that daily practices have been substantially resistant to improvement. Explanations may include diagnostic uncertainty about the possible presence of pneumonia, perceived patient (parental) demand for antibiotics, or time pressure.[47] Emerging evidence shows that GPs with training in communication skills and access to C-reactive protein near-patient tests wrote fewer antibiotic prescriptions for acute cough.[48,49] We do not know whether GPs in our study used decision support tools to diagnose acute bronchitis and we were not able to look closely at patients' characteristics to understand the circumstances of such prescribing patterns.

Pneumonia was treated with antibiotics most frequently. Still, up to 30% of cases did not receive antibiotics, which may raise questions about whether such 'under-treatment' practices are safe and unrelated to adverse outcomes. The results suggest that GPs may have restrained from empirical antibiotic prescribing for suspected viral pneumonia. In addition, GPs may be less confident about the diagnosis of complicated pneumonia in primary care, and refer serious cases to hospital immediately. Treatments not initiated by GPs are not included in the database, which might lead to an underestimation of antibiotic use in pneumonia. One Flemish study indicated that patients with pneumonia who did not receive antibiotics were actually referred to the emergency department by GPs working in OOH settings.[50] This is probably true for primary care during office hours as well, but we were not able to investigate referrals or complication rates in

(un)treated pneumonia cases. Nonetheless, a similar antibiotic prescription rate of 67% in paediatric pneumonia cases without reported complications was found in Norway.[43]

About 40% of pneumonia cases were prescribed macrolides or amoxicillin/clavulanate, instead of the first-choice antibiotic, amoxicillin. Due to their broader spectrum of antibiotic coverage, these antibiotics may have been considered a better choice for patients with severe conditions, allergy to penicillin or the risk of bacterial resistance. The estimated prevalence of patients' allergy to penicillins is 0.7% - 8%, while the most common bacterial pathogen of pneumonia in the Netherlands, Streptococcus pneumoniae, is susceptible to penicillin (1% - 3% of resistant strains).[51,52] However, high resistance to amoxicillin among b-lactamase-producing Haemophilus influenzae (17% in 2010) may necessitate other antibiotics.[51] In the main, current prescribing patterns have improved in comparison with amoxicillin use in 26% of pneumonia cases in the Dutch general population in 2001.[31]

Only half of strep throat and tonsillitis cases in our study were treated with recommended narrow-spectrum penicillins (phenethicillin and phenoxymethylpenicillin). Previous

paediatric studies highlighted similar problems of narrow-spectrum antibiotic underuse (63% in the Netherlands and 67% in Norway).[33,43] Again, this may be related to concerns about their limited activity, and broad-spectrum penicillins or macrolides may have been prescribed instead. Another factor for altered prescribing patterns might be the (un)availability of phenethicillin on the Dutch pharmaceutical market, which needs further confirmation. One more explanation for using macrolides may be their administrative convenience and preferential taste compared with the bittertasting phenoxymethylpenicillin, which can affect medication compliance in children.[53]

There were marked variations in antibiotic prescribing by practices in 2012, both for conditions that require antibiotics and for those that do not, such as bronchitis. The variability in the proportions prescribed antibiotics is broadly similar to the figures reported by a UK analysis of a large database of primary care consultations in 2011 (sore throat, 45%–78%; AOM, 63%–97%).[20]

Our findings about inter-practice variations in adherence are in agreement with other reports in Dutch primary care over the past decade.[39,54] An earlier study also indicated greater variations between general practices for first-choice antibiotics than for restrictive antibiotic prescribing. Its authors suggested that the quality of first-choice prescribing was more related to practice characteristics, while the quality of restrictive prescribing was more related to patient population characteristics. As suggested, differences between practices might be attributed in part to variations in diagnostic preferences and coding practices, given the high diagnostic uncertainty of RTIs. Therefore, further consultation-level analysis of practices and GPs' characteristics and patients' demographic and clinical features can improve our understanding of these variations and shape improvement strategies.

Implications for research and practice

RTIs form a major component of GP workload, but they are made challenging by diagnostic and prognostic uncertainties. Our results indicate that most paediatric fever and ear and respiratory infections in the Netherlands continue to be managed conservatively, with relatively low use of antibiotics. These figures could be used as indicators of attainable prescribing rates by other EU countries with higher antibiotic consumption.

In the Dutch context, further improvement efforts need to focus on reducing antibiotic use for acute bronchitis and increasing the use of first-choice antibiotics, especially narrow-spectrum penicillins. Progress may be achieved by targeting practices with lower adherence rates to guidelines. Better-performing practices may help develop suitable antibiotic indicators and set attainable standards for benchmarking purposes.[39] Near-patient testing and communication skills training for GPs seem promising in managing uncertainties for RTI treatment and dealing with patients' concerns and pressure.[55] New potential interventions suited to the local situation can make use of the Dutch professionalized and self-regulated peer group review system. During recent decades, this professional model

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has become a credible healthcare policy instrument in improving formulary adherence and assuring quality patient care.[56,57] We recommend that the effects of guidelines are actively monitored when it comes to antibiotic utilization, adherence, changes in clinical disease patterns and complication rates to demonstrate the benefits and safety of national implementation of prescribing advice.

ACKNOWLEDGEMENTS

REFERENCES

1. Akkerman AE, Kuyvenhoven MM, Verheij TJ, *et al*. Antibiotics in Dutch general practice: nationwide electronic GP database and national reimbursement rates. *Pharmacoepidemiol Drug Saf* 2008; 17: 378–83.

2. Peterson I, Hayward AC. Antibacterial prescribing in primary care. *J Antimicrob Chemother* 2007; 60 Suppl 1:i43–7.

3. Spinks A, Glasziou PP, Del Mar CB. Antibiotics for sore throat. *Cochrane Database Syst Rev* 2013; issue 11: CD000023.

4. Venekamp RP, Sanders SL, Glasziou PP, *et al*. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev* 2015: issue 6: CD000219.

5. Ahovuo-Saloranta A, Borisenko OV, Kovanen N, *et al*. Antibiotics for acute maxillary sinusitis. *Cochrane Database Syst Rev* 2008; issue 2: CD000243.

6. Smith SM, Fahey T, Smucny J, *et al*. Antibiotics for acute bronchitis. *Cochrane Database Syst Rev* 2014; issue 3: CD000245.

7. Hersh AL, Shapiro DJ, Andrew T, *et al*. Antibiotic prescribing in ambulatory paediatrics in the United States. *Pediatrics* 2011; 128: 1053.

8. Akkerman AE, van der Wouden JC, Kuyvenhoven MM, *et al*. Antibiotic prescribing for respiratory tract infections in Dutch primary care in relation to patient age and clinical entities. *J Antimicrob Chemother* 2004; 54: 1116–21.

9. Sharland M, Kendall H, Yeates D, *et al*. Antibiotic prescribing in general practice and hospital admissions for peritonsillar abscess, mastoiditis, and rheumatic fever in children: time trends analysis. *BMJ* 2005; 331: 328–9.

10. Keith T, Saxena S, Murray J, *et al*. Risk-benefit analysis of restricting antimicrobial prescribing in children: what do we really know? *Curr Opin Infect Dis* 2010; 23: 242–8.

11. Goosens H, Guillemot D, Ferech M, *et al*. National campaigns to improve antibiotic use. *Eur J Clin Pharmacol* 2006; 62: 373–9.

12. Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. *Cochrane Database Syst Rev* 2005; issue 4: CD003539.

13. Vodicka TA, Thompson M, Lucas P, *et al*. Reducing antibiotic prescribing for children with respiratory tract infections in primary care: a systematic review. *Br J Gen Pract* 2013; 63: e445–54.

14. Finkelstein JA, Stille C, Nordin J, *et al*. Reduction in antibiotic use among US children, 1996–2000. *Pediatrics* 2003; 112: 620–7.

15. Chai G, Governale L, McMahon AW *et al*. Trends in outpatient prescription drug utilization in US children, 2002–2010. *Pediatrics* 2012; 130: 23–31.

16. Vaz LE, Kleinman KP, Raebel MA *et al*. Recent trends in outpatient antibiotic use in children. *Pediatrics* 2014; 133: 375–85.

17. Schneider-Lindner V, Quach C, Hanley JA *et al*. Secular trends of antibacterial prescribing in UK paediatric primary care. *J Antimicrob Chemother* 2011; 66: 424–33.

18. Stanton N, Francis NA, Butler CC. Reducing uncertainty in managing respiratory tract infections in primary care. *Br J Gen Pract* 2010; 60:e466–75.

19. Malo S, Bjerrum L, Feja C *et al*. Compliance with recommendation on outpatient antibiotic prescribing for respiratory tract infections: the case of Spain. *Basic Clin Pharmacol Toxicol* 2015; 116: 337–42.

20. Hawker JI, Smith S, Smith GE *et al*. Trends in antibiotic prescribing in primary care for clinical syndromes subject to national recommendations to reduce antibiotic resistance, UK 1995–2011: analysis of a large

4.2

database of primary care consultations. *J Antimicrob Chemother* 2014; 69:3423–30.

21. Fierro JL, Prasad PA, Localio AR *et al.* Variability in the diagnosis and treatment of group A streptococcal pharyngitis by primary care paediatricians. *Infect Control Hosp Epidemiol* 2014: 35 Suppl 3: S79–85.

22. Forrest CB, Fiks AG, Bailey LC *et al.* Improving adherence to otitis media guidelines with clinical decision support and physician feedback. *Pediatrics* 2013; 131: e1071–81.

23. Goossens H, Ferech M, Vander Stichele R, Elseviers M. ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; 365: 579–87.

24. Adriaenssens N, Coenen S, Versporten A *et al.* European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe (1997–2009). *J Antimicrob Chemother* 2011; 66 Suppl 6: vi3–12.

25. The Dutch College of General Practitioners (NHG) Guidelines. Acute Otitis Media in Children (M09), 2006. http://assortment. bsl.nl/files/e27c6c2f-8fa3-4f91-9c60-39597b8ecf7d/voorbeeldhoofdstuk.pdf.

26. The Dutch College of General Practitioners (NHG) Guidelines. Acute Sore Throat (M11), 2007. In Dutch. https://www.nhg. org/standaarden/volledig/nhg-standaard-acute-keelpijn.

27. The Dutch College of General Practitioners (NHG) Guidelines. Rhinosinusitis (M33), 2005. In Dutch. https://www.nhg.org/ standaarden/volledig/nhg-standaard-acute-rhinosinusitis.

28. The Dutch College of General Practitioners (NHG) Guidelines. Children with Fever (M29), 2008. http://assortment. bsl.nl/files/e27c6c2f-8fa3-4f91-9c60-39597b8ecf7d/voorbeeldhoofdstuk.pdf.

29. The Dutch College of General Practitioners (NHG) Guidelines. Acute Cough (M78), 2011. https://guidelines.nhg.org/product/acute-cough.

30. van den Broek d'Obrenan J, Verheij TJ, Numan ME *et al.* Antibiotic use in Dutch primary care: relation between diagnosis, consultation and treatment. *J Antimicrob Chemother* 2014; 69: 1701–7.

31. Ong DSY, Kuyvenhoven MM, van Dijk L *et al.* Antibiotics for respiratory, ear and urinary tract disorders and consistency among GPs. *J Antimicrob Chemother* 2008; 62: 587–92.

32. Jansen AGSC, Sanders EAM, Schilder AGM *et al.* Primary care management of respiratory tract infections in Dutch preschool children. *Scand J Prim Health Care* 2006; 24: 231–6.

33. Uijen JHJM, Bindels PJ, Schellevis FG *et al.* ENT problems in Dutch children: trends in incidence rates, antibiotic prescribing and referrals 2002–2008. *Scand J Prim Health Care* 2011; 29: 75–9.

34. Netherlands Institute for Health Services Research. NIVEL Primary Care Database (NIVEL Zorgregistraties eerste lijn). http://www. nivel.nl/en/dossier/nivel-primary-care-database.

35. Lamberts H, Wood M, Hofman-Okkeks I. The International Classification of Primary Care in the European Community, With a Multilanguage Layer. 1st edn. Oxford, UK: Oxford University Press, 1987.

36. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC Classification and DDD Assignment 2013. Oslo, Norway: Norwegian Institute of Public Health. http://www.whocc.no/filearchive/publications/1_2013guidelines.pdf.

37. Dutch Civil Law. Article 7:458. http://www. dutchcivillaw.com/civilcodebook077.htm.

38. Nielen MMJ, Spronk I, Davids R et al. Accountability, Incidence and Prevalence of Health Problems in the Dutch General Practice in 2013. NIVEL Zorgregistraties

eerste lijn, 2013. In Dutch. http://www.nivel.nl/node/3619.

39. van Roosmalen MS, Braspenning JCC, De Smet PAGM et al. Antibiotic prescribing in primary care: first choice and restrictive prescribing are two different traits. Qual Saf Health Care 2007; 16: 105–9.

40. Adriaenssens N, Coenen S, Tonkin-Crine S et al. European Surveillance of Antimicrobial Consumption (ESAC): disease-specific quality indicators for outpatient antibiotic prescribing. BMJ Qual Saf 2011; 20: 764–72.

41. Westert GP, Hoonhout LHF, de Bakker DH et al. Huisartsen met en zonder elektronisch medisch dossier: weinig verschil in medisch handelen. [General practitioners with and without electronic patient records: little variation in medical care]. Huisarts Wet 2002; 45: 58–62. In Dutch.

42. van der Bij S, Khan N, ten Veen P et al. De kwaliteit van elektronische verslaglegging door huisartsen gemeten: EPD-scan regio Twente, eindrapport. [The Quality of Electronic Reporting by GPs. EPD Scan Region Twente, Final Report]. Utrecht: NIVEL, 2013. In Dutch. http://www.nivel.nl /sites/default/ files/ bestanden/ Rapport-Kwaliteit-elektronischeverslaglegging-Twente.pdf.

43. Fossum GH, Lindbaek M, Gjelstad S et al. Are children carrying the burden of broad-spectrum antibiotics in general practice? Prescription pattern for paediatric outpatients with respiratory tract infections in Norway. BMJ Open 2013; 3: e002285.

44. Coco A, Vernacchio L, Horst M et al. Management of acute otitis media after publication of the 2004 AAP and AAFP clinical practice guideline. Pediatrics 2010; 125: 214–20.

45. Gulliford MC, Dregan A, Moore MV et al. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: survey of 568 UK general practices. BMJ Open 2014; 4: e006245.

46. Barnett ML, Linder JA. Antibiotic prescribing for adults with acute bronchitis in the United States, 1996–2010. JAMA. 2014; 311:2020–2.

47. Ackerman SL, Gonzales R, Stahl MS et al. One size does not fit all: evaluating an intervention to reduce antibiotic prescribing for acute bronchitis. BMC Health Serv Res 2013; 13: 462.

48. Calls JW, Butler CC, Hopstaken RM et al. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. BMJ 2009; 338: b1374.

49. Little P, Stuart B, Francis N et al. on behalf of the GRACE consortium. Effects of internet-based training on antibiotic prescribing for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. Lancet 2013: 382: 1175–82.

50. Adriaenssens N, Bartholomeeussen S, Ryckebosch P et al. Quality of antibiotic prescription during office hours and out-of-hours in Flemish primary care, using European quality indicators. Eur J Gen Pract 2014; 20:114–20.

51. Working Group on Antibiotic Policy (SWAB) in the Netherlands. NethMap 2012 and MARAN 2012. http://www.swab.nl/swab/ cms3.nsf/ uploads/ E8426668DC 9BC944C1257A24006252DE/ $FILE/ Nethmap_Maran_2012.pdf.

52. Weiss ME, Adkinson NG. Immediate hypersensitivity reactions to penicillin and related antibiotics. Clin Allergy 1988: 18: 515–40.

53. Steele RW, Thomas MP, Begue RE. Compliance issues related to the selection of antibiotic suspensions for children. Pediatr Infect Dis J 2001; 20: 1–5.

4.2

54. vanDijk L, deJong JD,Westert GP *et al.* Variation in formulary adherence in general practice over time (2003–2007). *Fam Pract* 2011; 28: 624–31.

55. van der Velden AW, Piiper EJ, Kuyvenhoven MM *et al.* Effectiveness of physician-targeted interventions to improve antibiotic use for respiratory tract infections. *Br J Gen Pract* 2012; 62: e801–7.

56. Kringos DS, Klazinga N. Learning from Promising Primary Care Practice Models for the USA: A Case Study From The Netherlands. Academic Medical Centre—University of Amsterdam, Amsterdam for Training and Research Support Centre. 2014. ISSB: 978-0-7974-6098-0.

57. Wammes J, Jeurissen P, Westert G. The Dutch Health System. Radboud University Medical Center. Nederlandse Verenging Artsen Beleid Management Ondezoek. 2014. http://www.nvag.nl/afbeeldingen/2015/nscholing/Netherlands%20Health%20Care%20System%202014%20(PDF).pdf

CHAPTER 4.3

AGE-SPECIFIC ANTIBIOTIC PRESCRIBING AND ADHERENCE TO GUIDELINES IN PAEDIATRIC PATIENTS IN PRIMARY CARE

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ABSTRACT

Background

Most antibiotics in children are used to treat viral and self-limiting conditions. This study aims to compare physicians' adherence to guidelines on antibiotic prescribing in fever, ear and respiratory infections between children in different age groups in the Netherlands.

Methods

Data were used from the NIVEL Primary Care Database. For all paediatric episodes of fever, acute otitis media (AOM), strep throat, sinusitis, acute tonsillitis, acute bronchitis/bronchiolitis and pneumonia in 2012, we determined whether national guidelines were followed in regard to whether an antibiotic was prescribed, and the type of antibiotic.

Results

For diagnoses that generally do not require antibiotics, more prescriptions were found in episodes of adolescents compared to children aged 0-4 and 5-11 years (bronchitis: 52.0% vs. 42.4% and 42.7%, and fever: 16.8% vs. 9.0% and 14.2%). The same was true for diagnoses that require antibiotics (strep throat: 76.5% vs. 55.0% and 49.5%, pneumonia: 71.6% vs. 60.2% and 69.8%, and tonsillitis: 57.8% vs. 54.8% and 49.7%), except for AOM (43.9% vs. 52.4% and 39.6%). First-choice amoxicillin was prescribed more frequently in children aged 0-4 years than in age groups 5-11 and 11-17 years (AOM: 88.0% vs. 83.2% and 81.8%, and pneumonia:74.7% vs. 57.2% and 53.8%). First-choice narrow-spectrum penicillins were prescribed more often in adolescents than in age groups 0-4 and 5-11 years (strep throat: 72.0% vs. 63.6%, and 60.9%, and tonsillitis: 67.9% vs. 33.1 and 45.9%).

Conclusions

Worrisome adherence patterns include high antibiotic rates for bronchitis, particularly in adolescents, and underuse of narrow-spectrum penicillins in the 0-4 years group.

INTRODUCTION

Antibiotics are the most common medicines prescribed for children in primary care.[1] The majority of paediatric antibiotics are used to treat fever, ear and respiratory tract infections (RTI), due to fears of serious bacterial complications, although these conditions are often only viral and self-limiting.[2-4]

With antimicrobial resistance on the rise worldwide, it is needed that physicians prescribe antibiotics in accordance with evidence-based guidelines. International studies suggest that guidelines are theoretically accepted, but not necessarily implemented in daily clinical practice.[5-7] Both the decision to prescribe and the choice of antibiotics are complex processes, which are influenced by a variety of clinical and non-clinical factors.[8,9]

Where relevant, recommendations for antibiotic therapy also consider the age of the patient, along with the illness severity and the presence of underlying diseases. Advice may be age-specific if treatment evidence differs across paediatric age groups. It is well recognized that changes during child growth and development may affect the predisposition, manifestation and course of ear and respiratory infections. For instance, the relationship between age and consultation rates has already been reported; children below five years have respiratory symptoms more frequently and consult their physicians more often than older ones.[10,11] Moreover, RTI aetiologies are frequently age-dependent, and different causative organisms, such as bacteria or viruses, can be found in younger and older children.[12] Published data also show that the prevalence of antibiotic prescribing in childhood varies across age, with preschool children being mostly exposed to antibiotics.[13] However, less is known whether prescribers adhere better to guidelines on antibiotic use for certain age groups across different diagnoses.

Relative to other countries, the Netherlands has low rates of antibiotic use.[14] National guidelines, issued by the Dutch College of General Practitioners (NHG) are generally well accepted by physicians, and integrated in their clinical decision support.[15] Despite recommendations for restrictive antibiotic prescribing for RTIs, recent research has revealed potential areas of concern in primary care.[16] Namely, 40% of acute bronchitis episodes in Dutch children were treated with antibiotics contrary to the advice to avoid them, and first-line narrow-spectrum penicillins were used less than recommended. There is clearly room for improvement, and progress may be achieved by targeting interventions to age groups with potential inappropriate antibiotic exposure. Yet, limited knowledge is available on patterns of antibiotic use in children according to both their age and clinical condition.

Therefore, the purpose of our study was to compare the adherence to guidelines on antibiotic prescribing in fever, ear infections and RTIs between children having different ages. We aimed to determine antibiotic prescribing patterns for children stratified by age, both in terms of degree of prescribing per diagnosis and choice of antibiotics.

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METHODS

Data for 2012 used in this study were derived from the NIVEL Primary Care Database (NIVEL PCD), which collects routine electronic health records from general practitioners (GP) across the Netherlands.[17] The participating GPs constituted a representative sample of the total population of Dutch GPs, and their patients have similar demographic characteristics to the general Dutch population. Practices were included in our study if at least 70% of consultations included a registered diagnosis, and prescription and morbidity data were registered for at least 46 weeks of the year. For the present analysis, 101 practices were available. From these practices, data of all children (0-18 years) with physician-diagnosed fever, ear or respiratory infection (see details below), and a database history of at least one quartile of a year in 2012 were selected.

Our study was carried out according to Dutch legislation on privacy, which instructs that obtaining informed consent and/or approval by medical ethics committee is not obligatory for observational studies.[18] The NIVEL PCD database includes anonymous information on patients, including their year of birth, dates of consultation, clinical diagnoses (coded with the International Classification of Primary Care version 1 - ICPC-1 scheme) and prescriptions (coded with the Anatomical Therapeutic Chemical - ATC Classification Index).[19,20] Children were grouped into three age categories: 0-4,99 years (early childhood), 5-11,99 years (childhood), and 12-17,99 years (adolescents) according to national and UNICEF classification.[21-23]

The latest versions of the NHG guidelines for 1) fever, 2) acute otitis media (AOM), 3) acute cough, 4) acute sore throat and 5) rhinosinusitis were used as pertinent national resources to define fever, ear and respiratory infections and provide guidance on their management.[24-28] Seven ICPC codes were considered sufficiently specific to describe our diagnoses of interest: fever (A03), AOM (H71), strep throat/scarlet fever (R72), sinusitis acute/chronic (R75), acute tonsillitis (R76), acute bronchitis/bronchiolitis (R78) and pneumonia (R81).

