DISSERTATIONES
MEDICINAE
UNIVERSITATIS
TARTUENSIS
**203**

**JANA LASS**

# Epidemiological and clinical aspects of medicines use in children in Estonia

DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS
**203**

DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS
**203**

**JANA LASS**

# Epidemiological and clinical aspects of medicines use in children in Estonia

UNIVERSITY OF TARTU
PRESS
1632

Institute of Microbiology, University of Tartu, Estonia

Dissertation is accepted for the commencement of the degree of Doctor of Philosophy in Medicine on 19.12.2012 by the Council of the Faculty of Medicine, University of Tartu, Estonia.

Supervisor: Professor Irja Lutsar, MD, PhD
Institute of Microbiology, University of Tartu, Tartu, Estonia

Reviewers: Professor Jyrki Tapio Heinämäki, Dr. Pharm
Pharmacy Faculty, University of Tartu, Tartu, Estonia

Kersti Oselin, MD, PhD, specialist
State Agency of Medicines, Bureau of Clinical Assessment, Tartu, Estonia

Opponent: Professor Dr. Jörg Breitkreutz
Institute of Pharmaceutical Technology and Biopharmacy
Heinrich-Heine University, Düsseldorf, Germany

Commencement: 31st of January 2013

Publication of this dissertation is granted by Tartu University.

This research was supported by the European Regional Development Fund and by the European Social Fund



ISSN 1024–395X
ISBN 978–9949–32–204–6 (print)
ISBN 978–9949–32–205–3 (pdf)



University of Tartu Press
www.tyk.ee
Order No 654

# TABLE OF CONTENTS


LIST OF ORIGINAL PUBLICATIONS ..... 7

ABBREVIATIONS ..... 8

1. INTRODUCTION ..... 10

2. REVIEW OF LITERATURE ..... 11
   2.1. Licensing of medicines ..... 11
      2.1.1. Licensing of paediatric medicines ..... 12
   2.2. Paediatric drug utilisation studies ..... 14
      2.2.1. Methodology of drug utilisation studies in children ..... 14
      2.2.2. Paediatric drug utilisation studies in practice ..... 17
   2.3. Off-label (OL) and unlicensed (UL) use of medicines in children ... 18
      2.3.1. Definitions ..... 18
      2.3.2. Extent of OL/UL use of medicines ..... 20
      2.3.3. OL use according to the therapeutic groups and products ..... 28
      2.3.4. What problems may OL/UL use of medicines cause? ..... 28
      2.3.5. Data sources for paediatric medicines information ..... 30
   2.4. Pharmaceutical excipients ..... 32
      2.4.1. Paediatric and neonatal issues with pharmaceutical excipients ..... 33
   2.5. Summary of the literature ..... 36

3. AIMS OF THE RESEARCH ..... 38

4. PATIENTS AND METHODS ..... 39
   4.1. Ethics ..... 39
   4.2. Design of the studies and data collection ..... 40
   4.3. Age categories of study population ..... 41
   4.4. Assessment of licensing status of the medicines ..... 42
   4.5. Classification of excipients according to their potential toxicity to neonates ..... 43
   4.6. Analysis of the data ..... 43

5. RESULTS AND DISCUSSION ..... 45
   5.1. Demographics of the study populations ..... 45
      5.1.1. Ambulatory patients in Estonia and Sweden ..... 45
      5.1.2. Hospitalised neonates ..... 45
   5.2. Drug utilisation pattern ..... 47
      5.2.1. Ambulatory drug utilisation ..... 47
      5.2.2. Prescription pattern of antibiotics in Estonia compared to Sweden ..... 49
      5.2.3. Prescriptions for hospitalised neonates ..... 52
   5.3. OL use of medicines ..... 55
      5.3.1. Ambulatory OL use ..... 55

5.3.2. OL medicines use in hospitalised neonates ..... 62
5.3.3. Contraindicated medicines ..... 64
5.4. Extent of UL use of medicines ..... 66
5.5. Availability of paediatric medicines information ..... 67
5.5.1. Drug information for ambulatory prescriptions ..... 67
5.5.2. Neonatal medicines information ..... 70
5.6. Extent of excipient use ..... 72
5.6.1. Classification of excipients ..... 72
5.6.2. Neonatal exposure to excipients ..... 72

6. GENERAL DISCUSSION ..... 76
6.1. Studies on the paediatric prescription pattern and OL medicines use 76
6.2. Evidence-based paediatric drug information – from where should it come? ..... 76
6.3. Prioritisation of paediatric medicines research ..... 78
6.4. What to do with the UL medicines? ..... 80
6.5. Drug formulation excipients and safer neonatal pharmacotherapy ... 81
6.6. Limitations of the study ..... 82
6.7. Suggestions for future research ..... 83

7. CONCLUSIONS ..... 84

8. REFERENCES ..... 86

9. SUMMARY IN ESTONIAN ..... 96

ACKNOWLEDGEMENTS ..... 101

PUBLICATIONS ..... 103

CURRICULUM VITAE ..... 157

# LIST OF ORIGINAL PUBLICATIONS

I Lass J, Irs A, Pisarev H, Leinemann T, Lutsar I. Off-label use of prescription medicines in children in outpatient setting in Estonia is common. Pharmacoepid Drug Safety 2011; 20: 474–481.

II Lass J, Käär R, Jõgi K, Varendi H, Metsvaht T, Lutsar I. Drug utilisation pattern and off-label use of medicines in Estonian neonatal units. Eur J Clin Pharmacol 2011; 67:1263–1271.

III Lass J, Naelapää K, Shah U, Varendi H, Käär R, Turner M, Lutsar I. Hospitalised neonates commonly receive potentially harmful excipients. BMC Paediatrics 2012; 12: 136.

IV Lass J, Odlind V, Irs A, Lutsar I. Antibiotic prescription preferences in paediatric outpatient setting in Estonia and Sweden. Springer Plus 2012 (submitted)

Degree of the applicant's personal contribution to the publications: In all publications Jana Lass participated in study design, data collection, analysis and interpretation of data from studies. She drafted all manuscripts and was responsible for the responses and updates throughout the review process.

# ABBREVIATIONS

| | |
|---|---|
| ADR | Adverse drug reaction |
| BNFC | British National Formulary for Children |
| EHIF | Estonian Health Insurance Fund |
| EMA | European Medicines Agency |
| EOS | Early onset sepsis |
| EU | European Union |
| FDA | Food and Drug Administration |
| GCP | Good clinical practice |
| GA | Gestational age |
| GFR | Glomerular filtration rate |
| GW | Gestational weeks |
| ICH | The International Conference on Harmonization |
| ISPE | International Society for Pharmacoepidemiology |
| LOS | Late onset sepsis |
| MA | Marketing authorisation |
| NSAID | Non-steroidal anti infective drugs |
| OTC medicines | Over-the-counter medicines |
| OL | Off-label |
| PDCO | EMA Paediatric Committee |
| PICU | Paediatric intensive care unit |
| PIP | Paediatric investigation plan |
| PK | Pharmacokinetics |
| PMA | Postmenstrual age |
| PNA | Postnatal age |
| PUMA | Paediatric Use Marketing Authorisation |
| SPC | Summary of product characteristic |
| SSRI | Selective serotonin reuptake inhibitors |
| TCH | Tallinn Children's Hospital |
| TEDDY | Task-force in Europe for Drug Development for the Young |
| TUC | Tartu University Clinics |
| UL | Unlicensed |

# DEFINITIONS

| | |
|---|---|
| Crude 1 year prevalence of drug use | Proportion of the paediatric population who had one or more prescriptions issued during the study period. |
| Medicinal product authorised for a paediatric indication | Medicine, which is authorised for use in part or all of the paediatric population and in respect of which the details of the authorised indication are specified in the SPC. |
| Off-label (paediatric) use of medicines | Use of medicines, which have a local marketing authorisation (license), but do not have paediatric indications included in the marketing authorisation. |
| Pharmaceutical excipients | Substances other than the active ingredients, which have been appropriately evaluated for safety and are intentionally included in a drug delivery system (IPEC Europe. 2008). |
| Prescription rate | Ambulatory: number of prescriptions per 1000 children in the age group / per year.<br>Hospital: number of prescriptions per 100 admissions. |
| Prescription prevalence rate | Proportion of treated children of all children in the age group. |
| Unlicensed medicines | Use of medicines without local marketing authorisation. |

# 1. INTRODUCTION

All people, no matter what their age, should have access to safe and effective medicines. Still, while approximately quarter of the global population is under 15 years of age, children are not always treated in the most safe and effective way compared to adults and have even been called "therapeutic orphans" (Shirkey 1999). Many of the currently used medicines have not been clinically tested in children, thus have no paediatric labelling and are used off-label (OL). It has been shown that paediatric prescribing habits vary greatly between countries (Conroy *et al.* 2000), however, the high rates of OL medicines use have been widely described in the Western Europe and North America (Kimland *et al.* 2012), but data are scarce about the Eastern European countries.

The medicines designed for the adult population and also studied only in adults are not always suitable for treating children. Most importantly, children and especially neonates are different from adults in terms of their body composition and drug metabolising enzymes activity, which affects the pharmacokinetic (PK) profile of the active ingredients (Bartelink *et al.* 2006), but also drug formulation excipients. Thus the way in which children absorb, distribute, metabolise and eliminate drugs cannot be predicted from adult data.

In the absence of clinical trials, data on therapeutic doses for children often comes from the clinical experience of prescribers or case reports (Ceci *et al.* 2006) resulting in the wide variety of dosing recommendations in different drug information sources. The availability of dosing information in different information sources e.g. for different paediatric age groups, including neonates has been only selectively studied for a few drugs or drug groups.

Thousands of different pharmaceutical excipients are used in medicines, which make up, on average, about 90% of each medicinal product (Haywood & Glass 2011). Ideally, an excipient is pharmacologically inactive, non-toxic, and does not interact with the active ingredients or other excipients. However, in practice few excipients meet these criteria and the safety of pharmaceutical excipients is a growing concern for those treating children and especially neonates (Hall *et al.* 2004). There are currently many unknowns relating to the effects of drug formulation excipients in children, including toxicity. Several tragedies have occurred in the paediatric population as a result of the excipients, which had been tested only in the adult population. Still to this day only very few studies have been published on that topic mainly focusing on the limited number of known to be toxic excipients. It is not known how many toxic excipients are administered to children within their medicines or neither how many of the medicines that are used in children contain toxic excipients.

Drug utilisation studies involving mainly adult patients have been previously conducted in Estonia by R.A. Kiivet.

Pharmaceutical technology studies including the investigations of pharmaceutical excipients have been previously conducted in Tartu University by professor P. Veski and professor J. Heinämäki and K. Kogermann.

# 2. REVIEW OF LITERATURE

## 2.1. Licensing of medicines

According to current legislation all marketed medicines are required to have a marketing authorisation (MA), which defines their terms of use (European Parliament and the Council of the European Union 2001).

The licensing system of medicines was introduced in the 1960s in the aftermath of the thalidomide tragedy to establish certain basic safety procedures for MA (Permanand *et al.* 2006). The Kefauver-Harris amendment to the Food Drug and Cosmetic Act in 1962 in the US and European Directive requirements for MA in 1965 were the first legislations on licensing of medicines (Wong 2007). These documents did not include any specific guidance on the licensing of paediatric medicines.

Before a new medicine is available for use in humans, it will pass through several development phases such as preclinical and clinical studies. If there is enough data on the safety and efficacy, which is relevant to a particular clinical indication and a particular age group, a manufacturer can apply for a MA for the drug. A licence is a MA issued by the licensing authority. A licensed medicine has been assessed for efficacy, safety, and quality; has been manufactured to appropriate quality standards; and when placed on the market is accompanied by appropriate product information and labelling. An approved medicine has summary of product characteristic (SPC) which outlines the indication(s), recommended dose(s), contraindications, and special warnings and precautions for use on which the licence is based (European Parliament and the Council of the European Union 2001).

Formerly, new medicines were registered in each EU member state by the local regulatory authority. In several cases, the MA of the medicinal product was only intended in countries with a large population, such as Germany, France, the United Kingdom, Italy, and Spain. Smaller countries could obtain these medicines by import from a country that had licensed the medicinal product (Breitkreutz 2008).

Since 1995 the licensing system in Europe consists of a centralised system and a decentralised or national (European member states) system. The centralised system is administered by the European Medicines Agency (EMA) and enables the product to have a EU-wide marketing authorisation. The decentralised system is under the control of the member states and the granted MA may be recognised by other member states (Irs 2009).

In Estonia the medicines licensing system is currently administered by the State Agency of Medicines (SAM, Ravimiamet), a governmental body under the Ministry of Social Affairs. Procedures to obtain MA for the medicinal product in Estonia follows the international guidelines and is generally similar to that of other EU member states. The requirements of quality, safety and efficacy of medicines are based upon the Medicinal Products Act of 2005 (http://www.sam.ee/en/marketing-authorisation-medicinal-products).

In the US the Food and Drug Administration (FDA) gives marketing approvals to medicines (http://www.fda.gov), Therapeutic Goods Administration (http://www.tga.gov.au) is Australia's regulatory authority for therapeutic goods.

### 2.1.1. Licensing of paediatric medicines

The early regulatory medicines licensing documents did not include children into the drug development processes (Saint-Raymond & Seigneuret 2005). Additionally to the ambiguous regulatory situation, there were multiple factors limiting the number of paediatric clinical trials, such as difficult recruitment to studies due to the small number of children suffering from specific condition, more complex study design than adult studies (e.g. age-specific drug formulations needed) and technical challenges e.g. constraints associated with blood sampling, especially in very young children (Kemper *et al.* 2011, Stötterb 2007).

The first paediatric medicines regulations were established as late as in the middle on 1990s as shown in Table 1.

**Table 1.** Regulatory measures to increase the study and labelling of medicines for children (adopted from Hoppu *et al.* 2008 and Wong 2007)

| Regulations | Main aim | Year of approval |
|---|---|---|
| US | | |
| The Final Rule | Manufacturers should re-examine existing data to determine whether it could be modified to include paediatric use information to the SPC | 1994 |
| Paediatric Rule | Manufacturers should conduct studies to provide paediatric information on new/marketed drugs | 1998 |
| FDA Modernisation Act (FDAMA) | Paediatric exclusivity provision for manufacturers who voluntarily conduct studies in children | 1997 |
| Best Pharmaceuticals for Children Act (BPCA) | Renewed exclusivity provision under FDAMA, additional mechanism for obtaining paediatric data for OL drugs | 2002 |
| Paediatric Research Equity Act (PREA) | Renewed requirement for paediatric studies as a law. All applications for new drugs, indication, dosage form, dosing regimen or route of administration must contain a paediatric assessment. | 2003 |
| EU | | |
| Guidance document on the clinical investigation of medicinal products in children | Guidance to the safe, efficient and ethical study of medicines in children, had no legislative authority | 1997 EU |
| Better Medicines for Children | Provided a legislative framework to facilitate getting safety and efficacy information on paediatric drugs | 2002 EU |
| Medicinal products for paediatric use | Established a legislative framework of paediatric clinical studies | 2006 EU |
| The Paediatric Regulation No1901/2006 | Established a legislative framework for increasing the availability of paediatric medicines, the paediatric information and high quality research in children | 2007 EU |

Currently, The Paediatric Regulation is directly applicable in all EU Member States, including Estonia. The main aims of the Regulation are as follows:

- to make medicines available for children through increasing the development of medicines for children by ensuring that the medicines are subject to high quality research. At the same time avoiding unnecessary clinical trials in children and not delaying the authorisation of medicines for the adult population;
- to implement a new key element of the Regulation, a mandatory Paediatric Investigation Plan (PIP) to the process of MA;
- to create a Paediatric Committee (PDCO), which is responsible for co-ordinating the EMA's work on medicines for children.

According to the Regulation:

- Patented medicines:

For new medicinal products, indications, routes of administration or formulations of already patented products, pharmaceutical companies have to submit a PIP to the PDCO. The PIP sets out a programme for the development of a medicine in the paediatric population. PDCO considers whether the proposed studies will be of significant therapeutic benefit to the paediatric population. Also if there is evidence that the medicine is likely to be ineffective or unsafe in children, or that the targeted disease occurs only in adult populations or that the medicine does not represent a significant therapeutic benefit over existing treatments, the PDCO will issue a waiver. PDCO opinion on PIP is transformed into EMA decisions. Drugs that comply with the requirement get 6-months patent extension.

- Off-patent medicines:

A new type of MA, the Paediatric Use Marketing Authorisation (PUMA) allows 10 years of data protection for off-patent products (European Parliament 2004).
In the US the paediatric medicines licensing system is somewhat more flexible than in Europe. The FDA asks pharmaceutical companies a complete Paediatric Development Plan (equivalent to PIP in EU) providing any sufficient safety data, based on the adult population. When an OL drug is used for a long period, US authorities give a paediatric authorisation based on: 1) the number of paediatric patients already treated, 2) available efficacy and safety data collected among the paediatric population, 3) the life duration of the OL product use, 4) adequate safety data based on adults. Specific and justified paediatric clinical studies are demanded only if those points are not met (Knellwolf *et al.* 2011).

Historically, in 2006 around 75% of all centrally authorised medicines were relevant for children, but only half of these had indications for using in children (http://ec.europa.eu/health/files/paediatrics/2012-09_paediatric_report-annex1-2_en.pdf). Also the studies published before the approval of the Paediatric Regulation demonstrated a low number of paediatric labelling. The proportion of paediatric medicines approved each year under the EMA Centralised Procedure from 1995 to 2005 varied between 19% and 48%, with an average level of 33%

of the total EMA approvals (9.4% in neonates) (Ceci *et al.* 2006). Of new substances registered between 1995 and 2001, 58% were of potential use in children but only a quarter of those got paediatric authorisation (Strieker *et al.* 2002) and the median percentage of drugs authorised for children during these years was 35% of the total of commercially available drugs (Ceci *et al.* 2002). The medicines for younger age groups, especially neonates were rarely approved, the improvements occurred mainly for children over the age of six (Ceci *et al.* 2006, Grieve *et al.* 2005). Improvements in licensing of medicines were greatest in the US subsequent to the Paediatric Exclusivity Provision (Grieve *et al.* 2005).

## 2.2. Paediatric drug utilisation studies

As a part of the pharmacoepidemiology, drug utilisation studies show how medicines are used in real practice and are thus useful for identifying problems in paediatric pharmacotherapy. Qualitative drug utilisation studies include the concept of appropriateness and use in addition to the prescription data also parameters such as indications, daily dose and duration of therapy (Neubert *et al.* 2008a).

### 2.2.1. Methodology of drug utilisation studies in children

There are various study designs related to the observational research, all having their advantages and limitations. Still, the choice of the most appropriate study design to be used depends on the study question.

- Case report and case series are reports of individual patients or series of patients experiencing some unexpected event and are therefore of no particular use while studying drug utilisation.
- A cross sectional study measures both exposure to drugs and occurrence of disease in an individual or population at a specific time-point (Verhamme & Sturkenboom 2011) and has been used for describing drug utilisation in children (Nasrin *et al.* 2002) and OL medicines use (Schirm & Tobi 2002). Although cross-sectional studies are quick, easy and inexpensive (Verhamme & Sturkenboom 2011) they offer no real association between the exposure and outcome.
- A cohort study is a study where a group of people with a particular disease or taking a particular drug are followed up with regard to the occurrence of an outcome of interest. They can study rare exposure and allow the analysis of time to event, but are long lasting and expensive (Verhamme & Sturkenboom 2011). Cohort studies have been used to study paediatric drug utilisation patterns over time (Hugtenburg *et al.* 2004, Thrane & Sørensen 1999).

Some of the strengths and limitations of different data collection methods are described in the Table 2.

**Table 2.** Selected strengths and limitations of data collection methods/data sources used in paediatric drug utilisation studies

| Data source | Sample size | In-hospital medicines | Ambulatory prescriptions | Follow up period | Diagnoses included | OTC medicines | Drug purchased | Recall bias |
|---|---|---|---|---|---|---|---|---|
| Medicines charts | Small | + | – | Short | + | + | + | – |
| Prescription databases | Large | – | + | Long | +/– | – | + | – |
| Surveys | Small | +/– | + | Short | + | + | +/– | + |

The common measures that are used in drug utilisation studies are the following: 1) prevalence (number of children who received at least one prescription per 100 individuals in the general population) as a measure of exposure and 2) number of prescriptions and number of medication packages (boxes) as a measure of drug consumption (Sequi *et al.* 2012).

The measurement of drug exposure/consumption in children is somewhat different from the adult studies. As an example, the defined daily doses (DDD) is a parameter that is extensively used in adult studies (especially antibiotics use studies), but it cannot be used to measure drug consumption in children, since the dose recommendations for use in children vary according to age and body weight. The DDD is the assumed average maintenance dose per day for a drug in its main indication for adults and is commonly expressed with a certain population size denominator such as patient days, bed days, admission days, inhabitant days (http://www.whocc.no/filearchive/publications/2010guidelines.pdf.). The popularity of the DDD mainly originates from its general applicability and its advantage that comparison of the amount of drug use between different (international) settings and between different drugs based on grouped dispensing data is possible, without requiring utilisation data on the individual patient level. Based on the narrow range of body weights in the neonatal population, the investigators have recently developed a set of neonatal DDDs for antibiotics (Liem *et al.* 2010), however no studies using this method were currently identified.

The limitations of using prescription rate as a measure of drug exposure is the lack of information on the OTC medicines use.

According to a recently published literature review, the methodological quality of the paediatric drug utilisation studies is rather low. Of the 22 studies, all evaluating drug prescriptions published between 1994 and 2008, 10 reported the prevalence of drug prescriptions and 16 reported the number of prescriptions and/or medication packages. Only 12 studies reported the prevalence or the prescriptions of the most commonly prescribed therapeutic subgroup and 5 reported the prevalence of the most commonly prescribed drugs. All studies defined age groups in different ways, and there was no consistency in the choice of groups. The standard deviation (SD) was reported in 5, the range of values in 6, the 95 % CI in 5, and the median in 4 studies. Statistical analyses were performed in only 12 studies. Only in five of the 18 studies in which the mean was used was the SD also reported (Sequi *et al.* 2012).

In recent years, national and regional prescription and health maintenance organisation databases have been most commonly used in paediatric pharmacoepidemiological studies followed by data collected from physicians and questionnaires administered to parents (Sequi *et al.* 2012).

Claims databases are used in the US and health care databases in Europe. Health care databases consist of pharmacy, primary care and hospital databases (Verhamme & Sturkenboom 2011). Neubert *et al.* evaluated all of the 16 population-based European healthcare databases listed on the website of International Society of Pharmacoepidemiology (ISPE) and 9 databases known by

the members of the Task-force in Europe for Drug Development for the Young (TEDDY) pharmacoepidemiology expert group which could be used for paediatric medicines research. They found that all databases that participated in the survey collect information about prescription drugs and the units dispensed or prescribed, most of them also record the dosage regimen and are therefore particularly useful for studying drug utilisation (Neubert *et al.* 2008a).

### 2.2.2. Paediatric drug utilisation studies in practice

A great number of paediatric drug utilisation studies are conducted and published worldwide, however few have been focused on the use of medicines in neonates. For example, of the 128 paediatric drug utilisation studies published between 1994 and 2008, only 21 were analysing all of the drug groups and of these in turn only 11 evaluated drug prescriptions in the entire paediatric population, with 3 involving only infants (Clavenna & Bonati 2009). However, as a result of the increasing number of OL medicines use studies in neonatal units, the neonatal medicines use pattern of recent years has been relatively well described.

Most of the studies have been focusing on a specific drug class, most commonly on psychotropic medicines (46% of studies) and antibiotics (30%). Also great heterogeneity exists regarding the study types and parameters such as study methodology (e.g. prospective vs. retrospective study), population (sample size, age group) or setting (outpatient or hospitalised children, general practice or specialised unit, certain regional area) making the results of the studies hardly comparable (Clavenna & Bonati 2009).

Furthermore, markedly different data have been collected in trials excluding for example standard intravenous replacement solutions, blood products, oxygen therapy (Conroy *et al.* 1999), topical anaesthetic creams (Turner *et al.* 2009), drugs given via nebulisation or ear, eye and nose drops (Jain *et al.* 2008).

**Ambulatory practice.** The prescription prevalence rate in the paediatric ambulatory practice has been ranging from 51% in Denmark and Sweden to 70% in Greenland, and the prescription rate from 0.8 in Norway to 3.2 in the US (Clavenna & Bonati 2009, Olsson *et al.* 2011). Drug use has been the highest among infants decreasing until adolescence (Schirm *et al.* 2000).

Most commonly prescribed drug groups were systemic antibiotics, respiratory system medicines, analgesics, dermatologicals and ophthalmologicals (Mühlbauer *et al.* 2009, Schirm *et al.* 2000, Straand *et al.* 1998, Sturkenboom *et al.* 2008, Thrane & Sørensen 1999) while the most frequent active ingredients were amoxicillin, paracetamol, cetirizine and salbutamol (Bazzano *et al.* 2009, Morales-Carpi *et al.* 2010).

**Mixed paediatric population in the hospital, including neonates.** The median number of prescriptions per patient was from three (Pandolfini *et al.* 2002, t Jong *et al.* 2002) to six (Santos *et al.* 2008) ranging from 1 to 18. Similarly to

ambulatory prescribing pattern, the mean number of medications was higher in children <1 year old compared to other age groups (Santos *et al.* 2008).

The major therapeutic subgroups prescribed were the same as in the ambulatory practice – antibacterials for systemic use, respiratory system medicines and analgesics/antipyretics (Pandolfini *et al.* 2002, Santos *et al.* 2008).

The list of most frequently used active ingredients was more heterogeneous than in ambulatory practice, the most commonly used medicines being vitamin D, paracetamol, amoxicillin, beclomethasone, fluconazole, cefotaxime, caffeine, prednisolone, benzylpenicillin and nystatin (Hsu & Brazelton. 2009, Lindell-Osuagwu *et al.* 2009, Palčevski *et al.* 2012, Pandolfini *et al.* 2002, Santos *et al.* 2008).

**Hospitalised neonates** received a median number of three to four (Lindell-Osuagwu *et al.* 2009, Nguyen *et al.* 2011, Oguz *et al.* 2012) to 8.5 medicines (Kumar *et al.* 2008) ranging from 0–132.

Of all patients 72.5% (Palčevski *et al.* 2012) up to 99% (Neubert *et al.* 2010) received at least one drug during the hospitalisation.

According to the ATC classification system again antiinfectives for systemic use were prescribed most often followed by the central nervous system and respiratory system medicines (Neubert *et al.* 2010).

Most commonly used active ingredients were ampicillin, gentamicin, caffeine, paracetamol, cefotaxime, heparin, vitamins D and K, salbutamol, furosemide, dopamine, midazolam and benzylpenicillin (Clark *et al.* 2006, Hsu & Brazelton 2009, Kumar *et al.* 2008, Neubert *et al.* 2010, O'Donnell *et al.* 2002, Oguz *et al.* 2012, t Jong *et al.* 2001).

To conclude, the uniform methodology or large international studies could give more comparable data on the paediatric and neonatal medicines use pattern.