The analysis was based on constructed episodes per ICPC that included all the consultations related to the same health problem within a pre-set time frame. The used algorithm is described elsewhere.[16] To determine whether and which antibiotics were prescribed per diagnosis, antibiotics (ATC code J01) were linked to ICPC using prescription date and episode start and stop date. If more antibiotics were prescribed during an episode, the first prescription was used for the analysis.

Table 1 summarizes the recommendations on antibiotic prescribing from the NHG guidelines. Two sets of disease-specific indicators were used to measure the consistency in antibiotic prescribing between guidelines and GPs prescribing patterns for children in 2012. The first set of indicators examined GP adherence to guidelines on whether or not to prescribe antibiotics for the diagnoses. Antibiotics are generally not recommended for fever and bronchitis/bronchiolitis, so less episodes treated with antibiotics (lower indicator

Table 1. Recommended antibiotic prescribing per diagnosis by NHG with child age-specific considerations[24-28]

National guidelines	Diagnosis and ICPC	Indication for antibiotic prescription	Age-specific considerations for antibiotic use	Recommended antibiotics and age-specific considerations
Fever	**Fever** - A03	No antibiotics in general	None	None
Acute otitis media (AOM)	**Acute otitis media (AOM)** - H71	Restrictive antibiotic use	immediate antibiotic treatment: - children < 2 years with bilateral AOM - risk factors for complications (age < 6 months)	1st choice: Amoxicillin (J01CA04) 2nd choice: Azithromycin (J01FA10) or Cotrimoxazole (J01EE01) No age-specific recommendations
Acute cough	**Pneumonia** - R81	Antibiotic use	Risk factor for a complicated course of acute cough (age < 3 months)	1st choice: Amoxicillin (J01CA04) or Doxycycline (J01AA02) if > 8 years old 2nd choice: Azithromycin (J01FA10)
Acute cough	**Acute Bronchitis / Bronchiolitis** - R78	No antibiotics in general	None	/
Rhinosinusitis	**Sinusitis acute/ chronic** - R75	Restrictive antibiotic use	None	1st choice: Amoxicillin (J01CA04) or Doxycycline (J01AA02) if > 8 years old 2nd choice: Azithromycin (J01FA10) or Erythromycin (J01FA01)
Acute sore throat	**Strep throat / scarlet fever** - R72	Restrictive antibiotic use	None	1st choice: Pheneticillin (J01CE05) or Phenoxymethylpenicillin (J01CE02) 2nd choice: Azithromycin (J01FA10) if persists: Amoxicillin - clavulanate (J01CR02) or Clindamycin (J01FF01) No age-specific recommendations

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Table 1. (continued)

National guidelines	Diagnosis and ICPC	Indication for antibiotic prescription	Age-specific considerations for antibiotic use	Recommended antibiotics and age-specific considerations
Acute sore throat	**Acute Tonsillitis** - R76	Restrictive antibiotic use	None	1st choice: Pheneticillin (J01CE05) or Phenoxymethylpenicillin (J01CE02) 2nd choice: Azithromycin (J01FA10) if persists: Amoxicillin - clavulanate (J01CR02) or Clindamycin (J01FF01) No age-specific recommendations

values) mean better adherence to guidelines. In contrast, more episodes of pneumonia treated with antibiotics (higher indicator values) mean better adherence to guidelines. For diagnoses with restrictive antibiotic use (AOM, strep throat, sinusitis and tonsillitis), percentages of episodes treated with antibiotics may vary according to patient case mix, so the ideal indicator values could not be specified. The second set of indicators evaluated what antibiotics were prescribed for each of the five ICPCs that would require antibiotics according to the guidelines (H71, R72, R75, R76 and R81). Higher indicator values mean that more first-choice antibiotics were prescribed and thus represent better adherence to guidelines.

Analysis

At the start, we identified the age-specific advices for antibiotic prescribing in children in the selected NHG guidelines, as presented in Table 1. Next, the incidence rates for each ICPC were calculated per 1000 person-years by dividing the number of episodes by the total number of person-years in a specific age group. The incidence rates were required to quantify the extent of health problems by age categories and obtain numerators for the indicators.

The first sets of indicators for each age group were calculated by dividing the number of ICPC episodes with an antibiotic prescription by the total number of episodes for that ICPC. The second sets of indicators for each age group were calculated by dividing the number of ICPC episodes prescribed an antibiotic with a specific ATC code by the total number of the ICPC episodes prescribed an antibiotic.

Chi-square tests were used to compare differences in the degree of prescribing per diagnosis and first-choice antibiotics between age subgroups. Results with probability level of $p<0.05$ were considered as statistically significant. Data were analyzed with SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

During 2012, the total number of paediatric episodes with fever, ear or RTIs was 13,755. Across all ages, the most frequently reported episodes were related to AOM, fever, acute bronchitis/bronchiolitis and tonsillitis, while pneumonia, sinusitis and strep throat episodes were registered less frequently (Table 2). Table 2 also shows that children in the 0-4 years age group had the highest incidence rates for all studied ICPCs, except for sinusitis. Their most common reasons for GP consultations were AOM, fever and bronchitis/bronchiolitis (199, 135 and 61 episodes per 1,000 person-years, respectively). The 5-11 years age group most frequently reported AOM, tonsillitis and bronchitis (56, 17 and 16 episodes per 1,000 person-years, respectively). Adolescents had the lowest incidence rates for all ICPCs, except for sinusitis. They mostly suffered from tonsillitis, sinusitis and AOM (19, 15 and 14 episodes per 1,000 person-years, respectively).

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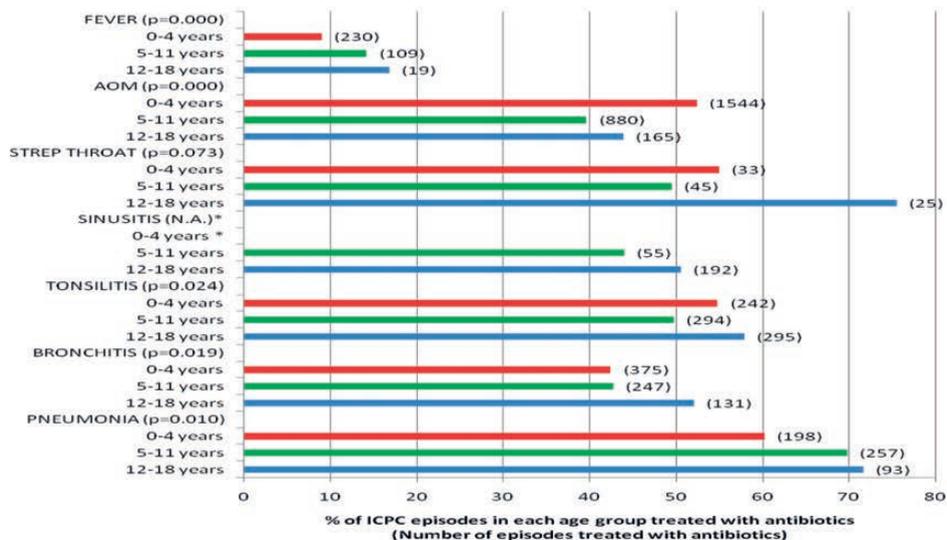
Figure 1. Percentages of episodes of fever, ear and respiratory infections treated with antibiotics according to age groups.
* - Total number of sinusitis episodes in the 0-4 years age group is 5.

Figure 1 presents GPs' adherence to recommendations on whether or not antibiotics were prescribed, stratified by ICPC and age. Overall, an antibiotic prescription was registered in 39.5% of all paediatric episodes, ranging from 36.4% in the 0-4 years age group to 51.3% in the adolescent group. For the majority of clinical conditions that require antibiotics, adolescent episodes were more frequently treated with antibiotics than episodes in the age groups 0-4 years and 5-11 years (strep throat: 76.5% vs. 55.0% and 49.5%, pneumonia: 71.6% vs. 60.2% and 69.8%, and tonsillitis: 57.8% vs. 54.8% and 49.7%). Only for AOM, more episodes in the 0-4 years age group were treated with antibiotics (52.4%) than in the 5-11 years age group (39.6%) and adolescents (43.9%). Since antibiotics are recommended for all children younger than two years with bilateral AOM, a subgroup analysis was done in this age group. It showed that 1008 (55.1%) of 1831 AOM episodes in children aged 0-2 years were treated with antibiotics, compared to 536 (47.9%) of 1118 AOM episodes in children aged 2-4 years, respectively. Concerning sinusitis, the small number of episodes in the 0-4 years age group ruled out any meaningful comparison on antibiotic treatment across age.

For those diagnoses where antibiotics are generally not recommended, more episodes in adolescents were treated with antibiotics as compared to the age groups 0-4 years and 5-11 years (bronchitis: 52.0% vs. 42.4% and 42.7%, and fever: 16.8% vs. 9.0% and 14.2%).

Table 3 shows GP adherence to first-choice antibiotics for diagnoses that require antibiotics, stratified by ICPC and age. AOM episodes in the 0-4 years age group were more frequently treated with first-choice amoxicillin (88.0%) compared to episodes in the 5-11 years age group (83.2%) and adolescents (81.8%). Similarly, 74.7% of pneumonia episodes

Table 2. Fever, ear and RTIs episodes and incidence rates (episodes/1000 person-years) by age groups

Clinical condition (ICPC)	Age category (years)	Number of episodes (% of total episodes in each age group)	Incidence rates as episodes per 1000 person-years
Fever (A03)	0-4	2544 (35.3%)	135.1
	5-11	768 (16.2%)	17.0
	12-17	113 (6.3%)	4.0
	0-17	**3425**	**41.9**
AOM (H71)	0-4,99	2949 (40.9%)	198.7
	5-11,99	2222 (46.8%)	55.7
	12-17,99	376 (21.0%)	13.9
	0-17,99	**5547**	**76.8**
Strep throat (R72)	0-4,99	60 (0.8%)	6.6
	5-11,99	93 (2.0%)	2.8
	12-17,99	34 (1.9%)	1.7
	0-17,99	**187**	**3.4**
Sinusitis (R75)	0-4,99	5 (0.1%)	0.8
	5-11,99	125 (2.5%)	4.2
	12-17,99	380 (21.2%)	15.1
	0-17,99	**510**	**7.10**
Tonsillitis (R76)	0-4,99	442 (6.0%)	34.8
	5-11,99	591 (12.5%)	16.6
	12-17,99	510 (28.4%)	19.2
	0-17,99	**1543**	**22.1**
Bronchitis (R78)	0-4,99	885 (12.3%)	60.5
	5-11,99	579 (12.2%)	15.9
	12-17,99	252 (14%)	9.9
	0-17,99	**1716**	**24.9**
Pneumonia (R81)	0-4,99	329 (4.6%)	24.5
	5-11,99	368 (7.8%)	9.9
	12-17,99	130 (7.2%)	4.7
	0-17,99	**827**	**11.7**

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in the 0-4 years age group was treated with first-choice amoxicillin, while the corresponding figures in the 5-11 years age group and adolescents were 57.2% and 53.8%, respectively. Conversely, more episodes in adolescents were prescribed first-choice narrow-spectrum penicillins than in the age groups 0-4 years and 5-11 years (strep throat: 72.0% vs. 63.6%,

Table 3. AB choice (%) for disease episodes according to age groups

ICPC diagnosis	AB treatment	0-4 years	5-11 years	12-17 years	p-value for differences between age groups (Chi-square test)
H71 (AOM)	in line with 1st choice	88.0	83.2	81.8	p=0.001
N=5547	in line with 2nd choice	5.5	6.7	4.8	p=0.408
	in line with 1st or 2nd choice	93.5	89.9	86.7	p=0.000
	Amoxi-clavulanate (J01CR02)	4.3	6,0	6.7	p=0.119
	Clarithromycin (J01FA09)	1.7	2.4	3.0	p=0.310
R72 (Strep throat)	in line with 1st choice	63.6	60.9	72.0	p=0.641
N=187	in line with 2nd choice	3.0	10.9	8.0	p=0.434 (small numbers)
	in line with 3rd choice	6.0	6.5	4.0	p=0.906 (small numbers)
	in line with 1st, 2nd or 3rd choice	72.7	78.3	84.0	p=0.590
	Amoxycillin (J01CA04)	15.2	19.6	12.0	p=0.695
R75 (Sinusitis)	in line with 1st choice	/*	78.2	74.0	p=0.774 (small numbers)
N=510	in line with 2nd choice	/*	12.7	13.0	p=0.799 (small numbers)
	in line with 1st or 2nd choice	/*	90.9	87.0	p=0.400 (small numbers)
	Claritromycin (J01FA09)	/*	1.8	4.7	p=0.594 (small numbers)
	Amoxi-clavulanate (J01CR02)	/*	7.3	6.8	p=0.888 (small numbers)
R76 (Tonsillitis)	in line with 1st choice	33.1	45.9	67.8	p=0.000
N=1543	in line with 2nd choice	10.3	6.5	5.4	p=0.075
	in line with 3rd choice	5.0	7.1	7.8	p=0.402
	in line with 1st or 2nd or 3rd choice	48.3	59.5	81.0	p=0.000
	Amoxicillin (J01CA04)	46.3	37.4	13.2	p=0.000
R81 (Pneumonia)	in line with 1st choice	74.7	57.2	53.8	p=0.000
N=827	in line with 2nd choice	9.1	17.1	11.8	p=0.040
	in line with 1st or 2nd choice	83.8	74.3	65.3	p=0.002
	Amoxi-clavulanate (J01CR02)	7.6	13.6	17.2	p=0.036
	Clarithromycin (J01FA09)	5.6	8.2	8.6	p=0.036

* - Total number of sinusitis episodes in the 0-4 years age group is 5.

and 60.9%, and tonsillitis: 67.9% vs. 33.1 and 45.9%). Once again, the small number of sinusitis episodes in the age group 0-4 years hampered any meaningful comparison on first-choice antibiotic treatment across age groups. First-choice doxycycline for pneumonia and sinusitis (with an age restriction) was not prescribed in any of the children.

DISCUSSION

In this study, AOM, fever, acute bronchitis/bronchiolitis and tonsillitis episodes were the most frequently reported diagnoses in all children. Stratified by age, the 0-4 years age group had the highest incidence rates for all ICPCs, except for sinusitis which was most prominent in adolescents. There was a considerable variation in antibiotic prescribing rates between different age groups and clinical entities. For the majority of clinical conditions that require antibiotics, adolescent episodes were most frequently treated with antibiotics (strep throat, pneumonia, and tonsillitis). Only for AOM episodes, antibiotic treatment was most common in the 0-4 years age group as a result of higher antibiotic rates in children 0-2 years, which corresponds to guideline recommendations. For the diagnoses where antibiotics are generally not recommended (bronchitis and fever), adolescent episodes were more commonly treated with antibiotics. In terms of first-choice antibiotics, we found two different prescribing patterns according to age groups. GP adherence to first-choice antibiotics (amoxicillin) in AOM and pneumonia episodes was better for the 0-4 years age group. In contrast, first-choice narrow-spectrum penicillins for strep throat and tonsillitis were more commonly prescribed in adolescents, and much less in the 0-4 years age group.

The main strength of the study is that the data come from a nationwide database, which contains information on diagnoses and prescriptions from a relatively large group of children. Further, individual patient records allow the assessment of the role of child age on disease frequencies and antibiotic prescribing patterns. As the age classification can be arbitrary and context-specific, our age groups were chosen for better comparability with literature on RTIs.

As described elsewhere, our study has several limitations which are inherent to the use of electronic patient records, such as quality and completeness of the GP records, as well as historic differences in antibiotic prescribing between NIVEL PCD participating and non-participating GPs.[16,29,30] It is however, expected that recent policy measures have improved and expanded routine data registration practices at national level.[31] Our results can be assumed to represent regular GP consultation behaviour in the Netherlands as much as possible.

In the present study, we did not control for clustering at practice level because of low patient numbers per age group and per diagnosis. But, our previous research on antibiotic prescribing in all children revealed that levels of adherence to guidelines varied largely between practices, especially for first-choice antibiotics.[16]

4.3

The present study showed that the 0-4 years age group had the highest incidence rates for fever, ear and RTIs, except for sinusitis. As expected, younger children were particularly vulnerable to (viral) infections, and visited their GPs more often due to parental concerns, the immaturity of the immune system and the developing anatomy of the airways.[32,33] Conversely, sinusitis was much more common in adolescents than in younger children, whose sinuses are not fully developed. Sinusitis can still occur at early age, although its distinction with other upper respiratory infections (adenoiditis, AOM) is more difficult.[34,35] We observed that AOM, fever and bronchitis/bronchiolitis were the three most common reasons for GP consultations in the 0-4 years age group. Age is a known risk factor for these conditions, and our results are comparable with earlier incidence rates reported in the Netherlands.[21,33,36,37]

In our study, adolescents had the lowest incidence rates for all ICPCs episodes, except sinusitis. But, they received antibiotics more commonly, both for episodes when antibiotics are recommended (pneumonia, strep throat, and tonsillitis), or not recommended (bronchitis, fever). These patterns may reflect adolescents' higher threshold of contacting GPs, and that they only went to visit their GPs when the disease was severe. The varying role of bacterial and viral infections between specific clinical entities and age groups may provide an additional explanation for differences in antibiotic treatment rates across ages.

The most common causes of pneumonia in infants and preschool children are viruses (respiratory syncytial virus, influenza, parainfluenza virus and human metapneumovirus). In older children, viruses as a sole cause of pneumonia are less common, with the exception of influenza.[38] These findings may explain the difference in the proportion of pneumonia episodes treated with antibiotics in the oldest (71.6%) and youngest age groups (60.2%). Also, more frequent referrals of younger children to hospital could perhaps lead to an underestimation of antibiotic use in pneumonia for the 0-4 age group. Besides the general indications for hospitalization, guidelines consider a lower threshold for admitting infants younger than 3 or 6 months of age to hospital because they may need more supportive care and monitoring, and it can be difficult to recognize subtle, sudden deterioration clinically.[26, 39] When a bacterial cause of pneumonia is found, this is *Streptococcus pneumoniae* in most cases.[38] *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are commonly occurring pathogens in older school children and adolescents.[40,41] Such age-specific etiology corresponds to our analysis on GP antibiotic selection for pneumonia by age groups. GP adherence to first-choice amoxicillin for *S. pneumoniae* was highest in children below 5 years (75%). But, over 40% in the other two age groups were treated with amoxicillin-clavulanate or macrolides (azythromycin, claritromycin) instead, possibly targeting the atypical pathogens. Nonetheless, we could not determine to what extent the choice of antibiotics was consistent with the etiologic agents present in the studied age subpopulations.

Only in AOM episodes, children aged 0-4 years were prescribed antibiotics more commonly than other age groups. In a previous Dutch study from 1998, antibiotics were also

prescribed in half of the AOM episodes in children up to five years old.[42] Higher antibiotic prescribing rates in this age group are in line with NHG guidelines that recommend antibiotics in all children under two years with bilateral AOM. At this age, the risk for bacterial infection is higher, as the Eustachian tube is shorter, wider and more horizontal, and provides bacteria with earlier passage from the nasopharynx to the middle ear.[33] GP adherence to first-choice amoxicillin was over 80% for AOM episodes in all age groups, ensuring a good coverage for its main etiological agent - *S. pneumoniae.*

Clinical implications

In general, we cannot regard the antibiotic under- and over-use as wrong treatment decisions in the absence of clinical golden standards, as in some patients, due to clinical characteristics, GPs may have to deviate from the recommendations. However, our results may point out at certain areas where improvements in prescribing behaviour are likely needed.

4.3

In the light of current acute cough guidelines, prescribing antibiotics in over 40% of bronchitis episodes in all children, and more than 50% in adolescents is unexpectedly high. It is difficult to understand the reasons for such practices, except for (adolescents) higher threshold of contacting GPs, resulting in high-risk samples of patients, where pneumonia or secondary bacterial infections cannot be easily excluded. Also, antibiotics may be requested for the persistent cough that usually accompanies bronchitis, even if that is of no benefit for most cases. Our results may be reflected on in the guidelines by promoting near-patients tests to tackle diagnostic uncertainties for lower RTIs where appropriate, and address patients' concerns and pressure for antibiotics.[43]

Furthermore, this study provides an age-specific insight into the concerning issue of underuse of first-choice narrow-spectrum penicillins (pheneticillin and phenoxymethylpenicillin) for sore throat and tonsillitis. GP adherence to prescribing these antibiotics for tonsillitis episodes was twice as low in children aged 0-4 years compared to the adolescents (33% vs. 67%). Instead, over half of tonsillitis episodes in the 0-4 years age group were treated with amoxicillin or macrolides. The palatable taste of these mixtures (compared to bitter testing penicillin liquids) and their administration convenience improve treatment compliance and are likely explanations for this practice.[44,45] Additionally, GPs might be inclined to cover a broader spectrum of bacteria than just *group A beta haemolytic streptococcus (GABHS)* in the youngest age group. On the contrary, higher percentage of tonsillitis episodes (67%) and RTIs episodes (70%) were treated with phenoxymethylpenicillin in the 0-6 years age group in Norway and Sweden respectively.[46,47] Such differences can be explained by the introduction of the quality indicator "80% of antibiotics used to treat RTIs in children aged 0-6 years should be phenoxymethylpenicillin" in the Swedish annual benchmarking of medical treatments and procedures, which may also be considered in the Netherlands.[47]

CONCLUSIONS

Our results showed variation in GP adherence to antibiotic prescribing for fever, ear and respiratory infections in different age groups. Adolescent episodes were most frequently treated with antibiotics for clinical conditions that require antibiotics (strep throat, pneumonia, and tonsillitis), except for AOM, where antibiotic rates were highest in vulnerable young children in line with recommendations. The low adherence to guidelines is worrisome for all children diagnosed with acute bronchitis, and particularly in adolescents, so such antibiotic prescribing patterns need more in-depth analysis. Another area to focus future efforts on is the underuse of first-choice narrow-spectrum penicillins for tonsillitis episodes in the 0-4 years age group. While the Netherlands has relatively low antibiotic consumption rates across all children, age-specific monitoring of antibiotic use can provide an useful perspective when setting priorities for further improvement of actions.

ACKNOWLEDGEMENTS

REFERENCES

1. Sturkenboom MCJM, Verhamme KMC, Nicolosi A, et al. Drug use in children: cohort study in three European countries. BMJ. 2008;337:a2245. doi:10.1136/bmj.a2245.

2. Nash DR, Harman J, Wald ER, *et al.* Antibiotic prescribing by primary care physicians for children with upper respiratory tract infections. *Arch Pediatr Adolesc Med* 2002;156:114-119.

3. Ciofi degli Atti ML, Massari M, Bella A, *et al.* Clinical, social and relational determinants of paediatric ambulatory drug presciptions due to respiratory tract infections in Italy. *Eur J Clin Pharmacol* 2006;62:749-755.

4. Elshout G, van Ierland Y, Bohnen AM, et al. Alarm signs and antibiotic prescription in febrile children in primary care: an observational cohort study. *Br J Gen Pract.* 2013;63(612):e437-44. doi: 10.3399/bjgp13X669158.

5. Vernacchio L, Vezina RM, Mitchell AA. Management of acute otitis media by primary care physicians: trends since the release of the 2004 American Academy of Pediatrics/American Academy of Family Physicians clinical practice guideline. Pediatrics. 2007;120:281–287.

6. Malo S, Bjerrum L, Feja C et al. Compliance with recommendation on outpatient antibiotic prescribing for respiratory tract infections: The case of Spain. Basic Clin Pharmacology Toxicology 2015;116(4):337-42.

7. Hawker JI, Smith S, Smith GE et al. Trends in antibiotic prescribing in primary care for clinical syndromes subject to national recommendations to reduce antibiotic resistance, UK 1995-2011: analysis of a large database of primary care consultations. J Antimicrob Chemother 2014;69(12):3423-3430.

8. Whaley LE, Businger AC, Dempsey PP, et al. Visit complexity, diagnostic uncertainty, and antibiotic prescribing for acute cough in primary care: a retrospective study. BMC Family Practice. 2013;14:120. doi:10.1186/1471-2296-14-120.

9. Lucas PJ, Cabral C, Hay AD, *et al.* A systematic review of parent and clinician views and perceptions that influence prescribing decisions in relation to acute childhood infections in primary care. *Scand J Prim Health Care* 2015;33(1):11–20.

10. Nyquist AC, Gonzales R, Steiner JF, et al. Antibiotic prescribing for children with colds, upper respiratory tract infections, and bronchitis. *JAMA*. 1998;279(11):875-877

11. Uijen JHJM, van Duijn HJ, Kuyvenhoven MM, et al. Characteristics of children consulting for cough, sore throat, or earache. *Br J Gen Pract* 2008;58(549):248-54.

12. Rogers P. Common Respiratory Infections. In: Strasburger VC, Brown RT, Braverman PK, Rogers PD, Holland-Hall C, Coupey SM, editors. Adolescent medicine: a handbook for primary care. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 40-46.

13. Blix HS, Engeland A, Litleskare I, et al. Age- and gender-specific antibacterial prescribing in Norway. *J Antimicrob Chemother.* 2007;59(5):971-6.

14. Adriaenssens N, Coenen S, Versporten A, et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe (1997-2009). *J Antimicrob Chemother* 2011;66 Suppl 6:vi3-12.

15. NHG Guidelines. Dutch College of General Practitioners (Netherlands Huisartsen Genootschap). Avalable at: https://guidelines.nhg.org/

16. Ivanovska V, Hek K, Mantel Teeuwisse AK, et al. Antibiotic prescribing for children in primary care and adherence to treatment guidelines. *J Antimicrob Chemother* 2016;71(6):1707-1714.

4.3

17. Netherlands institute for health services research. NIVEL Primary Care Database (NIVEL Zorgregistraties eerste lijn). http://www.nivel.nl/en/dossier/nivel-primary-care-database

18. Dutch Civil Law, Article 7:458. Avalable at: http://www.dutchcivillaw.com/civilcodebook077.htm

19. Lamberts H, Wood M, Hofman-Okkeks I. The International Classification of Primary Care in the European Community, with a Multilanguage Layer, 1st edition, 1987. Oxford University Press, Oxford, UK.

20. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC Classification and DDD Assignment 2013. Norwegian Institute of Public health, Oslo, Norway. Available at: http://www.whocc.no/filearchive/publications/1_2013guidelines.pdf

21. Uijen JHJM, Bindels PJ, Schellevis FG et al. ENT problems in Dutch children: Trends in incidence rates, antibiotic prescribing and referrals 2002-2008. Scand J Prim Health Care 2011;29:75-79.

22. Bloom B, Jones LI, Freeman G. Summary health statistics for U.S. children: National Health Interview Survey, 2012. Vital Health Stat 2013;10(258). Available at: http://www.cdc.gov/nchs/data/series/sr_10/sr10_258.pdf

23. UNICEF Situation Report # 19 - Sub-regional Libya crisis Date: 29 June 2011. Available at: http://reliefweb.int/sites/reliefweb.int/files/resources/Document1_18.pdf

24. The Dutch College of General Practitioners (NHG) Guidelines. Children with fever (M29), 2008. Available at: http://assortiment.bsl.nl/files/e27c6c2f-8fa3-4f91-9c60-39597b8ecf7d/voorbeeldhoofdstuk.pdf

25. The Dutch College of General Practitioners (NHG) Guidelines. Acute otitis media in children (M09), 2006. Available at: http://assortiment.bsl.nl/files/e27c6c2f-8fa3-4f91-9c60-39597b8ecf7d/voorbeeldhoofdstuk.pdf

26. The Dutch College of General Practitioners (NHG) Guidelines. Acute cough (M78), 2011_Available at:_https://guidelines.nhg.org/product/acute-cough

27. The Dutch College of General Practitioners (NHG) Guidelines. Acute sore throat (M11), 2007. Available at: https://www.nhg.org/standaarden/volledig/nhg-standaard-acute-keelpijn (in Dutch)

28. The Dutch College of General Practitioners (NHG) Guidelines. Rhinosinusitis (M33), 2005. Available at: https://www.nhg.org/standaarden/volledig/nhg-standaard-acute-rhinosinusitis (in Dutch)

29. Akkerman AE, Kuyvenhoven MM, Verheij TJ et al. Antibiotics in Dutch General Practice: nationwide electronic GP database and national reimbursement rates. Pharmacoepidemiol Drug Saf 2008; 17:378-383.

30. Westert GP, Hoonhout LHF, de Bakker DH et al. Huisartsen met en zonder elektronisch medisch dossier: weinig verschil in medisch handelen. [General practitioners with and without electronic patient records: little variation in medical care]. Huisarts Wet 2002;45: 58–62. (in Dutch)

31. van der Bij S, Khan N, ten Veen P et al. De kwaliteit van elektronische verslaglegging door huisartsen gemeten: EPD-scan regio Twente, eindrapport. [The quality of electronic reporting by GPs. EPD scan region Twente, Final Report] Utrecht; NIVEL, 2013. (in Dutch) Available at: http://www.nivel.nl/sites/default/files/bestanden/Rapport-Kwaliteit-elektronische-verslaglegging-Twente.pdf?

32. Buckley RH. In: Behrman RE, Kliegman RM, Jenson HB, editors. Nelson textbook of pediatrics. Philadelphia: W.B. Saunders; 2000. p. 494.

33. Rovers MM, Schilder AGM, Zielhuis GA, et al. Otitis media. Lancet 2004;363:465.

34. Aitken M, Taylor JA. Prevalence of clinical sinusitis in young children followed by primary care physicians. *J Allergy Clin Immunol* 1998;152(3):244–8.

35. Cherry JD, Mundi J, Shapiro NL. Rhinosinusitis. In: Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 7th ed, Cherry JD, Harrison GJ, Kaplan SL, et al (Eds), Elsevier Saunders, Philadelphia 2014. p.193.

36. Van der Linden MW, Westert GP, De Bakker DH, et al. Tweeded Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk: klachten en aandoeningen in de bevolking en in de huisartspraktijk. (Second National Study of diseases and procedures in general practice: complaints and conditions in the population and in general practice). Utrecht/Bilthoven: NIVEL/RIVM, 2004.

37. Venkatesh MP, Weisman LE. Prevention and treatment of respiratory syncytial virus infection in infants: an update. *Expert Rev Vaccines* 2006;5:261–268.

38. Farha T, Thomson AH. The burden of pneumonia in children in the developed world. Paediatric Respir Rev 2005;6:76-82.

39. Le Saux N, Robinson J. Pneumonia in healthy Canadian children and youth: Practice points for management. Paediatrics & Child Health. 2011;16(7):417-420.

40. Heiskanen-Kosma T, Korpii M, Jokinen C, et al. Etiology of childhood pneumonia: serologic results of a prospective, population-based study. Pediatr Infect Dis J 1998;17:986-991.

41. Wubbel L, Muniz L, Ahmed A, et al. Etiology and treatment of community-acquired pneumonia in ambulatory children. Pediatr Infect Dis J 1999;18:98-104.

42. Jansen AGSK , Sanders EAM , Schilder AGM , et al. Primary care management of respiratory tract infections in Dutch preschool children. Scand J Prim Health Care 2006; 24: 231-236.

43. Calls JW, Butler CC, Hopstaken RM, et al. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. BMJ 2009;338:b1374. doi: 10.1136/bmj.b1374.

44. Petursson P. GPs' reasons for «non-pharmacological prescribing of antibiotics. A phenomenological study. Scand J Prim Health Care 2005; 23: 120 – 125.

45. Steele RW, Thomas MP, Begue RE. Compliance issues related to the selection of antibiotic suspensions for children. Pediatr Infect Dis J 2001:20(1):1-5.

46. Fossum GH, Lindbaek M, Gjelstad S et al. Are children carrying the burden of broad-spectrum antibiotics in general practice? Prescription pattern for paediatric outpatients with respiratory tract infections in Norway. *BMJ Open* 2013;3(1). pii: e002285.

47. SWEDRES-SVARM 2013. Use of antimicrobials and occurrence of antimicrobial resistance in Sweden. Solna/ Uppsala ISSN 1650-6332 Available at: http://www.sva.se/globalassets/redesign2011/pdf/om_sva/publikationer/swedres_svarm2013.pdf

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CHAPTER 4.4

CHANGE IN PARENTAL KNOWLEDGE, ATTITUDES AND PRACTICE OF ANTIBIOTIC USE AFTER IMPLEMENTATION OF A NATIONAL INTERVENTION PROGRAMME

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ABSTRACT

Background

Self-medication with antibiotics contributes to the spread of antimicrobial resistance. Nation-wide multifaceted interventions were undertaken in Macedonia in September 2014 to improve antibiotic use.

Objectives

This study assessed the parental knowledge and attitudes about antibiotics, and self-medication practices in children, and evaluated the impact of interventions on these parameters.

Methods

Pre-post intervention surveys were conducted in May 2014, May 2015 and May 2016 in three administrative regions in Macedonia. Data were collected by interviewing parents of children younger than 15 years through a questionnaire. The analysis of knowledge, attitudes and antibiotic use involved descriptive quantitative statistics. The effects of interventions were assessed by a logistic and linear regression analysis.

Results

Data from 1203 interviewees showed that 80% of parents knew that antibiotics could kill bacteria, while 40% believed antibiotics could kill viruses. One third of parents expressed potential dissatisfaction with doctors who would not agree with them on antibiotic use. More parents received information about not taking antibiotics unnecessary after the interventions, but the rates decreased one year later. At baseline, 20% of the parents and 10% of the children who received antibiotics in previous year, took them without prescriptions. Parental self-medication rates did not change over time, while children rates decreased only in 2015.

Conclusion

The insignificant and short-term effects of the interventions demonstrate that interventions need to be implemented for a longer period of time, at a large scale, with active health providers' engagement, and accompanied by inspections to promote appropriate use of antibiotics and discourage self-medication.

INTRODUCTION

Irrational use of antibiotics includes self-medication by patients, which means taking antibiotics without consulting a medical doctor, either by getting antibiotics at the pharmacy without a prescription, or by using leftover antibiotics from previous treatments.[1] Use of antibiotics without medical guidance is inappropriate, as it may promote antimicrobial resistance (AMR) and cause adverse effects, drug toxicity, masked diagnoses, and superinfections.[2-4] Children are particularly prone to high rates of antibiotic use due to greater frequency of respiratory tract infections (RTI), and (often unnecessary) concerns about possible complications.[5-7]

Self-medication with antibiotics is an existing problem worldwide, mainly in developing countries. However, it has been also documented in a substantial number of European countries and the United States, in particular for cold and upper respiratory tract symptoms (URTI).[1,8-10] Research from developed countries indicates that self-medication with antibiotics is driven by a variety of determinants on different levels.[11] Individual attitudes toward use of antibiotics, poor knowledge of indications for use of antibiotics, and non-awareness of AMR have all been associated with higher rates of self-medication.[11] Over the counter (OTC) sales of antibiotics by pharmacists are often related to customer's pressure, weak regulatory mechanism, and professional conflicts of interest.[11-14] Cultural and socioeconomic factors, as well as disparities in health care systems (i.e. prescribing patterns, reimbursement policies, access to health care, and drug dispensing policies) also play a role.[11,15]

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As a result, the prevalence of self-medication in, for example, the European Union (EU) varies between 2 and 20 per 100 respondents among different countries, with the highest rates in eastern and southern European countries, and the lowest in northern and western European countries.[16] Given the complexity of the phenomenon of self-medication, simultaneous employment of multiple different interventions is needed to target all stakeholders. Multifaceted managerial and training strategies have proved effective in changing suboptimal prescribing practices.[17,18] As part of a broader strategy, promising interventions at population level include mass education campaigns on the rational use of antibiotics that change public attitudes and perhaps also behaviour, especially in countries with high antibiotic use.[19-21]

In contrast to the EU where self-medication with antibiotics has regularly been measured in Eurobarometer surveys, antibiotic use including self-medication has not been systematically studied in the non-EU countries in South-Eastern Europe.[16,22] Yet, recent studies have raised awareness of high resistance levels and inappropriate antibiotic use, including widespread, but under-reported OTC sales of antibiotics across this region.[23,24]

This may be of particular relevance in the Republic of Macedonia, where a recent study revealed that 18% of the respondents self-medicated themselves with antibiotics for URTI, and public knowledge on antibiotics was relatively low.[25] The Macedonian Government

has made fresh efforts to decrease the overuse of antibiotics by implementing nation-wide multifaceted antibiotic interventions.[26,27] The impact of these interventions on public knowledge and behaviour regarding antibiotics has not been assessed so far, while this might provide a useful guidance for future activities on the improvement of appropriate antibiotic use. Since children are an important target group with common RTI in need of appropriate treatment, and because the occurrence of AMR must be limited, part of the interventions in Macedonia were aimed at parents. This study aimed to: 1) assess the level of parental knowledge, attitudes and behaviors regarding use of antibiotics for RTI in children (and parents), and 2) evaluate the impact of national interventions on parental awareness and practice of antibiotic use.

METHODS

Setting

The Republic of Macedonia is a middle-income country with 2 million inhabitants, situated in the Balkan peninsula in Southeast Europe. The country has an universal access to healthcare, and its citizens register with primary healthcare doctors/paediatricians where they get free medical consultations.[28,29] National evidence-based guidelines have been developed for the management of most diseases, including RTIs.[30] Antibiotics are regulated as prescription-only medicines, and those on a positive list are reimbursed by the Health Insurance Fund.[31] Macedonia adopted its national AMR action plan in 2011, and conducted several interventions across the country to improve antibiotic use in 2014/2015, as described in Box 1a.[26,27]

Design

The impact of the national interventions has been evaluated through three community-based surveys, conducted in May 2014 (baseline), 2015 (post-1) and 2016 (post-2). The timeline of the three measurement points and related interventions are presented in Box1b.

The study was conducted in three out of eight administrative state regions (East Region, Southeast Region and Vardar Region), inhabited by half a million people (about 25% of the country population).[32] Respondents were recruited consecutively on randomly assigned days near shops and markets, pharmacies, paediatric consultation offices, schools, kindergartens and playgrounds in both urban and rural areas. Study participants were defined as parents with at least one child below 15 years of age. Medical professionals, more than one member of the same family, and inhabitants from other regions were excluded from the survey. A sample size of 400 respondents was determined using a 95% confidence level and 5% margin of error for an assumed 50% response distribution for self-medication.[33]

Box 1a: Description of national antibiotic interventions with a multifaceted approach during 2014-2015 [26, 27]

The following regulatory and health education strategies were introduced to raise awareness on adequate antibiotic use and danger of AMR:

1. Nation-wide mass media (TV) campaign on appropriate antibiotic use

- consisted of TV spots and health experts' video messages, broadcasted on national channels, with a key slogan: "Antibiotics are not your food!"
- conducted October – December 2014
- managed by the Ministry of Health

2. Kindergarten seminars for parents on RTI and appropriate antibiotic use

- consisted of 44 sessions with 1500 parents
- conducted September – November 2014 in 17 municipalities (five from our survey)
- managed by the National Drug Agency

3. Seminars for health workers on RTI management and antibiotic prescribing

- consisted of 21 sessions with 700 participants
- conducted October – December 2014 in 8 municipalities (two from our survey)
- managed by the Institute of Public Health and Health Insurance Fund

4. Regulations to further restrict antibiotic OTC sales in pharmacies

- amendment added on criminal provision/fines for OTC sales of prescription-only-medicines to the Law on Medicines
- put in force in May 2015

Box 1b. Timeline of surveys and interventions during 2014-2016
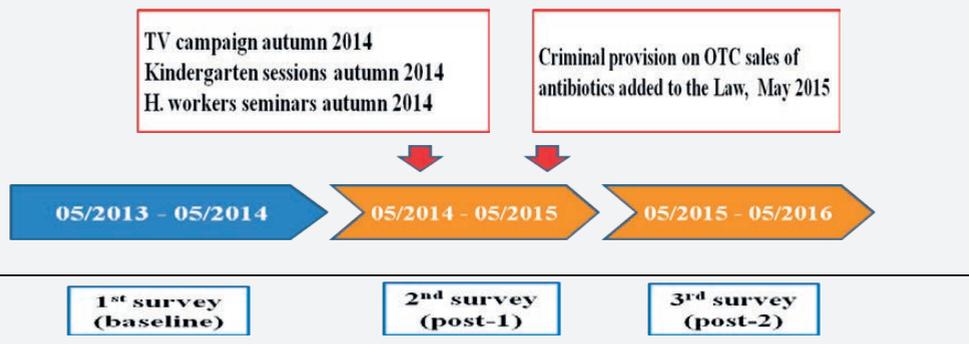
Box 1. The description and timeline of antibiotic interventions in the Republic of Macedonia.

Data collection

Data were collected through a structured questionnaire developed with validated questions from other studies, including the European Commission's Eurobarometer 407 on AMR.[22] The questionnaire was translated from English into national language, pretested on a small pilot population and finalized in early 2014. The questionnaires were distributed to trained volunteers during three consecutive years who conducted face-to-

face interviews. Respondents' verbal consent was obtained at the beginning of the survey. The confidentiality of the information was maintained by excluding personal identifiers, and all the data collected were processed and analyzed anonymously. The interviewees did not receive any financial or other compensation for participation in the study. The surveys were performed under the approval of the Ethics Committee of the Faculty of Medical Sciences in Stip, Macedonia.

The questionnaire consisted of 33 questions divided broadly into three sections: 1) socio-demographic characteristics of parents and their youngest children, 2) knowledge, attitudes and beliefs regarding antibiotic use and RTI, and 3) self-reported practices related to antibiotic use, including self-medication, in the preceding year. Answers to questions were either "yes, no, don't know", or multiple-choice answers. Commonly used terms to describe infectious conditions were used without providing a particular definition of the term, e.g., cold, sore throat, flu, etc. The questionnaire is included as a supplementary file.

Analysis

Questionnaire data were checked and coded identically in all three surveys. Collected data were recorded in Excel (Version 2007, Microsoft Office; USA), and the descriptive analysis was done in SPSS (Version 20; SPSS Inc., Chicago, IL, USA). Categorical data were summarized and reported as frequencies and simple proportions. Continuous data were summarized and reported as medians or means.

Differences in participants' socio-demographic characteristics between 2014 and 2015, and 2014 and 2016 were tested with the χ2 test or Fisher's exact test for categorical variables, and with the unpaired Student's *t* test and Mann-Whitney test for continuous variables. In the section on knowledge, "don't know" replies were grouped with the incorrect answers.

The effects of the interventions were assessed by comparing the differences in knowledge, attitudes and behaviour between 2014 and 2015, and between 2014 and 2016, using a logistic and linear regression analysis in Stata (version 14, StataCorp., TX, USA). In the model, years 2015 and 2016 were entered as dummies and year 2014 as a reference variable. The results were corrected for the differences in samples' socio-demographic composition. The statistical significance was determined at $p<0.05$.

RESULTS

Participant characteristics

In total, data of 1203 parents and their (youngest) children below 15 years of age were analyzed over the three years study period (n=403 in 2014, n=400 in 2015, and n=400 in 2016). Their socio-demographic characteristics were similar over the years, as summarized in Table 1. The average parents' age at baseline was about 33 years, and three-quarters of

Table 1. Study participants and their children's characteristics: demography and information related to antibiotics in the previous year, 2014 - 2016

Characteristics	2014 (n=403)	2015 (n=400)	2016 (n=400)
PARENTS			
Mean age in years (SD)	33 (6.4)	32.3 (6.3)	32.5 (6.5)
Female gender	308 (76.4%)	312 (78%)	298 (74.5%)
Minorities	51 (12.7%)	45 (11.2%)	51 (12.8%)
Urban residents	290 (72%)	273 (68.3%)	312 (78%)*
Married	381 (94.5%)	381 (95.3%)	371 (92.8%)
University degree	143 (35.5%)	147 (36.8%)	167 (41.8%)
Employed	277 (68.7%)	284 (71.3%)	297 (74.3%)
YOUNGEST CHILD IN FAMILY			
Median age in years (IQR)	5.9 (3;10)	4.5 (2.5;8) *	5 (2.5;9)
Younger than 5 years	195 (48.4%)	210 (52.5%)	196 (49%)
Female gender	181 (44.9%)	206 (51.5%)	186 (46.5%)
In kindergarten	105 (26.1%)	129 (32.5%)	131 (32.8%)*
With siblings (<18years)	181 (44.9%)	199 (49.8%)	176 (44%)

* p<0.05

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the respondents were females. More than 90% of parents were married, and lived in urban areas. Around half of the children in all the surveys were below 5 years of age.

Knowledge of antibiotics

Parental knowledge of antibiotics was tested with four statements about the nature and effectiveness of antibiotics and the risks associated with their unnecessary use (Table 2). At baseline, 82% of parents knew that antibiotics were effective against bacteria, and their percentage rose slightly over the years. Around 30% of parents understood that antibiotics were not effective against viruses in 2014, with a 9% (statistically insignificant) improvement over the years. Similar or higher percentages of parents expected that colds and flu improve faster with antibiotics (cold: 38%, 37% and 38%, and flu: 45%, 40%, and 48% in 2014, 2015 and 2016 respectively). In 2014, 76% of the respondents were aware of the possibility that antibiotics become ineffective if they are used inappropriately, and 85% knew about antibiotics' side effects. Both percentages increased in 2015, but dropped in 2016 lower than at baseline. The average number of correct answers out of 4 increased significantly from 2.7 to 2.9 between 2014 and 2015, and dropped again to 2.7 in 2016.