## 2.3. Off-label (OL) and unlicensed (UL) use of medicines in children

### 2.3.1. Definitions

One of the first definitions of OL/UL use of medicines was published more than 10 years ago (Turner *et al.* 1998) and later used in modified version. This defines OL use as use of a drug in situations not covered by the product license (e.g. administration of a greater dose or more often, administration for indications not described in the license, administration to children outside the age range for which the product is licensed, the use of alternative routes of administration, and use when the product is contraindicated). The UL use is defined as modifications to licensed drugs, drugs that are licensed but the particular formulation is manufactured under a special license, new drugs available under a special manufacturing license (such as caffeine injections for

apnoea of prematurity), use of chemicals as drugs, drugs used before a license has been granted, and imported drugs.

Turner's definitions were soon abandoned, probably due to the practicalities depending on the study methodology. For example as it is complicated to evaluate the real intake of medicines prescribed to ambulatory patients, it is also difficult to determine whether these drugs are used for licensed indications or in a licensed dose (McIntyre *et al.* 2000, Olsson *et al.* 2011).

In earlier drug utilisation studies generally broader definitions for OL were used, e.g. a drug use was classified OL if the dose, dosing frequency, or the age/weight of the patient was not in agreement with the labelling. In more recent studies, OL was mostly defined as a result of the lack of paediatric information and the use of a non-approved dose in relation to age (Kimland *et al.* 2012).

To overcome the unclarity around the terminology a Delphi survey was conducted in 2005 to develop shared definitions for UL/OL drug use in children to be used for research and regulatory purposes (Neubert *et al.* 2008b). The following definitions were created:

- OL use: all paediatric uses of a marketed drug not detailed in the SPC with particular reference to therapeutic indication, therapeutic indication for use in subsets, appropriate strength (dosage by age), pharmaceutical form and route of administration.
- UL use: all uses of a drug, which has never received a European MA as medicinal for human use in either adults or children.

A widely acceptable definition on the OL/UL use of medicines was still not agreed to extend to an international level (i.e. ICH—International Conference on Harmonisation) as the EMA opinion was that there is no need to do so from the regulatory point of view (Neubert *et al.* 2008a).

No uniform definitions across the studies exist for OL/UL medicines use making comparisons between studies very difficult if not impossible. As shown in Table 3 the OL and UL definitions are also overlapping. For example when adult medicine is modified (e.g. tablet is crushed) or when no paediatric dosage is available, medicines have been classified both – OL or UL. The list of definitions used in previous studies reveals many similarities but also crucial differences.

The OL use has been itself divided further to the OL with strong scientific support, and OL with limited or no scientific support (Radley *et al.* 2006). Some studies have not distinguished between OL and UL categories (Neubert *et al.* 2008b), some have abandoned the OL/UL definitions and assess the age-appropriateness of medicines (dose capability, suitability of the dosage form and inclusion of potentially harmful excipients) finding that paediatric medicines may not be age-appropriate, even if authorised (van Riet-Nales *et al.* 2011).

**Table 3.** Variability of definitions used by investigators while describing UL/OL prescribing

| Category | OL category consists | Reference |
|---|---|---|
| OL | D, F, I, A, RA, CI | (Turner *et al.* 1998) |
| | D, F, I, A, presentation* | (Carvalho *et al.* 2003) |
| | D, I, A, RA, CI, inadvisable co-prescription | (Horen *et al.* 2002) |
| | D, F, I, A, RA, formulation modification | (Pandolfini *et al.* 2002) |
| | D, F, I, A/weight, RA, CI, dosage form | ('t Jong *et al.* 2002) |
| | A, D, RA | (Bajcetic *et al.* 2005) |
| | A | (McKinzie *et al.* 1997, Pasquali *et al.* 2008, Shah *et al.* 2007) |
| | Clinically accepted OL indications | (Volkers *et al.* 2007) |
| UL | Formulation modifications, manufactured under special license, use of chemicals as drugs, used before a licence has been granted, imported drugs licensed for use in another country but not in UK | (Conroy *et al.* 1999, Turner *et al.* 1998) |
| | No MA | (Tuleu *et al.* 2010) |
| | No MA, formulation modification, extemporaneous | (Tuleu C. 2007) |
| | No MA, not recommended in children | (Serreau *et al.* 2004) |
| | Formulation modification | (Gavrilov *et al.* 2000) |
| | Formulation modification, CI, no paediatric dosage | ('t Jong *et al.* 2002) |
| | Not approved for use in children, CI, no paediatric dosage | (Carvalho *et al.* 2003) |
| | 'Unlicensed' for age | (Volkers *et al.* 2007) |
| | CI, extemporaneous, safety / efficacy in children not established | (Santos *et al.* 2008) |
| | Extemporaneous, drugs used as ''special'' formulations, without license | (DellAera *et al.* 2007) |

MA, marketing authorisation; D, dose; F, frequency; I, indication; A, age; RA, route of administration; CI, contraindication

*OL presentation – prescribers were not aware, that they are using a low viscosity paracetamol formulation (1ml = 30 drops) as best known product on the market is 1ml = 16–20 drops. Paracetamol was prescribed as though there were 20 drops / ml, leading to under-prescription of up to 50% less than intended

### 2.3.2. Extent of OL/UL use of medicines

As mentioned above the OL/UL prescribing has been extensively studied though mainly in Western Europe and US. According to the Neubert *et al*. a total of 66 publications relating to OL/UL drug use in children were identified from PubMed database between 1995 and 2005 (Neubert *et al.* 2008b).

Pandolfini *et al.* published a first systematic review of OL/UL use studies in 2003. They compared paediatric OL/UL drug use in seven European countries and across different settings such as neonatal and paediatric hospital wards and community setting. The OL/UL drug prescribing rates ranged from 19% of patients in community setting to 97% in neonatal wards, and from 11% to 80% prescriptions, respectively (Pandolfini & Bonati 2003).

A review article by the same authors published two years later included 30 studies from Medline and Embase from 1985–2004. Eleven studies involved paediatric hospital wards, seven neonatal hospital wards, and twelve the community setting. Most of the studies (21/30) were prospective. Similar OL/UL prescription rates were described as in their previous review – from

11% to 80%. The proportion of patients receiving at least one OL/UL drug on the neonatal wards was much higher than in the paediatric wards and ranged from 80% to 97% vs. 36 to 92%. The rates of OL/UL prescriptions in the community varied from 55% to 80% (Pandolfini & Bonati 2005).

Cuzzolin *et al.* published a review article in 2006. They identified 52 studies conducted between 1990 and 2006 assessing the OL/UL use of medicines from Medline and Embase database. Again the extent of paediatric UL/OL use was found to be higher in neonatal, paediatric intensive care and oncology wards, compared with primary care. OL/UL use ranged from 3.3 to 56% of prescriptions in community practice to 36 to 100% in hospital settings (median 40%) (Cuzzolin *et al.* 2006).

The most recent review by Lindell-Osuagwu *et al*. describes the OL/UL drug use in hospitalised children. Data were retrieved through electronic searches of Medline and International Pharmaceutical Abstracts. They included 24 studies from 12 different countries and found the proportion of children with at least one prescription for OL/UL drug ranging from 36 to 100%, including OL prescriptions rate from 18 to 60% and of UL prescriptions rate from 0 to 48%. Again UL/OL prescription rate was higher in neonates and small infants as compared with all children (98% vs. 88%, respectively) but the differences between these two groups were not as pronounced compared to the previous reviews (Lindell-Osuagwu *et al.* 2009).

With the literature review using Google scholar and Medline database with the search terms "off-label", "unlicensed", "children", "neonates" in May 2012 altogether 40 studies on the hospitalised children (including 7 in the neonatal wards) and 17 ambulatory OL/UL medicines use study performed between 1997 and 2012 were identified (Tables 4 and 5). Only studies in which the rates of OL/UL medicines use were reported were included. Again the OL use was higher in the hospital setting (median 35% in mixed population including neonates, 40% excluding neonates and 49% in pure neonatal studies) compared to median of 20% in the ambulatory studies. In contrast, more UL prescriptions were issued in the ambulatory setting (median 16%, range 0.3–17%) than in the hospital (median 9% in mixed population studies excluding neonates and median 12% in both – neonatal studies and mixed population studies including neonates). Studies have been mainly conducted in industrialised countries and seldom in low- or middle-income countries including Eastern Europe. Of the 20 countries where hospital-based OL/UL use has been studied, UK predominates with 8 studies, followed by The Netherlands (5 studies), Germany and Italy (4 in both) and Israel (3 studies). In other countries two or less hospital based OL studies have been conducted and published.

Compared to the hospital-based OL use studies the ones in ambulatory setting have been conducted even in few countries. As shown in Table 5 of eight countries again The Netherlands (4 studies) and UK (3 studies) prevail, followed by France, Germany, Sweden and United States (2 studies in each) and 1 in Italy and Spain. No studies originate from Eastern Europe or from the developing world.

**Table 4**. Review of the OL/UL rate studies in paediatric and neonatal hospital wards

| Reference/ country | Methodology, study duration | Paediatric wards / patients | Patients (n) | Age | Pre-scriptions (n) | OL % | UL % | Patients receiving OL/UL % | Most common reason for OL/UL |
|---|---|---|---|---|---|---|---|---|---|
| Mixed population studies including neonates | | | | | | | | | |
| US (McKinzie *et al.* 1997) | R 1 m | Emergency | 359 | <18y | NR | NR | NR | 43 | Age |
| UK (Turner *et al.* 1998) | P 13 w | Medical, surgical | 609 | 4d–20y | 2013 | 18.2 | 6.9 | 36 | Age |
| UK (Turner *et al.* 1999) | P 13 w | Surgical, medical, neonatal surgical, cardiac intensive care, general PICU | 1046 | 1d–18y | 4455 | 35 OL or UL | | 48 | NR |
| UK, Sweden, Germany, Italy, the Netherlands (Conroy *et al.* 2000) | P 4 w | General | 624 | 4d–16y | 2262 | 39 | 7 | 67 | Dose and frequency |
| The Netherlands (t Jong *et al.* 2000) | P 5 w | Medium-care, Intensive-care | 238 | 0–17y | 2139 | 18 | NR | 92 | Modification |
| The Netherlands (t Jong *et al.* 2001) | P 5 w | Paediatric, PICU | 237 | 0–17y | 2139 | 18 | 48 | 90% of patient-days contained UL drugs or OL prescription | Dose |
| The Netherlands (t Jong *et al.* 2002) | P 19 w | Paediatric, neonatology | 293 | 0–16.7y | 1017 | 44 | 28 | 92 | OL: dose/frequency UL: modification |
| UK (Dick *et al.* 2003) | R Over 6 m | Gastro-enterology outpatient | 308 | 20d–17y | 777 | 37 | 12 | NR | OL: indication UL: modification |
| Israel (Gavrilov *et al.* 2003) | R and P 3 and 4 m | PICUs | 158 | 6d –18y | 874 | 40 | 41 | 83 | Age |
| Germany (Neubert *et al.* 2004) | P 8 m | Isolation | 178 | 5d–17y | 740 | 26 | 0.4 | 52 | Age |

| Reference/ country | Methodology, study duration | Paediatric wards / patients | Patients (n) | Age | Pre-scriptions (n) | OL % | UL % | Patients receiving OL/UL % | Most common reason for OL/UL |
|---|---|---|---|---|---|---|---|---|---|
| Serbia and Montenegro (Bajcetic *et al.* 2005) | P 2 y | Cardiology | 544 | 1d–18y | 2037 | 47 | 11 | 76 | Dose |
| Switzerland (Di Paolo *et al.* 2006) | P 6 m | NICU, PICU, intermediate care, medical, surgical | 60 | 3d–14y | 483 | 25 | 24 | 100 | Lack of information |
| US (Eiland & Knight. 2006) | P 6 m | General, emergency, PICU | 403 | 3d–18y | 1383 | 31 | NR | 31 | Indication |
| US (Shah *et al.* 2007) | R 1 y | Paediatric tertiary care hospitals | 355409 | <18y | NR | NR | NR | 79 | Age |
| Germany (Hsien *et al.* 2008) | P 6 m | Paediatric | 417 | 1d–40y | 1812 | 31 | 0 | 61 | Age |
| US (Pasquali *et al.* 2008) | R 1 y | Database, inpatients, tertiary care paediatric hospitals | 31 432 | <18y | NR | 69 | NR | 78 | Age |
| Finland (Lindell-Osuagwu *et al.* 2009) | P 2 | NICU, general, surgical | 141 | <18y | 629 | 36 | 13 | 63 – 91 | Lack of information |
| UK, Italy, Greece (Porta *et al.* 2010) | P 2 w | NICU, general | 616 | <17y | 1244 | 4.1 NICU 1.7 others | NR | NR | Dose |
| Canada (Doherty *et al.* 2010) | R 1 m | NICU, PICU, operating room/post-anaesthetic care | 227 | 0–15y | 3391 | 60 | NR | 89–99 | Lack of information |
| Palestine (Khdour *et al.* 2011) | P 5 w | 4 paediatric wards (NICU, medical and surgical ward) | 387 | <18y | 917 | 35.3 | 7.1 | 49.6 OL 10.1 UL | NR |

| Reference/ country | Methodology, study duration | Paediatric wards / patients | Patients (n) | Age | Pre-scriptions (n) | OL % | UL % | Patients receiving OL/UL % | Most common reason for OL/UL |
|---|---|---|---|---|---|---|---|---|---|
| Croatia (Palčevski *et al.* 2012) | P 1 d each month during a 12 m period | Paediatric department | 691 | 1d–20y | 1643 | 13 | 12 | 48 | NA |
| Sweden (Kimland *et al.* 2012) | R two separate 2-day-periods | 41 hospitals | 2947 | <18y | 11294 | 41 | NR | 60 | Lack of information |
| Neonatal studies | | | | | | | | | |
| UK (Conroy *et al.* 1999) | P 13 w | NICU | 70 | Neonates | 455 prescription episodes* | 54.7 | 9.9 | 90 | Dose |
| Israel (Barr *et al.* 2002) | P 4 m | NICU | 105 | Neonates | 525 | 59 | 16 | 93 | Dose |
| Australia (O'Donnell *et al.* 2002) | P 10 w | NICU | 97 | Infants | 1442 | 47 | 11 | 80 | Indication / extemporaneous preparation |
| Italy (DellAera *et al.* 2007) | P 2 m | NICU | 34 | Neonates | 176 | 51 | 12 | 88 | Lack of information |
| Germany (Neubert *et al.* 2010) | P 11 m | NICU | 183 | Neonates | 1978 | 28 | 6 | 70 (100 for very preterm) | Lack of information |
| France (Nguyen *et al.* 2011) | P 4 m | Neonatal | 65 | Neonates | 265 | 30 | 17 | 71 | Age |
| Turkey (Oguz *et al.* 2012) | P 24h | NICUs | 464 | Neonates | 1315 | | 29 | 48 – 63 | OL: Lack of information UL: modification |
| Studies excluding neonates | | | | | | | | | |
| Australia (Turner. 1999) | P 5 w | Surgical and general | 200 | 49d–18y | 735 drug episodes † | 16% OL or UL | | 36 | OL: age |

| Reference/ country | Methodology, study duration | Paediatric wards / patients | Patients (n) | Age | Pre-scriptions (n) | OL % | UL % | Patients receiving OL/UL % | Most common reason for OL/UL |
|---|---|---|---|---|---|---|---|---|---|
| Israel (Gavrilov *et al.* 2000) | R<br>2 m | General ambulatory | 132 | 1m–18y | 222 | 26 | 8 | 42 | Dose |
| Italy<br>(Pandolfini *et al.* 2002) | P<br>12 w | General | 1461 | 1m–14y | 4265 | 60 | 0.2 | 89 | Dose |
| Brazil (Carvalho *et al.* 2003) | P<br>6 w | PICU | 51 | 1m–13y | 747 | 49.5 | 10.5 | 100 | Dose |
| UK<br>(Conroy *et al.* 2003) | P<br>4 w | Oncology | 51 | 0.6y–16.3y | 569 prescription episodes* | 26 | 19 | 100 | OL: Dose<br>UL: Modification |
| France (Serreau *et al.* 2004) | P<br>6 m | Psychiatry | 336 | 3y–15y | 295 | 25 | 23 | NR | OL: contraindicated<br>UL: not recommended for children |
| India<br>(Jain *et al.* 2008) | P,<br>2 m | General | 600 | 1m–12y | 2064 | 50.6 | NR | 90 | Dose |
| Brazil (Santos *et al.* 2008) | P,<br>5 m | General | 272 | 1m –16y | 1450 | 40 | 5.5 | 82 | OL: Dose / frequency |
| The Netherlands (van den Berg & Tak 2011) | P,<br>2 w | Oncology | 39 | 0.25y–17y | 268 | 43 | – | 87 UL | NR |
| Population not specified | | | | | | | | | |
| UK<br>(Conroy & Peden. 2001) | P<br>4 w | Acute medical and Surgical | NR | NR | 715 prescription episodes* | 33% | 0% | NR | Dose |
| Northern Ireland<br>(Craig *et al.* 2001) | P<br>2 m | Non-specialised | 32 | NR | 237 | 19.4 | 3.4 | NR | NR |

NICU, neonatal intensive-care unit; ICU, intensive care unit; PICU, paediatric intensive care unit; MCU, medium care unit; SICU, surgical intensive care unit; P, prospective; R, retrospective; d, day; y, year; m, month; w, weeks; NR, not reported

*Prescription episodes: each episode being a course of a drug or a single one off dose.

† Drug episodes: the sum of the number of different drugs administered during each patient admission.

**Table 5.** Review of the OL/UL studies in the community setting

| Reference | Methodology, data source, study period | Prescribers | Patients (n) | Age of patients | Prescriptions (n) | OL% | UL% | Patients receiving OL/UL% | Main reason for OL/UL |
|---|---|---|---|---|---|---|---|---|---|
| UK (McIntyre *et al.* 2000) | R, electronic prescribing system, 1y | Single suburban GP | 1175 | ≤ 12y | 3,347 | 10.5 | 0.3 | NR | Dose |
| France (Chalumeau *et al.* 2000) | P, survey, 1d | 77 office-based paediatricians | 989 | 2d –15y | 2,522 | 29 | 4 | 56 | Age |
| Germany (Bucheler *et al.* 2002) | R, electronic database, 3m | 6886 office based doctors | 455 661 | 0–16y | 1.74 million | 13.2 | NR | NR | Lack of information |
| The Netherlands (Jong *et al.* 2002) | Population based cohort, electronic database, 1y | 150 GP | 13 426 | 0–16y | 17,453 | 13.6 | 15.3 | NR | Lack of information |
| The Netherlands (Schirm & Tobi 2002) | Cross-sectional, prescription database | NR | 19 283 | <16y | 68,019 | 22.7 | 16.6 | NR | Lack of information |
| France (Horen *et al.* 2002) | P, 4m | 39 office-based physicians | 1419 | <16y | NR | 18.9 | NR | 42 | Indication |
| The Netherlands (Schirm *et al.* 2003) | Cross-sectional, pharmacy dispensing records, 1y | NR | 18 943 | <16y | 66 222 | 20.6 | 16.6 | NR | NR |
| Sweden (Ufer *et al.* 2003a) | R, electronic prescription database,1y | NR | NA | <16y | 575526 prescription items | 20.7 | NR | NR | NR |
| The Netherlands (t Jong *et al.* 2004) | P, population-based cohort study, GP | GP | 13426 | <16y | 5253 | 20.3 | 16.8 | NA | OL: Dose UL: |

| Reference | Methodology, data source, study period | Prescribers | Patients (n) | Age of patients | Prescriptions (n) | OL% | UL% | Patients receiving OL/UL% | Main reason for OL/UL |
|---|---|---|---|---|---|---|---|---|---|
| | practice database, 1y | | | | | | | | Modification |
| Scotland (Ekins-Daukes *et al.* 2004) | Electronic questionnaire, 1y | 161 GP practices | 167865 | <16y | NR | NR | NR | 26 | Dose |
| Italy (Pandolfini *et al.* 2005) | P, 13 weeks | GP practices | 9917 | <12y | 8476 | 17 | NR | 17 | Indication |
| US (Radley *et al.* 2006) | P, survey, 1y | NR | NR | NR | 725 million drug mentions among sampled drugs | 21 | NR | NR | |
| UK (McCowan *et al.* 2007) | P, periods between 2001- 2004 | 1188 GP practices | 17 163 | <16y | NR | NR | NR | 6.1 | Dose |
| US (Yoon *et al.* 2007) | R, 1y | Health care utilisation database | 4317 | <18y | 19109 prescription claims | 50 | NR | 42 to 53% | OL: Age |
| Germany (Mühlbauer *et al.* 2009) | R, Prescription database, 1y | Health insurance fund database | Approximately 289000 | <16y | 1429981 | 3.2 | NR | NR | NR |
| Spain (Morales-Carpi *et al.* 2010) | P, 14m | Questionnaire in the hospital emergency room | 462 | <14y | 667 | 51 | NR | 68 | OL: Dose / frequency |
| Sweden (Olsson *et al.* 2011) | R, Prescription database, 1y | Swedish Prescribed Drug Register | 968 465 | <18y | 2.19 million | 13.5 | NR | NR | OL: Lack of information |

P, prospective; R, retrospective; Y, year; m, month; NR, not reporte

### 2.3.3. OL use according to the therapeutic groups and products

Drug groups with the highest percentages of ambulatory OL use have found to be varying. These include cardiovascular medicines (Olsson *et al.* 2011, Radley *et al.* 2006), urologicals or sex hormones (mainly oral contraceptives) (Olsson *et al.* 2011, Schirm & Tobi 2002), ophthalmologicals/otologicals (Schirm *et al.* 2003), antidepressants (Lee *et al.* 2011, Volkers *et al.* 2007) and more specifically selective serotonin reuptake inhibitors (SSRIs) (Martin & Conroy. 1998), hypnotics (e.g. melatonin) and drugs for the musculoskeletal system (mainly non-steroidal anti-inflammatory drugs, NSAIDs) (Olsson *et al.* 2011) or respiratory medicines (Morales-Carpi *et al.* 2010, t Jong *et al.* 2004). It has been found that sixty percent of antidotes and poison treatment agents of children do not correspond to the demands of licensing systems (Lifshitz *et al.* 2001).

Often used OL products found in published neonatal studies are benzyl-penicillin (Conroy *et al.* 1999, Nguyen *et al.* 2011), amikacin (DellAera *et al.* 2007, Nguyen *et al.* 2011), furosemide, metoclopramide, fentanyl, salbutamol, paracetamol (Carvalho *et al.* 2003), ranitidine, tobramycin (DellAera *et al.* 2007), morphine, theophylline and aminophylline (O'Donnell *et al.* 2002).

### 2.3.4. What problems may OL/UL use of medicines cause?

The OL use of medicines is legal and sometimes the best practice. An example is the recommended use of gentamicin in the combination with ampicillin or penicillin in the empirical treatment of neonates at risk of early onset neonatal sepsis (Metsvaht *et al.* 2010) despite the lack of neonatal drug information in the Estonian SPC of gentamicin. The use of UL is neither illegal. The Article 5.11 of Directive 2001/83 allows using an UL medicinal product to meet the special needs of an individual patient under the direct personal responsibility of prescriber.

Real negative effects of OL/UL use of medicines have hardly been demonstrated in clinical practice or trials. Still, the suspected problems associated with OL/UL use of medicines are the following:

- Lack of suitable paediatric formulation (Tuleu *et al.* 2010) leading to non-compliance and potential for treatment failure;
- Lack of licensed paediatric doses, varying dose ranges in different drug information sources (Ceelie *et al.* 2010) leading to medication errors (Conroy 2011). There was for example underdosing of antiretrovirals in the UK partly attributable to confusing and inconsistent dosage strategies, failure to increase the dose with increases in height and weight or rounding down of doses, limitations in formulation (Menson *et al.* 2006).
- Lack of long-term safety and efficacy data (Stewart *et al.* 2007), risk of ADRs probably increased while OL medicines were used (Santos *et al.* 2008);

- Continuity of care after discharge from hospital – availability of OL/UL medicine in a public pharmacy once the patient is discharged, no reimbursement (Di Paolo *et al.* 2006, Wong *et al.* 2006);
- Concerns about the quality of UL product and compliance with Good Manufacturing Practice (GMP) by the manufacturer;
- Adequacy of the patient information – the language in package inserts of UL drugs is usually not the same as the official language in the country (Di Paolo *et al.* 2006);

Still, despite the aforementioned problems, there are currently large gaps in our understanding of how OL use affects children in real life situations (Smith *et al.* 2012).

Adverse drug reactions (ADRs) in children are a significant public health issue and have been associated with OL prescribing as shown by the prospective surveillance study in paediatric inpatients over a 9-month period. The OL prescriptions were responsible for 38% of inpatient ADRs and for 42% of the ADRs occurring in the community that led to hospitalisation. Urticaria, vomiting, rash and tremor were the most common ADRs. Eight ADRs (20%) were classified as severe (Impicciatore *et al.* 2002).

Horen *et al*. investigated the potential relationship between OL drug use and increased risk of ADRs in paediatric outpatients in France with a prospective survey of drug prescribing in office-based paediatricians. They found that the relative risk of ADRs with OL drug use was 3.44 (95% CI 1.26, 9.38), particularly when it was due to an indication different than that defined in the SPC (relative risk 4.42; 95% CI 1.60, 12.25) (Horen *et al.* 2002).

Ufer *et al.* investigated the extent and characteristics of OL prescribing for paediatric outpatients among drugs reported to have caused an ADR with a retrospective, cross-sectional, observational analysis of spontaneous ADR reports in Sweden in the year 2000. They identified 112 patient-linked reports corresponding to 158 ADRs of which 31% were serious. OL drug prescribing was 42.4% and it was more frequently associated with serious than non-serious ADRs and mostly due to a non-approved age or dose (Ufer *et al.* 2004).

Aagaard *et al*. analysed spontaneous ADR reports for children submitted to the Danish national ADR database from 1998 to 2007 with the aim to identify ADRs associated with OL prescribing. Of the 4388 of reported ADRs 17% were associated with OL use, 60% of them were serious. More than half of OL ADRs occurred in adolescents and serious ADRs due to OL prescribing were more likely to be reported for hormonal contraceptives, anti-acne preparations and allergens (Aagaard & Hansen. 2011).

Still, despite the generous amount of publications relating the OL use with ADRs and the magnitude of the risk remains unclear (Smith *et al.* 2012). A recent review concluded that although the results of previous studies have indicated that there may be some association between OL/UL medicine use and ADR risk there is still a lack of clarity (Mason *et al.* 2012).

### 2.3.5. Data sources for paediatric medicines information

As there is often a lack of paediatric data in official drug information sources such as the SPC, the information necessary for treating children is retrieved from paediatric textbooks, national formularies, guidelines etc. Differences in preference of drug information source exist between countries, hospitals, and even between physicians in the same institution (Kemper *et al.* 2011). For example, British community pharmacists most often use the British National Formulary (BNF) or the package insert leaflet for getting the paediatric medicines information rather than specialist formularies or guidelines (Stewart *et al.* 2007).

Different source documents have also been used to classify medicines into the OL category by investigators as shown in Table 6. The availability and reliability of paediatric drug dosing guidelines in medicines information sources varies.