Attitudes towards antibiotics

Figure 2 presents parental attitudes towards antibiotic prescribing and use. At baseline, 20% of parents preferred to give antibiotics - even if unnecessary - to their children over wait and see if the symptoms would resolve spontaneously. Around 30% of parents

Table 2. Parental knowledge on antibiotics 2014 - 2016

Statements on antibiotics with correct answers	2014 (n=403)	2015 (n=403)	2016 (n=400)
1. Antibiotics kill bacteria	330 (81.9%)	336 (84.0%)	336 (84.0%)
Answer: Yes			
2. Antibiotics kill viruses	124 (30.8%)	157 (39.3%)	158 (39.5%)
Answer: No			
3. If used inappropriately, antibiotics may become ineffective	307 (76.2%)	326 (81.5%)	290 (72.5%)
Answer: Yes			
4. Antibiotics may have side effects	342 (84.9%)	359 (89.8%)	314 (78.5%)*
Answer: Yes			

* p<0.05

were unsatisfied if no antibiotic was prescribed to their children when they considered it necessary, and similar percentage would seek another doctor as a result of that. About a quarter of parents would stop the antibiotic treatment when the symptoms of their child improve. The percentages of parents holding these attitudes did not change significantly over time.
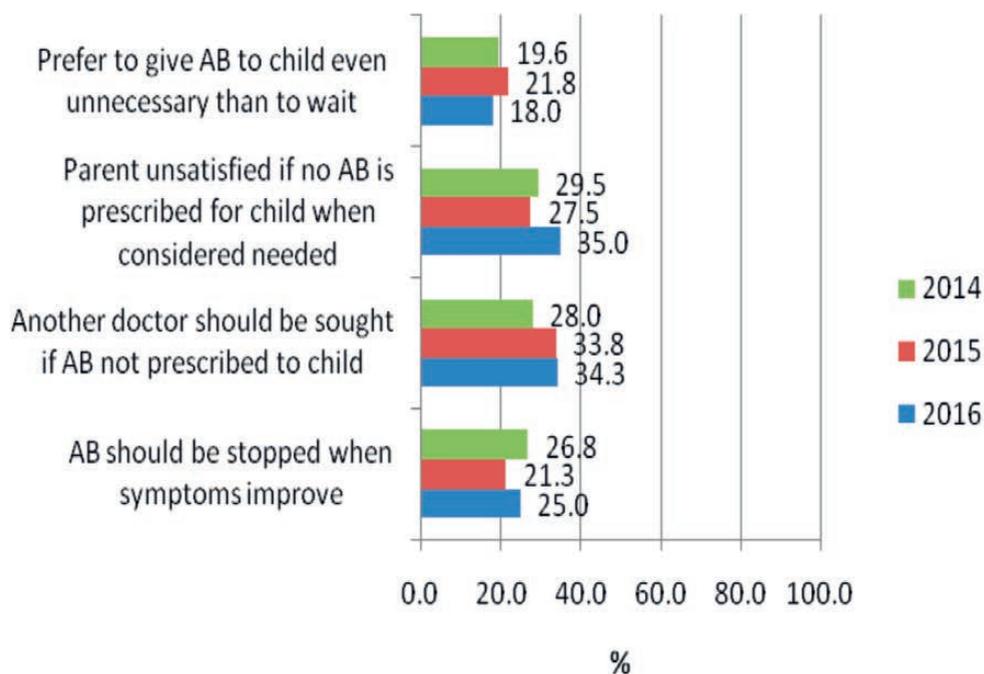
Figure 2. Parents' attitudes towards AB prescribing and use, 2014 - 2016

Information and appropriate use of antibiotics

At baseline, 65% of parents received information about not taking antibiotics unnecessary in the previous year. There was a significant increase to 78% in 2015, but a decrease one year later (63%).

At baseline, 79% of children were given antibiotics in the last year, while the corresponding figures were 84% in 2015 and 70% in 2016 (Table 3). In 2014, 89% of children that received antibiotics, were given antibiotics prescribed by doctors, while 6% and 4% were given antibiotics that were either purchased OTC, or kept at home from previous treatments, respectively. The percentage of children that were given antibiotics with prescriptions rose (significantly) to 95% in 2015, but decreased to 91% in 2016.

As for the parents, half of them took antibiotics in the last years at baseline, similarly to 2015 and 2016. In 2014, around 79% of those that used antibiotics took them with prescriptions, while the rest of the parents self-medicated themselves either with OTC (9%) or left-over (11%) antibiotics. The ways of obtaining antibiotics by parents did not change over the years.

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Table 3. Patterns of antibiotic provision for children and parents in the last year, 2014-2016

	2014 (n=403)	2015 (n=400)	2016 (n=400)
CHILDREN			
Antibiotic use in last year	n=319 (79.2%)	n=334 (83.5%)	n=279 (69.0%)*
Sources of antibiotics for children that took antibiotics in the last year			
Doctor's prescription	283 (88.7%)*	317 (94.9%)	254 (91.0%)
OTC sale in pharmacies	18 (5.6%)	4 (1,2%)	12 (4.3%)
Left-over AB at home	14 (4.4%)	13 (3.9%)	12 (4.3%)
Don't remember / Don't know	4 (1.3%)	0 (0%)	1 (0.4%)
PARENTS			
Antibiotic use in last year	n=203 (50.4%)	n=211 (52.8%)	n=201 (50.3%)
Sources of antibiotics for parents that took antibiotics in the last year			
Doctor's prescription	160 (78.8%)	167 (79.1%)	155 (77.1%)
OTC sale in pharmacies	18 (8.9%)	19 (9.0%)	20 (10%)
Left-over AB at home	22 (10.8%)	25 (11.8%)	26 (12.9%)
Don't remember / Don't know	3 (1.5%)	0 (0%)	0 (0%)

p<0.05

DISCUSSION

In this study among parents of children under age 15, 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. Less than 40% erroneously believed that antibiotics were effective against viruses and common URTIs. One third of the parents expressed potential dissatisfaction with doctors who would not agree with them on antibiotic use. At baseline, 20% of the parents and 10% of the children who received antibiotics in previous year, used OTC or left-over antibiotics. There were two short-term effects of the interventions in 2015: a significant increase in the percentage of parents stating to be informed about not taking antibiotics unnecessary, and a significant drop in the percentage of children self-medicated with antibiotics. Parental irrational patterns of antibiotic provision did not change during or after any of the interventions.

Despite relatively large sample sizes and diverse mix of participants, our study findings should be interpreted within the context of several limitations. First, the study was confined to the southeast and central regions in Macedonia with their own socio-demographic and health particularities, thereby possibly limiting the generalizability of the results to the whole country. However, a recent baseline study conducted in one western town in Macedonia mainly highlighted the overarching national healthcare culture and infrastructure.[34] Second, the results are based on self-reported practices, which may not represent the actual behavior, as they have the potential for recall bias, underreporting, or overreporting. Future research should therefore combine other methods (i.e. focus groups, observational studies, and pharmacy exit interviews) to validate and triangulate self-reported data.

The parental knowledge of antibiotics in our study is similar to average knowledge levels in adults across the EU, as reported by the Eurobarometer surveys. Yet, the proportion of those taking antibiotics in the previous year in Macedonia (50%) is much higher (EU average: 34%).[16,22] Likewise, our findings on parental non-prescribed antibiotic use are comparable to the countries with highest levels of self-medication in the EU, such as Greece (21%) and Romania (16%).[16] Our data show lower prevalence of self-medication with antibiotics in children compared to other studies. These studies found, for example that 12-23% of parents in Greece used non-prescribed antibiotics to treat symptoms in their children versus 36% of parents in China, and 42% of parents in Mongolia.[35-38] For many developed countries, however, the non-prescribed use of antibiotics in children is less often described in the literature, probably because of its infrequency in such contexts. Besides, findings may vary considerably among countries, because of different study methodologies, or differences in the disease burden and health-care delivery systems.

Although the non-prescription sale of antibiotics is illegal in Macedonia, our results show that pharmacies were an important source of antibiotics for self-medication. Such

antibiotic dispensing malpractice calls for more in-depth exploration of the OTC sales in the national context. Community pharmacists are the first point of contact in the health system, and are thereby, crucial in demystifying to patients the need to use antibiotics for minor ailments. Thus, more structured education for pharmacists, their active engagement in public health interventions, and innovative pharmacy service remuniration based on patient care may be effective strategies to improve antibiotic use in the community.[39]

Keeping leftover antibiotics at home is another important factor linked to the non-prescription use of antibiotics.[1,11,40] We found that the percentages of children and parents self-medicated with home-stored antibiotics were as high as those using OTC purchased antibiotics. This practice has also been described in other European countries (Austria: 5%, Estonia and Latvia: 4%).[22] A global survey found that living in a country where antibiotics are dispensed in fixed-count packs rather than as the exact numbers of pills was a strong predictor of the use of left-over antibiotics.[11] Stopping treatment earlier than prescribed is another source of leftover antibiotics.[41] In our study, 25% of parents believed that antibiotics should be stopped when symptoms improve. This practice can increase the risk of relapse, the development of resistant pathogens and produces leftovers for future self-medication. Thus, dispensing of antibiotics in exact numbers of doses should be recommended in addition to the development of information campaigns addressing the importance of completing antibiotic treatment, and discarding any leftover drugs.

Our results show that the national media campaign can lead to elevated percentage of parents informed about not taking antibiotics unnecessary. This is important, because surveys done after campaigns showed that those exposed to the campaigns were more likely to agree with standards of appropriate use of antibiotics and were less likely to expect antibiotics.[42] However, the available literature demonstrates that educating the public about the differences between infections caused by viruses or bacteria seems difficult. For example, in France, after successive campaigns over 5 years, 54% of the public still did not know that most upper respiratory tract infections are of viral origin and do not need treatment with antibiotics.[43] These findings mirror those in our study: parental knowledge on the use of antibiotics for viral infections did not significantly improve after the media campaign, and may need to be addressed with better targeted education on specific indications for antibiotics (the lack of need for antibiotics for treatment of cold and flu, for example) rather than on the use of antibiotics in general.

Our post-intervention data also revealed the short-term sustainability of the media campaign, as both improvements in terms of more informed parents about not taking antibiotics unnecessary, and less children self-medicated with antibiotics tended to revert to previous levels after 2015. This suggests the need for continuous educational initiatives to improve knowledge, or at least of longer duration or repetitive actions, followed by regular evaluation of their effects and fine-tuning of key messages to the public.

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It was also evident that the introduction of legal penalties to further control the OTC dispensing of antibiotics in 2015 did not immediately reduce self-medication practices by parents and children in 2016. Perhaps combining the regulatory measures with strong enforcement would be more beneficial to ultimately reduce the possibility of getting antibiotics from the pharmacies without prescription. Earlier interventions that succeeded in reducing the OTC antibiotic sales may offer some lessons. Sales of antibiotics without prescription in Zimbabwe decreased after the law against OTC sales was strictly enforced. Fear of losing their license was a factor mentioned by some pharmacists for their compliance to the rules.[44] Several Latin American countries have also implemented policies to enforce existing laws of restricting consumption of antibiotics only to patients presenting a prescription. After the regulations took place, an immediate and moderate decrease in the level of antibiotics consumption was seen in Colombia, Brazil and Mexico.[45,46] The effect was immediate and stronger in Chile, where the prohibition of OTC sales of antibiotics was accompanied by a simultaneous public education campaign and involvement of pharmacists. However, these actions were not sustained and the consumption in Chile started to increase again, which highlights the importance of multifaceted campaigns repeated over several years.[47] Implementing monitoring systems to track the implementation of the regulation in terms of consumption, such as part of our data, AMR and infections rates shall also be core components of a more comprehensive strategy.

CONCLUSIONS

A multifaceted intervention was performed for the first time in Macedonia, addressing the multiple factors that influence antibiotic use. The partial and short-term effects of the intervention on self-medication practices call for similar media campaigns to be implemented for longer period of time, at a large scale and with active providers' engagement to promote more appropriate use of antibiotics and discourage self-medication practices in the community. The intervention also provides a starting point for enforcement of certain aspects of dispensing practices, such as inspection of OTC sales, and implementation of regulatory measures that limit the number of antibiotic tablets dispensed in pharmacies.

REFERENCES

1. Grigoryan L, Haaijer-Rysjamp FM, Burgerhof JG, *et al*. Self-medication with antimicrobial drugs in Europe. *Emerg Infect Dis* 2006;12(3):452-459.

2. Thomas JK, Forrest A, Bhavnani SM, *et al*. Pharmacodynamic evaluation of factors associated with the development of bacterial resistance in acutely ill patients during therapy. *Antimicrob Agents Chemother* 1998;42:521–527.

3. Guillemot D, Carbon C, Balkau B, *et al*. Low dosage and long treatment duration of beta-lactam: risk factors for carriage of penicillin-resistant *Streptococcus pneumoniae*. *JAMA* 1998;279:365–370.

4. Liu YC, Huang WK, Huang TS, *et al*. Inappropriate use of antibiotics and the risk for delayed admission and masked diagnosis of infectious diseases: a lesson from Taiwan. *Arch Intern Med*. 2001;161:2366–70.

5. Akkerman AE, van der Wouden JC, Kuyvenhoven MM, *et al*. Antibiotic prescribing for respiratory tract infections in Dutch primary care in relation to patient age and clinical entities. *J Antimicrob Chemother* 2004;54:1116-1121.

6. Keith T, Saxena S, Murray J, *et al*. Risk-benefit analysis of restricting antimicrobial prescribing in children: what do we really know? *Curr Opin Infect Dis* 2010;23(3):2424-248.

7. Bauchner H, Pelton SI, Klein JO. Parents, physicians, and antibiotic use. Pediatrics, 1999;103:395-401.

8. Landers TF, Ferng Y, McLoughlin JW, *et al*. Antibiotic identification, use, and self-medication for respiratory illnesses among urban Latinos. *J Am Acad Nurse Pract* 2010;22(9):488-495.

9. Richman PB, Garra G, Eskin B, *et al*. Oral antibiotic use without consulting a physician: a survey of ED patients. *Am J Emerg Med* 2001; 19: 57–60. 4.

10. Morgan DJ, Okeke IN, Laxminarayan R, et al. Non-prescription antimicrobial use worldwide: a systematic review. *The Lancet infectious diseases*. 2011;11(9):692-701.

11. Grigoryan L, Burgerhof JG, Degener JE, *et al*. Determinants of self-medication with antibiotics in Europe: the impact of beliefs, country wealth and the healthcare system. *J Antimicrob Chemother* 2008;61(5):1172-1179.

12. Marković-Peković V, Grubiša N. Self-medication with antibiotics in the Republic of Srpska community pharmacies: pharmacy staff behavior. *Pharmacoepidemiol Drug Saf* 2012;21(10):1130-1133.

13. Plachouras D, Kavatha D, Antoniadou A, *et al*. Dispensing of antibiotics without prescription in Greece, 2008: another link in the antibiotic resistance chain. *Euro Surveill* 2010;15(7):19488

14. Gastelurrutia MA, Larrañaga B, Garay A, Echeveste F de A, Fernandez-Llimos F. Impact of a program to reduce the dispensing of antibiotics without a prescription in Spain. *Pharmacy Practice*. 2013;11(4):185-190.

15. Grigoryan L, Burgerhof JGM , Haaijer-Ruskamp FM, *et al*, SAR group. Is self-medication with antibiotics in Europe driven by prescribed use? *J Antimicrob Chemother* 2007;59(1):152-156.

16. European Commission. Special Eurobarometer 445. Antimicrobial Resistance. April 2016. Brussels: TNS Opinion & Social, 2016. Available at: http://ec.europa.eu/dgs/health_food-safety/amr/docs/eb445_amr_generalreport_en.pdf

17. Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. *Cochrane Database Syst Rev*. 2005;(4):CD003539.

18. Welschen I, Kuyvenhoven MM, Hoes AW, *et al*. Effectiveness of a multiple intervention to reduce antibiotic prescribing for respiratory

4.4

tract symptoms in primary care: randomised controlled trial. *BMJ* 2004;329(7463):431.

19. Huttner B, Goossens H, Verheij T, *et al*; CHAMP consortium. Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. *Lancet Infect Dis*. 2010;10(1):17-31.

20. Goossens G. Guillemot D, Ferech M, *et al*. National campaigns to improve antibiotic use. *Eur J Clin Pharmacol* 2006;62:373–379.

21. Chahwakilian P, Huttner B, Schlemmer B, *et al*. Impact of the French campaign to reduce inappropriate ambulatory antibiotic use on the prescription and consultation rates for respiratory tract infections. *J Antimicrob Chemother* 2011;66(12):2872-9.

22. European Commission. Special Eurobarometer 407. Antimicrobial Resistance. May-June 2013. Brussels: TNS Opinion & Social, 2013. Avalable at: http://ec.europa.eu/health/antimicrobial_resistance/docs/ebs_407_en.pdf

23. Versporten A, Bolokhovets G, Ghazaryan L, *et al*; WHO/Europe-ESAC Project Group. Antibiotic use in eastern Europe: a cross-national database study in coordination with the WHO Regional Office for Europe. *Lancet Infect Dis* 2014;14(5):381-7.

24. WHO Regional Office for Europe. Central Asian and Eastern European Surveillance of Antimicrobial Resistance. Annual report 2014. World Health Organization 2015. ISBN: 978 92 890 5108 8.

25. Ivanovska V, Zdravkovska M, Bosevska G *et al*. Antibiotics for upper respiratory infections: 386 public knowledge, beliefs and self-medication in the Republic of Macedonia. *Contributions (Macedonian Academy of Sciences and Arts, Section of Biological and Medical Sciences)* 2013;34:59-70.

26. WHO Regional Office for Europe. Promoting rational use of antibiotics in the former Yugoslav Republic of Macedonia. Avalable at: http://www.euro.who.int/en/countries/the-former-yugoslav-republic-of-macedonia/news/news/2014/10/promoting-rational-use-of-antibiotics-in-the-former-yugosalv-republic-of-macedonia

27. Centre for Regional Policy Research and Cooperation "Studiorum", Macedonia. Antibiotic awareness raising in Macedonia. Available at: http://studiorum.org.mk/amr2014/

28. Kamcev N, *Danilova M, Ivanovska V, et al*. General overview of the healthcare system in the Republic of Macedonia (FYROM): Health Indicators, Organization of Healthcare System and Its Challenges. In: Costigliola, Vincenzo. *Healthcare Overview: New Perspectives*. Dordrecht; New York: Springer, 2012.

29. European Observatory on Health Systems and Policies. The Former Yugoslav Republic of Macedonia. Health System Review. Health Systems in Transition;2006. WHO Regional Office for Europe.

30. Ministry of Health of the Republic of Macedonia. Recommendations for practicing Evidence-based medicine. (Ministerstvo za zdravstvo za Republika Makedonija. Upatstva za praktikuvanja na medicina zasnovana na dokazi.) Available at: http://zdravstvo.gov.mk/upatstva_update/

31. Health Insurance Fund of the Republic of Macedonia. List of medicines reimbursed by the Health Insurance Fund. (Fond za zdravstveno osiguruvanje na Makedonija. Lista na lekovi koi pagaat na tovar na Fondot za zdravstveno osiguruvanje na Makedonija). Available at: http://www.fzo.org.mk/ default.asp?ItemID= 8F44F37EC3802A43968F825481D42074

32. State Statistical Office of the Republic of Macedonia. The Nomenclature of Territorial Units for Statistics - NTES 2007 (Official Gazette

no. 158 of 28.12.2007). Available at: http://www.stat.gov.mk/OblastOpsto_en.aspx?id=1

33. Raosoft Inc: Sample size calculator. Available at: http://www.raosoft.com/samplesize.html

34. Alili-Idrizi E, Dauti M, Malaj L. Validation of the parental knowledge and attitude towards antibiotic usage and resistance among children in Tetovo, the Republic of Macedonia. *Pharm Practice* 2014;12(4):467.

35. Edwards DJ, Richman PB, Bradley K, *et al*. Parental use and misuse of antibiotics: are there differences in urban vs. suburban settings? *Acad Emerg Med*: *Off J Soc Acad Emerg Med*. 2002,9(1):22-26.

36. Mitsi G, Jelastopulu E, Basiaris H, *et al*. Patterns of antibiotic use among adults and parents in the community: A questionnaire-based survey in a Greek urban population. *Int J Antimicrob Agents* 2005,25(5):439-443.

37. Bi P, Tong SL, Parton KA. Family self-medication and antibiotics abuse for children and juveniles in a Chinese city. *Soc Sci Med* 2000,50(10):1445-1450.

38. Togoobaatar G, Ikeda N, Ali M, *et al*. Survey of non-prescribed use of antibiotics for children in an urban community in Mongolia. *Bull WHO* 2010;88(12):930-936.

39. Gebretekle GB, Serbessa MK. Exploration of over the counter sales of antibiotics in community pharmacies of Addis Ababa, Ethiopia: pharmacy professionals' perspective. *Antimicrob Resist Infect Control* 2016;5:2.

40. McNulty CA, Boyle P, Nichols T, et al. Antimicrobial drugs in the home, United Kingdom. *Emerg Infect Dis* 2006;12:1523-1526

41. Pechère JC, Hughes D, Kardas P, et al. Noncompliance with antibiotic therapy for acute community infections: a global survey. *Int J Antimicrob Agents* 2007;29:245-253.

42. Hemo B, Shamir-Shtein NH, Silverman BG, *et al*. Can a nationwide media campaign affect antibiotic use? *Am J Manag Care* 2009; 15:529–34.

43. National Health Insurance. Antibiotic programme: a first milestone is reached; the mobilization for the prudent use of antibiotics has to continue. Paris: National Health Insurance, 2008. http://www.ameli.fr/fileadmin/user_upload/documents/DP_Antibiotiques_10-01-2008.pdf

44. Nyazema N, Viberg N, Khoza S, *et al*. Low sale of antibiotics without prescription: a cross-sectional study in Zimbabwean private pharmacies. *J Antimicrob Chemother* 2007;59:718-726.

45. Wirtz VJ, Herrera-Patino JJ, Santa-Ana-Tellez Y, *et al*. Analysing policy interventions to prohibit over-the-counter antibiotic sales in four Latin American countries. *Trop Med Int Health* 2013;18(6):665-667.

46. Santa-Ana-Tellez Y, Mantel-Teeuwisse AK, Dreser A, *et al*. Impact of over-the-counter restrictions on antibiotic consumption in Brazil and Mexico. *PLoS One* 2013;16;8(10):e75550.

47. Bavestrello FL, Cabello MA. Consumo comunitario de antimicrobianos en Chile, 2000-2008. *Rev Chilena Infectol* 2011;28:107–112.

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SUPPLEMENTARY FILE

**Knowledge, attitudes and use of antibiotics
Parental questionnaire**

Date: _____

Dear parents,

We would like to invite you to take part in this research and answer few questions. Our aim is to understand parents' knowledge, attitudes and habits related to the use of antibiotics.

The following questionnaire will take approximately 10 minutes to complete. Your anonymity is guaranteed and no information will be used to reveal your identity.

If you have more than one child younger than 15 years of age, please relate your answers to your youngest child.