**Table 6.** Source documents used by investigators for categorising medicines into OL/UL

| Source | Description | Author(s) / reference |
|---|---|---|
| Official drug information | SPC | (Hsien *et al.* 2008, Jong *et al.* 2002, McIntyre *et al.* 2000, Mühlbauer *et al.* 2009, Schirm & Tobi 2002) |
| | USP DI 2001 | (Carvalho *et al.* 2003, Yoon *et al.* 2007) |
| | Swedish catalogue of medical products (FASS) | (Kimland *et al.* 2007) |
| Official drug information combined with the expert opinion | Micromedex database | (Carvalho *et al.* 2003, Yoon *et al.* 2007) |
| | BNFC | (Conroy *et al.* 1999, Conroy *et al.* 2003, Dick *et al.* 2003, Jain *et al.* 2008, McCowan *et al.* 2007, McIntyre *et al.* 2000, Porta *et al.* 2010, Turner *et al.* 1998, Turner 1999) |
| National compendiums (product licenses summarised) | The Association of the British Pharmaceutical Industry's data sheet compendium | (Conroy *et al.* 1999, Conroy *et al.* 2000, Conroy *et al.* 2003, Dick *et al.* 2003, Turner *et al.* 1998, Turner 1999) |
| | Repertorium (Dutch) | (Conroy *et al.* 2000, t Jong *et al.* 2000) |
| | *Rote Liste* (Germany) | (Conroy *et al.* 2000, Hsien *et al.* 2008, Mühlbauer *et al.* 2009) |
| | Israel Drug Compendium | (Gavrilov *et al.* 2000) |
| | Vidal (French) | (Chalumeau *et al.* 2000, Serreau *et al.* 2004) |
| | Swiss Drug Compendium | (Di Paolo *et al.* 2006) |
| Package insert | | (Conroy *et al.* 1999, Conroy *et al.* 2003, Di Paolo *et al.* 2006, Gavrilov *et al.* 2000, McIntyre *et al.* 2000, Porta *et al.* 2010, Turner *et al.* 1998, Turner 1999) |

| Source | Description | Author(s) / reference |
|---|---|---|
| National formularies | Informatore Farmaceutico (Italy) | (Conroy *et al.* 2000, Porta *et al.* 2010) |
| | Greek National Formulary | (Porta *et al.* 2010) |
| | Sweden | (Conroy *et al.* 2000, Ufer *et al.* 2003a) |
| Physician's Desk Reference | Israel | (Gavrilov *et al.* 2000) |
| | Paediatric drug reference book Medicines for Children | (Conroy *et al.* 2003) |

SPC – Summary of product characteristic
*Of the 30 studies conducted from 1998 to 2012, in 6 the manufacturer was contacted, 1 to 8 sources were used for classification drugs OL, 11 used only one source.

Description of different information sources:

- SPC: a legal document approved as part of the marketing authorization (MA) and its information is updated throughout the life cycle of the product as new data emerge. The drug manufacturer submits a dossier to the Medicine Competent Authority with a proposed SPC. A limitation of the SPC is that the data included is from the individual companies proposal to the regulatory authorities. The indications that are not claimed by the manufacturer are not included into the SPC.
- Micromedex database (including NeoFax database for neonatal medicines): contain both FDA-approved or "labelled" indications as well as unapproved or "off-label" indications for drug therapy which are the result of ongoing review and recommendations from the worlds' medical journals by the experts (http://www.micromedex.com/ evidence/). Smith *et al.* examined further the drugs without FDA-labelling for paediatric use to identify the strength of the evidence behind each indication according to the Micromedex website. They found that 41.7% of drugs have indications for which the strength of evidence is category C, meaning the evidence for use in paediatric patients is based on expert opinion, consensus, case reports, or case series, but not clinical trials (Smith *et al.* 2012). Similarly, Yoon et al. found that 27% of all drugs listed in the expert opinion-based Harriet Lane Handbook were not approved by the FDA for use in children (Yoon *et al.* 2006).
- BNF and BNFC: use a variety of sources for its information such as SPC, expert advisors, systematic literature review (staff editors monitor core medical and pharmaceutical journals, databases including the Cochrane Library and various web-based resources), consensus guidelines, textbooks and reference sources, statutory information, comments from readers and industry. Expert advisers provide an opinion in areas of controversy or when reliable evidence is lacking and advise on areas where BNF diverges from SPC (http://www.bnf.org/bnf/org_450015.htm).

An alarming difference in paediatric drug information in different sources is described (Hsu & Brazelton 2009) affecting the prescribing of medicines to children in different countries and settings. Significantly less prescriptions for hospitalised children were classified OL according to the two contemporary paediatric reference formularies (Lexi-Comp Pediatric Dosage Handbook and the Hospital for Sick Children Handbook and Formulary, and France's Dictionnaire Vidal) compared to the official Canadian Compendium of Pharmaceutical Specialties (Doherty *et al.* 2010). Almost two thirds of the drugs prescribed to the Turkish neonates were UL/OL according to national database and only 48% according to paediatric dosage handbook (Oguz *et al.* 2012).

Ceelie *et al.* assessed the availability of paediatric information in 4 information sources for all the prescribed drugs in 2 ICUs in the Netherlands in 2005 and 2006. For 34.7% of drugs the daily dosing recommendations differed by >100% compared with the formulary for the lowest daily dose to the highest daily dose. For 61% of drugs, dosing recommendations differed between formularies, whereas for 53.4%, the dosing regimen guidelines differed. The dosing guidelines for the three most prescribed drugs (paracetamol, midazolam, amoxicillin/clavulanic acid) were provided in all formularies and were largely in agreement. At the same time for some of the rarely prescribed drugs such as iloprost, no dosing information was given in any of the sources used (Ceelie *et al.* 2010).

## 2.4. Pharmaceutical excipients

In addition to active ingredients, most drug formulations contain pharmaceutical excipients. Excipients aid the manufacturing of the medicinal product and the administration to patients. They are used in medicines as tablet fillers, diluents and solvents, emulsifiers, binders, lubricants, glidants, disintegrants, sweeteners, preservatives and stabilising, flavouring or colouring agents etc. (Rowe *et al.* 2009).

Excipients are defined as substances other than the active ingredients, which have been appropriately evaluated for safety and are intentionally included in a drug delivery system (IPEC Europe. 2008). Their use is regulated by several documents. According to European guidelines (EMA. 2009), all excipients, which are present in the product, should be listed in the SPC, even those present in small amounts. In the United States the FDA has published a list entitled "Inactive Ingredient Guide" for excipients that have been approved in the marketed products providing also the relevant maximum dosage levels by route of administration or dosage form (FDA. 2010). WHO has also set an acceptable daily intake for several excipients, but despite the recommendation, the amount of excipients in the drug formulations has rarely reported in the SPCs. The description of excipients in the SPC is either always sufficient to evaluate the potential safety of the drug product. For example "orange aroma" could consist of 23 different substances, including benzyl alcohol (http://www.theriaque.org/

apps/recherche/rch_simple.php#) used as a solvent, which could vaporise during the manufacturing but may also stay in the medicinal product as a residual solvent. In some other medicinal products, the same generic term "orange aroma" includes only two excipients – natural orange essence and maltodextrine. It has been found that SPCs of medicinal products approved for sale in the United Kingdom and United States report more detail as regards special warnings and precautions for use regarding the excipients (Ursino *et al.* 2011).

Additionally, in contrast to the manufacturing system of active ingredients, excipient quality disasters have happened recently that have heightened awareness for the need to better regulate the excipients industry. For example, in 2008, 84 children died in Nigeria after consuming teething formula containing glycerine contaminated with diethylene glycol (DEG) and in 2006, 46 people died in Panama after taking cough syrup also contaminated with DEG (Monsuur *et al.* 2010).

### 2.4.1. Paediatric and neonatal issues with pharmaceutical excipients

Excipients generally lack pharmacological action and are therefore historically considered to be the inert/inactive ingredients of drug formulation (Fabiano *et al.* 2011). Still, some excipients are clearly not consistently inert in their biological activity.

Excipients have the potential to harm patients in two ways. First, by introduction of a chemical hazard (e.g. toxicity, physiological effect) or physical (e.g. irritation). Secondly, adversely affecting the drug products availability or performance (e.g. changes in the bioavailability or modified release) (Carter 2011).

Most of the medicines are administered orally to children, often in a liquid formulation. To increase palatability and thereby compliance, colourings, sweeteners and flavourings are often added to the preparation (Nunn & Williams 2005).

Excipients are safe in the majority of adult patients, but can possess danger to children for example due to their different PK parameters compared to the adults (Tuleu 2007). As an example, benzyl alcohol is oxidised to benzoic acid, then conjugated with glycine in the liver, and excreted as hippuric acid in the urine. As the pathways involved in the metabolism of benzyl alcohol in premature babies are immature, the accumulation of benzyl alcohol can cause gasping syndrome (Hall *et al.* 2004) (Table 7). Risks to children (Fabiano *et al.* 2011, Ursino *et al.* 2011) and particularly to neonates (Whittaker *et al.* 2009) have been emphasised in several publications and also recognised by the drug regulatory authorities (Carter 2011).

**Table 7**. Examples of excipients with the safety concerns while used in children / neonates based on the literature data with the examples from infants and adults (The exhaustive list of excipients and safety problems could be found in publication III, Table 3)

| | Excipient | Known safety concerns |
|---|---|---|
| Preservatives | Benzyl alcohol (BA) | Gasping syndrome – case report of 24GW neonate receiving i.v. clindamycin preserved with BA. After the third dose a profound desaturation and chest splinting occurred requiring resuscitation. (Hall *et al.* 2004) |
| | Parabens | Contact sensitization – 1,927 adult eczema patients were enrolled, patch test for parabens was positive for 1.1% (Dastychová *et al.* 2008) |
| Solvents | Diethylene glycol (DEG) | Acute renal failure – outbreak due to DEG-contaminated cough syrup in Panama (Rentz *et al.* 2008) |
| | Propylene glycol (PG) | Coma in a premature infant after receiving a wound dressing containing PG. An exceptionally high level of PG found in the urine. Cessation of the topical treatment resulted in complete recovery. (Peleg *et al.* 1998) |
| Stabilisers | Ethylenediamine | Anaphylactoid reaction – 31-year-old man with aminophylline (ethylenediamine salt of theophylline) allergy and positive intradermal test. (Asakawa *et al.* 2000) |

One of the first reports of excipient toxicity was from 1938 when a liquid preparation of sulphanilamide contaminated with diethylene glycol killed over 70 people (Geiling & Cannon 1938). In the 1980s intravenous vitamin E preparation (E-Ferol) was associated with the development of an unusual symptom complex of pulmonary deterioration, thrombocytopenia, liver failure, ascites, renal failure and fatalities among low birth weight (<1,500 g), premature infants in neonatal intensive care units. An inhibitory effect by this vitamin E preparation was observed on the *in-vitro* response of human lymphocytes to phytohemagglutinin mixture. Polysorbate 80 used as a carrier in E-Ferol was found to be responsible for the suppression (Alade *et al.* 1986).

Benzyl alcohol as a preservative in intravascular flush solutions has been associated with a number of deaths and intraventricular haemorrhage in low-birth-weight infants (Hiller *et al.* 1986).

Haemolysis, central nervous system depression, hyperosmolality, and lactic acidosis have been reported after intravenous administration of propylene glycol, commonly used in parenteral medication (Arulanantham & Genel 1978).

There are few data available about the extent to which premature babies and neonates are exposed to excipients. Still, it has been shown that neonates are exposed to several potentially harmful excipients with the potentially toxic doses while receiving routine treatment.

As shown by Shehab *et al.*, neonates who received medications by continuous infusion, median cumulative benzyl alcohol (BA) and propylene glycol (PG) exposures were approximately 21 and 180 times the acceptable daily intakes of BA and PG, respectively. As the study was retrospective using electronic pharmacy record data, possible ADRs to excipients were not recorded (Shehab *et al.* 2009).

Allegaert *et al.* assessed prospectively the renal, metabolic and hepatic tolerance of PG in 69 (pre)term neonates after i.v. administration of medicines containing PG. They found that unintended PG administration (34 mg/kg/24 h) for a maximum of 48 h seems to be tolerated in (pre)term neonates and does not affect short-term postnatal adaptations (Allegaert *et al.* 2010).

Whittaker *et al.* calculated the quantity of excipients found in the most commonly used eight oral liquid medications by retrospectively analysing the drug charts of 38 infants less than 30 GW. The amount of excipient each preterm baby received was determined on a per kg per week basis. Infants were exposed to over 20 excipients including ethanol, PG and high concentrations of sorbitol. Many of the infants in the study were exposed to excipient levels that were greater than the maximum accepted daily intake in adults (Whittaker *et al.* 2009).

Langley *et al.* reviewed the excipients levels in paediatric intensive care units. They collected data from 5 randomly selected patients and contacted manufacturers to ascertain the quantities of excipients present. Patients were taking 49 medicines, for only 22% of these the details about excipients were received from manufacturers (Langley *et al.* 2011, not published).

Cordner *et al*. aimed to review the suitability of formulations given to the hospitalised children and neonates. Excipients within medicines administered over 4 weeks in January to February 2010 were identified from SPC or contacting the manufacturer and the suitability of each individual excipient was assessed following literature review. 80 different medicines were administered and 44 excipients were identified that were potentially unsuitable for use in children and neonates. Excipients were grouped into four classes: excipients that have a potential harmful effect (such as acetone, aspartame, benzoic acid, benzyl alcohol, chloroform, citric acid, ethanol, galactose, methylhydroxybenzoate, phenol, polysorbate 20 and 80, PG, sodium benzoate, sodium bicarbonate, sodium chloride and sodium dihydrogen phosphate); excipients with potential harmful effects only in extremely high concentrations (e.g. diethanolamine, disodium edetate, hydrochloric acid, sodium carbonate anhydrous, sodium hydroxide, sucrose, sulphuric acid and triethyl citrate); excipients with potential to affect the gastrointestinal tract in excess and cause flatulence or act as a laxative (e.g. carboxymethylcellulose sodium, croscarmellose sodium, hypromellose, magnesium stearate, maltitol liquid and mannitol) and excipients with potential to cause an ADR, such as hypersensitivity and anaphylaxis (e.g. cetyl alcohol, lactose, polyoxyethylene hydrogenated castor oil, potassium sorbate, propylhydroxybenzoate and butylhydroxybenzoate, protamine sulphate,

saccharin sodium, sodium lauryl sulphate, sodium metabisulphate, sorbitol and tragacanth) (Cordner *et al.* 2012).

Studies of excipient exposure have until the present time only been based on the concentration in the medicinal product (Allegaert *et al.* 2010, Whittaker *et al.* 2009), but the concentration of most excipients in the blood of babies has never been measured.

The only earlier classification of excipients according to the potential safety / toxicity known to us has been developed by M. Turner (personal communication):

1. Excipient is known to cause harm in neonates in some circumstances;
2. No reports of excipient toxicity are available but the excipient is metabolised by pathways known to be immature in neonates;
3. Excipient is known to cause harm in older age groups but effects on neonates not clear;
4. There are other uncertainties;
5. Unlikely to cause harm in neonates because they do not cause harm in older age groups and metabolism is fully understood.

## 2.5. Summary of the literature

Throughout the last decade, safer and more evidence-based paediatric pharmacotherapy has become a target for clinical practitioners and regulatory bodies worldwide. Up to now, many of the medicines are not licensed for use in paediatrics (are used OL) or have no marketing authorisation (UL).

Additionally to the legislative initiatives aiming to increase the paediatric medicines licensing status, a substantial amount of paediatric drug utilisation studies and OL/UL medicines use studies have been performed and greater attention is paid to the quality of these studies.

The rates of OL/UL use have not been falling in recent years notwithstanding the combined effort of different specialities. Despite the methodological heterogeneity and various OL/UL definitions used, it has been shown that 6 to 100% of children in various age categories, different countries and treatment settings have received at least one OL /UL medicine. The extent of OL use, however, has been not previously studied in the Eastern-European countries or any of the developing or middle-income countries.

Also the rates of the UL medicines use have wide inter-country ranges – from no UL prescriptions to 48%. There is a lack of studies evaluating UL use of medicines (mainly defined as the use of medicines with no marketing authorisation) in small countries such as Estonia, where the availability of medicines is compromised compared to the countries with a larger populations.

If the medicine is not studied in clinical trials in children, official drug information such as SPC is generally lacking. Different information sources are then used in practice with the varying dosing guidance and evidence of information. It has not been previously shown how the selection of drug information

source affects the general rate of OL/UL prescribing and how does the availability of drug information differ between official drug information source e.g. SPC and expert-consensus based sources such as guidelines and reference books.

Almost every medicinal product contains some pharmaceutical excipient. Compared with active ingredients the data on excipients (their content in medicines, tolerability and safety in vulnerable populations etc.) is even less well known. Furthermore, even if their safety has been evaluated the studies have been conducted in adults only or in experimental animals. Despite the limited physiological effects in adult population, toxicity resulting from the use of pharmaceutical excipients in children has been reported. The highest concern is the safety of excipients in neonates, as this is the most vulnerable population also presenting the biggest variations in maturation of drug metabolising processes. Limited published studies describing the neonatal excipient exposure have been focusing on the few well-described toxic excipients, which is only a modest fraction of the total excipient list. Still, toxicity or ADR reports have been published for many of the substances also used as pharmaceutical excipients. The extent of excipient use, especially of those with known toxicity in paediatric population is largely unknown. No validated classification system exists until the present time for categorising the pharmaceutical excipients according to their potential safety / harmfulness to young children.

# 3. AIMS OF THE RESEARCH

Our general aim was to describe the current situation of paediatric pharmacotherapy in terms of the prescription pattern and use of OL/UL medicines in the ambulatory and hospital setting and the extent of pharmaceutical excipient exposure in hospitalised neonates.

The specific aims were as follows:

1. To describe the Estonian paediatric drug utilisation pattern in the outpatient setting and in the neonatal wards;
2. To compare the paediatric ambulatory antibiotic prescription pattern between Estonia and Sweden;
3. To investigate the labelling status of prescribed medicines according to the Estonian SPC;
4. To identify the critical areas in paediatric / neonatal pharmacotherapy where drugs are used most commonly and where the information in SPC is most often lacking;
5. To compare the availability of paediatric / neonatal information in Estonian SPCs with other widely used drug information sources such as BNFC and Thomson Micromedex database;
6. To develop a classification of excipients depending on their potential toxicity present in medicines used in neonatal wards in Estonia;
7. To describe the presence of toxic and potentially toxic excipients in neonatal medicines;
8. To describe the extent of inpatient neonatal exposure to excipients in general and potentially harmful excipients.

# 4. PATIENTS AND METHODS

The thesis consists of three studies and additional analysis of the data collected on the neonatal use of medicines as presented in Table 8.

**Table 8.** Description of studies and analyses of the thesis

| Study characteristic | Timing | Population / prescriptions | Primary aim | Publication |
|---|---|---|---|---|
| Cross-sectional drug utilisation study | 1.01.2007 – 31.12.2007 | 467 334 prescriptions dispensed to 151 476 subjects up to 18.99 y from the EHIF database | To describe the accordance of the ambulatory paediatric prescriptions to the Estonian SPCs | I |
| Prospective cohort study in neonatal wards | 1.02. – 1.08.2008 in TUC and 1.02. –1.08.2009 in TCH | 348 neonates PNA <29d | To investigate the labelling status of prescribed drugs according to the Estonian SPC | II |
| Excipients use study | *Post-hoc* analysis of neonatal study data | 348 neonates PNA <29d | To estimate the extent of excipient exposure in hospitalised neonates | III |
| Comparative antibiotic use study | 1.01.2007 – 31.12.2007 | 159 304 prescriptions from EHIF and 681 954 from SPDR database for children up to 17.99y | To compare the paediatric outpatient antibiotic use in Estonia and Sweden | IV |

EHIF, Estonian Health Insurance Fund; PNA, postnatal age; SPC, summary of product characteristic; SPDR, Swedish Prescribed Drug Register TUC, Tartu University Clinics; TCH, Tallinn Children's Hospital; y, year; d, days

## 4.1. Ethics

Prescription database studies did not need the ethics committee approval as no personal identifiers were collected.

Prospective cohort study was approved by the Ethics Review Committee of the University of Tartu (No 167/T–9, received 28.01.2008). The study used anonymised data collected in routine clinical practice and did not require individual consent of the parent.

## 4.2. Design of the studies and data collection

**Drug utilisation studies on dispensed ambulatory prescriptions** were based on the Estonian Health Insurance Fund (EHIF) prescription database and Swedish Prescribed Drug Register (SPDR) databases. The period of prescriptions dispensed that was extracted from both databases was from 1.01.2007 to 31.12.2007. Estonian data for the comparative antibiotic use study was a subset of cross-sectional drug utilisation study data.

Both databases are nationwide prescription databases, containing electronically submitted data of all prescription medicines dispensed by the pharmacies to individuals receiving ambulatory care. The Estonian database contains individual patient and physician identification numbers and is diagnosis-linked. The Swedish database contains product identification and patient's age but no information with regard to dose or indication.

**Table 9.** Data used for cross-sectional drug utilisation and comparative antibiotic use study

| Study | Data-base | Age group studied | Data extracted |
|---|---|---|---|
| Cross-sectional drug utilisation study | EHIF | Up to18.99 y | EHIF: Age and identification code of patient, drug data (package code, WHO ATC code, brand name and INN, formulation, content per dose unit), number of packages dispensed, subsequent diagnoses |
| Comparative antibiotic use study | EHIF SPDR | Up to 17.99y | EHIF: same as in cross-sectional study and additionally prescriber speciality<br>SPDR: aggregated data on the number of prescriptions for each active substance for each age group |

ATC, Anatomical Therapeutic Chemical code; INN, International Non-proprietary name; WHO, World Health Organization

Population data were obtained from the Statistics Estonia (http://pub.stat.ee/px-web.2001/Database/Rahvastik) and from Statistics Sweden (http://www.scb.se).

**Neonatal drug utilisation study** was a prospective cohort study conducted in the neonatal intensive care units (NICU) and intermediate-level neonatal wards of Tartu University Hospital's (TUC) Children Clinics and Tallinn Children's Hospital (TCH). All medicines prescribed to neonates with postnatal age <29 days who were treated at TUC between 1 February and 1 August 2008 and at TCH between 1 February and 1 August 2009 were recorded twice weekly from the medicines charts by the 3 investigators, including author of the thesis.

The following information was collected from the hospital records twice a week: demographic data [gestational age (GA), birth weight, gender, date of

birth], all diagnoses, admission and discharge dates and all prescriptions (international non-proprietary or product names (INN), doses and duration of treatment and formulations). If only INN name was collected from the patient record, the product names were specified from the pharmacy database. We did not record the use of standard intravenous replacement solutions, blood products, oxygen, nutritional and technical products (including contrast agents), basic creams and ointments, parenteral nutrition solutions, vaccines and vitamins (including colecalciferol).

**Excipients use study** was a *post-hoc* analysis based on the data collected during the prospective cohort study in neonatal wards described above. All of the pharmaceutical excipients in medicines used during the study period were primarily determined from the SPCs. If the drug product was not registered in Estonia in September 2009 and thus the SPC was lacking, the package inserts were used. The names of the excipients and synonyms were double-checked from the Rowe's Handbook of Pharmaceutical Excipients (Rowe *et al.* 2009) and classified into the safety categories based on the literature review. The following literature sources were used for classification: Rowe's Handbook of Pharmaceutical excipients 6th ed., European Commission guidelines on the excipients in the label and package leaflet of medicinal products for human use (European Commission 2003), EMA reflection paper formulations of choice for the paediatric population, 2006 (EMA CHMP 2006), article by Fabiano *et al*. (Fabiano *et al.* 2011) and book from Costello *et al.* (Costello *et al.* 2007). A PubMed database search was conducted by using the name of each identified excipient AND/OR synonyms AND "human toxicity" as search terms; no other limiters or terms were used to narrow or widen the search. If there were no results in the PubMed search or other abovementioned information sources, Google scholar (http://scholar.google.com; last accessed 24th September 2011) search was conducted using the same search terms. In this study, all excipients for which according to the abovementioned sources there were some safety concerns, including the data from experimental studies, and there was no neonatal data demonstrating that these are safe were classified as "potentially harmful" (Table 11).

## 4.3. Age categories of study population

The age categories recommended by the ICH were used in studies for dividing children into the subgroups. These age ranges reflect biological changes – the changes after birth (preterm neonates born before 37 gestation weeks and term neonates); the early growth spurt (infants and toddlers from 28 days to 23 months); gradual growth from 2–11 years; the pubertal and adolescent growth spurt and development towards adult maturity (12–18 years) (Stötterb 2007).

In the prescription database studies the age group 2–11 years was further subdivided in terms of the child's ability to accept and use different dosage forms into pre-school children (2–5 years) and school children (6–11 years).

The group of preterm neonates was further subdivided into extremely preterm (gestational age (GA) <28 weeks), very preterm (28–31 weeks) and late preterm (32–36 weeks).

## 4.4. Assessment of licensing status of the medicines

The following four SPC sections of the medicinal products were reviewed for paediatric information as of February 2009 (ambulatory prescriptions) and as of September 2009 for neonatal information (prescribed to hospitalised neonates): indication (4.1), administration (4.2), contraindications (4.3) and warnings (4.4).

Products with the same active substance but different brand name, dosage and formulation were evaluated separately as they have separate SPCs.

Drugs were then categorised to labelled, OL in terms of age and UL as presented in the Table 10.

A drug was considered OL if it was prescribed to a child below the lowest approved age or outside of the age brackets mentioned in the SPC. We did not classify drugs to OL based on the indications, formulations and routes of administration. OL use was further divided into two groups – OL because of lack of paediatric information and OL because of contraindication (CRI).

**Table 10.** Categories of drugs according to the information in SPC

| Category | | Information in SPC |
|---|---|---|
| L | L for all children | Information about paediatric / neonatal use available in point 4.1 or / and 4.2*; not CRI for children |
| | L for specific age group | Information about paediatric / neonatal use available in 4.1 or / and 4.2*; Indicated for children over certain age, for children able to swallow oral solid dosage forms, for children over certain weight |
| | L for specific age group and diagnosis | Indicated for children over certain age and with specific diagnosis |
| OL | No data | Children / neonates not mentioned in SPC or the following sentence used: “no data for use in children”, “for using in children exists limited information / experience”, “not recommended for children because of the limited information / experience”, “not recommended for children because of the drug formulation is not appropriate” |
| | CRI | CRI for children / neonates |
| | CRI for use in specific age group | CRI under certain age, CRI for children under certain weight |
| UL | | Product has no MA in Estonia, chemicals that were prepared into a formulation within the hospital pharmacy |

*SPC topics: indication (point 4.1), administration (point 4.2).

CRI, contraindicated; L, labelled; OL, off-label; UL, unlicensed; MA, marketing authorisation

There were four products (less than 0.3% of all prescriptions) prescribed to outpatient children for which, for the consistency, the weight-based recommendations were transformed to the age-based. Enalapril, azitromycin and doxycyclin tablets were recommended for children over 15, 20, 45 and 50 kg, respectively. The weights were transformed to the matching age as follows: if the product was licensed for use over 15 kg, it got classified as to be licensed for children older than 5 years and over 20 kg, for those older than 12 years. If the product was labelled for children who are able to ingest solid dosage formulations or for school-aged children, it was considered to be licensed for children over 6 years old.