****

Please first provide some general information about you and your child:

1.   Parent's age

_____ years

2.   Parent's gender

a.   Male

b.   Female

3.   Child's age

_____ years_____ months

4.   Child's gender

a.   Male

b.   Female

5.   Does your child goes to a kindergarten?

a.   Yes

b.   No

6.   Do you have other children under 18 years of age?

a.   Yes

b.   No

7.   Place of living

a.   Town

b.   Village

8. **Your municipality**

_____

9. **Your nationality**

_____

10. **Marital status**
a. Married
b. Single parent
c. Divorced
d. Widow

11. **Completed educational level**
a. None
b. Primary school
c. High school
d. University degree and higher

12. **Employment status**
a. Unemployed
b. Employed (part, full time)
c. Other (student, retired)

13. **Do you have a health insurance?**
a. Yes
b. No

14. **How do you judge your social and economic situation?**
a. Bad
b. Good
c. Excellent

We would now like to ask about your knowledge and attitudes related to antibiotics.

15. **Antibiotics can kill bacteria.**
a. Yes
b. No
c. Don't know

16. **Antibiotics can kill viruses.**
a. Yes
b. No
c. Don't know

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17. **Unnecessary use of antibiotics makes them become ineffective.**
a. Yes
b. No
c. Don't know

18. **Antibiotic therapy can have side effects.**
a. Yes
b. No
c. Don't know

19. **Which symptoms improve faster if treated with antibiotics?**
    (Please choose one or more answers.)
a. Cough
b. Cold
c. Flu
d. Earache
e. Sore throat
f. Clear thick mucus in nose
g. Green colored mucus in nose
h. Nothing from above

20. **I would rather give my child an antibiotic that may not be needed than wait to see if the child gets better without it.**
a. Yes
b. No
c. Don't know

21. **If I expected an antibiotic for my child, I am less satisfied with the doctor's visit if an antibiotic is not received.**
a. Yes
b. No
c. Don't know

22. **If a doctor does not prescribe an antibiotic when I think one is needed, I will take my child to another doctor.**
a. Yes
b. No
c. Don't know

23. **Do you think you should stop taking antibiotics once you feel better?**
a. Yes
b. No
c. Don't know

24. **In the last year, did you get any information about not taking antibiotics unnecessarily, for example for a cold or the flu?**

a. Yes

b. No

c. Don't know

If "No" or "Don't know" in 24, please go directly to question 26.

If "Yes" in 24, please answer question 25.

25. **How did you first get this information about not taking any antibiotics unnecessarily?**
     (Please choose one or more answers.)

a. A doctor talked to you about it

b. A pharmacist talked to you about it

c. A friend, colleague, or a family member talked to you about it.

d. You saw/heard a TV, radio or newspapers advertisement about it.

e. You saw it in a poster, brochure, or a leaflet

f. You saw it in the internet

g. You heard about it during a kindergarten presentation

h. Other, please explain: _____

i. Don't know

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The next group of questions is about your child' recent use of antibiotics.

26.   **Has your child taken any antibiotic (tablets, capsules or syrups) in the last year?**

a. Yes

b. No

c. Don't know

If "No" or "Don't know" in 26, please go directly to question 30.

If "Yes" in 26, please answer question 27.

27. **What was the reason for last taking antibiotic that your child used?**
     (Please choose one or more answers.)

a. Pneumonia

b. Bronchitis

c. Sore throat

d. Cold

e. Cough

f. Flu

g. Running nose

h. Earache

i. Diarrhoea

j.   Urinary tract infection

k.   Wound or skin infection

l   Other reason *(Please specify):* _____

m.   Don't know

28.   How did your child obtain the last course of antibiotics?

a.   From a medical prescription

b.   Without prescription from a pharmacy

c.   Left over antibiotics from previous course

d.   Don't remember

If "From a medical prescription" or "Don't remember" in 28, please go to question 30.

If "Without prescription from a pharmacy" or "Left over antibiotics from previous course" in 28, please answer question 29.

29.   Why did you give your child an antibiotic without prescription?

a.   Did not have time to take the child to a doctor

b.   Did not consider the illness to be serious

c.   Doctor prescribed the same antibiotic to my child for the same symptoms in the past

d.   Other reason *(Please specify):* _____

The last group of questions is about your personal recent use of antibiotics.

30.   Have you yourself taken any antibiotic (tablets or capsules) in the last 12 months?

a.   Yes

b.   No

c.   Don't remember

If "No" or "Don't know" in 30, you have completed the questionnaire.

If "Yes" in 30, please answer question 31.

31.   What was the reason for last taking antibiotic that you used?
    (Please choose one or more answers.)

a.   Pneumonia

b.   Bronchitis

c.   Sore throat

d.   Cold

e.   Cough

f.   Flu

g.   Running nose

h.   Earache

i.   Diarrhoea

ji.   Urinary tract infection

k.   Wound or skin infection

l   Other reason *(Please specify)*: _____

m.   Don't know

32. How did you obtain the last course of antibiotics?

a.   From a medical prescription

b.   Without prescription from a pharmacy

c.   Left over antibiotics from previous course

d.   Don't remember

If "From a medical prescription" or "Don't remember" in 32, you have completed the questionnaire.

If "Without prescription from a pharmacy" or "Left over antibiotics from previous course" in 32, please answer question 33.

33. Why did you take an antibiotic without prescription?

a.   Did not have time to see a doctor

b.   Did not consider the illness to be serious

c.   Doctor prescribed me the same antibiotic for the same symptoms in the past

d.   Other reason *(Please specify)*: _____

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Thank you for your participation.

CHAPTER 5

GENERAL DISCUSSION

INTRODUCTION TO CONTINUED PROGRESS FOR BETTER MEDICINES FOR CHILDREN

The position of children in our society has changed dramatically during the last century. Society has acknowledged that children are different from adults, and need to be better protected, educated and cared for. Their recognition as a vulnerable group by the UN Convention on the Rights of the Child in 1989 and the global development framework of the UN Millennium Declaration in 2000 is a clear evidence of the evolving commitment to children.[1,2] Such prospects have ultimately encouraged people to become more child-centered, and entire industries have evolved around them (i.e. toys, clothing, entertainment, literature, etc). They have taken a more prominent role in health care as well. Paediatrics is a rather young academic discipline compared to the history of other medical sub-specialties. But, following from the mainstream of medical progress and innovation, children in modern society enjoy the best medical care that has ever been available in history.[3]

Nevertheless, children's particular needs in pharmacotherapy, related mainly to differences in children's growth and maturating physiology, as well as the need for specific pharmaceutical formulations, have gone largely ignored.[4,5] The availability of authorised paediatric medicines has been lagging behind that of adults, resulting in insufficient information and inadequate dosing recommendations for safe and efficacious use of medicines in children. For decades, off-label and unlicensed use was considered acceptable practice for treating paediatric patients, even though age-inappropriate formulations can cause administrative errors, suboptimal clinical outcomes, unexpected side effects, and lack of therapeutic compliance.[6,7] The lack of suitable, authorised medicinal products to treat conditions in children can be best explained by the fact that frequently pharmaceutical companies did not carry out the necessary R&D to adapt medicines to the needs of children. The underlying reason being that medicine development for paediatric patients is accompanied by numerous challenges, such as the diversity of children in different age groups, the consent and recruitment process, limited investigational infrastructure and expertise, and the relatively small and segmented market size.[8]

Fortunately, all stakeholders (society, health care providers, the pharmaceutical industry, regulatory agencies, and academia) have become progressively aware of the relevance of more evidence-based paediatric pharmacotherapy. We observe today a new focus on improvement of drug treatment of children, which reflects further advances not only in paediatrics, but also in the methodology of clinical research, and of a number of related scientific fields. The last decades have witnessed a significant expansion of knowledge related to greater understanding of growth and maturation of the paediatric patients, the disease progression, clinical end points, and drug pharmacokinetics and pharmacodynamics.[9-12] The still changing regulatory environment is at present pushing the demands for better age-adapted formulations for children. New global partnerships have been established to

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ensure that the progress and innovation in paediatric drug development address the disease burden and the needs of children in developing countries.[13-16]

There are equal challenges to ensure not only that medicines for children are safe and effective, but also that they are used in a rational manner. This is rightly justified by global estimations that over 50% of all medicines are prescribed, dispensed or sold inappropriately and that half of all patients fail to take medicines correctly.[17] The focus of improvement has been on the challenges of improving antibiotic prescribing, as these remain among the most commonly prescribed drugs used in human medicine, and their inappropriate use leads to antimicrobial resistance (AMR) globally.[18] From the child health perspective, the appropriate use of antibiotics is critically important, given their wide use in children, and the impact of infections on child morbidity and mortality.[19-20] The World Health Organization (WHO) has been instrumental in producing an Essential Medicines List for Children (EMLc) in order to help prescribers choose the most appropriate paediatric medicines, including antibiotics.[21] Furthermore, a number of guidelines and formularies, both international and national, have been produced to help healthcare professionals prescribe, supply, and administer medicines for childhood disorders. Understanding the extent of antibiotic consumption is an essential starting point to monitor and improve prescribing and use patterns.[22-24] But, while medicines prescribing and use practices have generally been well documented in high-income countries, there are inadequate data for low- and middle-income countries, especially in children.

Despite the increasing interest and initial progress to improve paediatric treatments, there is a need for readjustments and continuing advocacy for better evidence, better adjusted formulations, and better use of medicines in children. The final integration of efforts in this field must be achieved through a consensus on priority areas for action, that include development of safe and effective medicines that children are able and willing to take, and research in areas where knowledge is still scarce and fragmented.

Built on this, the overall aim of the present thesis was to document some of the recent advancements with respect to priority needs for medicines in children, and conduct additional research focusing on age-appropriate medicines and use of antibiotics in children across different regions and income levels. In this chapter, we provide a brief overview of the impact of recent paediatric legislation and global initiatives on paediatric drug research, and present the progress in the field of age-appropriate formulations in more details. We also point out the setbacks and unmet therapeutic paediatric needs, and discuss some alternative solutions to meet public health goals. Our work in the area of drug use offers certain lessons about methodological issues and challenges in conducting research in low-resource settings. We also analyse prescribing and drug use patterns in children, highlight main aspects of concern and discuss interventions to improve the situation. Finally, we make suggestions about the way forwards to better medicines for children.

PRIORITY MEDICINES AND PHARMACEUTICAL GAPS: A PUBLIC HEALTH PERSPECTIVE

In chapter 2 of this thesis, we explored the priority needs for medicines in children within the broader context of WHO 2013 Priority Medicines Report for Europe and the World.[25] This report has provided a medicines R&D agenda with a global public health perspective, which can be seen as a rather complex decision-making exercise. It entailed taking into account an extensive range of health needs of both Europe and the world, and establishing a well-balanced system of priorities for pharmaceutical research. Priority setting, also known as rationing or resource allocation, is a universal challenge for policy makers in health systems throughout the world.[26] Both public and private sector research funders have to make difficult decisions about which fields and specific studies to support with their limited resources. National populations and the global population add a broader perspective to priority-setting and add significant dimensions to international collaboration in health research.[26] That complexity is evident in the WHO 2013 Priority Medicines Report, as it focuses on different populations whose priority health needs differ, overlap and/or constantly change over time, and need to be interpreted in the context of various models of healthcare systems.

Accordingly, the primary aim of research priority setting is to gain consensus about areas where increased research effort including collaboration, coordination and investment will have wide benefits to societies.[27] The decision-making is facilitated by the use of a systematic, explicit and transparent process of setting priorities to ensure that the funded research has the greatest potential public health benefit, that research funding and outputs are aligned with the needs of decision makers, and that there is efficient and equitable use of limited resources, without duplication of research effort.[28,29] Priority setting should be as evidence-based as possible, while also incorporating the views of a wide range of stakeholders (i.e. patients, healthcare providers, the pharmaceutical industry, regulatory agencies, funders, and academia).[30] In that sense, decision-making may be justified on a number of grounds including human rights, health needs, ability to pay, likely health benefits, and the presence of risk.

There is generally no consensus on the "best practice" regarding which, or whose, values should guide decisions about allocation of research funding and how these values should inform priority setting.[31] There are two broad approaches to setting priorities for health research: the use of technical analyses, which rely on quantifiable epidemiologic, clinical, financial or other data; and the use of interpretive assessments, which rely on consensus views of informed participants.[26] Technical approaches depend on the availability of data, and priorities tend to be based on measurable units such as diseases (burden of disease) or interventions (with respect to their costs and use). The difficulty with quantitative methodology is that it hides value judgments that might reflect those of stakeholders not involved in the methodology. In contrast, interpretive or consensus stakeholder

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approaches relying on the subjective judgments of participants deal with value judgments and multifaceted assumptions. The search for good methods in priority setting in health care has shown that the best solution is to combine different approaches where both explicit and implicit methods are used simultaneously.[26]

The WHO 2013 Priority Medicines Report has also used several complementary methods to establish the priorities for biomedical research: an evidence-based approach (burden of disease and mortality data), future projections approach, risk factor approach, and social solidarity approach. [25] In the report, priority medicines were defined as medicines designed to fill pharmaceutical "gaps", and a systematic methodology was provided for identifying priority diseases with pharmaceutical "gaps". According to the criteria, pharmaceutical "gaps" were categorized as pharmaceutical treatments for a disease/condition which: 1) does not yet exist or is not sufficiently effective, 2) are likely to become ineffective in the future (e.g. due to AMR), or 3) are available but the delivery mechanism or formulation is not appropriate for the target patient group (e.g. children or elderly).[26]

As discussed in chapter 2, the unmet needs for medicines in children are mostly related to Gap 3, because children often have particular needs in terms of drug delivery mechanism and/or formulations, particularly at younger age. Some of the priority diseases for which existing treatments lack child-specific formulations 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 Gap 1, as more research is required to develop new therapies for diseases and conditions restricted to children, such as preterm births, neonatal sepsis, and birth asphyxia.

The existing frameworks in the European context seem to result in both matching and complementary decisions on unmet paediatric needs and priority areas of actions, which further needs to be linked to allocated financial resources for research. In chapter 2, we also point at another priority list, made by the EU, to serve as a basis for the special funding for research on off-patent medicines with therapeutic interest for children. The first financial support for this research was provided through the EU Seventh Framework Programme for Research (FP7-FPRP), which derived directly from the European Paediatric Regulation mandate.[32] In order to ensure that funds are directed into researching medicines with the highest needs, the Paediatric Committee of the European Medicines Agency (PDCO-EMA) has established a priority list of off-patent active substances for which studies are required.[33] In 2003, the original list of priority off-patent medicines was prepared from a public health perspective, prioritising conditions based on severity of disease, non-availability of treatment alternatives, affected paediatric age groups, and paediatric prevalence data. Later, a literature review on these off-patent medicines has been conducted to help select medicines with evidence of efficacy and no evidence of major safety issues. For the revision in 2008, the medicines on the list were prioritised by taking into account

the WHO list of essential medicines for children, the US FDA/National Institute of Child Health and Human Development' list of products, and further paediatric needs expressed by scientific and paediatric societies. Finally, the 2010 survey of all paediatric uses of medicinal products in Europe, and its identified areas of extensive off-label use were also considered to get a wider basis for the inventory of therapeutic needs, and a guide on whether paediatric development of medicines should take place.[7] The current list covers off-patent priority medicines for 17 therapeutic fields (e.g. infections, neonatology, oncology). Indicated research priorities range from requests for additional data on drug pharmacokinetics, efficacy and safety, to development of age-appropriate formulations. Up to 2013, 21 projects covering 24 off-patent active substances have received EU funds, amounting to total support of EUR 108 million.[34] But, despite the positive results achieved for the development of off-patent drugs, the specific EU funding programme setup from 2007 to 2013 has not been renewed in Horizon 2020. Since these completed projects cover a limited number of off-patent medicines and many unmet priority therapeutic needs in paediatrics remain, we urge for new similar initiatives in forthcoming European funding programmes.

The WHO 2013 Priority Medicines Report acknowledged that, while there are common priorities for Europe and the world, there are still many specific priorities for less developed countries that require a continued attention (e.g. HIV/AIDS, tuberculosis, neglected diseases and malaria).[25] Over the years, a number of coordinated, systematic efforts on a global level have been made to support countries make choices about priority medicines for paediatric use. Such examples include the creation of WHO Essential Medicines List for Children (EMLc) in 2007, and the UN list of priority medicines for maternal and child health in 2012, both based of the global burden of disease, and the evidence of efficacy and safety for preventing or treating newborn and child mortality and morbidity.[21,35] Lack of medicines is not the single most important health problem of children in developing countries, but access to appropriate medicines could make a potential difference in child survival and health, and thereby, contribute to the quantifiable achievements of the Millennium Development Goal (MDG) 4.[2]

The MDG era came to conclusion in 2015 with significant advances made in increasing life expectancy and reducing child mortality.[36] But, the target of a two-thirds reduction of 1990 mortality levels by the year 2015 was not reached, mostly because the progress was uneven across the globe, and deeply rooted in child poverty and inequalities. In response, the new 2030 UN Agenda for Sustainable Development adopted a more rounded vision for tackling the unfinished child survival goals, by integrating social, economic and environmental issues into its new global prioritization strategy.[37] The new Sustainable Development Goal target 3.2 is set to specifically achieve neonatal mortality of 12 or fewer deaths per 1000 live births and under-5 mortality of 25 or fewer deaths per 1000 live births by 2030. This has been translated into several global initiatives that include prevention

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and treatment of pneumonia, diarrhoea, malaria, and newborn care, and ultimately keeps the focus of further development and access to better medicines for children.[37]

PARADIGM SHIFT IN PAEDIATRIC DRUG DEVELOPMENT
The impact of EU paediatric legislation on paediatric drug research

The adoption of paediatric regulatory initiatives in the US and then in Europe has significantly changed the worldwide legislative frameworks. The amount of work done to study medicines for children is significantly greater than in the past.

In chapter 2, we summarize the major milestones achieved since the implementation of the EU Pediatric Regulation. Primarily, there is a fundamental change of culture, as the impetus of incentives and regulatory requirements have induced companies to screen every new adult product for its potential paediatric value. Likewise, the new legislative and regulatory framework has brought about closer international cooperation among medicines agencies, capacity building in the area of paediatric medicines research, establishment of comprehensive networks with paediatric expertise, and publication of scientific paediatric guidelines.

The science of the paediatric drug development has developed considerably, and the advances in clinical trial and statistical analysis designs especially relevant for paediatric populations have been reflected in the revised regulatory guidance on clinical investigation of medicinal products in the paediatric population - ICH E11(R1), recently opened for public consultation.[38,39] Moreover, the data from the EMA and others provides encouraging markers about the process of paediatric drug research. Yet, the question as to whether the implementation of the regulation has delivered what was expected in paediatric practice needs to be critically answered.

The five-year report to the European Commission showed a mixed start of the regulation, with a stable number of paediatric clinical trials per annum, but an increasing participation of children up to 2 years, who were previously neglected in trials.[40] The initial status quo is probably due to many deferred paediatric clinical trials, that were requested to avoid delays in the authorisation of adult medicines. The number of trials is expected to grow in the coming years, as suggested by the 25% increase of paediatric studies in 2015 compared to 2014.[41] Still, the trend in clinical trial registrations does not necessarily correlate to the increase in approved pediatric medicines. By the end of 2012, only 33 of all 600 approved PIPs have been completed, resulting in approvals of new paediatric medicines.[40] Given the length of the drug development cycles, the number of new paediatric medicines cannot be determined before the 10-year evaluation of the EU regulation, due in 2017.

Chapter 2 flags the modest impact of the EU Paediatric Regulation on high priority and unmet therapeutic paediatric needs, including rare diseases or diseases that occur only in children (e.g. paediatric oncology, pain, neonatal morbidity).[40] The paediatric therapeutic areas addressed by the industry since 2007 have been mostly aligned with adult

drug development, which comes from the fact that the starting point for the majority of PIPs is an ongoing R&D program for adult medicines. So, an intrinsic consequence of this approach is that these products primarily target adult population, but neglect diseases that are specific and exclusive to children. As a corrective measure, the PIP class waiver list was revised in 2015 to ensure that each molecule is reviewed for childhood disease, so that medicines for children can now be developed independently from the adult indication.[42] The European Commission may consider a new incentive approach for companies willing to go beyond their adult indications and investigate neglected paediatric diseases.

As outlined in chapter 2, the PUMA concept to stimulate research in off-patent medicines for children is an innovative type of marketing authorisation. However, to date, only two PUMAs have been granted, with a few more projects currently in the pipeline.[40,43] It appears that the incentive is insufficient to reassure the return of investments, and companies fear that market exclusivity will not prevent the use of competitor products with the same ingredient off-label, at lower costs. National pricing and reimbursement rules in the EU often don't reward the PUMA research in price negotiations, which then opens a gap between paediatric drug approval by PDCO-EMA and drug market access. To endorse the PUMA concept, more collaborative efforts between manufacturers, regulatory agencies, national payers, and caregivers are needed to align R&D with access and use of medicines in children. But, developing a more appropriate financial incentive is of major relevance for the future, since (generic) companies may be lacking investment sources for paediatric research. Finally, the regulatory requirements for PUMA may need to be revised, so that they are less burdensome for companies in comparison with drug applications of new molecules, while still obtaining the necessary data on efficacy, quality and safety.

Progress in formulating medicines for children

The EU Paediatric Regulation endorses the critical importance of suitable formulations for optimal adherence and efficiency in paediatric patients. The regulation requires that every PIP includes a description of measures to make the medicines acceptable, safe and effective for different subsets of the paediatric population.[32] The critical points in the evaluation of the PIP are the route of administration, appropriateness, excipients, taste and palatability, delivery devices, rate of infusion, volume to be administer (i.e. fluid load or size of solid oral formulations), and wastage. The development of formulations suitable for children is a major challenge that separates drug development in children from that in adults. To overcome the difficulties, new EU funding opportunities and collaborative research initiatives have been created to support development of paediatric formulations in a more structured way.

In chapter 3.1. we stressed the shifting trends observed in the industry toward oral solid formulations with a focus on innovative preparations.[44] 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 in developing countries.[45] More contemporary solid formulations include multiparticulate, (or) odispersible and chewable dosage forms, that offer key advantages in terms of formulation characteristics, and end-user needs.[46] The important advantages to paediatric patients and caregivers include the provision of easy, safe and convenient dose delivery, and in terms of resource-limited settings - superior stability in hot climate zones, and easier transport and storage.[47] Solid formulations also minimize the problems with confidentiality and social stigma, facilitating both adherence and in some cases clinical outcomes for malaria and HIV/AIDS treatments among children in Africa.[48,49]

However, there have been examples of low-uptake of novel solid formulations, such as dispersible paediatric formulations of fixed-dose antiretroviral therapies in some regions. This can be influenced by a variety of factors, including the lack of attachment to specific programs, unfamiliarity with the formulation, and historic use of liquids. Thus, patient and health care professionals' education about novel formulations, more research on their added value for children, and wider supply may be needed to support the acceptance in clinical practice.

In chapter 3.1. we focus on the evolution of minitablets, that are identified as potential solid formulations that can be used in very young children. Emerging evidence of suitability demonstrates that children as young as 6 months old are able to swallow 2mm minitablets, and in many cases, even preferred them to glucose syrup.[50] Nevertheless, considering the limited dose loading per individual minitablet, multiple minitablets may be required to provide the appropriate dose, which requires further evaluation on administration (errors), and patient acceptance.