Amongst the ambulatory prescriptions 20 most often prescribed OL medicines were chosen to compare the differences in the availability of paediatric information in SPC, British National Formulary for children (BNFC) (BMJ Group. 2009); Micromedex database (Thomson Reuters Micromedex 2.0), and Harriet Lane Handbook 18th ed. (Custer J.W & Rau R.E. 2009).

## 4.5. Classification of excipients according to their potential toxicity to neonates

The classification system of excipients was developed for the study purpose and excipients were divided into four categories as detailed in Table 11 based on the literature sources described in section 4.2.

**Table 11**. Classification of excipients to which studied neonates were exposed according to the literature review

| Category | Safety status | Description |
|---|---|---|
| 1 | Potentially safe | No ADRs reported |
| 2 | Potentially harmful and known to be harmful | ADRs reported |
| 3 | No safety data found | No data found in the literature on human exposure and toxicity |
| 4 | Description of the excipient in SPC or PIL unspecific | Description does not allow a specific literature search |

ADR, adverse drug reaction; PIL, product information leaflet

## 4.6. Analysis of the data

The prescriptions were categorised based on the World Health Organisation's Anatomical Therapeutic Chemical (ATC) classification system (http://www.whocc.no/atc_ddd_index/).

Descriptive statistics was used in all of the studies for prescription data and demographics. For ambulatory prescriptions the prescription rate in general and

in each age group, in ATC group and specific product level (number of prescriptions per 1000 children aged up to 18.99 years or per number of children in the age group) and crude 1 year prevalence of drug use in children (proportion of patients of the paediatric population who had one or more prescriptions issued) were calculated.

The paediatric antibiotic use was expressed as number of prescriptions for systemic antibiotics (ATC code J01) per 1000 children aged up to 17.99 years in the population/year and calculated the 95% confidence intervals (CIs) by using R64 software (http://www.r-project.org/).

For neonatal medicines use study in the interest of completeness the data of both hospitals and wards was pooled as both hospitals are in general similar and follow the same treatment guidelines. The prescription rates (the number of prescriptions per 100 admissions) for each hospital (and CIs), drug group and each individual drug were calculated. If two or more courses of the same agent were given within the same hospitalisation it was reported only once. StatsDirect software (ver. 2.7.8) and Welch's two sample two-tailed t test were used to compare continuous variables and the chi-squared test was used to compare categorical values. Cochran-Armitage trend test was used to evaluate the trends of prescription rates in different GA groups.

# 5. RESULTS AND DISCUSSION

## 5.1. Demographics of the study populations

### 5.1.1. Ambulatory patients in Estonia and Sweden

Altogether 151 476 subjects aged up to 18.99 years were identified from the Estonian Health Insurance Fund (EHIF) prescription database in 2007 as seen in Table 12.

**Table 12.** Number of Estonian children who had been receiving a prescription medicine during year 2007 divided into the age groups and total number of children in age groups in Estonia.

| Age group (years) | Treated children in Estonia (unique subjects) | Total number of children Estonia |
|---|---|---|
| < 2 | 22 949 | 29 091 |
| 2–5 | 37 689 | 52 233 |
| 6–11 | 33 034 | 74 202 |
| 12–18.99 | 57 798 | 102 989 |
| Children total | 151 476 | 277 265 * |

* The total number was 258,515 when children aged up to 17.99 years counted for the antibiotics use study

The paediatric population of children aged up to 17.99 years in 2007 was 7.5 times smaller in Estonia (n = 258,515) as compared to Sweden (n = 1, 933,920). As the Swedish database contains only aggregated data on the number of prescriptions for each active substance for each age group, the number of unique children with the prescription was not available to us.

### 5.1.2. Hospitalised neonates

A total of 490 neonates were admitted to the study centres during the study periods as seen in Figure 1.

About 40% of admitted neonates were preterm, of whom 8% were extremely premature babies. The ratio of preterm neonates in TUC was higher than that in TCH [46%, 95% CI 40%; 53% vs. 37%, 95%CI 31; 42; p = 0.028], but the proportion of extremely preterm neonates was greater in TCH compared with TUC (10%, 95% CI 7; 15 vs. 5%, 95% CI 3; 9; p = 0.047).

The proportions of neonates receiving pharmacotherapy were slightly different in the two study centres: 156/203 in TUC (77%, 95% CI 71; 82) and 192/287 in TCH (67%, 95% CI 61; 72), but the difference was not statistically different (Chi-square test value 0.017).

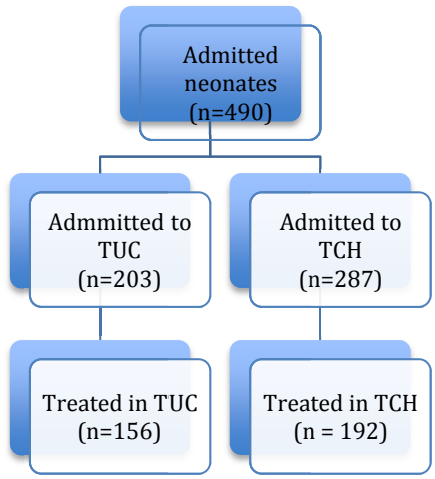


**Figure 1.** Flow-chart of the neonates hospitalised and treated in TUC and TCH

The prescription rates were in general similar between the hospitals – 405 (95% CI 377; 434) per 100 admissions in TUC and 397 (95% CI 374; 421) in TCH (p = 0.65). Despite the small variations the data from both hospitals was decided to pool.

Neonatal hyperbilirubinaemia (n = 192), perinatal infections (n = 103) including neonatal sepsis (n = 50) and respiratory distress syndrome (n = 83) were the most common reasons for hospitalisation. The same diagnoses prevailed also in other neonatal studies making our data representative to neonatal population in general and not specifically for Estonia (Altman *et al.* 2011, Jakuskiene *et al.* 2011, O'Donnell *et al.* 2002).

**Table 13.** Demographics of the neonatal study population

| | Extremely preterm neonates | Very preterm neonates | Late preterm neonates | Term neonates | Total |
|---|---|---|---|---|---|
| No of children admitted (male) | 41 (22) | 53 (27) | 105 (49) | 291 (170) | 490 (268) |
| Median No of hospitalisation days (IQR) | 28 (12–80) | 31 (24–41) | 15 (10–21) | 8 (5–11) | 10 (5–19) |
| Average birth weight* (g) + SD | 739 (209) | 1370 (412) | 2084 (448) | 3455 (618) | 2446 (1124) |
| Survival (%) | 71 | 94 | 98 | 99 | 96 |

* Birth weight was not available for 3 children
IQR, inter quartile range; SD, standard deviation

## 5.2. Drug utilisation pattern

### 5.2.1. Ambulatory drug utilisation

A total of 467 334 prescriptions to 851 products with 309 unique active substances or combinations were dispensed, making the crude 1 year prevalence of 54.6% and prescription rate 1.7 per child. Those aged below 6 years received twice as many prescriptions (2.5 prescriptions per child) as children over 6 years old (1.2 and 1.4 prescriptions per child for 6–11 years old and for 12–18 years old children, respectively). There was a statistically significant difference of the prescription rates between all age groups.

We observed similar prescription rates as shown by others (Clavenna & Bonati. 2009, Olsson *et al.* 2011). Also our finding that preschoolers receive more prescriptions than older children is consistent with previous studies from other countries (Clavenna *et al.* 2009, Madsen *et al.* 2001, Schirm *et al.* 2000, Thrane & Sørensen 1999). Why more medicines is given to preschool children has not been systematically studied but one could speculate that it probably reflects the difference in illness prevalence between age groups due to immature immune systems, lack of appropriate hygiene and crowding in the day care settings, the youngest children have more illness episodes, especially infections, than older children (Straand *et al.* 1998, Thrane & Sørensen 1999).

#### 5.2.1.1. Ambulatory prescription pattern according to the ATC groups

Anti-infectives were the most commonly prescribed ambulatory medicines in all age groups, followed by respiratory and dermatological medicines contributing together 77% of the total prescriptions (Figure 2). Our finding that antibiotics are the most commonly prescribed medicines in children has been described almost in all studies (Olsson 2011; Clavenna 2009).

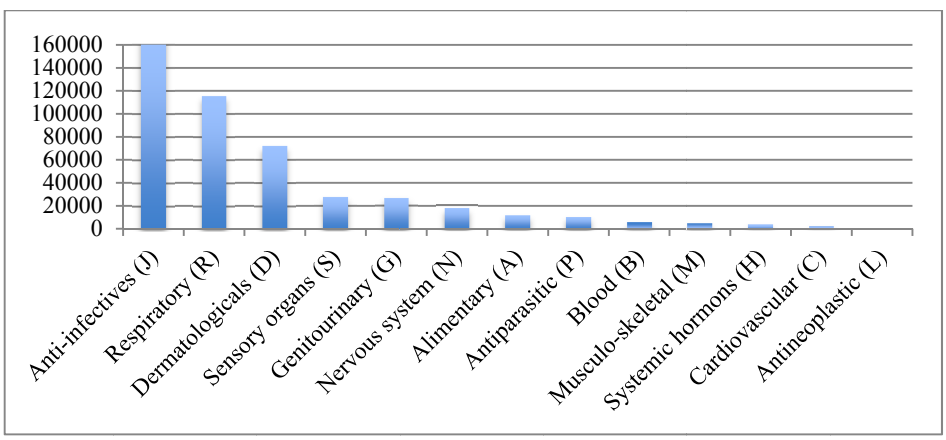


**Figure 2.** Number of ambulatory prescriptions (y axis) according to the ATC groups (x axis)

The 20 most commonly prescribed chemical agents comprised 57% of all prescriptions, which was less than in Norway – 75.3% (Straand *et al.* 1998).

The **respiratory medicines** is a heterogeneous ATC group, which can be divided into drugs for cough or asthma and drugs for allergy. As seen from the Table 14, antihistamines for systemic use were by far most commonly used respiratory medicines.

Cetirizine drops and desloratadine syrup prevailed for <12 year old children and cetirizine + pseudoephedrine tablets and desloratadine tablets lead the list for adolescents.

Second common group selective beta-2 adrenoreceptor agonists for systemic use consisted mainly of salbutamol, which was prescribed extensively for children of all ages.

Leukotriene receptor antagonist montelukast tablets were used often in the age group 2–5 years.

Of the local antibiotics fusafungin spray was prescribed, most often to 2 to 5 year old children.

**Table 14.** Ambulatory prescription rate of respiratory medicines for Estonian children (No of prescriptions per 1000 users)

| | Age groups (years) | | | | |
|---|---|---|---|---|---|
| ATC subgroup (ATC code) | <2 | 2–5 | 6–11 | 12–18 | Total |
| Antihistamines for systemic use (R06A) | 291 | 218 | 78 | 70 | 657 |
| Selective beta-2 adrenoreceptor agonists for systemic use (R03AC) | 156 | 179 | 52 | 13 | 400 |
| Leukotriene receptor antagonists (R03DC) | 54 | 126 | 42 | 5 | 227 |
| Glucocorticoids for inhalation (R03BA) | 29 | 61 | 41 | 11 | 142 |
| Nasal corticosteroids (R01AD) | 4 | 39 | 54 | 50 | 147 |
| Mucolytics (R05CB) | 30 | 70 | 18 | 7 | 125 |
| Throat preparations, local AB (fusafungin, R02AB03) | 11 | 49 | 33 | 29 | 122 |
| Others | 31 | 56 | 48 | 48 | 183 |
| Total | 607 | 797 | 367 | 232 | 2003 |

AB, antibiotics

Respiratory medicines were on of the most commonly used drug group similarly to us also in Sweden, Spain and Germany (Morales-Carpi *et al.* 2010, Mühlbauer *et al.* 2009, Olsson *et al.* 2011) and salbutamol (Bianchi *et al.* 2010, Sturkenboom *et al.* 2008) and cetirizine (Schirm *et al.* 2000) were amongst most commonly used respiratory medicines.

**Dermatological products** were by far more often used in children younger than 2 years compared to older children as seen in Table 15. Most commonly used drug groups for pre-school children were topical corticosteroids and for

adolescents anti-acne products. Generally, topical products containing fusidic acid and hydrocortisone + chlorhexidine (80 and 78 prescriptions / 1000, respectively) were most often prescribed.

Dermatological medicines were in the third place also in Sweden (Olsson *et al.* 2011) and similarly to Estonia, topical corticosteroids were most frequently used among the <2-year-old Danish children (Thrane & Sørensen 1999). Fusidic acid (1518 and 6273 users / 1000) and hydrocortisone (1287 and 12310) were also the most common individual dermatological drugs used in The Netherlands and UK, nevertheless the prescription prevalence was considerably higher there than in Estonia.

Not surprisingly, anti-acne preparations comprised an increasing proportion among the oldest children also in Denmark (Thrane & Sørensen 1999).

**Table 15.** Ambulatory prescription rate for dermatological medicines for Estonian children (No of prescriptions per 1000 users)

| | Age group (years) | | | | |
|---|---|---|---|---|---|
| ATC subgroup | <2 | 2–5 | 6–11 | 12–18 | Total |
| Topical corticosteroids, combinations (D07B) | 252 | 99 | 42 | 34 | 427 |
| Topical corticosteroids, plain topical (D07A) | 127 | 65 | 37 | 41 | 270 |
| Topical anti-acne products (D10) | 2 | 1 | 5 | 169 | 177 |
| Pimecrolimus (D11AH02) | 51 | 30 | 5 | 4 | 90 |
| Local antifungal products (D01A) | 34 | 13 | 12 | 14 | 73 |
| Local antibacterial products (D06A) | 39 | 35 | 16 | 12 | 102 |
| Local anti-psoriatic products (D05A) | 0.1 | 1 | 5 | 11 | 17.1 |
| Other | 3 | 3 | 2 | 5 | 13 |
| Total | 507 | 247 | 124 | 288 | 1166 |

### 5.2.2. Prescription pattern of antibiotics in Estonia compared to Sweden

#### 5.2.2.1. Quantitative differences

The total paediatric antibiotic use was almost twice as high – 616 per 1000 (95%CI 613; 619) in Estonia versus 353 per 1000 (95%CI 352; 354) in Sweden (Figure 3).

As antibiotic prescribing depends antimicrobial susceptibility as well as on local prescription habits the quantitative and qualitative regional variations in the antibiotics prescription profile are understandable (Clavenna & Bonati 2011, Rossignoli *et al.* 2007). As of many examples, in Italy the antibiotic prescription rate was twice as high compared with Denmark (67 Defined Daily Doses per 1000 inhabitants per day (DDD/TID) vs. 35 DDD/TID, respectively) (Lusini *et al.* 2009) and the children in British Columbia received substantially more

antibiotic prescriptions than Danish counterparts (608 versus 385 prescriptions per 1000 children, respectively) (Marra *et al.* 2007).

However, the quantitative differences seen in our study could not be simply explained by dissimilarities in resistance levels of common outpatient micro-organisms, which have been reported to be low in general in both countries. For example, in 2005 to 2009, the proportion of methicillin resistant *S. aureus* has ranged between 2% to 9% in Estonia and 0.5% to 1% in Sweden (EARS-NET).

Similarly to the general prescription pattern in Estonia, the preschool children were also most exposed age group to antibiotics. The probable reasons for this phenomenon are discussed in the previous section 5.2.1. The highest prescription rate of antibiotics in Estonia was found among 2 to 6 year old children whereas in Sweden it was highest among those less than 2 years old (Figure 3). Adolescents had the lowest rate of antibacterial prescriptions in both countries but the difference in favour of Sweden as in all other age groups was observed.

In concordance with our results, the pre-school children have shown to be the most exposed age group to antibiotics also by others (prevalence 72%; prescription rate 2.2) compared to the older children (prevalence from 14 to 57% (mean 34%), prescription rate from 0.2 to 1.3) (Rossignoli *et al.* 2007). Previously, a striking difference in antibiotic prescribing between Italy and Denmark has been highlighted for children aged from 0 to 9 years (Vaccheri *et al.* 2002).

#### 5.2.2.2. Differences in the selection of antibiotics between Estonia and Sweden

A total of 55 different active substances (22 in Estonia and 50 in Sweden) were used. However, 90% of prescriptions in both countries were covered by 8 agents, as seen in Table 1, paper IV.

Penicillins were the most widely prescribed antibiotics with the similar prescription rate in both countries (Figure 3) but the ratio of penicillins of all prescriptions was significantly greater in Sweden than in Estonia (74% vs. 49%).

In addition, the qualitative selection of penicillins differed considerably – extended spectrum penicillin amoxicillin or its combination with beta-lactamase inhibitor (amoxicillin + clavulanic acid) were commonly prescribed in Estonia whereas narrow spectrum penicillins (e.g. phenoxymethylpenicillin) covered half of the prescriptions in Sweden (Figure 4).

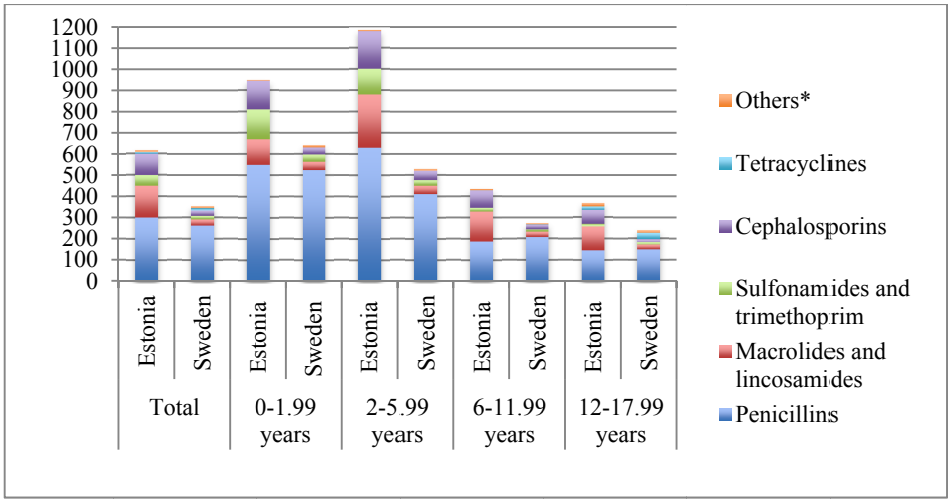


**Figure 3.** Number of prescriptions per 1000 children (y axis) of systemic antibacterials (ATC group J01) by age groups in Estonia and Sweden (x axis)
* Includes monobactams (J01DF), carbapenems (J01DH), aminoglycosides (J01G), quinolones (J01M) and other antibacterials (J01X)

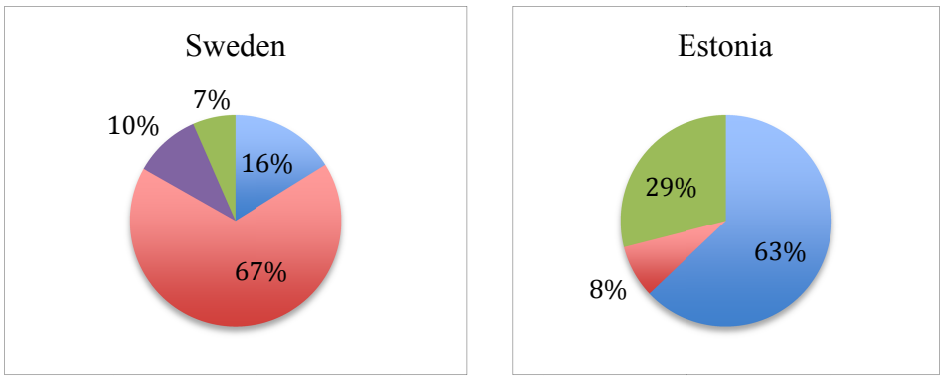


**Figure 4.** Proportion of different penicillins used in Estonia and Sweden
Blue: Penicillins with extended spectrum (J01CA; ampicillin, amoxicillin, pivmecillinam, piperacillin)
Red: Beta-lactamase sensitive penicillins (J01CE; benzylpenicillin, phenoxymetylpenicillin)
Green: Combinations of penicillins, incl. Beta-lactamase inhibitors (J01CR; amoxicillin + clavulanic acid, sultamicillin, piperacin + tazobactam)
Purple: Beta-lactamase resistant penicillins (J01CF; dicloxacillin, flucloxacillin)

Similarly to our results for Estonia, extended-spectrum penicillin amoxicillin has also been reported to be the most frequently prescribed antibiotic in the Netherlands and Canada and amoxicillin with clavulanic acid combination in Italy (Clavenna & Bonati 2011).

The reasons why Estonian physicians tend to prescribe more often wide spectrum agents compared to Swedish colleagues have not been systematically studied but the likely reasons could involve the relatively liberal guideline recommendations. For example, for acute tonsillitis, the Estonian guidelines (http://www.haigekassa.ee/raviasutusele/ravijuhendid/andmebaas/tunnustatud), in addition to phenoxymethylpenicillin recommend amoxicillin despite the fact that *S. pyogenes* is uniformly susceptible to penicillin (Hraoui *et al.* 2011). Other reasons could involve the pressure from parents to receive the newest agents, a limited option for etiologic diagnosis in outpatient setting, the promotional activities of pharmaceutical industry, the lack of detailed knowledge due to poor dissemination of guidelines or simply poor adherence to guidelines (Hedin *et al.* 2006). The latter reason could apparently be supported by the significant amount of antibiotic prescriptions for acute bronchitis, a disease not requiring antibiotic treatment at all.

Macrolides accounting for 24% of prescriptions were extensively used in Estonia (149 prescriptions per 1000) in all age groups, with the highest rates observed among children aged 6 to 17 years whereas in Sweden they were used less frequently (29 prescriptions per 1000; 8% of all prescriptions) (Figure 3). The extended use of macrolides has been related to increased carriage of penicillin non-susceptible *S.pneumoniae* (Lusini *et al.* 2009) and considered as a major driver for the increase in beta-lactam resistance (EARS-Net 2010). The inappropriate prescription of that group of antibiotics was one of the initial targets for STRAMA programme in Sweden (Mölstad *et al.* 2009) and macrolide treatment of upper respiratory infections is only recommended if the patient is allergic to penicillins (Högberg *et al.* 2005).

Also the types of macrolides also differed between countries – clarithromycin predominated in Estonia while the parent drug erythromycin was mainly used in Sweden (Table 1, paper IV). The preference of clarithromycin by Estonian prescribers could possibly be explained by the easier administration scheme – twice as compared to four times daily. Slightly better tolerability in terms of gastrointestinal side effects of clarithromycin compared to erythromycin has also been reported (Lee *et al.* 2008).

### 5.2.3. Prescriptions for hospitalised neonates

A total of 1981 prescriptions for 115 products and 105 active substances were administered to 348 neonates. The prescription rate was 5.7 (Table 16), which is higher than the ambulatory prescription rate in Estonia (1.7 / 1000), but similar to studies from other countries (range from 3 to 7) (Conroy *et al.* 1999, DellAera *et al.* 2007, O'Donnell *et al.* 2002, Oguz *et al.* 2012). However, the extent of neonatal drug exposure has found to be varying between studies

depending on one hand on the used methodology and on the other hand on the treatment habits and guidelines.

The median number of products per child (n = 4; range 1 to 26) in our study was broadly similar to that in Italy (n = 5.5; range 1 to 15) (DellAera *et al.* 2007) and Finland (n = 4.2; range 0 to 19) (Lindell-Osuagwu *et al.* 2009) but was more than half lower that in a recent study from Germany – 8. The latter study did not exclude the vitamins and included also the medications given prior to the admission to the neonatology ward (e.g. drugs given in the delivery room), which could partly explain differences from our study (Neubert *et al.* 2010).

The prescription rate in preterm neonates was greater than in term neonates as seen in Table 16. All of the extremely preterm neonates received pharmacotherapy compared to the 59% of full-term babies. Preterm neonates received 68% of all prescriptions. There was a negative correlation between prescription rate and GA, which has been also reported elsewhere (Kumar *et al.* 2008, Neubert *et al.* 2010, Warrier *et al.* 2006).

**Table 16.** General prescription pattern in hospitalised neonates

| | Extremely preterm neonates | Very preterm neonates | Late preterm neonates | Term neonates | Total |
|---|---|---|---|---|---|
| No of children admitted (male) | 41 (22) | 53 (27) | 105 (49) | 291 (170) | 490 (268) |
| No of children who received drugs (%) | 41 (100) | 48 (91) | 87 (83) | 172 (59) | 348 (71) |
| No of prescriptions | 596 | 367 | 376 | 642 | 1981 |
| Prescription rate* | 14.5 | 7.6 | 4.3 | 3.7 | 5.7 |
| No of products used | 66 | 66 | 65 | 85 | 115 |
| No of active substances used | 62 | 62 | 61 | 81 | 105 |

* Number of prescriptions per treated neonate in GA group

#### 5.2.3.1. Prescription pattern according to the ATC groups for hospitalised neonates

The drug utilisation pattern in very preterm infants (<31 weeks GA) was different compared with newborns with a higher GA. Similarly to outpatient medicine use antiinfectives for systemic use were the most commonly prescribed in all GA categories. These were followed by cardiovascular agents in extremely and very preterm neonates, alimentary medicines in late preterm neonates and nervous system drugs in term neonates (Figure 5). The same ATC groups have been most often prescribed in other neonatal studies (Clark *et al.* 2006, Warrier *et al.* 2006).

In line with prescription rates, the number of different products used during our study period was the highest for cardiovascular (n = 24), systemic anti-infectives and nervous system drugs (n = 20 for both).

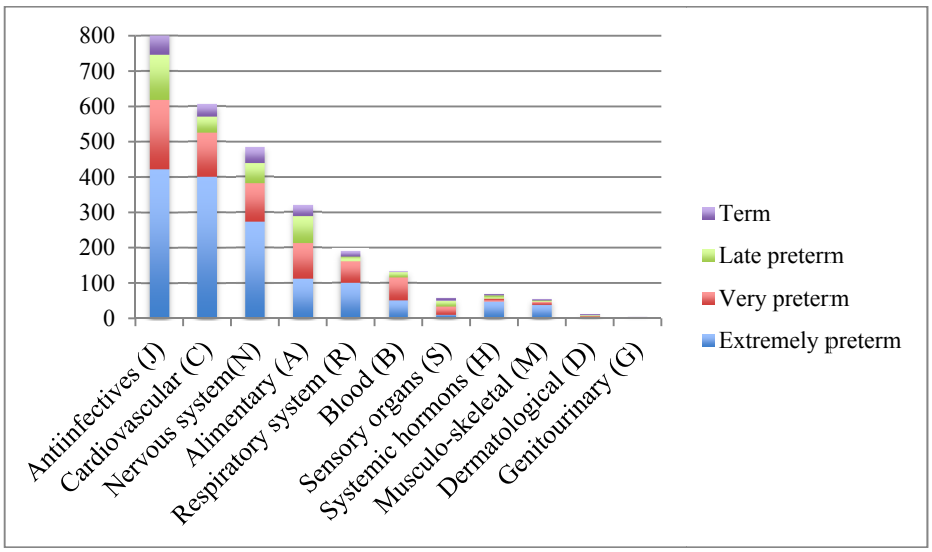


**Figure 5.** Prescription rates per 100 neonatal admissions (y axis) by GA and ATC groups (x axis)

Of the antiinfectives gentamicin (prescription rates per 100 admissions from 31 to 82 depending on GA) and ampicillin (prescription rates from 4 to 32) were used most commonly in all of the GA groups (Paper II, Table 3). Gentamicin, as an antibiotic recommended for empiric treatment of early onset sepsis (EOS) and late onset sepsis (LOS) by most guidelines has been reported to be the most frequently used antibiotics in hospitalised neonates in the UK (Conroy *et al.* 1999), US (Clark *et al.* 2006) and Australia (O'Donnell *et al.* 2002). In other countries other aminoglycosides prevail – amikacin in Italy (DellAera *et al.* 2007) and tobramycin in Germany (Neubert *et al.* 2010).

The heterogeneity of antibiotics selection indicates that empiric antibiotic treatment varies among neonatal intensive care units and countries and there are currently no consensus guidelines regarding the choice of empiric antibiotics (Venkatesh & Garcia-Prats 2008). Still, it has been shown that ampicillin or penicillin G combined with gentamicin are equally effective and safe agents in the early initial empiric treatment of neonates with risk factors of early onset sepsis (Metsvaht 2009).

Of the cardiovascular medicines, most often catecholamine dobutamine was prescribed to the extremely and very preterm neonates (24 prescriptions per 100 admissions in both GA groups) (Paper II, Table 3). Similarly to our study, the most frequently used diuretic was furosemide also in the neonatal unit in Germany (Neubert *et al.* 2010).

Of the central nervous system drugs, fentanyl (from 8 to 30 prescriptions per 100 admissions depending on the GA) and midazolam (from 5 to 32 prescriptions per 100 admissions) showed a high number of prescriptions. Paracetamol parenteral solution and rectal suppositories (9 and 22 prescriptions per 100 admissions, respectively) were used often in term neonates, but compared to our study, it was prescribed rarely in Germany (Neubert *et al.* 2010).

Neonates received medicines mainly via parenteral route (61/107). The other routes like oral administration of manipulated crushed tablets or opened capsules (19/107), oral liquids (8/107), topical ointments and creams (6/107), ophthalmic (5/107), rectal (4/107) and inhalation (4/107) medicines were rarely used. The general problems with manipulated dosage forms are lack of information on the bioavailability and stability of the manipulated drug (Nahata & Allen Jr 2008). Some studies have shown the equal bioavailability of crushed tablets with non-manipulated product, for example for the voriconazole (Ashley *et al.* 2007). At the same time administration of crushed tablet of oral angiogenesis inhibitor pazopanib increased area under the curve (AUC (0–72)) by 46% compared with the whole tablet administration, Cmax was increased by twofold and Tmax decreased by 2h (Heath *et al.* 2011).

Differences in the rates of medicines use according to the ATC classes between study centres were observed. These were mainly caused by few active substances. Cardiovascular drugs, consisting mainly of dopamine and epinephrine were prescribed more often in TCH (89/100, 95% CI 78–100 vs. 62/100, 95% CI 52–74 in TUC), and antibacterials were prescribed more often in TUC (150/100, 95% CI 133–168 vs. 107/ 100, 95% CI 94–118 in TCH). Intra-country difference in prescription prevalence has been also described previously (Bianchi *et al.* 2010; Rossignoli *et al.* 2007). Although the reasons of such in-country differences were not studied one could speculate that lack of evidence-based guidelines in treating several neonatal conditions could be one of them.

## 5.3. OL use of medicines

### 5.3.1. Ambulatory OL use

Altogether 31% of ambulatory prescriptions were OL in terms of age. The majority of those (29%) did not have any information of paediatric use in the SPC and 2% were contraindicated (CRI) for the respective age. It is hard to put our findings into the context with others due to the great variability in previous studies – ranging from 3.2% of OL use in Germany (Mühlbauer *et al.* 2009) up to 51% in Spain (Morales-Carpi *et al.* 2010). However, when looking at the median rate of OL use (20%) our results are still higher (Table 4).

The great variability of OL medicines use rates found in different studies is at least partly attributable to the various definition, number and quality of reference sources used for classifying medicines into the OL category but also to the study patients and medicines selection. The lower end of OL use has been

generally described in the studies using more than one reference source for classification.

The wide variation of the OL medicines use rates is most probably explained by the classification differences. Relatively low OL rate (13.6) was described in the Netherlands (Jong *et al.* 2002) as all of the medicines with no paediatric information in SPC were classified quite the contrary to most other studies UL instead of OL. At the same time, in the study with the highest OL rate (51%) performed in Spain, the broadest definition of OL was used including the age, indication, dosage, frequency, route of administration, and also lack of paediatric information (Morales-Carpi *et al.* 2010).

In addition, significant differences in the content of the SPCs between countries have been observed, which explain partly the differences in OL prescription rates in various studies (Sturkenboom *et al.* 2008). Surkenboom *et al.*, when comparing the SPCs with that of the UK, Holland and Italy, reported that only 25% of the agents had the same age limit from which the drug was approved (Sturkenboom *et al.* 2009). These differences are likely to be minimised after implementation of mutual recognition in drug approval process.

Although we found that almost half of the prescriptions for infants and adolescents are OL, the proportions in preschool and schoolchildren are only approximately 10 and 20%, respectively (Figure 6). Previous data in this respect vary. The vast majority similar to us have also reported that infants, neonates and adolescent receive more often OL medicines than children of other age groups (Bucheler *et al.* 2002, Chalumeau *et al.* 2000, Di Paolo *et al.* 2006, Kimland *et al.* 2012, Palčevski *et al.* 2012, Schirm *et al.* 2003). However, there are other studies in which OL prescription rates were not dependent on age (Ekins-Daukes *et al.* 2004, Horen *et al.* 2002).

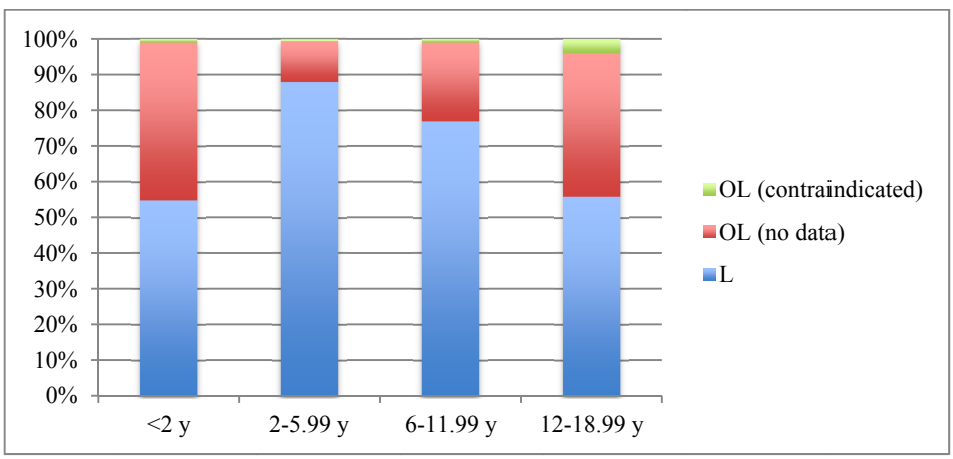


**Figure 6.** The proportion of ambulatory prescriptions classified as labelled (L) or off-label (OL) (y axis) in age groups (x axis)

### 5.3.1.1. Ambulatory OL ATC groups and products

The OL rate was the highest in genitourinary drugs group (97%), followed by dermatological (74%) and cardiovascular drugs (61%) (Figure 7). The most commonly prescribed ATC group anti-infectives were generally labelled for use in children (88% of prescriptions were labelled).

Drug groups with the highest percentages of ambulatory OL use have found in previous studies to be varying but similar to us (Morales-Carpi *et al.* 2010, Olsson *et al.* 2011, Radley *et al.* 2006, Volkers *et al.* 2007).

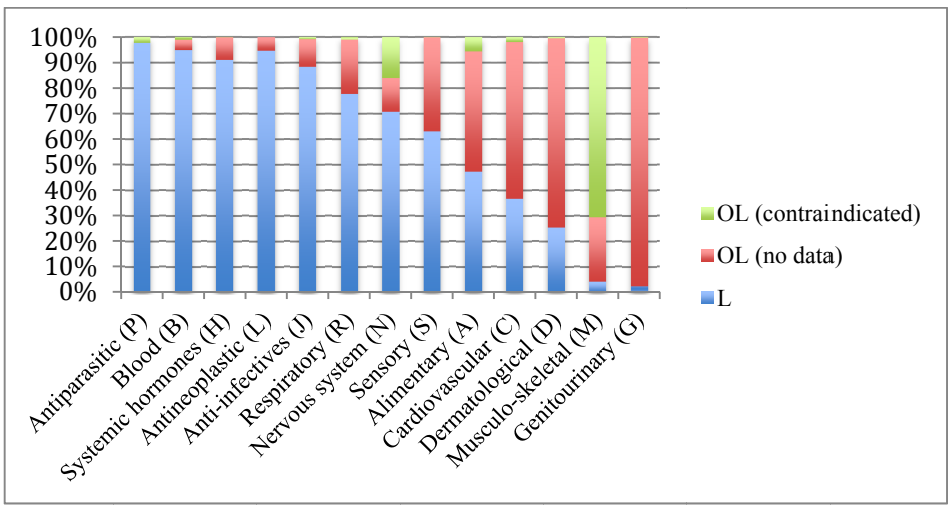


**Figure 7.** Percentage of ambulatory prescriptions (y axis) according to the ATC groups classified as being labelled or OL (x axis)

The most commonly prescribed OL products came from the frequently prescribed ATC groups – systemic antibacterials, dermatological and respiratory system drugs as seen in the Table 17. Prescriptions for drugs which are OL because of lack of data counted for 98% of the prescriptions for genitourinary drugs in adolescents, consisting mainly prescriptions for hormonal contraceptives. Also, over half of the prescriptions for alimentary drugs had no information in the SPCs for children aged less than 12 years.

For children younger than 2 years the highest OL prescription rate was for topical corticosteroids, cetirizine oral drops and salbutamol syrup.

The most commonly administered OL/UL medicines in the ambulatory setting have similarly to us found to be salbutamol (Bazzano *et al.* 2009, Chalumeau *et al.* 2000, Jong *et al.* 2002, Morales-Carpi *et al.* 2010, Pandolfini *et al.* 2005, Radley *et al.* 2006), amoxicillin (Bazzano *et al.* 2009, McIntyre *et al.* 2000, Morales-Carpi *et al.* 2010, Radley *et al.* 2006) and also paracetamol (Kimland *et al.* 2012, Morales-Carpi *et al.* 2010). The latter was not documented in our study as we did not collect data on the use of OTC medicines.

**Table 17.** Most commonly prescribed OL products in ambulatory practice in Estonia described as a number of OL prescriptions per 1000 children in population

| ATC group | Age group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | <2y (n = 29 805) Drug product / OL prescription rate | | 2–6y (n = 53 105) Drug product / OL prescription rate | | 6–12y (n = 74 044) Drug product / OL prescription rate | | 12–18y (n = 120 311) Drug product / OL prescription rate | |
| Alimentary (A) | Lipase+ amylase + protease caps | 12 | Drotaverine tabl | 4.9 | Drotaverine tabl | 9.4 | Drotaverine tabl | 12 |
| | Metoclopramide supp | 4.3 | Lipase+ amylase + protease caps | 3.4 | Insulin aspart (Novomix®) | 2.9 | Insulin lispro (Humalog®) | 5.8 |
| | Drotaverine tabl | 2.1 | Metoclopramide supp | 2.9 | Short- and middle acting human insulin (Mixtard®) | 1.4 | Omeprazol caps (Omeprazol ratiopharm®) | 2 |
| Blood (B) | NR | NR | NR | NR | NR | NR | Tranexamic acid tabl | 1.2 |
| Cardio-vascular (C) | Trandolapril caps | 0.7 | NR | NR | NR | NR | Trimetasidine tabl | 1.8 |
| | NR | NR | NR | NR | NR | NR | Nebivolol tabl | 1.6 |
| Dermato-logicals (D) | Hydrocortisone + chlorhexidine cream | 207 | Hydrocortisone + chlorhexidine cream | 60 | Hydrocortisone + chlorhexidine cream | 18 | Clindamycin topical sol | 58 |
| | Pimecrolimus cream | 51 | Pimecrolimus cream | 30 | Mometasone cream / ointment/ topical sol | 13 | Aselainic acid cream | 42 |
| | Fusidic acid cream /ointment | 27 | Fusidic acid cream /ointment | 30 | Betamethasone + fusidic acid cream | 12 | Adapalene cream / gel | 35 |
| Genitouri-nary (G) | NR | NR | Oxybutynin tabl | 1.2 | Oxybutynin tabl | 2.4 | Ddrospirenone + ethinyloestradiol tabl | 60 |
| | NR | NR | NR | NR | NR | NR | Gestodene + ethinyoestradiol | 50 |
| | NR | NR | NR | NR | NR | NR | Dienogest + ethinyloestradiol tabl | 23 |

| ATC group | Age group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | <2y (n = 29 805) Drug product / OL prescription rate | | 2–6y (n = 53 105) Drug product / OL prescription rate | | 6–12y (n = 74 044) Drug product / OL prescription rate | | 12–18y (n = 120 311) Drug product / OL prescription rate | |
| Systemic hormons (H) | NR | NR | NR | NR | NR | NR | Methylprednisolone tabl | 0.8 |
| Anti-infectives (J) | Sulfamethoxazole + trimetoprim syrup (L, but CRI for neonates) | 123 | Azitromycin tabl /caps | 6 | Amoxicillin + clavulanic acid tabl (Augmentin®)* | 39 | Amoxicillin + clavulanic acid tabl (Augmentin®)* | 39 |
| | Cefuroxime susp gran (L, but no data for neonates) | 62 | Amoxicillin + clavulanic acid tabl | 4.3 | Clarithromycin tabl | 35 | Clarithromycin tabl | 9.4 |
| | Cefprozil susp gran (L, but no data for neonates) | 48 | Clarithromycin tabl | 4.3 | Azitromycin tabl /caps | 13 | Ciprofloxacine tabl | 8.2 |
| Antineoplastic (L) | NR | NR | NR | NR | NR | NR | NR | NR |
| Musculo-skeletal (M) | Diclofenac supp | 4 | Diclofenac supp | 2.6 | Diclofenac topical gel | 0.7 | Dexketoprofene tabl | 7.5 |
| | NR | NR | NR | NR | NR | NR | Diclofenac topical gel | 4.5 |
| | NR | NR | NR | NR | NR | NR | Glucosamine tabl/powder | 4.5 |
| | NR | NR | NR | NR | Nortriptyline tabl | 2.2 | Escitalopram tabl | |
| Nervous system (N) | NR | NR | NR | NR | Piracetam tabl | 2 | Citalopram tabl | 3.1 |
| | NR | NR | NR | NR | Sertraline tabl | 1.3 | Fluoxetine tabl | 2.5 |
| Antiparasitic (P) | NR | NR | Hydroxychloroquin tabl | 2.9 | NR | NR | NR | NR |
| Respiratory (R) | Cetirizine oral drops | 254 | Momethasone nasal spray | 14 | Desloratadine tabl | 8 | Montelukast tabl | 2.9 |
| | Salbutamol syrup | 156 | Montelukast tabl | 9.2 | Cetririzine + pseudoephedrine tabl | 4.2 | NR | NR |
| | Ventolin resp sol (L, no data for neonates) | 17 | Beclomethasone nasal spray | 7.9 | Pseudoephedrine + loratadine tabl | 2.4 | NR | NR |

| ATC group | Age group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | <2y (n = 29 805) Drug product / OL prescription rate | | 2–6y (n = 53 105) Drug product / OL prescription rate | | 6–12y (n = 74 044) Drug product / OL prescription rate | | 12–18y (n = 120 311) Drug product / OL prescription rate | |
| Sensory organs (S) | Chroramphenicol opth drops | 66 | Chroramphenicol opth drops | 39 | Chroramphenicol opth drops | 10 | Dexamethasone + cloramphenicol opth sol, ointment | 7.5 |
| | Tobramycin opth sol, ointment (L, no data for neonates) | 39 | Dexamethasone + cloramphenicol opth sol, ointment | 18 | Dexamethasone + cloramphenicol opth sol, ointment | 8.5 | Chroramphenicol opth drops | 5.6 |
| | Dexamethasone + cloramphenicol opth sol, ointment | 17 | Dexamethasone opth sol, ointment | 5.7 | Dexamethasone opth sol, ointment | 4.2 | NR | NR |

Caps – capsules; gran – granules; NR, not relevant – the OL use of medicines in specific ATC group is low; opth – ophthalmic; sol – solution; supp – suppositories; susp – suspension; tabl – tablets;

Our results highlight that the following products could be included in the priority list of medicines needing paediatric trials:

- Dermatological drugs (D):
  Topical corticosteroids and local antibacterials for <12y (hydrocortisone + chlorhexidine and fusidic acid products; pimecrolimus for <6y; betamethasone and mometasone products for >6 y);
  Anti-acne products for adolescents (clindamycin, aselainic acid and adapalene topical products);
- Opthalmic drugs (S) for all age groups (chloramphenicol and dexamethasone products);
- Respiratory medicines (R):
  Antihistamine cetirizine oral drops for <2y;
  Anti-asthmatic medicines: montelukast tablets for >2y;
- Alimentary drugs: metoclopramide supp <6y; lipase+ amylase + protease caps <6y; drotaverine tabl <6y; insulin analogues (aspart, lispro) >6y;
- Genitourinary medicines (G): urinary antispasmodics oxybutynin tablets for 2–12y and oral contraceptives for adolescents;
- Antiinfectives: Clarithromycin for 2–18y, azitromycin for 2–12y
- Nervous system drugs (N): nortriptylline tablets for 6–12y.

In addition, there are medicines which SPCs should probably just updated regarding the paediatric use according to the available literature data such as for the use of salbutamol syrup in children <2y and amoxicillin capsules for adolescents.

#### 5.3.1.2. Ambulatory OL products vs. OL prescriptions and topical vs. systemic medicines

In all age groups, the proportion of OL prescriptions was lower than for OL products (Figure 8). This is a consequence of the lower prescription rate of the OL products when compared to the drugs with adequate labelling.

Also compared with topical drugs, a markedly smaller proportion of systemic agents (less than 40% in all age categories and 10% of prescriptions for the 2–5 years old) were OL for children (Figure 8). The proportion of OL topical drugs in our study was the highest for those under 2 years old and for adolescents— less than 40% of prescriptions had paediatric label.

It has been also described by others, that systemic drugs are less likely to be prescribed UL/OL than non-systemic (Chalumeau *et al.* 2000, Olsson *et al.* 2011, Schirm *et al.* 2003, Ufer *et al.* 2003b). The clinical relevance of this is debatable. On one hand, ADRs have been disproportionately more often reported on systemic than in topical drugs (Schirm *et al.* 2004). On the other hand, however, several cases of significant systemic absorption of topical and ophthalmic drugs leading to severe side effects have been observed (Dahshan & Donovan 2006, Hutcheson 2007, Phillips 2008). It is widely known that the relative systemic exposure of topically applied drugs in children may exceed

that of adults (Kearns *et al.* 2003), thus demonstrating a need to increase the available amount of information about the use of topical drugs in children.

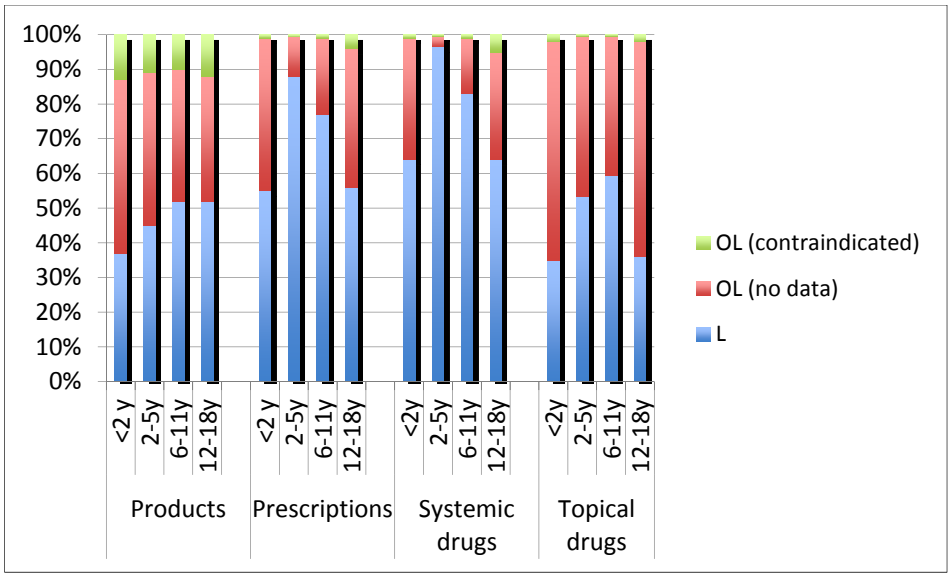


**Figure 8.** Proportion of systemic (a) and topical (b) agents and products (c) / prescriptions (d) being labelled, OL due to the lack of data or contraindication

### 5.3.2. OL medicines use in hospitalised neonates

OL medicines were an essential part of neonatal care – all preterm and 97% of treated term neonates received at least one OL/UL prescription suggesting that OL use in Estonia is in the upper end as compared to previous studies (48% – 100%)(Table 5).

Altogether 65% of prescriptions were for OL medicines (Table 19), which is higher than found in previous studies with the median rate of 49%, ranging from 28% (Neubert *et al.* 2010) to 59% (Barr *et al.* 2002) (Table 5).

While almost three-quarters (67/85, 72%) of drug products used in term neonates were OL, the respective rates in extremely preterm, very preterm and late preterm neonates were all >90% (respectively, 61/66, 92%; 62/66, 94%; 62/65, 95%).

The higher proportion of OL medicines found in our study could not be only explained by the methodological differences described previously in the review section.

The extent of UL/OL use in Estonian neonatal wards was found to be markedly higher than the general OL rate in the ambulatory setting. This is not surprising and is described by others that more OL prescriptions are seen in the neonatal, paediatric intensive care, oncology and haematology wards, compared

with primary care (Cuzzolin *et al.* 2006, Palčevski *et al.* 2012). This suggests that if paediatric studies are conducted they will mostly exclude patients with severe illness or at extreme age groups. However, namely in these populations the PK/PD of the drug is most unpredictable.

Among the preterm neonates, the markedly higher rate of OL medicines was seen in the group of late preterm neonates (Table 18). This phenomenon is not well understood. It may be that late preterm infants born at 34 through 36 GW are often the size and weight of term infants and may be managed as though they are developmentally mature as term neonates (Engle *et al.* 2007) affecting also the selection of medicines. In contrary to our results, higher prevalence of OL prescriptions have been found within the full-term neonates compared to pre-term neonates (DellAera *et al.* 2007).

**Table 18.** Number (%) of labelled (L), off-label (OL) and unlicensed (UL) medicines prescribed for hospitalised neonates according to the Estonian SPC

| | Extremely preterm neonates | Very preterm neonates | Late preterm neonates | Term neonates | Total |
|---|---|---|---|---|---|
| L | 62 (10) | 33 (9) | 16 (4) | 151 (24) | 200 (10) |
| OL | 369 (62) | 249 (68) | 300 (80) | 369 (57) | 1287 (65) |
| UL | 165 (28) | 85 (23) | 60 (16) | 122 (19) | 432 (22) |
| Total | 596 | 367 | 376 | 642 | 1981 |

### 5.3.2.1. OL ATC groups and products for hospitalised neonates

The proportions of OL/UL prescriptions differed greatly between ATC groups (Figure 9). There were only 5 drugs labelled for preterm neonates – phospholipids (2.5% of prescriptions), midazolam (2.4%), epoetin beta (1.6%), ibuprofen (1.6%) and amikacin (0.1%).

All alimentary, genitourinary, musculoskeletal and sensory system drugs were used OL, whereas the proportion of OL prescriptions was the lowest among the dermatologicals, drugs for blood and blood-forming organs and respiratory medicines. Of the antibiotic prescriptions used to treat term neonates, 83% were for 7 different OL medicines. The highest proportion of OL prescriptions for previously mentioned drug groups has been also shown by others (DellAera *et al.* 2007).

Most commonly prescribed OL products in our study were gentamicin for all age groups, heparin for very preterm neonates and simeticone for very-, late- and term neonates (Paper III, Table 3).

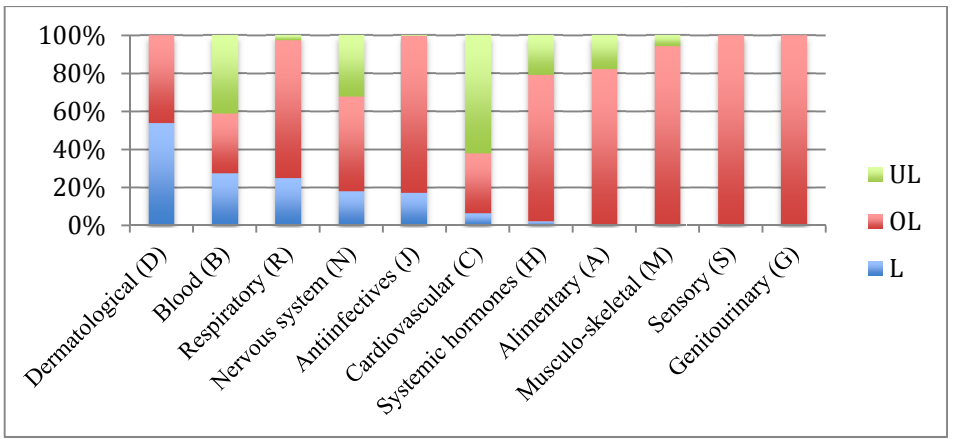


**Figure 9.** Percentage of prescriptions to hospitalised neonates according to the ATC groups classified as being labelled (L), off-label (OL) or unlicensed (UL)

### 5.3.3. Contraindicated medicines

**Ambulatory.** There were 2% of prescriptions for 106 products, which were contraindicated for paediatric use according to the SPC. For almost half of the products (42%) the contraindication was because of possible ADR in children. There was not enough experience or no clinical trials conducted in children for 29% of contraindicated products, in 22% the reason was not specified, in six cases (6%), the dose of the product was too high for children and in one product the excipients were not appropriate for children. The rate of medicines contraindicated because of the lack of paediatric clinical data was considerably higher than in our study in French (79%) and Germany (75%) (Bensouda-Grimaldi *et al.* 2007, Bucheler *et al.* 2002). Also in contrary to us, it has been shown that contraindication was seldom based on possible toxic effects in children (Bensouda-Grimaldi *et al.* 2007).

The proportion of contraindicated prescriptions was the highest amongst musculoskeletal (69%) and nervous system (16%) drugs. The same drug groups were often classified as OL because of contraindication also by others (Bensouda-Grimaldi *et al.* 2007, Olsson *et al.* 2011, Smith *et al.* 2012).

The most commonly prescribed contraindicated medicines are shown in Table 19. For pre-school children antiparasitic drug hydroxychloroquine (3/1000) and for older children selective serotonin receptor inhibitor escitalopram (6/1000) were most commonly prescribed CRI medicines. Anti-infectives also had one of the biggest proportions of contraindicated prescriptions for adolescents because of the prescription rate of 11/1000 for quinolones.