The administration of paediatric oral formulations is often facilitated by paediatric dosing devices, and we documented a parallel progress in their development too.[44] While novel devices (e.g. medicated dosing straw, medicated pre-filled spoon, solid dosage pen, minitablets dispenser, etc) offer tangible patient benefits, there are very few available on the market, due to their high costs, so prior alignment and coordination among all stakeholders is necessary.

Improving age-appropriate medicines for children in low-resource settings

The progress made in developing new formulations needs to be extended for the benefit of children globally, especially in LMICs, as they are most acutely affected by lack of child-friendly medicines. In 2007, the Sixtieth World Health Assembly (WHA) adopted the resolution 'Better medicines for children' (WHA60.20) to improve access to better medicines for children, and requested the development of the WHO Model EMLc.[51] The intention of the separate list for children was to recognise special paediatric needs for medicines, and promote the inclusion of paediatric formulations in national procurement programs. It is important that the EMLc reflects new evidence-based treatment options, so

that progress made in the developed countries can be extended for the benefit of a large number of children in LMIC.

In chapter 3.2 we explored whether more formulations of certain antibiotics existed globally, but were not on the EMLc. Our analysis focused on 26 EMLc antibiotics, and we compared several medicines lists (mainly from developed countries) versus EMLc to identify new paediatric formulations that could be potentially considered for inclusion on the EMLc. Overall, seven oral and two parenteral formulations on the comparator lists were considered clinically relevant for children use. Frequently quoted benefits of the oral formulations included filling the gap of unmet therapeutic needs in certain age/weight groups, and simplified administration and supply advantages. In terms of injections, the lower doses of ampicillin and cefazolin could simplify the dosing in neonates and infants, and reduce the waste of medicines, but target age/weight groups for the new strengths may be narrow.

Overall, introducing some of these formulations on the lists may improve safety and ease of delivery in children, but may also lead to a complex procurement of multiple strengths and formulations, and less efficient drug management, including prescribing, particularly in resource-constrained settings. Nevertheless, it is important to create a global platform to provide the information about the benefits, shortcomings and availability of age-appropriate formulations for children, and advocate for their rational use. Besides, it is also vital to consider the implementation issues at field level and the translation of the (longer) WHO EML to national EMLs. There is considerable evidence that listing in the current WHO EML does not always translate into demand for the products at country level.[52-54] For example, there is very low demand/uptake for zinc preparations despite being listed in the WHO EML for a number of years, and apparently low demand for dispersible amoxicillin formulations.[55,56] So, more research may be needed to understand the barriers and facilitators to better incorporate novel, beneficial age-appropriate paediatric formulations on national lists, and use them in clinical practice.

One step further in tackling the gaps in suitable formulations is to reformulate antibiotics with potential for treatment improvements. In chapter 3.2. we argue that the priority agenda for reformulation is best guided by critical absences of high-demand, off-patent products that industry does not invest in. Some of them, as indicated by the EMA inventory list of needs for research and development of paediatric medicines may include age appropriate oral formulations for ampicilin, cloxacillin, clindamycin, and vancomycin.[57] Other agencies, have also looked at how to develop user-friendly formulations suited for LMICs at acceptable costs. For instance, the Gates Foundation has supported innovations in the treatment of pneumonia with amoxicillin in children younger than 5 years, including a rectal formulation, an oil-based formulation, a thixotropic system for oral delivery, and a peanut butter-based formulation that boosts nutrition.[58] Further, WHO priorities involve solutions for missing paediatric injection strengths, such as 20mg/ml gentamicin injections,

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and the most promising innovations for administering (low-dose) gentamicin seem to be fixed-dose presentations for needles and syringes, and prefilled injection systems.[25,59] These examples may provide further opportunities for a future EMLc that improve the treatment of children.

Future research in paediatric drug development

Despite the advances in optimizing paediatric treatments, the new paediatric formulations are still only a small part of the full therapeutic arsenal needed to serve all paediatric patients. Therefore, at the end of chapter 3.1. we suggested five approaches to guide future research on what needs to be done towards better medicines for children.

First, the focus on continuous prioritization process shall be on unmet public health issues and true clinical needs in children. These priorities include drug delivery in neonates, treatments gaps in paediatric cancers and diseases in developing countries, which are economically unattractive areas of paediatric R&D.[25,43] Although there has been progress with including neonates in new clinical trials, developing more paediatric ARV formulations, and requiring a screening of each oncology molecule for childhood disease as per recent revision of the PIP class waiver list, there is still a long way to go. These diseases serve special attention and dedication beyond market considerations, and there is a need to explore incentive options further than those currently available. The most effective response seems to be the promotion of international partnerships and consortiums that focus on specific disease areas, such as cancer and global public health threats (e.g. malaria and HIV), to cover scientific investigations and care for children, as well as data sharing up to the point of intellectual property rights issues.

Second, existing adult data shall be better used to facilitate paediatric drug research. Promising developments include the creation of enabling trial formulations that bridge existing adult formulations and potential paediatric market formulations, use of adult in-vitro gastrointestinal models to study drug bioavailability in children, and refinement of criteria for extrapolation of adult efficacy data to children.[60-62] To communicate current regulatory discussions on extrapolation, the EMA published a reflection paper in July 2016. Its framework defines the principle steps on how to ensure a reliable and valid extrapolation to the paediatric population, how to deal with the uncertainty and risk during extrapolation, and how extrapolation can be applied through the life cycle of product development.[63]

Third, recent technological advances shall be accompanied by practice-based evidence on the impact of novel formulation on efficacy, safety, patient acceptability, preferences, and adherence to new formulations, which is currently lacking.[64] Relevant patients outcome studies can inform future development of paediatric formulations with clear clinical advantages. The literature shows that information is mostly available on the relationship between the type of formulation and children/patient acceptability and preference. Studies seem more driven by marketing considerations in preferring one product over the other, then interested to obtain knowledge on how formulation aspects would relate to patient

outcomes.[64] Obviously, there is a lack of clear definitions of the patient related outcomes in the published literature, further emphasizing the need for a taxonomy suitable for categorization in paediatric medicines research.

In addition, EMA paediatric guideline requires that the end-user acceptability is assessed as an integral part of development studies.[46] Companies are now frequently requested to propose child acceptability studies in the PIP, however, the choice of the method and its justification is left to the companies themselves.[65] That suggests a need for internationally developed and harmonized methods and acceptance criteria, taking into consideration not only children, but also parents, caregivers, and healthcare professional, where appropriate.

Fourth, paediatric research on formulations shall benefit from existing and novel technologies for adults, such as novel smart polymer-based drug delivery systems, nanoparticle-targeted therapy including dendrimers, and remote triggering devices.[66-69] There is a limited extent of paediatric research conducted in nanotechnology, and it ranges from preliminary in-vitro studies to preclinical and clinical trials aiming to treat paediatric infectious diseases and paediatric solid tumors.[68] This is related to the market constraints and challenging paediatric clinical trials, as well as the absence of specific regulatory rules for evaluating toxicological properties of nanoproducts, and the appropriateness and safety of clinical protocols.[68] Controlled release systems in general can also be attractive in children, because they can potentially provide remote, non-invasive, repeatable and prolonged duration of effect from a single administration. Yet, triggerable drug delivery systems might not be easy for use by children, and the devices might need to be controlled by their parents or health professionals. [69]

Overall, the Paediatric Committee's-Formulation Working Group of EMA can be a starting point that supports the development of innovative paediatric formulations. The existing paediatric networks may also be interested to discuss the multifaceted challenges, including the financial impact, in the implementation of innovative medicines in children in the future.

Fifth, the affordability of paediatric medicines is crucial for their development for the global market, especially LMICs. The utilization of cost-effective and available technologies can maximize the affordability of medicines, and benefit paediatric patients. Therefore balance between innovative technologies and patient access to medicines must be sought.

Fortunately, there are cases where age-appropriate formulations are not only favorable for children, but also for other special patient groups, including elderly and adults with reduced capability to swallow conventional solid formulations.[70] Targeting a larger patient population may improve the commercial viability of paediatric products, but caution must be taken to ensure that this practice does not undermine the requirements of each individual patient group. Further research is required to generate evidence-based data that support the utilization of a particular formulation in different age groups.

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In the long term, regulatory obligations and incentives may help to build a global paediatric research infrastructure, with a sufficient economy of scale and sustainability. In the short term, however, financial support remains critical to maintain and enhance the growing but fragile infrastructure. Some approaches include a more globalized procurement, new funding mechanisms, particularly for off-patent medicines, that include tax breaks, premiums and exclusivity, as well as   public-private partnerships for less profitable therapeutic areas.[71]

OPTIMIZING ANTIBIOTIC PRESCRIBING AND USE IN CHILDREN

Introduction to (ir)rational use of medicines

Beyond the development and regulatory approval of child-specific medicines, it is equally important that these medicines are made accessible to patients, and that they are used rationally within healthcare systems. Medicine use is rational when patients receive the appropriate medicines, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost both to them and the community.[72] Common types of irrational use of medicine include the use of too many medicines per patient (polypharmacy), inappropriate use of antibiotics for non-bacterial infections, over-use of injections when oral formulations would be more appropriate, failure to prescribe in accordance with clinical guidelines, and inappropriate self-medication of prescription-only medicines.[73] The inappropriate use of medicines results in significant patient harm in terms of poor patient outcomes and adverse drug reactions, and also raises the cost of medical treatment, including out-of-pocket payments by patients. The over-use of antibiotics, for example, is leading to increased antibiotic resistance, while the use of non-sterile injections is leading to the transmission of hepatitis, HIV/AIDS and other blood-borne diseases. Irrational use of medicines can stimulate inappropriate patient demand, and lead to reduced access and attendance rates due to medicine stock-outs and loss of patient confidence in the health system.[73]

Nonetheless, WHO estimates that less than half of all countries have implemented the basic policies or programs to ensure appropriate use of medicines. Those include: regular monitoring of use, regular updating of clinical guidelines, and having a medicine information centre for prescribers or drug and therapeutics committees in hospitals.[74]

The optimization of the use of antibiotics is an important aspect of rational use of medicines, given the rapidly changing patterns of infections and the emergence and spread of antibiotic resistance. Antibiotic resistance represents one of the biggest threats to global health today, and the magnitude of the problem is now well recognised. The AMR infections currently cause approximately 50,000 deaths a year in Europe and the US alone, increasing to 700,000 deaths when other countries are included.[75] The continuing

rise in AMR could result in more infections that are resistant to antibiotics, becoming a leading cause of death by 2050, killing about 10 million people annually. AMR also has an economic cost, and it will potentially reach up to US$100 trillion per year by 2050.[75] Most of the direct and much of the indirect impact of AMR will fall on LMICs, that lack the infrastructure, and human and financial resources to deal with the epidemics. It is well documented that, although antibiotic resistance occurs naturally, the misuse of antibiotics in humans accelerates the process.[76] Thus, the surveillance of antibiotic usage and resistance is widely recommended as part of ongoing management and containment plans. This is also true for children, as antibiotics remain the medicines most widely prescribed for the paediatric population.

Studies on antibiotic use across different settings

Systematic data on rational prescribing in relation to children, especially in low- and middle-income countries (LMICs) is very sparse. Chapter 4.1. presents the first attempt to document trends in the treatment of acute childhood illnesses in developing and transitional countries between 1990 and 2009, and evaluated the effectiveness of interventions designed to promote appropriate prescribing. The analyses 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, as more cases (from 14% to 60%) were treated with oral rehydration salts (ORS). However, the rates of treating pneumonia with appropriate antibiotics have remained below 80% over time. Also, the rates of over-treatment of viral upper respiratory tract infections (URTI) with antibiotics increased from 42% to 72%. We found that not many interventions for rational use of medicines in children were implemented and evaluated in the LMICS, and only 19% of the interventional studies were of methodologically adequate design. Among the studies evaluated, multi-component interventions resulted in larger improvements than single-component ones.

Despite the fact that multiple interventions work better, treatment guidelines are always an important instrument for evidence-based use of antibiotics. The development of treatment guidelines is an intervention increasingly used to inform healthcare professionals whether or not to prescribe antibiotics and which antibiotics to prescribe, although their implementation is a complex process. Chapter 4.2. examined the guideline adherence to antibiotic prescribing for fever, acute respiratory and ear infections in children in the Netherlands during 2010-2012, and explored the potential variations across Dutch general practices. We found that most of these paediatric infections in the Netherlands are treated with antibiotics rather conservatively. About two-thirds of patients with pneumonia and half of the cases with restrictive antibiotic use (i.e. acute otitis media - AOM, strep throat, tonsillitis and sinusitis) were treated with antibiotics. One potential aspect of concern is that 40% of children with acute bronchitis were prescribed antibiotics, opposite to the guidelines, though the antibiotic rates were still lower than in other Western

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countries. The second alarming aspect on guideline adherence is related to the lower use of first-choice antibiotics, especially narrow-spectrum penicillins. We found marked variations in antibiotic prescribing by practices, especially for first-choice antibiotics. This study indicates the areas in which there is a room for improvement in antibiotic use, even in the Netherlands

In chapter 4.3. the analysis on antibiotic use in the Netherlands went a step further, as we stratified the children by age groups (0-4/5-11/12-17 years) to determine antibiotic prescribing patterns in each group, in terms of degree of prescribing per diagnosis and choice of antibiotics. The results showed that for the diagnoses that generally do not require antibiotics (i.e. bronchitis and fever), more prescriptions were found in adolescents than in other age groups. Half of all adolescent cases with acute bronchitis were prescribed antibiotics vs. 40% in all children, which was unexpectedly high. Likewise, more adolescents were prescribed antibiotics for diagnoses that require antibiotics (i.e. strep throat, pneumonia, and tonsillitis) except for AOM. Underuse of narrow-spectrum penicillins was mostly seen in the 0-4 years age group. General practitioners (GP) adherence to prescribing pheneticillin and phenoxymethylpenicillin for tonsillitis episodes was twice as low in children aged 0-4 years compared to the adolescents (33% vs. 67%).

Chapter 4.4. explored one more aspect of irrational use of antibiotics, i.e. self-medication, which is mostly pronounced in case of cold and upper respiratory tract symptoms (URTI). Our study described recent nation-wide multifaceted interventions to improve antibiotic use in Macedonia, and assessed its impact on parental awareness and action on antibiotic use, including self-medication. 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 analysis did not show changes in parental knowledge on antibiotics after the intervention. At baseline, 20% of the parents and 10% of the children who received antibiotics in previous year, were self-medicated with OTC or left-over antibiotics. The parental self-medication rates did not change during or after the interventions. The percentage of children that were self-medicated with antibiotics dropped to 5% during the intervention, but increased again to 9% in 2016.

As shown in chapter 4, the inappropriate use of medicines, and of antibiotics in particular, is a global issue of concern. Despite the differences in epidemiology and human development index among countries, our studies point to some common themes in irrational or suboptimal use of antibiotics in children observed in developed and developing settings, alike.

For instance, the irrational use of antibiotics includes the foremost universal practice of prescribing antibiotics when they are not indicated, such as respiratory infections that

are mainly viral and self-limiting (e.g. URTI and bronchitis). This is likely to be a prevalent problem globally, in view of the high incidence of such infections in children. The other commonality across countries is not prescribing effective therapy, or prescribing ineffective or suboptimal therapy. This includes the situations where, even though specified antibiotic is recommended for certain bacterial infections, another (mostly broad-spectrum instead of narrow-spectrum) antibiotic is chosen. A similar issue is illustrated by the irrational treatment of acute diarrhoea, when simple but effective ORS is not prescribed, and unnecessary antibiotics are given instead.

On the other hand, there are patterns of irrational use of antibiotics, such as self-medication, that are inherent to LMICs, and are facilitated by their inadequate health infrastructure, supply systems, and regulations. In these settings, self-medication is perceived as a norm by many patients (and parents), and, despite its prevalence, remains poorly documented.[77]

Another distinct feature among countries are different methods employed to measure use of medicines (antibiotics). In many developed countries, medicines use is routinely monitored with a focused evaluation method through insurance data, prescriptions and electronic medical records.[74] These data may allow disaggregation of drug use data based on patient characteristics (gender, age), or indication for which the medicine is used. This facilitates the assessment of clinical practice against agreed protocols and treatment guidelines, and enables peer reviewing, and benchmarking.

Other countries may use an aggregate method to compare drug consumption, such as the Anatomical Therapeutic Classification (ATC)/Defined Daily Dose (DDD) methodology.[74] But, the ATC/DDD methodology is not suitable for children, as it fails to reflect variation in paediatric dosing with bodyweight and surface area.[78] Unlike patient-level data, consumption data is only a proxy measure to drug use. Another option is the rapid appraisal of prescriptions, using standard methods and indicators, such as the WHO/INRUD (International Network for the Rational Use of Drugs) and the WHO/IMCI (Integrated Management for Childhood Illness) indicators, which identify general prescribing problems and quality of care, but may lack data consistency.[74] As an illustration, our data in chapter 4.1. were derived from the WHO database with a large body of collected evidence about medicines use in primary care in LMICs, based on WHO/INRUD and WHO/IMCI indicators. Yet, the database suffers from a number of methodological limitations, as standard indicators and the collection manual have often not been used by researchers, and certain data have been poorly described in the studies. Due to the heterogeneity of studies and methods, our analysis on intervention impact had a descriptive focus, and lacked a more sophisticated cross-temporal meta-analysis approach, which might have attempted to detect and control for the influence of possible biases. Thus, our study represents one practical approach to assessing medicines use in children in primary care in LMICs by compiling information from existing reports.

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The way forward in improving antibiotic use in children

It is now evident that adherence to a sound standard research methodology is needed to improve the scientific evidence on antibiotic use in many LMICs. An important step to correcting irrational use of medicines is to measure it first, and as we can see from our study only few LMICs monitor their prescribing practices, or took sufficient action to correct the situation.

The need to improve antibiotic use and act collectively on AMR has been acknowledged by the world leaders at the UN General Assembly in September 2016.[79] This strong political commitment builds upon the Global Action Plan (GAP) on AMR, that was adopted at the World Health Assembly (WHA68.7) in 2015.[80] The GAP urged member states to develop national action plans on AMR, and implement a global framework for the development of new antibiotics, while preserving existing antibiotics. The need for both effective strategies to ensure improved access to antibiotics and strategies to ensure that prescribers and patients use them appropriately is at the cornerstone of tackling antibiotic resistance in LMIC contexts. That implies the need for stronger systems to monitor antibiotic use, and in 2016 WHO developed a common methodology for the measurement of antibiotic consumption in LMICs.[81] The standardised reporting metric will facilitate the monitoring of trends at national level, and comparisons between countries, although measuring consumption data is not optimal to capture paediatric use data. But, with experience and as more sophisticated data sources become available (e.g. e-prescribing records) in LMICs, there will be hopefully, more emphasis on the need to measure the actual antibiotic use in children, and share best practices globally. New surveys are needed to provide updated evidence on medicines use in children, and assess whether the recent impetus on the fight against the AMR helps improve antibiotic use for ARI in children.

Many health system factors and stakeholders can influence the use of medicines including antibiotics, so antibiotic stewardship programs should focus not only on appropriate use, but also on ensuring sustainability of behavioural change at all levels of the system and change social and institutional norms.[74] Solutions need to focus on multifaceted and multilevel interventions that define local barriers and beliefs, which can vary widely between countries. It is important that LMICs adopt the cross-cutting approach, ensure sufficient leadership, commitment, and funding for programs, and restructure health systems to "institutionalize" the promotion of the rational use of medicines. But, paediatric issues can easily go unconsidered when national programs for rational use of medicines are being developed, implemented or evaluated. It is therefore vital that explicit policies or programs are integrated in the system to systematically identify and address issues specific to the paediatric population. The paediatric expertise can prove essential to advice on appropriate prioritisation and relevant resourcing to meet important paediatric needs for rational use of medicines. 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.

Our studies show that within Europe and wider, the Netherlands has comparatively low antibiotic use and good adherence to treatment guidelines for childhood infections in primary care. Its national disease-specific antibiotic outcomes can be used as values for attainable prescribing rates by other EU countries with higher antibiotic consumption. Even so, the continuing progress in appropriate antibiotic use may be achieved by targeting the potential aspects of concern - inappropriate antibiotic prescribing for acute bronchitis and the underuse of some first-choice antibiotics. The large inter-practice variations indicate there is room for improvement with regard to choice of type and indication of antibiotics. Better performing practices may set attainable standards for benchmarking purposes. The Dutch monitoring system has the opportunity to screen the effects of guidelines when it comes to antibiotic utilization, adherence, changes in clinical disease patterns and complication rates, and that can be used to further improve the national implementation of prescribing advice.

Some of the reasons for the irrational treatment of bronchitis may include the diagnostic uncertainty about the possible presence of pneumonia, perceived patient (parental) demand for antibiotics, or prescribers' time pressure.[82] Therefore, future efforts to improve the situation 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.

A recent Cochrane Review has shown that the interventions aiming to promote communication with patients, and shared decision making in primary care, significantly reduced antibiotic prescribing for acute respiratory infections (ARI) by almost 40% compared with usual care in the short term.[83] Shared decision making between clinicians and patients is increasing seen as an important part of patient-centered care. It is important that future research focuses on the impact of such intervention on antibiotic prescribing for children as well, and its applicability to LMICs settings. Children are a specific patient population, and the social construction of child vulnerability and the perceived need of extra protection may additionally influence the shared decision making on ARI management in children.

Rapid diagnostic tests may help rule out bacterial infections in children, and optimize antibiotic prescribing, but it is needed to evaluate potential barriers for their use in children (i.e. diagnostic accuracy and value for children in primary care, and financial implications for parents).[84] Affordability of rapid tests can be a critical issue, especially in resource-limited settings, and the diagnostic uptake can be undermined if the empiric use of existing antibiotics on the market remains a cheaper option. The recommendations for rapid tests often take their starting point in high income country contexts with already established and well-functioning health care systems and infrastructures.[85] However, such

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recommendations may not always be appropriate or applicable in LMICS, where the basics of diagnosis and prescribing may not even be doctor-driven or driven by guidelines, and are performed in facilities with minimal infrastructure. Technological and health care needs are likely to be quite different in LMICS, and more insight is needed so that the adaptation of rapid tests happens in a satisfactory manner.

In terms of underuse of recommended narrow-spectrum antibiotics, the bitter taste of penicillin liquids and their frequent administration are likely explanations for the preference of amoxicillin or macrolides in young infants, highlighting the importance of age-appropriate formulations for young children.[86] On the other hand, better prescribing of narrow-spectrum penicillins in Scandinavia shows not only their consensus to use narrow-spectrum penicillins in a broader range of paediatric ARI, but also the value of their annual benchmarking exercise.[87] These strategies may be considered by other countries, in line with national data on resistance patterns. The study from Macedonia reminds us that self-medication with antibiotics is still a widespread practice in some pockets of Europe, and it requires significant efforts to eradicate such irrational patterns of use.[88] The analysis did not show changes in the parental knowledge on antibiotics after the intervention, which mirrors the literature that poor knowledge on antibiotic use for viral infections does not necessarily improve after the media campaigns.[89] Our findings suggest to implement a targeted educational approach towards specific viral conditions that do not require antibiotic use (e.g. colds, flu, runny and congested nose, etc), which may not be easily identifiable by the public under the general term of 'viral infections,' used in wide-ranging campaigns.