**Table 19.** TOP 10 most commonly prescribed contraindicated medicines, number of prescriptions per 1000 chi ldren in the population, reasons for being CRI according to the SPC and alternative with paediatric license if available

| Active substance (ATC group) | Pre-scription rate | Reasons for CRI | Alternative with paediatric licence |
|---|---|---|---|
| Dexketoprofen tabl (N) | 6.2 | Not tested in children | Ibuprofen |
| Ciprofloxacin tabl (J) | 6 | Not specified | Alternative AB |
| Escitalopram tabl (N) | 4.9 | No efficacy; increased risk of self harm and suicidal thoughts | NA* |
| Diclofenac gel (M) | 3.9 | Not enough data | NA |
| Norfloxacine tabl (J) | 2.5 | Not enough data, possible increased risk of tendon rupture | Alternative AB |
| Nortriptylline tabl (N) | 2.5 | No efficacy; increased risk of self harm and suicidal thoughts | NA* |
| Glucosamine tabl (M) | 2 | Not clinically tested in children | NA |
| Omeprazol caps (ratiopharm®) (A) | 1.8 | Not enough experience in children | Some products licensed |
| Etoricoxib tabl (M) | 1.7 | Not specified | Ibuprofen |
| Fluoxetine caps (N) | 1.2 | No efficacy; increased risk of self harm and suicidal thoughts | NA* |

AB, antibiotics; NA, not available

* Drug from the same ATC group included into the EMA priority list for studies in children

Contraindicated respiratory system drugs were rarely used for older children, but the prescription rate in infants and toddlers was 24/1000 (containing mainly fusafungin spray). For pre-school children, contraindicated clemastine tablets (2/1000) were prescribed.

Of the musculoskeletal system medicines, mainly non-steroidal anti-inflammatory drugs (NSAIDs) were contraindicated. As an example, diclofenac suppositories were prescribed at a rate of 4/1000 for infants, the drug being indicated above the age of 1 year.

**Neonates.** There were only five contraindicated products used in neonates – diclofenac, drotaverine, metoclopramide, heparin sodium ointment and ursodeoxycholic acid tablets. They were used in small number of patients and none of these were prescribed for extremely preterm neonates, still most of these medicines are needed in neonatal pharmacotherapy and recommended by the guidelines.

## 5.4. Extent of UL use of medicines

There were 0.05% of ambulatory prescriptions for six products (etosuximide capsules (Petnidan® and Suxilep®), salbutamol prolonged release tablets (Volmax®), fludrocortisone tablets (Florinef®), hydrocortisone tablets and vigabatrine tablets (Sabril®)) that had no MA in Estonia and were categorised as being UL. This is much lower than the median UL rate 16% in other studies (Table 4) ranging from 0.3 (McIntyre *et al.* 2000) to 16.8 (t Jong *et al.* 2004). As mentioned above here the UL definition plays the most important role, as all of the studies reporting high ambulatory UL rate have been conducted in The Netherlands and have classified medicines as being UL if the medicinal preparation was modified, drug lacked paediatric information or was contraindicated (Table 3). Also, as reported by the authors, the amount of prescriptions that is prepared by the Dutch pharmacies is approximately 5%, contributing also to the higher rate of UL medicines (Schirm *et al.* 2003).

The amount of UL drugs in the Estonian neonatal wards was in a contrary high (22% of prescriptions, and 25% of products used). This is again in the upper end of UL rate found in the literature review (range 6–29%, Table 5). As for a comparison, not a single UL medicine was used in the paediatric ward in Germany (Hsien *et al.* 2008). Differences between countries might reflect the variations in the national approval status. The higher proportion of UL medicines in neonatal wards could express the small market for specific medicinal products only used in neonatology leading to the lack of interest for drug companies to register these products. As an example, caffeine was used for treating apnoea in 29/41 extremely and 20/53 very preterm neonates and was UL in Estonia during the study period. Parenteral furosemide and heparin were the most commonly used cardiovascular drugs in term and extremely preterm neonates, and dobutamine was often used in preterm neonates for treating

hypotension associated with postnatal adaption and transitional circulation. All of these drugs were UL.

## 5.5. Availability of paediatric medicines information

Notable differences were found when paediatric information in the Estonian SPCs of the frequently used OL medicines was compared with other paediatric drug information sources. Discrepancies in paediatric drug information in different sources exist due to the following reasons:

- Principal differences of the source documents e.g. official information in the SPC vs. expert-opinion based sources such as BNFC;
- Regulatory discrepancies e.g. EMA and European indications in the SPC, BNFC and UK based indications, FDA indications in the Micromedex database.

### 5.5.1. Drug information for ambulatory prescriptions

Differences existed most often in nervous system medicines and anti-infectives. The main discrepancy between the information sources was due to different age-related indications/contraindications (Table 20).

There were several products containing the same active ingredient and present in the same pharmaceutical formulation, but produced by different drug companies having completely different paediatric information in the SPCs. For example, in the SPC of cetirizine oral solution, for the brand name Aceterine® (Hexal AG), the SPC states that the product is contraindicated for children aged under 2 years; whereas the SPC of Zyrtec® (UCB Pharma Oy) does not state such contraindication. The drug formulations, including excipients of these two products are exactly the same. According to the BNFC, cetirizine is not indicated for use in children aged less than 6 years except for 2–6 year olds for the treatment of seasonal allergic rhinitis. According to the Thomson Micromedex, cetirizine is indicated for children aged over 6 months for the treatment of perennial allergic rhinitis and also chronic urticaria. The 16$^{th}$ edition of Harriet Lane Handbook recommends cetirizine for children aged over 2 years without mentioning specific indications or contraindications.

**Table 20.** 20 most commonly prescribed OL medicines and the information in SPCs, BNFC and Micromedex

| Drug (ATC group) | SPC | BNFC | Micromedex |
|---|---|---|---|
| Cetirizine oral drops (Zyrtec, Aceterin) (R) | Zyrtec: not recommended<2y; Aceterin: CRI | NL <6y, doses for >1y | Doses for >6 months |
| Salbutamol syrup (R) | Doses for >2y | NL <2y, doses for >1 month | L >2y |
| Amoxicillin + clavulanic acid granules for oral suspension (J) | Not recommended <2 months | L, doses for neonates and older | L <3 months and older |
| Chloramphenicol eye drops (S) | Children mentioned only in warnings | L, starting from neonates | Safety & efficacy not established, doses for neonates given |
| Diclofenac suppositories (M) | CRI, dose too high | NL < 6y | Safety & efficacy not established |
| Fusidic acid cream (D) | Children not mentioned | L | NA |
| Mometasone nasal spray (R) | L > 6y | L > 6y | L > 2y |
| Hydroxychloroquine tabl (P) | CRI < 6y | L >1 month | L for malaria suppression |
| Metoclopramide tabl (A) | CRI < 14y | L, starting from neonates | Safety & efficacy not established, doses starting from neonates |
| Amoxicillin + clavulanic acid tabl (J) | Children not mentioned | L, starting from neonates | L <3 months |
| Clarithromycin tabl (J) | Oral suspension is recommended for <12y | L, starting from neonates | L |
| Nortriptyline tabl (N) | CRI | L > 6y | L adolescents |
| Escitalopram tabl (N) | CRI | NL for use in children | Safety & effectiveness not established; doses >12y |
| Sulpiride tabl (N) | CRI <14y | For Tourette syndrome doses >2y | NA |
| Sertraline tabl (N) | CRI | NL for depression; doses for obsessive-compulsive disorder > 6y, doses for depression > 12y | For obsessive-compulsive disorder > 6y |
| Clindamycin topical solution (J) | Children not mentioned | L | Acne vulgaris: >12y |

| Drug (ATC group) | SPC | BNFC | Micromedex |
|---|---|---|---|
| Drospirenone + ethinylestradiol tabl (G) | Children not mentioned | L | Contraception: after menarche, same dose as adults; Acne vulgaris >14y |
| Dienogest + ethinylestradiol tabl (G) | Children not mentioned | L | NA |
| Adapalene cream (D) | Only information in SPC: not tested <12y | L, dose starting from neonates | afety & efficacy not established 12y; for acne vulgaris >12y |
| Ciprofloxacin tabl (J) | CRI | L > 5y for pseudomonal infections in cystic fibrosis & for other children/other infections where benefit outweighs potential risks | NL < 18y except for treatment of anthrax and complicated urinary tract infections |

CRI, contraindicated; NL, not labelled; L, labelled, NA, not included into the handbook or database

Another contradictory area in the SPCs is related to the recommendations for liquid and solid oral formulations. Although it is generally accepted but not thoroughly studied that children aged above 6 years are able to swallow tablets, the upper age for liquid formulation is often not specified or is much greater than 6 years. For example, amoxicillin/clavulanic acid (Amoksiklav® [Sandoz d.d.], Augmentin® [GlaxoSmithKline]) tablets are most likely suitable for children aged above 6 years, but the SPC dosing recommendations for adolescents were given only for powder for oral suspension. There was no reference to paediatric use in the SPC of Augmentin® tablets, at the same time the SPC of Augmentin® suspension granules gives dosing information starting from 2 months of age. These results are even more intriguing because amoxicillin clavulanate has been extensively studied in paediatric population; the MEDLINE database search for the term 'amoxicillin clavulanate' identified 265 randomised controlled studies conducted in the age group of 0–18 years. We believe that the SPCs should be updated, as the oral suspension may not be the best formulation for subjects who could otherwise swallow tablets. However, we accept that the prescription of amoxicillin clavulanate tablets to adolescents is OL legally and not medically, provided that the bioequivalence between the tablets and the liquid formulation has been demonstrated.

### 5.5.2. Neonatal medicines information

Main licensing status variations between drug information sources for the medicines used in hospitalised neonates were encountered among term neonates (Table 21), while the amount of information for preterm neonates was equally scarce in all studied sources as presented in (Figure 10). Neonatal information was most frequently available in the BNFC and lacking in the SPCs. For term neonates, the information was available for 67%, 38% and 24% of prescriptions according to the BNFC, Micromedex and Estonian SPC, respectively.

Similar to older children great differences regarding the neonatal drug information in drug information sources in terms of specific drug products were found. For example, according to the SPC, metoclopramide is contraindicated for children less than 2 years of age. According to the BNFC it is not licensed for use in neonates as a prokinetic, however the doses are still given. According to the Micromedex metoclopramide is only licensed for intestinal intubation, but doses for neonates are given for treating gastroesophageal reflux disease (GERD). Metoclopramide is widely used as prokinetics in neonates despite the descriptions of several side effects and lack of evidence to support the use for GERD in infants (Hibbs & Lorch 2006).

Povidone iodine ointment is licensed according to the SPC, has no directions for using in neonates according to BNFC and Micromedex and is contraindicated for preterm neonates according to the BNFC. Micromedex warns against using povidone iodine, as significant transcutaneous absorption of iodine may occur after the topical application in infants and raised plasma iodine levels could interfere with metabolic and thyroid function (Hudaoglu *et al.* 2009).

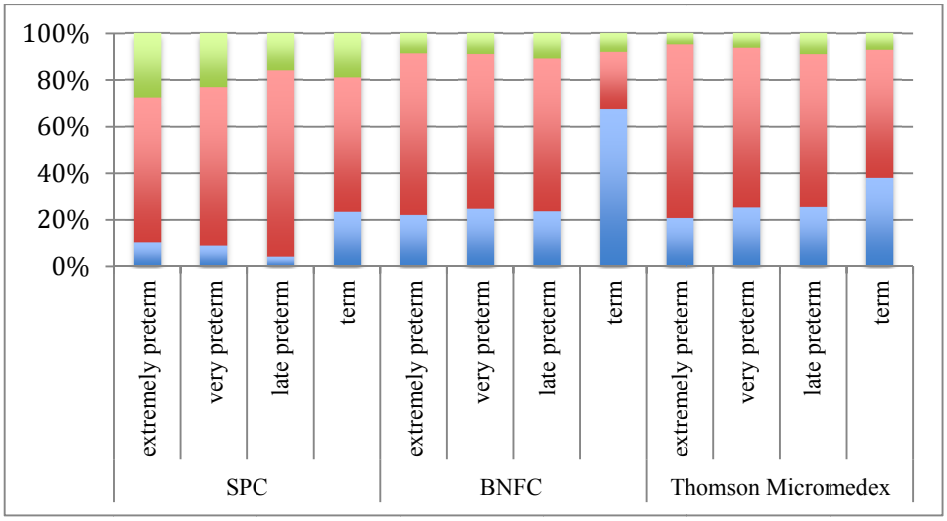


**Figure 10.** Neonatal labelling status according to SPC, BNFC 2009 and Thomson Micromedex database
Blue bars – L; red bars – OL; green bars – UL

**Table 21.** Neonatal drug information according to BNFC 2009 and Thomson Micromedex database (TMD) for ten most often used drugs in preterm and term neonates. Blue boxes – L; green boxes – OL; white boxes – UL

| Preterm neonates | | | | Term neonates | | | |
|---|---|---|---|---|---|---|---|
| | SPC | BNFC | TMD | | SPC | BNFC | TMD |
| 1 Gentamicin | | | | Gentamicin | | | |
| 2 Ampicillin | | | | Dimeticone /Simeticone | | | |
| 3 Heparin | | | | Ampicillin | | | |
| 4 Dimeticone /Simeticone | | | | Benzylpenicillin | | | |
| 5 Fentanyl | | | | Fentanyl | | | |
| 6 Laurylsulphate + sodiumcitrate | | | | Furosemide iv sol | | | |
| 7 Furosemide iv sol | | | | Salbutamol | | | |
| 8 Dextriferrone | | | | Midazolam | | | |
| 9 Dobutamine | | | | Heparin | | | |
| 10 Fluconazole | | | | Paracetamol supp | | | |

Parenteral heparin, preserved with benzyl alcohol (BA), is used UL in Estonian neonatal units as it has no local or central EU MA. Some preparations containing no BA are licensed in children according to the BNFC, and Micromedex, but it is stated that solutions preserved with BA should not to be used in neonates as BA has been related to the "gasping syndrome" (Thomson Reuters Micromedex 2.0). The neonatal safety issues with pharmaceutical excipients are further discussed in the following section 5.6.

## 5.6. Extent of excipient use

In total 93 of 107 medicines (87%) and 1620 of 1961 prescriptions (83%) contained at least one excipient. The total number of different excipients was 123.

### 5.6.1. Classification of excipients

One third of excipients (42/123) was classified as potentially safe (Category 1, described in Table 11).

Another third (47/123) was classified as potentially harmful (Category 2), including eight excipients already known to be harmful in neonates e.g. parabens, saccharin sodium, sodium benzoate, benzyl alcohol, benzalkonium chloride, propylene glycol, polysorbate 80 and ethanol.

For the remaining 34 excipients human safety / toxicity data was not found in the literature (Category 3) or the chemical entity of excipient was not described in the SPC thus allowing not conducting the literature search (15/34; Category 4) (Paper III, Table 2). Many of the excipients of the previous category were flavouring agents such as banana, strawberry, raspberry flavour etc.

### 5.6.2. Neonatal exposure to excipients

Almost all treated neonates (339/348; 97%) received medicines with at least one potentially harmful excipient (Category 2) and as many as 88% (307/348) received at least one of the eight excipients known to be harmful in neonates (Paper III, Table 2).

The proportion of medicines containing potentially harmful excipients in preterm neonates was even higher in our study than the general rate – 77%. At the same time the percentage of used medicines that contained only potentially safe excipients was the same in both populations (22%).

### 5.6.3. Presence of potentially and known to be harmful excipients (category 2) in the medicines

From the medicines prescribed, the median number of included excipients known to cause harm in neonates was two (interquartile range (IQR) 5–2; pre-

term neonates median of 3, range 1 to 15, IQR 4–2; term neonates median of 1, range 1 to 11, IQR 3–1).

As illustrated in the Figure 11 approximately two thirds (73 products /107, 68%) of all the medicines used contained at least one category 2 excipient including 31/107; 31% containing at least one known to be harmful excipient. The median number of category 2 excipients per medicinal product was two and maximum was five (in simeticone oral suspension).

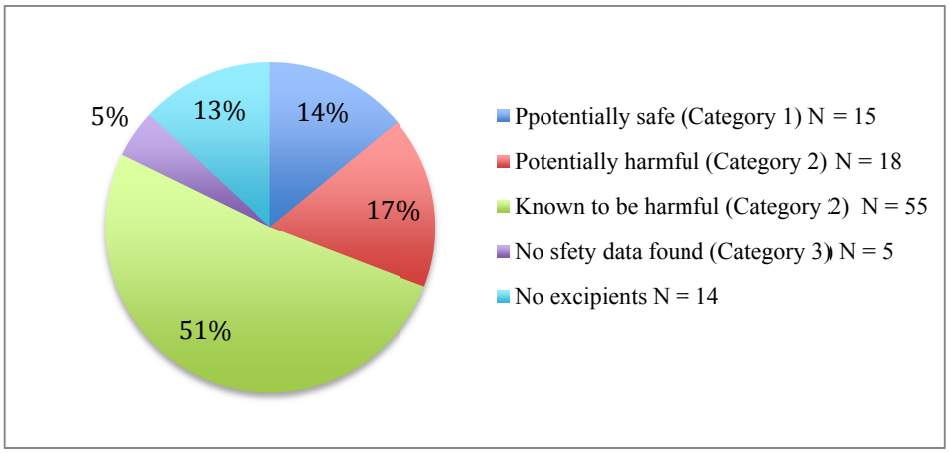


**Figure 11.** Proportion of prescribed medications to neonates, containing at least one excipient, in each safety category (every drug is listed once according to the worst-case scenario – into the most harmful category).

The most common excipients that are known to cause harm were propylene glycol and ethanol, both present in seven products. In relation to prescription frequency, the most common excipients known to cause harm were parabens (methyl- and propylparahydroxybenzoate) used as preservatives in the most commonly used medicine – parenteral gentamicin, which was given to 57% of treated neonates. However, a paraben-free gentamicin product is also registered in Europe. The gentamicin product also included another potentially harmful excipient, namely sodium metabisulphite (Table 22).

With this our data are in line with van Riet-Nales et al. who also showed that for 22% of oral liquid paediatric medicines contain potentially harmful excipients. Whilst at the same time an alternative formulation lacking the potentially harmful excipient being available with the same active chemical entity (van Riet-Nales *et al.* 2011). This may indicate that health professionals have a low awareness on safety of excipients.

**Table 22.** Most commonly prescribed medicines (received by >10 neonates) containing known to be harmful or potentially harmful excipients

| Rank | Active substance, drug formulation | No of Pre-scrip-tions | Potentially harmful or known to be harmful excipients |
|---|---|---|---|
| 1 | Gentamicin, inj solution | 200 | Parabens, sodium metabisulphite |
| 2 | Simeticone, oral suspension | 108 | Sodium benzoate, saccharin sodium, silicium dioxide, sodium cyclamate, sorbic acid |
| 3 | Heparin, inj solution | 86 | Benzyl alcohol, Parabens |
| 4 | Laurilsulphate + Sorbitol + Sodium citrate, rectal solution | 60 | Sorbic acid |
| 5 | Salbutamol, nebulisation solution | 54 | Benzalkonium chloride, propylene glycol |
| 6 | Dobutamine, inj solution | 45 | Sodium metabisulphite |
| 7 | Epinephrine, inj solution | 36 | Sodium metabisulphite |
| 8 | Iron, oral solution | 32 | Parabens, saccharin sodium |
| 9 | Budesonide, nebulisation solution | 31 | Polysorbate 80, disodiumedetate |
| 10 | Chloramphenicol, opthalmic solution | 29 | Benzalkonium chloride, polysorbate 80, borax, boric acid |
| 11 | Caffeine, solution | 29 | Sodium benzoate |
| 12 | Phenobarbital, tablet | 29 | Silicium dioxide, gelatin |
| 13 | Paracetamol, suppository | 29 | Disodium hydrogen phosphate |
| 14 | Piperacillin+ tazobactam, inj solution | 25 | Disodium edetate |
| 15 | Paracetamol, inj solution | 24 | Disodium hydrogen phosphate |
| 16 | Hydrocortisone, inj solution | 23 | Benzyl alcohol, disodium hydrogen phosphate |
| 17 | Epoetin beta, inj solution | 22 | Disodium hydrogen phosphate, glycine, calcium chloride dihydrate, leucine, |
| 18 | Ibuprofen, inj solution | 21 | Trometamol |
| 19 | Hyoscine butylbromide, tablet | 20 | Silicium dioxide |
| 20 | Spironolactone, tablet | 18 | Silicium dioxide |
| 21 | Zidovudine, oral solution | 17 | Sodium benzoate, saccharin sodium |
| 22 | Fusidic acid, ophthalmic solution | 16 | Benzalkonium chloride, disodium edetate |
| 23 | Morphine, inj solution | 14 | Sodium metabisulphite |
| 24 | Phenobarbital, inj solution | 13 | Benzyl alcohol, propylene glycol |
| 25 | Heparin sodium, topical gel | 12 | Parabens, ethanol, trietanolamine, |
| 26 | Insulin, inj solution | 11 | Cresol |

Inj – injection

Simeticone oral suspension was the second most commonly prescribed medicine, given to 31% of neonates. The simeticone product contained two excipients known to cause harm – saccharin sodium and sodium benzoate, and also three other potentially harmful excipients – colloidal anhydrous silica, sorbic acid and sodium cyclamate (Table 22).

Two products contained 3 known to be toxic excipients – cetirizine oral drops (parabens, saccharine sodium and propylene glycol) and miconazole ointment (parabens, polysorbate 80, ethanol). The number of different potentially toxic excipients to which neonates are exposed is not studied before, but it has been shown that on paediatric wards some products contained up to five potentially harmful excipients (Cordner *et al.* 2012).

The proportion of medicines containing potentially harmful excipients in our study is higher than the recently published in the Netherlands where 52% of oral liquid formulations and 7% of all parenteral products for the entire paediatric population were containing some toxic excipients (van Riet-Nales *et al.* 2011). This difference is most likely explained by the methodological variations, regional characteristics in marketed product ranges and by differences in classifying excipients into the toxicity categories. In the Dutch study only "known to be toxic" excipients were taken into the analysis while in our study a very conservative approach was taken and the excipients were classified into the "potentially harmful" category even if only some data on human toxicity had been published (also when used as a substance) as one could not assure that the same agent does not cause any harm when used in small quantities as an excipient.

Approximately two thirds of parenterally used products (29/47) contained some potentially harmful excipients. The situation was even worse for other drug formulations – all of the prescribed rectal, topical, inhalation, oral solutions and oral suspensions contained at least one potentially harmful excipient. The use of topical agents in neonates was rare, only 8/33 products contained excipient known to be toxic to neonates. Only one of the 19 orally administered solid drug formulations and one of the five ocular formulations were free of potentially harmful excipients. Not surprisingly, most of medicines free from potentially harmful excipients were parenteral single-dose antibacterial or antifungal formulations (13/ of all the 35 medicines without harmful excipients).

A total of 19 medicines were licensed for use in neonates (6 for preterm and all for term neonates). Approximately half of them (3/6 in preterm and 8/19 in term neonates) contained at least one potentially harmful excipient. For example epoetin beta product contains leucine, which is moderately toxic by the subcutaneous route, glycine which is moderately toxic by the intravenous route and mildly toxic by ingestion, disodium hydrogen phosphate that can cause gastrointestinal disturbances including diarrhea, nausea, and vomiting when used as an excipient and calcium chloride dihydrate which is toxic by subcutaneous route and can also cause dermatitis (Rowe *et al.* 2009). It has also described by others that the paediatric medicines may not be age-appropriate concerning the excipients even if the drugs are authorised for use in children (van Riet-Nales *et al.* 2011).

The amount of the excipients in the drug formulation was present in the SPCs for only two medications (metoclopramide injection solution and esomeprazole powder for injection). The detailed characteristics of excipients and their potential safety issues are described in Paper III, Table 3.

# 6. GENERAL DISCUSSION

## 6.1. Studies on the paediatric prescription pattern and OL medicines use

Paediatric medicines use has been abundantly studied in recent decades as the creation of healthcare databases has broadened the possibilities for pharmaco-epidemiological studies. However, due to the high heterogeneity among the paediatric drug utilisation studies, the systematic and continuous monitoring of the drug use in children by conducting multinational collaborative studies is still a burning need to improve the rational use of drugs in children (Clavenna & Bonati 2009). With our study we demonstrate that cross-national analyses of drug utilisation data can aid in highlighting the possible flaws in pharmaco-therapy such as in our case the great difference in antibiotics use between Estonia and Sweden despite the similar resistance profile of most common pathogens. On the basis of our results, the prescribing of antibiotics in Estonian children may not always be appropriate and these results should motivate initiatives with the aim of improving antibiotics prescribing.

As one of the subsections of the pharmacoepidemiological studies, the OL medicines use has been studied extensively during the last number of years. As a result, the current OL status of the many commonly used medicines in paediatrics has been meticulously proven for different kinds of treatment settings and regions. With our studies we show that the OL medicines use rates in an Eastern European country are broadly similar with the results of the studies conducted in the Western Europe, thus the further studies focusing on the general OL use rates are apparently of no great value. We suggest that the differences in OL between various studies (Tables 4 and 5) are not caused by the interregional differences but are mainly driven by different methodology and most of all by differences in the definitions used.

## 6.2. Evidence-based paediatric drug information – from where should it come?

Licensed medicines represent the gold standard for treatment quality, safety and efficacy. In comparison to adults, children are commonly treated with medicines that are not studied in the paediatric population and are thus often with unknown safety and efficacy profile. As we are also exhaustively showing, these medicines generally lack official paediatric drug information and are used solely based on the expert opinion.

There are strict recent regulations for the drug companies while acquiring marketing authorisation for a new medicine, such as need for PIP. As a result, in the 2 years after the acceptance of the Paediatric Regulation, 564 PIPs / waivers were submitted by the pharmaceutical companies, covering nearly 870 indications (Rocchi *et al.* 2010). By the end of 2011 the evaluation of 682 PIPs

was completed by the PDCO, of these 476 opinions (70%) resulted in an agreement of a PIP and 29 PIPS were completed. The completed PIPS have been leading to new paediatric indications for 24 medicines and to a drug formulation appropriate for the children for 7 medicines. Thirty-four new medicines have been centrally authorised since 26 January 2007 with a paediatric indication at the time of initial MA, out of these 7 were authorised for a use only in the paediatric population (http://ec.europa.eu/health/files/paediatrics/2012-09_paediatric_report-annex1-2_en.pdf).