As per actual parental behaviour, the short-term impact of the interventions on reduced self-medication rates in children suggests the need for continuous educational initiatives to improve the knowledge, or at least of longer duration or repetitive actions for the dynamic cohort of young parents, followed by regular evaluation of their effects to adjust the key messages to the public.

As shown by previous research in the developed world, public education, and strengthened laws about prescription-only medicines can help decrease the rate of self-medication.[90] There is a global call to reduce the (unnecessary) demands for antibiotics, and change behaviours by improving the awareness of AMR across the board (i.e. patients, prescribers, policy makers) with massive public awareness campaigns.[75] The current focus of public awareness campaigns and the attention on AMR has however, happened through a 'top-down' approach led primarily by governments, philanthropies and academia. For a better public reception, the rational use of medicines and self-medication in particular, may need a stronger rooting in dedicated civil society organisations and patient advocacy groups to convey messages adjusted to the local circumstances, and all year round. Moreover, educational efforts to optimize antibiotic use must be expanded towards children, in the attempt to educate parents through children. A variety of new European

programs have now been focused on teaching children about microbes and antibiotics, hygiene and the spread of infection.[91] Although education alone might not be powerful enough as an intervention, it generates knowledge that is essential for children and families, and public in general to understand and support the resistance control programmes. Education should be tailored and started early on in life to shape behaviour rather than having to change it. This may be particularly relevant for Macedonia and other countries with higher antibiotic consumption.

Besides the knowledge and attitudes, an important opportunity which drives people to self-medicate themselves is the availability of antibiotics without a medical prescription from community pharmacists.[92] The effects of the legal penalties to curb the OTC dispensing of antibiotics may need more time, and shall be accompanied by rigorous and targeted inspections. A recent survey from Latin America showed that enforcement of legislation to restrict OTC sales of antibiotics led to less antibiotic use, especially penicillins and probably also more appropriate use, since the seasonal variation diminished after the intervention.[93] The legal and restrictive measures are to be aligned with better professional cooperation by community pharmacists to attain sustainable changes in antibiotic use across the health system. More collaborative, patient-oriented activities are needed to engage the pharmacist to participate actively in public education campaigns, and contribute to the national efforts to restrict OTC sales of antibiotics.

The achievement of progress towards adopting and integrating interventions for improved use of antibiotics depends on effective governance mechanisms, accurate evaluation systems and inclusive partnerships, at regional, national and global level.

CONCLUSIONS

Safe and effective paediatric pharmacotherapy requires medicines adjusted to the clinical needs, acceptability and preferences (of each subpopulation) of children. 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 the 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 is 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.

REFERENCES

1. U.N. General Assembly. Document A/RES/44/25 (12 December 1989): *Convention on the Rights of the Child*. Available at: www.un.org/ga/search/view_doc.asp?symbol=A/RES/44/25

2. *The United Nations*. Millennium Development Goals (MDGs). Goal 4: Reduce Child Mortality. Available at: *www.un.org/millenniumgoals/childhealth.shtml*

3. Colon AR, P.A. Colon. *Nurturing children: a history of pediatrics*. 1999, Greenwood Pub Group. Westport.

4. Nahata MC. Lack of pediatric drug formulations. *Pediatrics* 1999;104 (suppl 3):607–609.

5. Shirkey H. Therapeutic orphans. *J Pediatr* 1968;72(1):119–120.

6. Ceci A, Felisi M,Baiardi P, *et al*. Medicines for children licensed by the European Medicines Agency (EMEA): the balance after 10 years. *Eur J Clin Pharmacol*. 2006;62(11):947–952.

7. European Medicines Agency. *Report on the survey of all paediatric uses of medicinal products in Europe*. EMA/794083/2009. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101006.pdf 8. Mulberg AE, Murphy MD, Dunne J, Mathis LL. *Pediatric drug development: concepts and applications*. Second edition. ed., Wiley, Hoboken, New Jersey, USA, 2013.

8. Kearns GL, Abdel-Rahman SM, Alander SW, *et al*. Developmental pharmacology--drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003;349(12):1157-67.

9. *European* Medicines Agency (*EMEA*). *Reflection Paper: Formulations of Choice for the paediatric population*. 2006.

10. International Conference on Harmonization (ICH). Topic *E-11*. *Clinical Investigation of Medicinal Products in the Paediatric Population*. 2001.

11. Giacoia GP, Taylor-Zapata P, Zajicek A. Eunice Kennedy Shriver National Institute of Child Health and Human Development Pediatrics Formulation Initiative: proceedings from the Second Workshop on Pediatric Formulations. *Clin Ther* 2012;34(11):S1-10.

12. Ruperto N, Eichler I, Herold R *et al*. A European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA). *Arch Dis Child* 2012;97:185–188.

13. TEDDY - European Network of Excellence for Paediatric Clinical Research. Available at: www.teddyoung.net/

14. GRIP - Global Research in Paediatrics: Network of Excellence. Available at: www.grip-network.org

15. DNDi - *Drugs* for Neglected *Diseases* initiative (DNDi). Avalable at: www.dndi.org

16. World Health Organization. 2010. *Medicines: rational use of medicines*. Fact sheet N°338. Available at: www.who.int/mediacentre/factsheets/fs338/en

17. World Health Assembly. Resolution: WHA 67.25/2014. Antimicrobial Resistance. Available at: http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R25-en.pdf?ua=1&ua=1

18. Liu L, Oza S, Hogan D, *et al*. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* 2015;385 (9966):430-440.

19. Le Doare K, Barker CIS, Irwin A, *et al*. Improving antibiotic prescribing for children in the resource-poor setting. *Br J Clin Pharmacol* 2015;79(3):446-455.

20. World Health Organization. The Selection and Use of Essential Medicines. Geneva: WHO; 2009. Report of the WHO Expert Committee October 2009. Technical series report vol. 958.

5

21. World Health Organization. WHO Model Formulary for Children 2010. Geneva: WHO; 2010. Available at: www.who.int/selection_medicines/list/WMFc_2010.pdf

22. National Institute for Health and Care Excellence (NICE). British National Formulary for Children (BNFc). Available at: www.evidence.nhs.uk/formulary/bnfc/current

23. Nederlands Kenniscentrum voor Farmacotherapie bij Kinderen (Dutch Knowledge for Pharmacotherapy in Children). Kinderformularium. - in Dutch. Available at: www.kinderformularium.nl/

24. Kaplan W, Wirtz VJ, Mantel-Teeuwisse A, Stolk P, Duthey B, Laing R. *Priority Medicines for Europe and the World 2013 Update*. Geneva: World Health Organization in collaboration with Utrecht University and Boston University; 2013.

25. Kaplan W. *Background Paper 3 - Approaches to Priority Setting*. in Kaplan W, Wirtz VJ, Mantel-Teeuwisse A, Stolk P, Duthey B, Laing R. *Priority Medicines for Europe and the World 2013 Update*. Geneva: World Health Organization in collaboration with Utrecht University and Boston University; 2013.

26. Health and Medical Research Strategic Review. *The Virtuous Cycle: Working Together for Health and Medical Research*. Canberra, Australia: Commonwealth of Australia; 1998.

27. Working Group on Priority Setting Priority setting for health research: lessons from developing countries. *Health Policy Plan* 2000;15(2):130–136.

28. Fleurence RL, Togerson DJ. Setting priorities for research. *Health Policy* 2004;69:1–10.

29. Lomas J, Fulop N, Gagnon D, *et al*. On being a good listener: setting priorities for applied health services research. *Milbank Q* 2003;81:363–388.

30. Viergever RF, Olifson S, Ghaffar A, *et al*. A checklist for health research priority setting: nine common themes of good practice. *Health Res Policy Syst* 2010, 8:36.

31. The European Parliament and the Council of the European Union. Regulation EC No. 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use. 2006.

32. European Medicines Agency. *Paediatric needs*. Available at: www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000096.jsp&mid=WC0b01ac05800260a1

33. Ruggieri L, Giannuzzi V, Baiardi P, *et al*. Successful private–public funding of paediatric medicines research: lessons from the EU programme to fund research into off-patent medicines. *Eur J Pediatr* 2015; 174(4): 481–491.

34. World Health Organization. *Priority live-saving medicines for women and children 2012*. Geneva: World Health Organization, 2012 (WHO/EMP/MAR/2012.1). Available at: http://apps.who.int/iris/bitstream/10665/75154/1/WHO_EMP_MAR_2012.1_eng.pdf?ua=1

35. United Nation Inter-Agency Group for Child Mortality Estimation (IGME). *Levels and trends in child mortality - report 2015*. United Nations Children's Fund, World Health Organization, the World Bank and the United Nations Population Division. New York, 2015. Available at: www.childmortality.org/files_v20/download/IGME%20report%202015%20child%20mortality%20final.pdf

36. United Nations General Assembly. Resolution 70/1/2015: Transforming our World: the 2030 Agenda for Sustainable Development. Available at: www.un.org/ga/search/view_doc.asp?symbol=A/RES/70/1&Lang=E

37. International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Harmonised Guideline. *Addendum to ICH E11: Clinical investigation of Medicinal products in the Pediatric Population E11(R1).* 2016. Available at: www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/ICH_E11_R1_Step_2_25Aug2016_Final.pdf

38. Ceci A, Giannuzzi V, Bonifazi D, *et al.* Chapter 12: Clinical Trials in Paediatrics — Regulatory and Methodological Aspects. in Vallisuta O, Olimat S. *Drug Discovery and Development - From Molecules to Medicine.* InTech, 2015. Available at: www.intechopen.com/books/drug-discovery-and-development-from-molecules-to-medicine/clinical-trials-in-paediatrics-regulatory-and-methodological-aspects

39. European Medicines Agency with its Paediatric Committee. *5-year Report to the European Commission. General report on the experience acquired as a result of the application of the Paediatric Regulation.* EMA/428172/2012 2012. Available at: www.ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf.

40. European Medicines Agency. *Annual Report 2015.* Available at: www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2016/05/WC500206482.pdf

41. Chin WWL, Joos A. Moving toward a paradigm shift in the regulatory requirements for pediatric medicines. *Eur J Pediatr* 2016. DOI 10.1007/s00431-016-2781-z.

42. European Medicines Agency. *Press release: European Medicines Agency gives second positive opinion for a paediatric-use marketing authorisation*. 2014. Available at: www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/02/WC500161967.pdf

43. Ivanovska V, Rademaker CM, van Dijk L, et al. Pediatric drug formulations: a review of challenges and progress. *Pediatrics.* 2014;134(2):361-72.

44. World Health Organization. 17th meeting of the Expert Committee on Selection and Use of Essential Medicines. Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children. December 2008. Available at: www.who.int/selection_medicines/committees/expert/17/application/paediatric/Dosage_form_reportDEC2008.pdf

45. European Medicines Agency. Guideline on pharmaceutical development of medicines for paediatric use. 2013. Available at: http://www.ema.europa.eu/ docs /en_GB/document_library/ Scientific_guideline/2013/ 07/ WC500147002.pdf

46. World Health Organization. *Development of paediatric medicines: points to consider in formulation*. Geneva, Switzerland: World Health Organization, 2012. WHO Technical Report Series, No.970, Annex 5.

47. Ansha EK, Gyapong JO, Agyepong IA, *et al*. Improving adherence to malaria treatment for children: the use of pre-packed chloroquine tablets vs. choloroquine syrup. *Trop Med Int Heal* 2001;6:496-504.

48. Bagenda A, Barlow-Mosha L, Bagenda D, *et al*. Adherence to tablet and liquid formulations of antiretroviral medication for paediatric HIV treatment at an urban clinic in Uganda. *Ann Trop Paediatr* 32:235-245.

49. Spomer N, Klingmann V, Stoltenberg I, et al. Acceptance of uncoated minitablets in young children: results from a prospective exploratory cross-over study. *Arch Dis Childhood* 2012;97(3):283--6.

50. World Health Assembly, 2007. *Resolution WHA60.20 Better medicines for children.* Available at: www.who.int/entity/childmedicines/publications/WHA6020.pdf

5

51. Robertson J, Forte G, Trapsida J, *et al.* What essential medicines for children are on the shelf? *Bull World Health Organ* 2009;87:231–237.

52. Gitanjali B, Manikandan S. Availability of five essential medicines for children in public health facilities in India: A snapshot survey. *J Pharmacol Pharmacother* 2011;2:95–99.

53. Balasubramaniam R, Beneragama BV, Sri Ranganathan S. A national survey of availability of key essential medicines for children in Sri Lanka. *Ceylon Med J* 2011;56:101–7.

54. Fischer Walker CL, Fontaine O, Young MW, *et al.* Zinc and low osmolarity oral rehydration salts for diarrhoea: a renewed call to action. *Bull World Health Organ* 2009;87:780–6.

55. Nsabagasani X, Ogwal-Okeng J, Mbonye A, et al. The "child size medicines" concept: policy provisions in Uganda. J Pharm Policy Pract. 2015; 8(1):2.

56. European Medicines Agency. Inventory of paediatric therapeutic needs, infectious diseases. EMA/PDCO/287222/2012. Available at: www.ema.europa.eu/docs/en_GB/document_library/Other/2014/05/WC500166168.pdf

57. The Bill & Melinda Gates Foundation. Grand Challenges Explorations: Awarded grants. New Ways to Reduce Childhood Pneumonia Deaths Through Delivery of Timely Effective Treatment (Round 15). Available at: http://gcgh.grandchallenges.org/grants?f[0]=field_challenge%253Afield_short_title%3APneumonia

58. Coffey P, Kelly K, Baqui A, *et al.* Case study: injectable antibiotics for treatment of newborn sepsis. 1–24 p. United Nations Commission on Commodities for Women's and Children's Health, 2012. Available at: http://pdf.usaid.gov/pdf_docs/pnady703.pdf

59. Ricci BM. Bridging studies in support of oral pediatric formulation development. *Int J Pharm* 2013;457(1):323-6.

60. Dunne J, Rodriguez WJ, Murphy MD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. *Pediatrics* 2011;128(5):e1242-9.

61. European Medicines Agency. List of criteria for screening PIPs with regard to paediatric specific Quality issues and referring them to the PDCO FWG for discussion. EMA/174404/2013. Available at: http://www.ema.europa.eu /docs /en_GB/document_library /Other /2014 /01 / WC500159380.pdf

62. European Medicines Agency. *Reflection paper on extrapolation of efficacy and safety in paediatric medicine development.* Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/04/WC500204187.pdf

63. van Riet-Nales DA, Schobben AF, Egberts TC, *et al.* Effects of the pharmaceutical technologic aspects of oral pediatric drugs on patient-related outcomes. *Clin Ther* 2010;32(5):924-938.

64. Kozarewicz P. Regulatory perspectives on acceptability testing of dosage forms in children. *Int J Pharm* 2014;469(2):245-248.

65. Menjoge AR, Kannan RM, Tomalia DA. Dendrimer-based drug and imaging conjugates: design considerations for nanomedical applications. *Drug Discov Today* 2010;15(5-6):171-85.

66. Krishnan V, Xu X, Barwe SP, *et al.* Dexamethasone-loaded block copolymer nanoparticles induce leukemia cell death and enhance therapeutic efficacy: a novel application in pediatric nanomedicine. *Mol Pharm* 2013;10(6):2199-210.

67. Sosnik A, Carcaboso AM. Nanomedicines in the future of pediatric therapy. *Advanced Drug Delivery Reviews* 73 (2014) 140–161.

68. Timko BP, Kohane DS. Materials to clinical devices: technologies for remotely triggered drug delivery. *Clin Ther* 2012;34(11):S25-35.

69. Breitkreutz J, Boos J. Paediatric and geriatric drug delivery. *Expert Opin Drug Deliv* 2007;4(1):37-45.

70. Milne CP, Bruss JB. The economics of pediatric formulation development for off-patent drugs. *Clin Ther* 2008;30(11):2133-45.

71. World Health Organization. The rational use of drugs. Report of the Conference of Experts. Geneva, World Health Organization, 1985.

72. World Health Organization. Promoting Rational Use of Medicines: Core Components - WHO Perspective on Medicines. No. 005, 2002. Geneva, World Health Organization. Available at: http://apps.who.int/medicinedocs/en/d/Jh3011e/

73. Holloway K, van Dijk L. *Rational Use of Medicines*. in: *The World Medicines Situation 2011*. Geneva, WHO, 2011.

74. O'Neill J. Tackling drug-resistant infections globally: Final report and recommendations. The review on antimicrobial resistance. Government of the United Kingdom, 2016.

75. Goossens H. Antibiotic consumption and link to resistance. Clin Microbiol Infect 2009 ;15 Suppl 3:12-5.

76. Ocan M, Obuku EA, Bwanga F, *et al*. Household antimicrobial self-medication: a systematic review and meta-analysis of the burden, risk factors and outcomes in developing countries. *BMC Public Health* 2015;15:742.

77. Le Doare K, Barker CIS, Irwin A, *et al*. Improving antibiotic prescribing for children in the resource-poor setting. *Brit J Clin Pharmacol* 2015;79(3):446-455.

78. General Assembly of the United Nations. Press Release: High-level Meeting on Antimicrobial Resistance. 21 September 2016, the UN Headquarters, New York. Available at: http://www.un.org/ pga /71/2016 /09 /21 /press- release- hl- meeting- on- antimicrobial- resistance/

79. WHA68.7 - Global Action Plan on Antimicrobial Resistance. WHA Resolution; Sixty-eighth World Health Assembly, 2015, Geneva. Available at: http://apps.who.int/ medicinedocs/ documents/ s21889en/ s21889en.pdf

80. World Health Organization. Methodology for a global programme on surveillance of antimicrobial consumption. Geneva, 2016. Available at: http://www.who.int/ medicines/areas/ rational_use/ WHO_ AMCsurveillance_ 1.0.pdf?ua=1

81. Ackerman SL, Gonzales R, Stahl MS, *et al*. One size does not fit all: evaluating an intervention to reduce antibiotic prescribing for acute bronchitis. *BMC Health Serv Res* 2013;13:462.

82. Coxeter P, Del Mar CB, McGregor L, *et al*. Interventions to facilitate shared decision making to address antibiotic use for acute respiratory infections in primary care. *Cochrane Database of Systematic Reviews* 2015, Issue 11. Art. No: CD010907. DOI: 10.1002/14651858.CD010907.pub2.

83. Calls JW, Butler CC, Hopstaken RM *et al*. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. *BMJ* 2009; 338: b1374.

84. Buckland Merrett GL, Bloom G, Wilkinson A, *et al*. Email authorTowards the just and sustainable use of antibiotics. *J Pharm Policy Pract* 2016;9:31.

85. Steele RW, Thomas MP, Begue RE. Compliance issues related to the selection of antibiotic suspensions for children. *Pediatr Infect Dis J* 2001; 20: 1–5.

86. SWEDRES-SVARM 2013. Use of antimicrobials and occurrence of antimicrobial resistance in Sweden. Solna/Uppsala ISSN 1650-6332. Available at: http://www.sva.se/ globalassets/

5

redesign2011/ pdf/ om_sva/ publikationer/ swedres_svarm2013.pdf

87. Huttner B, Goossens H, Verheij T, *et al*; CHAMP consortium. Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. *Lancet Infect Dis*. 2010;10(1):17-31.

88. European Commission. Special Eurobarometer 445. Antimicrobial Resistance. April 2016. Brussels: TNS Opinion & Social, 2016.

89. Furst J, Cizman M, Mrak J, *et al.* The influence of a sustained multifaceted approach to improve antibiotic prescribing in Slovenia during the past decade: findings

and implications. *Expert Rev Anti Infect Ther* 2015;13(2):279–289.

90. Lee C-R, Lee JH, Kang L-W, *et al.* Educational Effectiveness, Target, and Content for Prudent Antibiotic Use. *BioMed Research International*. 2015;2015:214021. doi:10.1155/ 2015/ 214021.

91. World Health Organization. *Antibiotic resistance: Multi-country public awareness survey*. Geneva, 2015.

92. Santa-Ana-Tellez Y, Mantel-Teeuwisse AK, Leufkens HG, et al. Seasonal variation in penicillin use in Mexico and Brazil: analysis of the impact of over-the-counter restrictions. *Antimicrob Agents Chemother* 2013;59(1):105-110.

CHAPTER 6

SUMMARY AND SAMENVATTING

CHAPTER 6.1

SUMMARY

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

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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 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.

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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.

6.1

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.

CHAPTER 6.2

SAMENVATTING

SAMENVATTING

Kinderen zijn geen kleine volwassenen, maar een aparte en heterogene groep patiënten met specifieke behoeften ten aanzien van hun behandeling. De ontwikkeling van kinderen is een dynamisch proces vanaf de geboorte tot aan hun volwassenheid. Zij worden vaak geconfronteerd met andere ziekten dan volwassenen. Voor de behandeling van kinderen met geneesmiddelen is het daarom van belang dat deze middelen tegemoet komen aan de specifieke behoeftes, acceptatie en voorkeuren van (subgroepen) kinderen.

De introductie (**hoofdstuk 1**) beschrijft de wereldwijde vooruitgang in het terugdringen van de kindersterfte tussen 1990 en 2015. De afname in sterfte van kinderen onder vijf jaar was in die periode 53%. Dit is een aanzienlijke verbetering, maar niet genoeg om aan milleniumdoel 4 van de Verenigde Naties - een afname met twee derde - te voldoen. Ongeveer de helft van de gerealiseerde vermindering is toe te schrijven aan betere preventie en behandeling van longontsteking, diarree, mazelen en malaria. Veel van deze aandoeningen kunnen worden voorkomen of behandeld met interventies waarvan het nut bewezen is, waaronder geneesmiddelen voor kinderen en vaccins. Maar er valt nog veel te verbeteren ten aanzien van de preventie en behandeling van infecties bij kinderen, onder andere omdat de juiste vaccins en geneesmiddelen vaak niet voorhanden zijn.

Het onvermogen om aan de specifieke behoeftes voor geneesmiddelen bij kinderen te voldoen werd reeds beschreven in het Priority Medicines for Europe and the World rapport uit 2004. Dit rapport benadrukte het belang van onderzoek naar geneesmiddelen voor kinderen en deed aanbevelingen om de ontwikkeling van dergelijke geneesmiddelen, waaronder kinderformuleringen voor alle leeftijdsgroepen, te stimuleren.

Naast de ontwikkeling van geneesmiddelen voor kinderen is ook de beschikbaarheid en het doelmatig gebruik van deze middelen binnen de gezondheidszorg van groot belang. In hoofdstuk 1 wordt het belang van het verbeteren van het gebruik van antibiotica benadrukt. Irrationeel gebruik van antibiotica komt wereldwijd veelvuldig voor en de antibioticaresistentie neemt mede daarom toe. En hoewel antibiotica de meest voorgeschreven geneesmiddelen bij kinderen zijn, zijn systematisch verzamelde gegevens met betrekking tot antibioticagebruik bij kinderen beperkt voorhanden. Dit geldt met name voor lage-inkomenslanden.

Gelukkig hebben stakeholders steeds meer oog voor de noodzaak van goed onderzoek naar farmacotherapie bij kinderen en de ontwikkeling van kindergeneesmiddelen. Desondanks is verdere actie nodig om aan de behoeftes van kinderen tegemoet te komen. Het doel van dit proefschrift was het beschrijven van recente ontwikkelingen op het gebied van farmacotherapie bij kinderen en het doen van aanvullend onderzoek naar kinderformuleringen en gebruik van antibiotica door kinderen in verschillende landen en omstandigheden.

Hoofdstuk 2 presenteert een update van het achtergrondartikel over geneesmiddelen voor kinderen dat hoort bij het Priority Medicines for Europe and the World rapport

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uit 2004. De noodzaak voor betere geneesmiddelen voor kinderen bestaat nog steeds, met name op het gebied van toedieningsvormen die geschikt zijn voor jonge kinderen. Tot de ziektes waarvoor geen of te weinig specifieke kinderformuleringen aanwezig zijn, behoren HIV/AIDS, tuberculose, kanker, weesziektes, malaria, longontsteking, hart- en vaatziekten, infecties (door het optreden van resistentie) en vele tropische ziektes. Ook is meer onderzoek nodig om geneesmiddelen te ontwikkelen voor omstandigheden en aandoeningen die alleen bij kinderen voorkomen, zoals vroeggeboortes, neonatale sepsis en verstikkingsgevaar bij de geboorte.

In 2007 heeft de Europese Unie nieuwe wetgeving geïmplementeerd, waarbij wettelijke eisen gepaard gaan met financiële prikkels om bedrijven te stimuleren om geneesmiddelen te formuleren, testen en registreren voor gebruik bij kinderen. Dit heeft bewerkstelligd dat geneesmiddelen voor volwassenen vaker worden gescreend op het mogelijk gebruik bij kinderen. Ook is de onderzoekscapaciteit en samenwerking op het gebied van onderzoek naar kindergeneesmiddelen toegenomen. Echter, hoewel de hoeveelheid klinisch onderzoek bij kinderen is toegenomen, lijkt het erop dat de farmaceutische industrie zich bij geneesmiddelenontwikkeling nog steeds meer laat leiden door behoeften bij volwassenen dan bij kinderen. De European Medicines Agency (EMA), de Europese registratieautoriteit, heeft daarom een overzicht gemaakt van aandoeningen waarbij off-label gebruik door kinderen veelvuldig voorkomt en van aandoeningen waarbij gegevens voor kinderen volledig ontbreken. Met deze overzichten wil de EMA inzichtelijk maken waar behoeften bij kinderen liggen en zo de farmaceutische industrie stimuleren zich op deze gebieden te richten. Dergelijke overzichten moeten wel gepaard gaan met een adequaat beloningssysteem voor investeringen in de ontwikkeling van geneesmiddelen voor kinderen. De commerciële levensvatbaarheid van kindergeneesmiddelen zou verder kunnen worden verbeterd door schaalvergroting (globalisering, naast toepassing bij kinderen ook toepassing bij andere patiëntengroepen zoals geriatrische patiënten en volwassenen met slikproblemen), nieuwe financiële prikkels (bijvoorbeeld voor geneesmiddelen die uit patent zijn) en publiek-private samenwerkingsverbanden die de ontwikkeling van weesgeneesmiddelen en geneesmiddelen voor andere minder winstgevende nichemarkten ondersteunen.

Hoofdstuk 3 richt zich op geneesmiddelformuleringen voor kinderen in verschillende leeftijdsgroepen. In **hoofdstuk 3.1** wordt de vooruitgang op dit gebied geïllustreerd voor de groep van orale middelen. In toenemende mate komen nieuwe geneesmiddelen beschikbaar die een grotere flexibiliteit op het gebied van dosering hebben: minitabletten, kauwtabletten en orodispergeerbare tabletten voor jonge kinderen en toedieningsvormen die dispergeerbaar zijn tot drankjes of met voedsel kunnen worden vermengd. Deze trend sluit aan bij de consensus die bereikt werd tijdens een WHO expert forum in 2008. Hier werd gesteld dat flexibele vaste orale toedieningsvormen voordelen hebben ten opzichte van de klassieke vloeibare preparaten, met name bij jongere kinderen en bij kinderen in ontwikkelingslanden. Waar er wel onderzoek is naar de ontwikkeling van dergelijke

nieuwe kinderformuleringen, ontbreekt gedegen onderzoek naar de effecten van deze ontwikkelingen voor de patiënt in de klinische setting (bijvoorbeeld impact met betrekking tot het optreden van bijwerkingen, verdraagbaarheid en medicatiefouten). Dergelijk onderzoek is van belang voor verdere bevordering van technologische vooruitgang op dit gebied. Daarnaast worden sommige van deze nieuwe vaste toedieningsvormen slechts beperkt gebruikt vanwege de hoge kosten en de onbekendheid met deze formuleringen. Daarom is betere voorlichting over deze nieuwe toedieningsvormen aan patiënten en medewerkers in de gezondheidszorg nodig. Tot slot is meer onderzoek nodig naar de toegevoegde waarde van kinderformuleringen in termen van effectiviteit, veiligheid, acceptatie door en voorkeuren van patiënten en therapietrouw om acceptatie in de klinische praktijk te bevorderen.

Aangezien het tekort aan adequate geneesmiddelen vooral kinderen in lage-inkomenslanden treft, is er wereldwijd aandacht geweest voor het borgen van toegang tot geneesmiddelen voor aandoeningen die kinderen veelvuldig treffen. Het resultaat hiervan is de WHO Essential Medicines List for Children (EMLc) uit 2007. Deze lijst bevat een overzicht van de meest noodzakelijke geneesmiddelen voor kinderen en hun toedieningsvormen. Het doel is de speciale behoeftes van kinderen te benadrukken en het opnemen van geneesmiddelen voor kinderen in nationale inkoopprogramma's van geneesmiddelen te stimuleren. De vraag is in hoeverre deze lijst alle relevante formuleringen bevat. **In hoofdstuk 3.2** zijn daarom kinderformuleringen voor antibiotica vergeleken tussen nationale kinderformularia van het Verenigd Koninkrijk, Australië en Nederland en de WHO EMLc. Dit om inzicht te krijgen in kindergeneesmiddelen die potentieel aan de WHO EMLc toegevoegd zouden kunnen worden. Alle kinderformuleringen in de nationale formularia die afweken van de formuleringen in de WHO EMLc in termen van toedieningsroute, doseervorm en sterkte werden geëvalueerd om hun klinische en/of financiële meerwaarde ten opzichte van de huidige formuleringen op de WHO EMLc vast te stellen. Er werden zeven orale en twee parenterale kinderformuleringen gevonden die mogelijk een klinisch voordeel zouden kunnen geven in lage inkomenslanden, waaronder een eenvoudigere toediening of een verhoogde doseernauwkeurigheid. Deze formuleringen zouden dus voor opname in de WHO EMLc in aanmerking zouden kunnen komen. Aan de andere kant moet ook het effect op de complexiteit van de inkoop en het hanteren van verschillende doseringen en formuleringen in overweging worden genomen. Tevens moet nagedacht worden over het implementeren van nieuwe kinderformuleringen in de dagelijkse praktijk, aangezien bekend is dat het opnemen in de WHO EML zich niet altijd vertaald in daadwerkelijk gebruik.

6.2

Naast het ontwikkelen en beschikbaar stellen van kinderformuleringen vormt ook het goed gebruik van geneesmiddelen een grote uitdaging. Het in kaart brengen van (de mate van) geneesmiddelengebruik is een essentieel startpunt voor het monitoren en verbeteren van het voorschrijven en gebruiken van geneesmiddelen. De focus van **hoofdstuk 4** is

het meten en verbeteren van goed gebruik van antibiotica, omdat antibiotica veelvuldig door kinderen worden gebruikt en infecties wereldwijd een grote impact hebben op ziekte en sterfte onder kinderen. In **hoofdstuk 4.1** zijn voorschrijfpatronen voor acute infectieziektes bij kinderen in de eerste lijn in ontwikkelingslanden tussen 1990 en 2009 bestudeerd. Tevens zijn de effecten van interventies om de behandeling van deze infectieziektes te verbeteren geanalyseerd. De gegevens werden geëxtraheerd uit de WHO Medicines Use Database en bestonden uit 344 onderzoeken bij kinderen uit 78 landen. De resultaten lieten een gemengd beeld zien, waarbij in grote lijnen werd vastgesteld dat veel aspecten van de behandeling van infectieziektes nog niet optimaal waren. Er was een verbetering zichtbaar in de behandeling van diarree met toenemend gebruik van oraal rehydratiezout, hoewel de waargenomen trend niet statistisch significant was (van 14% voor 1990 tot 60% in de periode 2006-2009, p=0.57). Het percentage gevallen van longontsteking dat met het juiste antibioticum werd behandeld, bleef echter onder de 80% gedurende de gehele studieperiode. Tevens was er een niet-significante toename van onjuist gebruik van antibiotica voor de behandeling van bovenste luchtweginfecties met een virale oorsprong (van 42% voor 1990 tot 72% in 2006-2009, p=0.07). Van de 226 studies naar interventies om het gebruik van geneesmiddelen bij infectieziektes te verbeteren hadden er slechts 44 (19%) een methodologisch kwalitatief goede opzet. Interventies waarin meerdere aspecten van onjuist gebruik werden aangepakt waren effectiever dan interventies die zich op één aspect richtten. Het gemiddelde effect van de interventie op juist geneesmiddelengebruik nam met 28% toe bij interventies waarin case-management binnen de leefgemeenschap plaatsvond, met 18% als zowel voorschrijvers als consumenten beter werden voorgelicht en slechts met 9% als alleen voorschrijvers beter werden voorgelicht. Oplossingen om juist gebruik van geneesmiddelen bij infectieziektes te verbeteren moeten dus een brede aanpak kennen, waarbij herstructurering van de gezondheidszorg soms nodig is om bevordering van goed gebruik van geneesmiddelen te "institutionaliseren". Ook zijn standaard systemen om geneesmiddelgebruik te meten essentieel, maar ontbreken die momenteel vaak nog in lage en midden inkomenslanden.

In **hoofdstuk 4.2** is gekeken in hoeverre het voorschrijfgedrag van huisartsen bij koorts bij kinderen, acute luchtwegontstekingen en oorontstekingen in overeenstemming was met behandelrichtlijnen in Nederland in de periode 2010-2012. Hierbij werd tevens gekeken naar verschillen tussen huisartspraktijken. De gegevens over diagnoses en voorschriften voor antibiotica waren afkomstig uit de NIVEL Zorgregistraties, een elektronische database waarin onder anderen morbiditeit en voorschrijfgegevens van huisartsen beschikbaar zijn. Bij de helft van alle luchtweg- en oorinfecties waarbij men terughoudend zou moeten zijn met antibiotica (acute middenoorontsteking, keelontsteking, sinusitis en tonsillitis) en bij 65% van de episodes van longontsteking werden antibiotica voorgeschreven. Dit duidt op een relatief conservatief antibioticagebruik in Nederland voor deze infecties. Deze percentages zouden als indicatoren kunnen gelden voor wat haalbaar is in andere landen in

de Europese Unie waar het antibioticumgebruik momenteel hoger ligt dan in Nederland. Een zorgwekkend aspect is echter dat 40% van de kinderen met een acute bronchitis antibiotica kreeg voorgeschreven, wat niet in overeenstemming met de richtlijnen is. Daarnaast gold voor alle infecties dat 15-50% van de diagnoses niet werd behandeld met het antibioticum van eerste keuze. Vooral het juist gebruik van smalspectrum penicillines is een uitdaging. Tot slot werd een opvallende variatie tussen huisartspraktijken gevonden in het voorschrijven van antibiotica, vooral voor eerstekeuze antibiotica. Inspanningen om het juist gebruik van antibiotica verder te bevorderen zouden zich vooral op deze praktijken moeten richten.

In **hoofdstuk 4.3** werd nader ingegaan op specifieke voorschrijfpatronen van antibiotica bij verschillende leeftijdsgroepen (0-4/5-11/12-17 jaar) uit het vorige onderzoek. De resultaten laten zien dat bij adolescenten meer episodes van bronchitis werden behandeld met een antibioticum dan bij kinderen van 0-4 en 5-11 jaar (52.0% vs. 42.4% en 42.7%). Ook kregen adolescenten vaker antibiotica voorgeschreven bij infecties waarbij antibiotica geïndiceerd zijn (keelontsteking, longontsteking en tonsillitis). Een uitzondering hierop was acute middenoorontsteking. Ondergebruik van smalspectrum penicillines werd meer gezien bij jonge kinderen van 0-4 jaar dan bij kinderen van 5-11 jaar en adolescenten (bij keelontsteking: 60.9% vs. 63.6% en 72.0%, bij tonsillitis: 33.1% vs. 45.9% en 67.9%). De onderzoeken in hoofdstuk 4.2 en 4.3 geven aan waar, ook in Nederland, ruimte is voor verbetering van antibioticagebruik. Toekomstige initiatieven om antibioticagebruik bij specifieke aandoeningen verder te optimaliseren zouden onder andere gericht kunnen zijn op het trainen van voorschrijvers om weerstand te bieden aan de vraag naar antibiotica door patiënten en het gebruik van snelle diagnostische testen die lage luchtweginfecties van virale en van bacteriële oorsprong kunnen onderscheiden. Verder onderzoek zou zich moeten richten op barrières bij het voorschrijven van eerstekeuze antibiotica, vooral bij kleine kinderen.

Het doel van het onderzoek in **hoofdstuk 4.4** was om verschillende aspecten van zelfmedicatie met antibiotica bij kinderen in Macedonië te bestuderen en de impact van nationale interventies op kennis van ouders over antibioticagebruik en zelfmedicatie bij hun kinderen te analyseren. De interventies kenden verschillende elementen, waaronder een massamedia (TV) campagne over het juist gebruik van antibiotica, discussies met ouders over luchtweginfecties en antibioticumgebruik op kinderdagverblijven en seminars voor medewerkers in de gezondheidszorg over de behandeling van luchtweginfecties en het juist voorschrijven van antibiotica. Gegevens werden verzameld door middel van gestructureerde enquêtes onder 1203 ouders gedurende een periode van 3 jaar (2014-2016). Er werd gevonden dat kennis van ouders over het gebruik van antibiotica vergelijkbaar was met het kennisniveau van volwassenen in de gehele Europese Unie. Meer dan 80% van de ouders wist dat onjuist gebruik kan leiden tot verminderde effectiviteit of bijwerkingen en dat antibiotica bacteriën kunnen doden. Circa 40% van de ouders geloofde echter ten onrechte

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dat antibiotica effectief zijn bij virale infecties en eenvoudige bovenste luchtweginfecties. De kennis van ouders veranderde niet significant na de interventies. Voor de interventies gebruikte 20% van de ouders en 10% van de kinderen antibiotica als zelfmedicatie (gekocht zonder recept of ongebruikte antibiotica van een eerdere infectie). Zelfmedicatie onder ouders veranderde niet tijdens of na de interventies, terwijl zelfmedicatie bij hun kinderen verminderde tot 5% tijdens de interventies maar weer steeg tot 9% na afloop van de interventies in 2016. Dit duidt op de noodzaak van continue voorlichting of tenminste herhaalde acties om publieke kennis over en juist gebruik van antibiotica te verbeteren. Dit moet gepaard gaan met restrictieve maatregelen om vrij gebruik van antibiotica terug te dringen en samenwerking met apothekers om duurzame veranderingen op dit gebied te bereiken.

In de algemene discussie in **hoofdstuk 5** worden de belangrijkste bevindingen van dit proefschrift gepresenteerd en bediscussieerd in relatie tot de vooruitgang op het gebied van kinderformuleringen en antibioticagebruik bij kinderen in verschillende regio's en inkomenslanden en de uitdagingen die daar nog liggen. Het onderzoek in dit proefschrift beschrijft hoe de praktijk van het ontwikkelen en gebruik van geneesmiddelen bij kinderen is geëvolueerd binnen de recente regulatoire kaders voor kindergeneesmiddelen en de wereldwijde initiatieven om betere geneesmiddelen voor kinderen te bewerkstelligen. Er is vooruitgang geboekt op het gebied van de beschikbaarheid van nieuwe kinderformuleringen voor verschillende leeftijdsgroepen. Desalniettemin blijven specifieke behoeftes bestaan en vervolgstappen in het geneesmiddelonderzoek bij kinderen zijn nodig op basis van een continue proces van prioritering, beter gebruik van nieuwe technieken zoals toegepast bij volwassenen en feedback vanuit de klinische praktijk.

Een even belangrijk onderdeel van dit proefschrift is de evaluatie van antibioticagebruik bij kinderen in verschillende gezondheidszorgsystemen en financiële omstandigheden. De resultaten in dit proefschrift kunnen bijdragen aan een beter begrip van zowel juiste keuzes bij het voorschrijven van antibiotica als zorgwekkende aspecten en de range aan interventies die geïmplementeerd zijn om antibioticagebruik bij kinderen te verbeteren. Het onderzoek heeft laten zien dat hiervoor ook meer nadruk gelegd moet worden op het meten van antibioticagebruik in gebieden met weinig financiële middelen en op het meten van zelfmedicatie. Gegevens hierover zijn nu beperkt voorhanden. Er is nog veel werk te doen en oplossingen moeten zich concentreren op interventies op meerdere niveaus die zich op meerdere aspecten van antibioticagebruik richten. Deze interventies moeten niet alleen lokale barrières identificeren maar ook bevorderen dat goed gebruik van antibiotica bij kinderen geïntegreerd wordt in het gezondheidszorgsysteem.

CHAPTER 7

ADDENDUM

CHAPTER 7.1

ACKNOWLEDGEMENTS

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7.1

CHAPTER 7.2

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CHAPTER 7.3

SCIENTIFIC PUBLICATIONS

SCIENTIFIC PUBLICATIONS INCLUDED IN THIS THESIS

Verica Ivanovska, Hubert G. Leufkens, Carin Rademaker, Elizabeta Zisovska, Mariëlle W. Pijnenburg, Liset van Dijk, Aukje K. Mantel-Teeuwisse. Are age-appropriate antibiotic formulations missing from the World Health Organization List of Essential Medicines for Children? A comparison study. Arch Dis Child 2017;0:1–5. doi:10.1136/archdischild-2016-311933

Verica Ivanovska , Karin Hek, Aukje K. Mantel-Teeuwisse, Hubert G. M. Leufkens, Mark M. J. Nielen, Liset van Dijk. Antibiotic prescribing for children in primary care and adherence to treatment guidelines. J Antimicrob Chemother 2016;71(6):1707-14.

Kathleen A. Holloway, Verica Ivanovska, Anita K. Wagner, Catherine Vialle-Valentin, Dennis Ross-Degnan. Prescribing for acute childhood infections in developing and transitional countires, 1990-2009. Paed Int Child Health 2015;35(1)5-13.

Verica Ivanovska, Carin M.A. Rademaker, Liset van Dijk, Aukje K. Mantel-Teeuwisse. Pediatric Drug Formulations: A Review of Challenges and Progress. Pediatrics 2014;134(2):361-72.

Verica Ivanovska, Aukje K. Mantel-Teeuwisse, Liset van Dijk. Background paper. Priority medicines for children. Priority Medicines for Europe and the World Update Report, WHO, Geneva, 2013.

Verica Ivanovska, Karin Hek, Aukje K. Mantel-Teeuwisse, Hubert G. Leufkens, Liset van Dijk. Age-specific antibiotic prescribing and adherence to guidelines in paediatric patients in primary care. Submitted.

Verica Ivanovska, Bistra Angelovska, Liset van Dijk, Milka Zdravkovska, Hubert G. Leufkens, Aukje K. Mantel-Teeuwisse. Change in parental knowledge, attitudes and practice of antibiotic use after implementation of a national intervention programme. Submitted.

7.3

PUBLICATIONS NOT INCLUDED IN THIS THESIS

Medicines use in primary care in developing and transitional countries. Fact Book summarizing results from studies reported between 1990 and 2006. WHO/EMP/MAR/2009.3

Verica Ivanovska. Pharmacy practice in the Republic of Macedonia. South Med Rev 2011;4(2):88-91

Alexander K. Rowe, Samantha Y. Rowe, Kathleen Anne Holloway, Verica Ivanovska, Lulu Muhe, Thierry Lambrechts. Does shortening the training on Integrated Management of Childhood Illness guidelines reduce its effectiveness? A systematic review. Health Policy Plan 2012;27(3):179-93

Nikola Kamcev, Marina Danilova, Verica Ivanovska, Gordana Kamceva, Nevenka Velickova, Kneginja Richter. A General Overview of the Healthcare System in the Republic of Macedonia: Health Indicators, Organization of Healthcare System and its challenges. in: Costigliota V. (ed) Healthcare Overview. New Perspectives. Advances in Prediditive, Preventive and Personalised Medicine vl.1 2012. Springer Science.

Verica Ivanovska, Kathleen Anne Holloway. Interventions to Improve Antibiotic Prescribing in Upper Middle Income Countries: A Systematic Review of the Literature 1990 - 2009. Maced J Med Sci 2013; 6(1):84-91

Kathleen A. Holloway, Verica Ivanovska, Anita K. Wagner, Catherine Vialle-Valentin, Dennis Ross-Degnan. Have we improved use of medicines in developing and transitional countries and do we know how to? Two decades of evidence. Trop Med Int Health. 2013;18(6):656-64

Verica Ivanovska, Milka Zdravkovska, Golubinka Bosevska, Bistra Angelovska. Antibiotics for upper respiratory infections: public knowledge, beliefs and self-medication in the Republic of Macedonia. Contributions Sec of Med Sci MASA 2013;34(2):59-70

Karin Hek, Verica Ivanovska, Aukje K. Mantel-Teeuwisse, et al. Voorschrijven van antibiotica bij kinderen. (Antibiotic Prescribing in children). Huisarts Wet 2016;59:410 [in Dutch].

CHAPTER 7.4

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ABOUT THE AUTHOR

Verica Ivanovska obtained a Master's degree in Pharmacy in 1998 at the University of Skopje, Macedonia. During her study, she completed an exchange research programme at the Faculty of Pharmacy, University of Granada, Spain.

Upon graduation, Verica worked as a humanitarian aid pharmacist in the Western Balkans for two years. In 2001, she continued her higher education in the United Kingdom, and obtained a Master in Public Health (MPH) at the Faculty of Medicine, Glasgow University. Her studies were supported by the UK Government's Chevening scholarship.

From there Verica went on to work at the World Health Organization in Geneva between 2002 and 2004 as Technical Officer in the Department of Essential Medicines and Pharmaceutical Policies, on assignments related to rational use of medicines. She later continued with a consultancy work until 2007, when the WHA Resolution 60.16 - Progress in the Rational Use of Medicines was adopted.

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Verica is married to Bojan Ugrinovski and they have a son Joan (2008).

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