It was stated more than 10 years ago that when a drug is already extensively used there is no commercial incentive for a pharmaceutical company to seek an amendment to the product licence (Turner *et al.* 1998). From our studies the examples of such OL "old" medicines are diclofenac, metoclopramide or drotaverine and there are around 1000 products authorised for adults but used also for treating children on the market in Europe at the present time (Kimland *et al.* 2012). Inadequate paediatric labelling of drugs is often attributed to the lack of scientific documentation in children due to the lack of clinical trials. However, in some cases, the available evidence outside the drug labelling might be sufficient to extend the indications to children without further clinical studies. For example, of five proton pump inhibitors (PPI) marketed in EU only omeprazole has a paediatric indication, but in US 3 out of 5 are authorised for children. Still, despite the lack of paediatric data in SPC, the paediatric PK, efficacy and safety data of PPIs in the age ranges that are not covered by SPC is available in the literature (Tafuri *et al.* 2009). Similarly, we conclude that high rate of OL medicines use is probably the combination of missing clinical study data and nature of the regulatory approval process delaying the reflection of study results in the SPC. For example when searching in the PubMed database (accessed on 19 August 2012) using the key words "neonate", "pharmacokinetics" and "gentamicin", we identified 201 publications, several of which provide dosing recommendations. However, there is still no mention of neonates in the Estonian SPC (http://193.40.10.165/SPC/Hum/SPC_12524.pdf, confirmed in the Estonian State Agency of Medicines in March 2011). It would appear that regardless of the number of studies, the dosing recommendations and safety data are still not readily available to physicians. Furthermore different dosing recommendations for gentamicin are given in various guidance documents (e.g. BNFC, NeoFax, Textbook for Paediatric Infectious Diseases) for neonates, which may also confuse the prescribers.

It has been suggested that the review of the SPCs of some drugs, together with the monitoring of clinical practice and with new clinical research, may be a step forward to reduce the OL use in children (Marchetti *et al.* 2007). A system how to increase the availability of official paediatric medicines information for the "old" OL medicines that have been used for years is currently established through the Paediatric regulation (PUMAs) and EU FP7grants. In order to update the SPC with the relevant paediatric information, the EU Paediatric Regulation states that paediatric studies that have not previously been assessed by the authorities "shall be submitted by the MA holder for assessment to the

competent authority" (Paediatric Regulation, articles 45 and 46). The competent authority may then update the SPC and may vary the MA accordingly (Kimland *et al.* 2012). According to the EMA 5-year Report, up to the end of 2011 more than 18,000 paediatric studies (also published studies) of about 1000 active substances have been submitted to the PDCO by the Marketing Authorisation Holders and the assessment of these studies has resulted in 65 SPC changes. Also the development of 20 off-patent medicines for paediatric use was funded by the EU 7th Framework programme (http://ec.europa.eu/health/files/paediatrics/2012-09_paediatric_report-annex1-2_en.pdf).

Recently, a national law was adopted in France with the aim of strengthening the safety of medicines called "Temporary Recommendations for Use" (TRUs). This law provides a regulatory process for temporarily supervising the prescribing of medicines for indications for which they are not yet licensed. A TRU is issued a single time for a medicine for 3 years, it allows to assess the benefits and risks of a marketed drugs for an unlicensed indication, to collect scientific information and gives pharmaceutical companies the responsibility for controlling the OL prescribing. Companies must monitor prescriptions' adherence to MAs and if unconventional prescribing is observed, they must inform the National Agency of Medicines (Emmerich *et al.* 2012).

In an ideal world similarly to the pharmacotherapy of adults the SPC would also be the leading source of drug information for the treatment of children. Still, taking into account the limitations of the officially approved SPC, which is mainly a manufacturer-lead uni-directional provision of clinical trial based information (or often a statement of the lack of this information) and, on the other hand, the comprehensive information management of the selected medicines formularies such as BNFC, the choice of the drug information source by the practitioner and accordingly the drug dosage for children probably remains an "educated guess" also in the near future.

## 6.3. Prioritisation of paediatric medicines research

An important aim of the OL/UL studies is to show in detail which medicines, groups of medicines or specialties need to be inserted into the paediatric priority lists with the highest need to be studied. As the prescribing habits may vary between countries and settings, also the list of priority medicines may differ and results of a new OL/UL use study either affirm the list or add new priorities. Still, one of the important flaws of the OL/UL medicines use studies is the lack of uniform definitions leading to the incomparable study results restricting the straightforward transformation of study results to the universal paediatric priority list.

There are two recently published lists of paediatric priority medicines having different aims and also content. Global Model List of Essential Medicines for Children intended for use for children up to 12 years of age by the WHO (http://whqlibdoc.who.int/hq/2011/a95054_eng.pdf) comprises of data from 89

unique country priority lists. It represents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. The medicines were selected on the basis of global burden of disease and the evidence of efficacy and safety for preventing or treating maternal, neonatal, and child mortality and morbidity. The list includes medicines for treating pneumonia, diarrhoea, malaria, vitamin A deficiency, medicines for paediatric palliative care, HIV/TB prophylaxis and medicines for neonatal care (Hill *et al.* 2012).

According to the EMA revised priority list for studies into off-patent paediatric medicinal products published in January 2012 (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004017.pdf), the following areas are always considered to be of high priority: development of age-appropriate drug formulations, data in neonates, in infants with oncological conditions and for refractory paediatric epilepsy syndromes. It has also been shown by investigators that children from 2 to 6 years receive significantly more often than other age groups of medicines that are contraindicated due to the inappropriate drug formulation and infants tend to receive the drugs which are contraindicated for their age on the basis of toxic effects (Bensouda-Grimaldi *et al.* 2007) confirming the recommendations from the priority list.

The EMA priority list for off patent medicines used in children is a basis for the 7$^{th}$ Framework Programme of the European Commission, which the manufacturing companies can apply for funding studies for medicines, which are in the list.

The priority list should provide guidance on which medicines are the most important to be studied. Still, it is acknowledged that the identification of the priorities for the research into the medicinal products for paediatric use is partly based on subjective criteria and that the identified priorities may change over time (van Riet-Nales *et al.* 2011). The country-specific and systematic studies of the OL/UL use of medicines are therefore helpful for improving the priority list.

In our studies we identified that the most commonly prescribed OL products come from the frequently prescribed ATC groups – systemic antibacterials, dermatological and respiratory system drugs. This highlights also the general priorities of including these ATC groups in the priority lists in addition to the less commonly used medicines for which the paediatric clinical data is lacking.

Our results are supported by the Olsson *et al*. who suggested that topically used medicines should be considered in greater need of paediatric clinical studies (Olsson *et al.* 2011) and also by the European survey of the paediatric medicines use (http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101006.pdf) which states that among others, the most frequent OL medicines are antiasthmatics and antimicrobials (macrolides, betalactams plus betalactamase inhibitors and carbapenems).

However, we believe that the most commonly used OL medicines should be critically evaluated before adding new medicines to the priority lists. For example, according to our results, instead of including the commonly used beta-blocker nebivolol, which is OL for children to the list, the use of the licensed

medicine metoprolol from the same drug group could probably be recommended in the clinical practice. Also the contraindicated dexketoprofen should not be added to the priority list but rather be substituted in the clinical practice with the NSAID labeled for the use in children such as ibuprofen. The use of contraindicated prescriptions is certainly inappropriate if the labelled alternative exists within the same therapeutic group.

To conclude, the clinical studies are mostly needed for the most commonly used OL medicines and also for those in which no alternatives in paediatric pharmacotherapy exist.

## 6.4. What to do with the UL medicines?

The UL rates in different studies have been found to be even more erratic than OL rates. However, again the UL definition could have various meanings. For example, the drug formulation needs to be modified before it can be administered to child (Gavrilov *et al.* 2000), medicine is not recommended to be given to a child (Serreau *et al.* 2004) or the drug product has no marketing authorisation in the country where the study is conducted, but it is licensed for use in an other country (Turner *et al.* 1998). All of these previously mentioned reasons for medicines being UL need different handling and solutions for reducing the UL use rates.

Similarly to most other studies (Table 3) we classified medicinal product UL if the product had no MA in Estonia nor centrally in the EU. Chemicals that were prepared into a formulation within the hospital pharmacy were also categorised UL. Generally the UL medicines lack the official drug information (SPC) and are supplemented solely with patient information sheets, which are not in local language. The number of such medicines was remarkably high (22% of prescriptions, and 25% of products) in the neonatal units highlighting the need for regulatory action.

We show that the UL prescribing is a significantly larger problem in the neonatal pharmacotherapy compared to the paediatric ambulatory practice. However, very few of the UL medicines were specific for neonates such as vitamin K and caffeine. Most of the UL medicines are also used in adults (are thus also UL in adults), to mention only a few – atropine, furosemide, heparin, fenobarbital or petidine injection solutions. Unfortunately none of these products have either a central EU marketing authorisation.

If there are no alternatives for the substitution of the UL medicines with the licensed medicines in clinical practice, one way forward in reducing the UL medicines usage rates could be the implementation of regulatory initiatives. These initiatives could force the manufactures of such medicines to apply for a MA or at least to make available the clinical trial documentation. As a result the respective regulatory authorities could then provide an official guidance on the use of the specific product in the clinical practice.

## 6.5. Drug formulation excipients and safer neonatal pharmacotherapy

We show that hospitalised neonates often receive medicines with potentially harmful drug formulation excipients. However, despite the existing literature reports about the possible ADRs of pharmaceutical excipients in children, this area has up to now received no appropriate attention, as the excipients were relative recently called inactive ingredients of the drug formulation. Therefore, the awareness of the potential problems with the excipients, especially in neonates has remained low in the medical community. We aimed to increase the awareness and have highlighted that in addition to the active ingredients medicines also contain a lot of excipients which may cause side effects especially in neonates (e.g. ethanol, propylene glycol and benzoic acid).

To date very few medicines have been designed with the needs of the neonates in mind and there are few direct data on the safety of specific excipients in infants (Nunn & Williams 2005). Still, due to the immature metabolizing systems, excipients that are not harmful to older age groups could be harmful to neonates even in very low doses. It is possible that even if the excipient is known to be harmful, the daily intake will not exceed the toxic threshold due to the small quantities used in drug formulations. The general lack of quantitative information of the excipients amount in the SPC limits the possibility of the practitioner to make an informed decision. For example, from using a parenteral gentamicin product, a premature infant weighting 500g and receiving a daily dose of 2mg gets a maximum of 0.1mcg of parabens (methyl- and propylparahydroxybenzoate, parenteral formulations contain up to 0.75% parabens). When comparing this value to the allowed daily intake of 10mg/kg body weight in adults it is obvious that the quantities are far below the toxic threshold. However, the fact that in neonates organs and thus the PK pathways are not fully matured may change the situation drastically (Fabiano *et al.* 2011).

Up to now, even the toxicity of known toxic excipients has not been clearly proven in clinical practice. Thus it has not been established how extensive is the possible clinical harm that may be caused by the formulation excipients. For example, Allegaert *et al*. showed recently that a short duration of unintended propylene glycol administration at a median dose of 34 mg/kg over 48 hours was well tolerated by (pre)term neonates (Allegaert *et al.* 2010). However, the authors stress that the long-term safety of propylene glycol is still not established. We believe that the well-known toxic or potentially harmful excipients need careful safety assessment and determination of the PK/PD profiles in neonates.

There is an increasing trend for the companies producing cosmetics to remove the unwanted excipients from their products. For example, Johnson and Johnson are removing all excipients from their baby care products, including parabens. If this would also happen in the pharmaceutical industry, a substitution in clinical practice between the generic products free from potentially toxic excipients could be possible while treating neonates.

One way to reduce the neonatal exposure to the potentially toxic excipients could be the therapeutic substitution of medicinal products containing only potentially safe excipients. The possibility of substitution will be hopefully proven by the European Study of Neonatal Exposure (ESNEE, http://www.esnee.eu/index.html) project, which is partly taking place also in Estonia. As a part of the project, service evaluation questionnaire was carried out to collect the list of medicinal products used in the European neonatal intensive care units. The excipient content of the almost 2000 different medicinal products reported was collected using the SPCs and PILs. The preliminary results show several options for substitution, for example the currently used gentamicin product could be substituted by the parabens-free product. However, before these results are published, withholding the medicines is at the moment often the only means of avoiding exposure to the excipients in neonatology.

## 6.6. Limitations of the study

Some limitations of the studies should be noted, which in our opinion do not affect the general reliability of the results.

In the studies for ambulatory medicines use we were not able to register over-the-counter drug use, but only prescription medicines. Thus we are showing the usage pattern only for the prescription medicines.

The main weakness in the antibiotics use study comes from the fact that the Swedish data collection is not diagnose-linked so we were not able to assess the guideline adherence in Sweden. Nor was it possible to describe the between-country variability of the dose regimens and of the duration of treatment. In order to study the between-country variability in treatment practices including the choice of antibiotics for different conditions, a prospective study would be required.

We also only captured ambulatory data collected within 1 year and thus were unable to analyse the trends in the prescription medicines and also in the systemic antibacterials use. However, the drug prescription pattern is found to be relatively stable, and even if changes occur, they are seen between specific drugs rather than between drug classes.

The major limitation to the neonatal medicines use study is that we addressed a subsection of the issue of the OL use in neonatology, as only the drugs prescribed to the hospitalised neonates were included. However, we believe that these limitations did not obviate the adequacy of our conclusions on neonatal drug exposure rates and on OL use in Estonia. We did collect data about the doses and duration of the treatment, but were unfortunately not able to use this information as the doses expressed per body weight often change daily in neonates.

The most important limitation of the excipients exposure study is the lack of the information on the exact amounts of excipients in the medicines, which

precludes us making any conclusions on the quantitative excipient exposure. This limitation was beyond our control because manufacturers do not disseminate this information. The other challenges are the use of a novel and non-validated classification system and the restriction of the study to one country only. We did not collect information about the dosage regimens since this would have been un-interpretable in the absence of the quantitative information about the excipient content of the prescribed medicines. Another issue, possibly characteristic also to other small markets, was the significant use (22%) of unlicensed medicines and thus the unavailability of the SPCs. In these cases the excipient content was recorded according to the package insert leaflets. Although we appreciate that only excipients of intravenous, topical and ophthalmic products and known to be toxic excipients have to be declared in the package leaflet, we assume that this will not significantly affect our conclusions. Finally the study was conducted in a small country and thus these results cannot be generalised to other countries. These limitations do not undermine our findings that neonates are frequently exposed to a range of potentially harmful and known to be toxic excipients.

## 6.7. Suggestions for future research

Taking into account the various methodological problems in the OL/UL medicines use studies such as various definitions and study methodologies used, we believe that the future studies on the OL/UL use of medicines in children should rather be prospective studies with the focus on the real clinical impact of the OL/UL medicines use in children. For example, what is the impact of the OL/UL use to the efficacy and safety of the paediatric medicines or to which extent the OL/UL use of medicines in paediatrics could be avoided. For the OL medicines, it should be detected whether there is a real lack of clinical data in the literature or there is a need for the SPC update while selecting the medicines into the priority list.

As discussed above numerous clinical studies have already been performed with some agents and there is hardly any need to conduct another study. Thus, instead of conducting another PK study, a meta-analysis of all existing data together with the re-analysis of the already collected data by using population kinetics and modelling could be a step forward in providing appropriate dosing and safety information to practicing physicians.

Also, before the discussions into the reformulation of medications with safer excipients for neonatal use start, the possible harm from excipients must be balanced against the positive effect of the medicine and the hazard (how does the excipient harm the child) must be adequately characterised. Therefore, further studies should make a clinical link between the excipient exposure and outcomes focusing on the excipients disposition (PK), clinical consequences associated with the excipient exposure and the level of safe exposure, including the long-term safety data in neonates.

# 7. CONCLUSIONS

I The reports of paediatric ambulatory prescription and in-hospital medicines use show that a substantial amount of medicines are prescribed to Estonian children. This highlights the need for in-depth diagnoses-linked pharmaco-epidemiological studies in more commonly prescribed pharmacotherapeutic subgroups for ensuring the rationality of paediatric pharmacotherapy.

II Significant qualitative and quantitative differences in ambulatory antibiotics use between Estonian and Swedish children exist. The higher rate of antibiotic consumption in Estonia and the apparent high use of broad-spectrum antibiotics emphasises the need for national activities similar to the Swedish STRAMA programme in order to prevent misuse of antibiotics. Thus, auditing activities should focus on rational use of antibiotics and compliance to evidence based guidelines.

III Compared with Western Europe the rates of OL / UL medicines use in the ambulatory and hospital setting in Estonia are similarly high. Larger proportion of topical than systemically administered medicines was OL. Also children under 2 years received OL medicines more often than older age groups. This is showing a priority of including the younger paediatric age groups and topical drugs into the priority list of medicines that need to be studied in children.

IV There were very few ambulatory prescriptions for UL medicines. The prescription rate of UL drugs in most vulnerable group hospitalised neonates was in a contrary high (22% of prescriptions, and 25% of products used), indicating the lack of medicines with local marketing authorisation needed for treating hospitalised neonates. Clinical trials in neonatal population and regulatory initiatives forcing the manufactures of such medicines for applying MA could ease the situation.

V The majority of prescriptions were classified OL due to the lack of data on the paediatric / neonatal use in the SPC. There is a distinctly higher availability of information in the paediatric handbooks (e.g. BNFC) and databases (e.g. Micromedex) compared to the official documents (SPC). As for many OL medicines the literature search reveals substantial amount of paediatric studies, our results shall bring the attention of the authorities to the need for taking action in updating the SPCs. The reasons for a drug not being recommended for paediatric use should be provided to inform the practitioners and to avoid ineffective and potentially dangerous use of medicines in children.

VI One third of excipients used in hospitalised neonates were classified as potentially harmful but of these only eight have been previously classified as known to be harmful in neonates (e.g. parabens, saccharin sodium, sodium benzoate, benzyl alcohol, benzalkonium chloride, propylene glycol, polysorbate 80 and ethanol). There is a need for validated classification system regarding the potential neonatal toxicity of excipients.

VII As almost all treated neonates received medicines with at least one potentially harmful excipient, there is an urgent need for the careful toxicological assessment of excipients as the information in the published literature is extremely limited. Information about the possible harm resulting from excipients and also the quantitative data regarding the excipients amount in specific drug products should be made available to pharmacists and neonatologists. This will assist the selection of the most appropriate medicines for neonates. When excipients cannot be avoided, professionals should have access to quantitative and qualitative information that allows them to assess risk, substitute products while toxic-excipient free products are available and monitor vulnerable patients appropriately.

# 8. REFERENCES


Aagaard L & Hansen EH. (2011) Prescribing of medicines in the Danish paediatric population outwith the licensed age group: characteristics of adverse drug reactions. Br J Clin Pharmacol 71(5): 751–757.

Alade SL, Brown R & Paquet A. (1986) Polysorbate 80 and E-Ferol toxicity. Pediatrics 77(4): 593–597.

Allegaert K, Vanhaesebrouck S, Kulo A, Cosaert K, Verbesselt R, Debeer A & de Hoon J. (2010) Prospective assessment of short-term propylene glycol tolerance in neonates. Arch Dis Child 95(12): 1054–1058.

Altman M, Vanpée M, Cnattingius S & Norman M. (2011) Neonatal morbidity in moderately preterm infants: a Swedish national population-based study. J Pediatr 158(2): 239–244.

Arulanantham K & Genel M. (1978) Central nervous system toxicity associated with ingestion of propylene glycol. J Pediatr 93(3): 515–516.

Asakawa H, Araki T, Yamamoto N, Imai I, Yamane M, Tsutsumi Y & Kawakami F. (2000) Allergy to ethylenediamine and steroid. J Invest Allergol Clin Immunol 10(6): 372–374.

Ashley ESD, Zaas A, Fang A, Damle B & Perfect J. (2007) Comparative pharmacokinetics of voriconazole administered orally as either crushed or whole tablets. Antimicrob Agents Chemother 51(3): 877–880.

Bajcetic M, Jelisavcic M, Mitrovic J, Divac N, Simeunovic S, Samardzic R & Gorodischer R. (2005) Off label and unlicensed drugs use in paediatric cardiology. Eur J Clin Pharmacol 61(10): 775–779.

Barr J, Brenner-Zada G, Heiman E, Pareth G, Bulkowstein M, Greenberg R & Berkovitch M. (2002) Unlicensed and off-label medication use in a neonatal intensive care unit: a prospective study. Am J Perinatol 19(2): 67–72.

Bartelink IH, Rademaker C, Schobben AFAM & Van Den Anker JN. (2006) Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. Clin Pharmacokinet 45(11): 1077–1097.

Bazzano ATF, Mangione-Smith R, Schonlau M, Suttorp MJ & Brook RH. (2009) Off-Label Prescribing to Children in the United States Outpatient Setting. Academic Pediatrics 9(2): 81–88.

Bensouda-Grimaldi L, Sarraf N, Doisy F, Jonville-Béra AP, Pivette J & Autret-Leca E. (2007) Prescription of drugs contraindicated in children: a national community survey. Eur J Clin Pharmacol 63(1): 99–101.

Bianchi M, Clavenna A & Bonati M. (2010) Inter-country variations in anti-asthmatic drug prescriptions for children. Systematic review of studies published during the 2000–2009 period. Eur J Clin Pharmacol 66(9): 929–936.

BMJ Group. (2009) BNF for Children. London, UK: RPS Publishing.

Breitkreutz J. (2008) European perspectives on pediatric formulations. Clin Ther 30(11): 2146–2154.

Bucheler R, Schwab M, Morike K, Kalchthaler B, Mohr H, Schroder H, Schwoerer P & Gleiter CH. (2002) Off label prescribing to children in primary care in Germany: retrospective cohort study. Br Med J 324(7349): 1311–1312.

Carter D. (2011) Risk Assessment for Excipients for Enhanced Patient Safety. Pharm Technol 35: s29-s33.

Carvalho P, Carvalho CG, Alievi PT, Martinbiancho J & Trotta EA. (2003) Prescription of drugs not appropriate for children in a Pediatric Intensive Care Unit. J Pediatr 79(5): 397–402.
Ceci A, Felisi M, Baiardi P, Bonifazi F, Catapano M, Giaquinto C, Nicolosi A, Sturkenboom M, Neubert A & Wong I. (2006) Medicines for children licensed by the European Medicines Agency (EMEA): the balance after 10 years. Eur J Clin Pharmacol 62(11): 947–952.
Ceci A, Felisi M, Catapano M, Baiardi P, Cipollina L, Ravera S, Bagnulo S, Reggio S & Rondini G. (2002) Medicines for children licensed by the European Agency for the Evaluation of Medicinal Products. Eur J Clin Pharmacol 58(8): 495–500.
Ceelie I, van der Starre C, Tibboel D, Stol K, Koren G & de Wildt SN. (2010) Evaluation of drug formularies for pediatric intensive care. Pediatric Crit Care Medicine 12(1): 14–18.
Chalumeau M, Treluyer J, Salanave B, Assathiany R, Chéron G, Crocheton N, Rougeron C, Mares M, Bréart G & Pons G. (2000) Off label and unlicensed drug use among French office based paediatricians. Arch Dis Child 83(6): 502–505.
Clark RH, Bloom BT, Spitzer AR & Gerstmann DR. (2006) Reported medication use in the neonatal intensive care unit: data from a large national data set. Pediatrics 117(6): 1979–1987.
Clavenna A, Berti A, Gualandi L, Rossi E, De Rosa M & Bonati M. (2009) Drug utilisation profile in the Italian paediatric population. Eur J Pediatr 168(2): 173–180.
Clavenna A & Bonati M. (2009) Drug prescriptions to outpatient children: a review of the literature. Eur J Clin Pharmacol 65: 749–755.
Clavenna A & Bonati M. (2011) Differences in antibiotic prescribing in paediatric outpatients. Arch Dis Child 96(6): 590–595.
Conroy S. (2011) Association between licence status and medication errors. Arch Dis Child 96(3): 305–306.
Conroy S, Choonara I, Impicciatore P, Mohn A, Arnell H, Rane A, Knoeppel C, Seyberth H, Pandolfini C & Raffaelli MP. (2000) Survey of unlicensed and off label drug use in paediatric wards in European countries. Br Med J 320(7227): 79–82.
Conroy S, McIntyre J, Choonara I, Hull P. (1999) Unlicensed and off label drug use in neonates. Arch Dis Child Fetal Neonat ed 80(2): F142–145.
Conroy S, Newman C & Gudka S. (2003) Unlicensed and off label drug use in acute lymphoblastic leukaemia and other malignancies in children. Ann Oncol 14(1): 42–47.
Conroy S & Peden V. (2001) Unlicensed and off label analgesic use in paediatric pain management. Pediatric Anesthesia 11(4): 431–436.
Cordner C, Caldwell N & Elliot P. (2012) What else is in our children's medicine? Arch Dis Child 97(5): e2-e3.
Costello I, Long PF, Wong IK, Tuleu C, Yeung V (ed) (2007) Paediatric Drug Handling. Great Britain: Pharmaceutical Press.
Craig JS, Henderson CR & Magee FA. (2001) The extent of unlicensed and off-label drug use in the paediatric ward of a district general hospital in Northern Ireland. Ir Med J 94(8): 237–240.
Custer JW & Rau RE. (2009) The Harriet Lane Handbook. Pennsylvania: Elsevier Mosby.
Cuzzolin L, Atzei A & Fanos V. (2006) Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. Exp Opin Drug Safety 5(5):703–718

Dahshan A & Donovan GK. (2006) Severe methemoglobinemia complicating topical benzocaine use during endoscopy in a toddler: a case report and review of the literature. Pediatrics 117(4): e806.
Dastychová E, Necas M & Vasku V. (2008) Contact hypersensitivity to selected excipients of dermatological topical preparations and cosmetics in patients with chronic eczema. Acta Dermatovenerol Alpina, Panonica, et Adriatica 17(2): 61–68.
DellAera M, Gasbarro AR, Padovano M, Laforgia N, Capodiferro D, Solarino B, Quaranta R & Dell'Erba AS. (2007) Unlicensed and off-label use of medicines at a neonatology clinic in Italy. Pharm World & Science 29(4): 361–367.
Di Paolo ER, Stoetter H, Cotting J, Frey P, Gehri M, Beck-Popovic M, Tolsa J, Fanconi S & Pannatier A. (2006) Unlicensed and off-label drug use in a Swiss paediatric university hospital. Swiss medical weekly 136(13/14): 218–222.
Dick A, Keady S, Mohamed F, Brayley S, Thomson M, Lloyd B, Heuschkel R & Afzal N. (2003) Use of unlicensed and off-label medications in paediatric gastroenterology with a review of the commonly used formularies in the UK. Aliment Pharmacol Ther 17(4): 571–575.
Doherty DR, Pascuet E, Ni A, Stewart P, Splinter W & Vaillancourt R. (2010) Off-label drug use in pediatric anesthesia and intensive care according to official and pediatric reference formularies. Can J Anesth 57(12): 1078–1088.
Eiland LS & Knight P. (2006) Evaluating the off-label use of medications in children. Am J Health Syst Pharm 63(11): 1062–1065.
Ekins-Daukes S, Helms PJ, Simpson CR, Taylor MW & McLay JS. (2004) Off-label prescribing to children in primary care: retrospective observational study. Eur J Clin Pharmacol 60(5): 349–353.
EMA. (2009) A guideline on summary of product characteristics.
Emmerich J, Dumarcet N, Lorence A. (2012) France's new framework for regulating off-label drug use. New Eng J Med 367: 1279–1281.
Engle WA, Tomashek KM & Wallman C. (2007) "Late-Preterm" Infants: A population at risk. Pediatrics 120(6): 1390–1401.
European Commission. (2003) The Rules Governing Medicinal Products in the European Union. Excipients in the Label and Package leaflet of Medicinal Products for Human Use. Eudralex Collection 2011(August, 2011).
European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). (2006) Reflection paper: Formulations of choice for the paediatric population. 2011(August, 11).
European Parliament. (2004) Directive 2001/83/EC of the European Parliament and of the council of the Community Code relating to medicinal products for human use. 2012(April 8).
European Parliament and the Council of the European Union. (2001) Directive 2001／20／EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. OJEC L121(34–44).
Fabiano V, Mameli C & Zuccotti GV. (2011) Paediatric pharmacology: Remember the excipients. Pharmacol Res 63(5):362–365.
FDA. (2010) Inactive ingredients database. 2012(April, 14).
Gavrilov V, Berkovitch M, Ling G, Brenner-Zadda G, Lifshitz M & Gorodischer R. (2003) Unapproved prescriptions in two pediatric intensive care units in Israel. Curr Ther Res 64(9): 734–742.

Gavrilov V, Lifshitz M, Levy J & Gorodischer R. (2000) Unlicensed and off-label medication use in a general pediatrics ambulatory hospital unit in Israel. Isr Med Assoc J 2(8): 595–597.
Geiling E & Cannon PR. (1938) Pathologic effects of elixir of sulfanilamide (diethylene glycol) poisoning. J Am Med Assoc 111(10): 919.
Grieve J, Tordoff J, Reith D, Norris P. (2005) Effect of the pediatric exclusivity provision on children's access to medicines. Br J Clin Pharmacol 59(6): 730–735.
Hall C, Milligan D & Berrington J. (2004) Probable adverse reaction to a pharmaceutical excipient. Arch Dis Child Fetal Neonat Ed 89(2): F184.
Haywood A & Glass B. (2011) Pharmaceutical excipients–where do we begin? Australian Prescriber 34(4)112–114.
Heath EI, Forman K, Malburg L, Gainer S, Suttle AB, Adams L, Ball H & LoRusso P. (2011) A phase I pharmacokinetic and safety evaluation of oral pazopanib dosing administered as crushed tablet or oral suspension in patients with advanced solid tumors. Invest New Drugs 30(4), 1566–1574.
Hedin K, Andre M, Håkansson A, Mölstad S, Rodhe N & Petersson C. (2006) A population-based study of different antibiotic prescribing in different areas. Br J Gen Pract 56(530): 680–685.
Hibbs AM & Lorch SA. (2006) Metoclopramide for the treatment of gastroesophageal reflux disease in infants: a systematic review. Pediatrics 118(2): 746–752.
Hill S, Yang A & Bero L. (2012) Priority Medicines for Maternal and Child Health: A Global Survey of National Essential Medicines Lists. PloS one 7(5): e38055.
Hiller JL, Benda GI, Rahatzad M, Allen JR, Culver DH, Carlson CV & Reynolds JW. (1986) Benzyl alcohol toxicity: impact on mortality and intraventricular hemorrhage among very low birth weight infants. Pediatrics 77(4): 500–506.
Horen B, Montastruc JL & Lapeyre-Mestre M. (2002) Adverse drug reactions and off-label drug use in paediatric outpatients. Br J Clin Pharmacol 54(6): 665–670.
Hraoui M, Boutiba-Ben Boubaker I, Doloy A, Samir E, Ben Redjeb S & Bouvet A. (2011) Epidemiological markers of Streptococcus pyogenes strains in Tunisia. Clin Microbiol Infec 17(1): 63–68.
Hsien L, Breddemann A, Frobel AK, Heusch A, Schmidt KG & Läer S. (2008) Off-label drug use among hospitalised children: identifying areas with the highest need for research. Pharm World Science 30(5): 497–502.
Hsu B & Brazelton T. (2009) Off-label medication use in an academic hospital pediatric critical care unit. Wis Med J 108(7): 343–348.
Hudaoglu OG, Uçar SK, Atlihan F, Dizdarer C & Büyükgebiz A. (2009) The effects of topical iodine containing antiseptics on thyroidal status of preterm versus term babies. Saudi Med J 6: 783–787.
Hugtenburg J, Heerdink E & Egberts A. (2004) Increased psychotropic drug consumption by children in the Netherlands during 1995–2001 is caused by increased use of methylphenidate by boys. Eur J Clin Pharmacol 60(5): 377–379.
Hutcheson KA. (2007) Steroid-induced glaucoma in an infant. J AAPOS 11(5): 522–523.
Impicciatore P, Mohn A, Chiarelli F, Pandolfini C & Bonati M. (2002) Adverse drug reactions to off-label drugs on a paediatric ward: an Italian prospective pilot study. Paediatr Perinat Drug Ther 5(1): 19–24.
IPEC Europe. (2008) Qualification of excipients for pharmaceutical use.
Irs A. (2009) Ravimite kasutusele lubamine Eestis ja Euroopa Liidus. Eesti Arst 88(10): 697–701.

Jain SS, Bavdekar S, Gogtay NJ & Sadawarte PA. (2008) Off-label drug use in children. Indian J Pediatr 75(11): 1133–1136.

Jakuskiene R, Vollmer B, Saferis V & Daugeliene D. (2011) Neonatal outcomes of very preterm infants admitted to a tertiary center in Lithuania between the years 2003 and 2005. Eur J Pediatr 170: 1–11.

Jong G, Eland IA, Sturkenboom MCJM, van den Anker JN & Stricker BHC. (2002) Unlicensed and off label prescription of drugs to children: population based cohort study. BMJ 324(7349): 1313–1314.

Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS & Kauffman RE. (2003) Developmental pharmacology-drug disposition, action, and therapy in infants and children. N Engl J Med 349(12): 1157–1167.

Kemper EM, Merkus M, Wierenga PC, Van Rijn PC & Van der Werff D. (2011) Towards evidence-based pharmacotherapy in children. Pediatr Anesth 21(3): 183–189.

Khdour MR, Hallak HO, Alayasa KSA, AlShahed QN, Hawwa AF & McElnay JC. (2011) Extent and nature of unlicensed and off-label medicine use in hospitalised children in Palestine. Int J Clin Pharm 33:650–655.

Kimland E, Bergman U, Lindemalm S & Böttiger Y. (2007) Drug related problems and off-label drug treatment in children as seen at a drug information centre. Eur J Pediatr 166(6): 527–532.

Kimland E, Nydert P, Odlind V, Böttiger Y & Lindemalm S. (2012) Paediatric drug use with focus on off-label prescriptions at Swedish hospitals–a nationwide study. Acta Paediatrica 101(7):772–778.

Knellwolf AL, Bauzon S, Alberighi ODC, Lutsar I, Bácsy E, Alfarez D, Panei P, Jiao F, Zhang X, Bai T. (2011) Framework conditions facilitating paediatric clinical research. Ital J Pediatr 37(1): 1–6.

Kumar P, Walker JK, Hurt KM, Bennett KM, Grosshans N & Fotis MA. (2008) Medication use in the neonatal intensive care unit: current patterns and off-label use of parenteral medications. J Pediatr 152(3): 412–415.

Lee E, Teschemaker AR, Johann-Liang R, Bazemore G, Yoon M, Shim KS, Daniel M, Pittman J, Wutoh AK. (2011) Off-label prescribing patterns of antidepressants in children and adolescents. Pharmacoepid Drug Saf 21:137–144.

Lee PI, Wu MH, Huang LM, Chen JM & Lee CY. (2008) An open, randomized, comparative study of clarithromycin and erythromycin in the treatment of children with community-acquired pneumonia. J Microbiol Immunol Infect 41(1): 54–61.

Liem TBY, Heerdink ER, Egberts ACG & Rademaker CMA. (2010) Quantifying antibiotic use in paediatrics: a proposal for neonatal DDDs. Eur J Clin Microbiol Inf Dis 29(10): 1301–1303.

Lifshitz M, Gavrilov V & Gorodischer R. (2001) Off-label and unlicensed use of antidotes in paediatric patients. Eur J Clin Pharmacol 56(11): 839–841.

Lindell-Osuagwu L, Korhonen M, Saano S, Helin-Tanninen M, Naaranlahti T, Kokki H. (2009) Off-label and unlicensed drug prescribing in three paediatric wards in Finland and review of the international literature. J Clin Pharm Ther 34(3): 277–287.

Lusini G, Lapi F, Sara B, Vannacci A, Mugelli A, Kragstrup J & Bjerrum L. (2009) Antibiotic prescribing in paediatric populations: a comparison between Viareggio, Italy and Funen, Denmark. Eur J Public Health 19(4): 434–438.

Madsen H, Andersen M & Hallas J. (2001) Drug prescribing among Danish children: a population-based study. Eur J Clin Pharmacol 57(2): 159–165.

Marchetti F, Bua J, Ventura A, Notarangelo LD, Di Maio S, Migliore G & Bonati M. (2007) The awareness among paediatricians of off-label prescribing in children: a survey of Italian hospitals. Eur J Clin Pharmacol 63(1): 81–85.

Marra F, Monnet DL, Patrick DM, Chong M, Brandt CT, Winters M, Kaltoft MS, Tyrrell GJ, Lovgren M & Bowie WR. (2007) A comparison of antibiotic use in children between Canada and Denmark. Ann Pharmacother 41(4): 659–666.

Martin RM & Conroy S. (1998) Unlicensed and off label drug use for paediatric patients. Br Med J 317(7152): 204–204.

Mason J, Pirmohamed M & Nunn T. (2012) Off-label and unlicensed medicine use and adverse drug reactions in children: a narrative review of the literature. Eur J Clin Pharmacol 68: 21–28.

McCowan C, Hoskins G & Neville RG. (2007) Clinical symptoms and 'off-label'prescribing in children with asthma. Br J Gen Pract 57(536): 220–222.

McIntyre J, Conroy S, Avery A, Corns H & Choonara I. (2000) Unlicensed and off label prescribing of drugs in general practice. Arch Dis Child 83(6): 498–501.

McKinzie JP, Wright SW & Wrenn KD. (1997) Pediatric drug therapy in the emergency department: Does it meet FDA-approved prescribing guidelines? Am J Emerg Med 15(2): 118–121.

Menson EN, Walker AS, Sharland M, Wells C, Tudor-Williams G, Riordan FAI, Lyall E & Gibb DM. (2006) Underdosing of antiretrovirals in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997–2005: cohort study. Br Med J 332(7551): 1183–1187.

Metsvaht T. (2009) Optimal Antibacterial Therapy of Neonates at Risk of Early Onset Sepsis. Dissertation, University of Tartu.

Metsvaht T, Ilmoja ML, Parm Ü, Maipuu L, Merila M & Lutsar I. (2010) Comparison of ampicillin plus gentamicin vs. penicillin plus gentamicin in empiric treatment of neonates at risk of early onset sepsis. Acta Paediatrica 99(5): 665–672.

Morales-Carpi C, Estañ L, Rubio E, Lurbe E & Morales-Olivas FJ. (2010) Drug utilization and off-label drug use among Spanish emergency room paediatric patients. Eur J Clin Pharmacol 66(3): 315–320.

Mühlbauer B, Janhsen K, Pichler J & Schoettler P. (2009) Off-Label Use of Prescription Drugs in Childhood and Adolescence: An Analysis of Prescription Patterns in Germany. Deutsches Arzteblatt International 106(3): 25–31.

Nahata MC & Allen Jr LV. (2008) Extemporaneous drug formulations. Clin Ther 30(11): 2112–2119.

Nasrin D, Collignon PJ, Roberts L, Wilson EJ, Pilotto LS & Douglas RM. (2002) Effect of β lactam antibiotic use in children on pneumococcal resistance to penicillin: prospective cohort study. Br Med J 324(7328): 1–4.

Neubert A, Dormann H, Weiss J, Egger T, Criegee-Rieck M, Rascher W, Brune K & Hinz B. (2004) The impact of unlicensed and off-label drug use on adverse drug reactions in paediatric patients. Drug safety 27(13): 1059–1067.

Neubert A, Lukas K, Leis T, Dormann H, Brune K & Rascher W. (2010) Drug utilisation on a preterm and neonatal intensive care unit in Germany: a prospective, cohort-based analysis. Eur J Clin Pharmacol 66(1): 87–95.

Neubert A, Sturkenboom MCJM, Murray ML, Verhamme K, Nicolosi A, Giaquinto C, Ceci A & Wong ICK. (2008a) Databases for pediatric medicine research in Europe – assessment and critical appraisal. Pharmacoepidemiol Drug Saf 17(12): 1155–1167.

Neubert A, Wong ICK, Bonifazi A, Catapano M, Felisi M, Baiardi P, Giaquinto C, Knibbe CAJ, Sturkenboom MCJM & Ghaleb MA. (2008b) Defining off-label and

unlicensed use of medicines for children: results of a Delphi survey. Pharmacol Res 58(5–6): 316–322.
Nguyen KA, Claris O & Kassai B. (2011) Unlicensed and off-label drug use in a neonatal unit in France. Acta Paediatrica 100(4): 615–617.
Nunn T & Williams J. (2005) Formulation of medicines for children. Br J Clin Pharmacol 59(6): 674–679.
O'Donnell CPF, Stone RJ & Morley CJ. (2002) Unlicensed and off-label drug use in an Australian neonatal intensive care unit. Pediatrics 110(5): e52.
Oguz SS, Kanmaz HG & Dilmen U. (2012) Off-label and unlicensed drug use in neonatal intensive care units in Turkey: the old-inn study. Intern J Clin Pharmacy 34: 136–141.
Olsson J, Kimland E, Pettersson S & Odlind V. (2011) Paediatric drug use with focus on off-label prescriptions in Swedish outpatient care – a nationwide study. Acta Paediatrica 100: 1272–1275.
Palčevski G, Skočibušić N & Vlahović-Palčevski V. (2012) Unlicensed and off-label drug use in hospitalized children in Croatia: a cross-sectional survey. Eur J Clin Pharmacol 68(7): 1073–1077.
Pandolfini C & Bonati M. (2003) Off-label drug use in children in Europe: a major health issue. Pharm Developm Regul 1(2): 133–143.
Pandolfini C & Bonati M. (2005) A literature review on off-label drug use in children. Eur J Pediatr 164(9): 552–558.
Pandolfini C, Campi R, Clavenna A, Cazzato T & Bonati M. (2005) Italian paediatricians and off-label prescriptions: Loyal to regulatory or guideline standards? Acta Pædiatrica 94(6): 753–757.
Pandolfini C, Impicciatore P, Provasi D, Rocchi F, Campi R & Bonati M. (2002) Off-label use of drugs in Italy: a prospective, observational and multicentre study. Acta Paediatrica 91(3): 339–347.
Pasquali SK, Hall M, Slonim AD, Jenkins KJ, Marino BS, Cohen MS & Shah SS. (2008) Off-label use of cardiovascular medications in children hospitalized with congenital and acquired heart disease. Circulation: Cardiovasc Qual Outcomes 1(2): 74–83.
Peleg O, Bar-Oz B & Arad I. (1998) Coma in a premature infant associated with the transdermal absorption of propylene glycol. Acta Paediatrica 87(11): 1195–1196.
Permanand G, Mossialos E & McKee M. (2006) Regulating medicines in Europe: the European Medicines Agency, marketing authorisation, transparency and pharmacovigilance. Clin Med, J Royal College of Physicians 6(1): 87–90.
Phillips C. (2008) Risk of systemic toxicity from topical ophthalmic chloramphenicol. Scott Med J 53(3): 54–55.
Porta A, Esposito S, Menson E, Spyridis N, Tsolia M, Sharland M & Principi N. (2010) Off-label antibiotic use in children in three European countries. Eur J Clin Pharmacol 66(9): 919–927.
Radley DC, Finkelstein SN & Stafford RS. (2006) Off-label prescribing among office-based physicians. Arch Intern Med 166(9): 1021–1026.
Rentz ED, Lewis L, Mujica OJ, Barr DB, Schier JG, Weerasekera G, Kuklenyik P, McGeehin M, Osterloh J & Wamsley J. (2008) Outbreak of acute renal failure in Panama in 2006: a case-control study. Bull WHO 86(10): 749–756.
Rocchi F, Paolucci P, Ceci A & Rossi P. (2010) The European paediatric legislation: benefits and perspectives. Ital J Pediatr 36: 56.

Rossignoli A, Clavenna A & Bonati M. (2007) Antibiotic prescription and prevalence rate in the outpatient paediatric population: analysis of surveys published during 2000–2005. Eur J Clin Pharmacol 63(12): 1099–1106.

Rowe RC, Sheskey PJ, Quinn ME. (2009) Handbook of Pharmaceutical Excipients. London: Pharmaceutical Press.

Saint-Raymond A & Seigneuret N. (2005) Medicines for children: time for Europe to act. Paediatr Perinatal Drug Ther 6(3): 142–146.

Santos DB, Clavenna A, Bonati M & Coelho HLL. (2008) Off-label and unlicensed drug utilization in hospitalized children in Fortaleza, Brazil. Eur J Clin Pharmacol 64(11): 1111–1118.

Schirm E & Tobi H. (2002) Unlicensed and off label drug use by children in the community: cross sectional study. Br Med J 324(7349): 1312–1313.

Schirm E, Tobi H & de Jong-van den Berg LTW. (2003) Risk factors for unlicensed and off-label drug use in children outside the hospital. Pediatrics 111(2): 291–295.

Schirm E, Tobi H, van Puijenbroek EP, Monster-Simons MH & de Jong-van den Berg LTW. (2004) Reported adverse drug reactions and their determinants in Dutch children outside the hospital. Pharmacoepidemiol Drug Saf 13(3): 159–165.

Schirm E, Van Den Berg P, Gebben H, Sauer P & De Jong-van den Berg, L. (2000) Drug use of children in the community assessed through pharmacy dispensing data. Br J Clin Pharmacol 50(5): 473–478.

Sequi M, Campi R, Clavenna A & Bonati M. (2012) Methods in pharmaco-epidemiology: a review of statistical analyses and data reporting in pediatric drug utilization studies. Eur J Clin Pharmacol 1–6.

Serreau R, Le Heuzey M, Gilbert A, Mouren M & Jacqz-Aigrain E. (2004) Unlicensed and off-label use of psychotropic medications in French children: a prospective study. Paediatr Perinat Drug Ther 6(1): 14–19.

Shah SS, Hall M, Goodman DM, Feuer P, Sharma V, Fargason Jr C, Hyman D, Jenkins K, White ML & Levy FH. (2007) Off-label drug use in hospitalized children. Arch Pediatr Adolesc Med 161(3): 282–290.

Shehab N, Lewis CL, Streetman DD & Donn SM. (2009) Exposure to the pharmaceutical excipients benzyl alcohol and propylene glycol among critically ill neonates. Pediatr Crit Care Med 10(2): 256–263.

Shirkey H. (1999) Editorial comment: therapeutic orphans. Pediatrics 104(Supplement): 583.

Smith MC, Williamson J, Yaster M, Boyd GJC & Heitmiller ES. (2012) Off-Label Use of Medications in Children Undergoing Sedation and Anesthesia. Anesth Analg (in press).

Stewart D, Rouf A, Snaith A, Elliott K, Helms PJ & McLay JS. (2007) Attitudes and experiences of community pharmacists towards paediatric off-label prescribing: a prospective survey. Br J Clin Pharmacol 64(1): 90–95.

Stötterb KRH. (2007) ICH E 11: Clinical investigation of medicinal products in the paediatric population. Guide to Paediatric Clinical Research. Basel, Karger, pp 33–37.

Straand J, Rokstad K & Heggedal U. (1998) Drug prescribing for children in general practice. A report from the Møre & Romsdal Prescription Study. Acta Paediatr 87(2): 218–224.

Strieker BHC, Choonara I & Anker J. (2002) Lack of effect of the European guidance on clinical investigation of medicines in children. Acta Paediatr 91(11): 1233–1238.

Sturkenboom M, Felisi M, Manfredi C, Neubert A, Cantarutti L, Padula R, Sen F & Verhamme K. (2009) Paediatric status and off-label use of drugs in children in Italy, United Kingdom and the Netherlands. Pharmaceuticals Policy Law 11(1): 51–59.

Sturkenboom MCJM, Verhamme KMC, Nicolosi A, Murray ML, Neubert A, Caudri D, Picelli G, Sen EF, Giaquinto C & Cantarutti L. (2008) Drug use in children: cohort study in three European countries. Br Med J 337: a2245.

t Jong G, van der Linden P, Bakker E, Van der Lely N, Eland I, Stricker B & van den Anker J. (2002) Unlicensed and off-label drug use in a paediatric ward of a general hospital in the Netherlands. Eur J Clin Pharmacol 58(4): 293–297.

't Jong G, van der Linden P, Bakker E, Van der Lely N, Eland I, Stricker B & van den Anker J. (2002) Unlicensed and off-label drug use in a paediatric ward of a general hospital in the Netherlands. Eur J Clin Pharmacol 58(4): 293–297.

t Jong GW, Vulto AG, de Hoog M, Schimmel KJM, Tibboel D & van den Anker JN. (2000) Unapproved and off-label use of drugs in a children's hospital. N Engl J Med 343(15): 1125–1125.

t Jong GW, Vulto AG, de Hoog M, Schimmel KJM, Tibboel D & van den Anker JN. (2001) A survey of the use of off-label and unlicensed drugs in a Dutch children's hospital. Pediatrics 108(5): 1089–1093.

t Jong G, Eland I, Sturkenboom M, van den Anker J & Stricker B. (2004) Unlicensed and off-label prescription of respiratory drugs to children. Eur Resp J 23(2): 310–313.

Tafuri G, Trotta F, Leufkens HGM, Martini N, Sagliocca L & Traversa G. (2009) Off-label use of medicines in children: can available evidence avoid useless paediatric trials? Eur J Clin Pharmacol 65(2): 209–216.

Thomson Reuters Micromedex 2.0. 2010.

Thrane N & Sørensen H. (1999) A one-year population-based study of drug prescriptions for Danish children. Acta Paediatrica 88(10): 1131–1136.

Tuleu C. (2007) Paediatric Formulation in Practice. In: Costello I, Long PF, Wong I, Tuleu C, Yeung V (ed) Paediatric Drug Handling. London: Pharmaceutical Press: 43.

Tuleu C, Solomonidou D & Breitkeutz J. (2010) Paediatric formulations. In: Rose K & Van den Anker JN (eds) Guide to Paediatric Drug Development and Clinical Research. Karger Pub. pp:117–128.

Turner M, Lewis S, Hawcutt D & Field D. (2009) Prioritising neonatal medicines research: UK Medicines for Children Research Network scoping survey. BMC Pediatrics 9(1): 50.

Turner S. (1999) Unregistered and off-label drug use in paediatric inpatients. Australian Journal of Hospital Pharmacy 29(5): 265–268.

Turner S, Longworth A, Nunn AJ & Choonara I. (1998) Unlicensed and off label drug use in paediatric wards: prospective study. Br Med J 316(7128): 343–345.

Turner S, Nunn A, Fielding K & Choonara I. (1999) Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. Acta Paediatrica 88(9): 965–968.

Ufer M, Kimland E & Bergman U. (2004) Adverse drug reactions and off-label prescribing for paediatric outpatients: a one-year survey of spontaneous reports in Sweden. Pharmacoepidemiol Drug Saf 13(3): 147–152.

Ufer M, Rane A, Karlsson Å, Kimland E & Bergman U. (2003a) Widespread off-label prescribing of topical but not systemic drugs for 350,000 paediatric outpatients in Stockholm. Eur J Clin Pharmacol 58(11): 779–783.

Ufer M, Rane A, Karlsson Å, Kimland E & Bergman U. (2003b) Widespread off-label prescribing of topical but not systemic drugs for 350,000 paediatric outpatients in Stockholm. Eur J Clin Pharmacol 58(11): 779–783.

Ursino MG, Poluzzi E, Caramella C & Ponti FD. (2011) Excipients in medicinal products used in gastroenterology as a possible cause of side effects. Regul Toxicol Pharmacol 60(1): 93–105.

Vaccheri A, Bjerrum L, Resi D, Bergman U & Montanaro N. (2002) Antibiotic prescribing in general practice: striking differences between Italy (Ravenna) and Denmark (Funen). J Antimicrob Chemother 50(6): 989–997.

van den Berg H & Tak N. (2011) Licensing and labelling of drugs in a paediatric oncology ward. Br J Clin Pharmacol 72(3): 474–481.

van Riet-Nales DA, de Jager KE, Schobben AFAM, Egberts TCG & Rademaker C. (2011) The availability and age-appropriateness of medicines authorized for children in the Netherlands. Br J Clin Pharmacol 72(3): 465–473.

Venkatesh MP & Garcia-Prats JA. (2008) Management of neonatal sepsis by Gram-negative pathogens. Expert Rev Anti Infect Ther 6(6): 929–938.

Verhamme K & Sturkenboom M. (2011) Study designs in paediatric pharmaco-epidemiology. Eur J Clin Pharmacol 67: 67–74.

Volkers AC, Heerdink ER & van Dijk L. (2007) Antidepressant use and off-label prescribing in children and adolescents in Dutch general practice (2001–2005). Pharmacoepidemiol Drug Saf 16(9): 1054–1062.

Warrier I, Du W, Natarajan G, Salari V & Aranda J. (2006) Patterns of drug utilization in a neonatal intensive care unit. J Clin Pharmacol 46(4): 449–455.

Whittaker A, Currie AE, Turner MA, Field DJ, Mulla H & Pandya HC. (2009) Toxic additives in medication for preterm infants. Arch Dis Child Fetal Neonatal Ed 94(4): F236–40.

Wong I. (2007) Updates and Regulations Around the World. In: Costello I, Long PF, Wong IK, Tuleu C, Yeung V (ed) Paediatric Drug Handling. London: Pharmaceutical Press: 75–84.

Wong ICK, Basra N, Yeung V & Cope J. (2006) Supply problems of unlicensed and off-label medicines after discharge. Arch Dis Child 91(8): 686–688.

Yoon EY, Davis MM, El-Essawi H & Cabana MD. (2006) FDA labeling status of pediatric medications. Clin Pediatr 45(1): 75–77.

Yoon EY, Dombkowski KJ, Rocchini A, Lin JJ & Davis MM. (2007) Off-label utilization of antihypertensive medications in children. Ambul Pediatrics 7(4): 299–303.

# 9. SUMMARY IN ESTONIAN

## Ravimikasutuse epidemioloogilised ja kliinilised aspektid Eesti lastel

Lapsed moodustavad suure osa kõigist ravimite tarvitajatest, kuid võrreldes täiskasvanutega on nende ravimine sageli keerulisem. Kuna lastel on ravimiuuringuid tehtud oluliselt vähem kui täiskasvanutel, ravitakse lapsi sageli vaid täiskasvanutel uuritud ravimitega. Sellisest olukorrast tingituna on kasutusel kaks mõistet:

- näidustuseta ravimid (ingl. k. *off-label,* OL) – ravimit kasutatakse erinevalt ravimiomaduste kokkuvõttes märgitust (näiteks erineval näidustusel, vanuserühmal, annuses ja/või manustamisviisil) või on ravim lastele vastunäidustatud;
- litsentseerimata (ingl. k. *unlicenced, UL*) ravimid pole Euroopa Liidus kasutamiseks registreeritud ei täiskasvanutele ega lastele.

OL ravimite kasutamine on Lääne-Euroopas ja Põhja-Ameerikas levinud (Kimland *et al.* 2012), kuid vastavad andmed Ida-Euroopa kohta seni puudusid.

Täiskasvanutele mõeldud ja vaid täiskasvanutel uuritud ravimid või ravimite annused ei sobi alati laste ravimiseks. Lapsed ja eriti veel vastsündinud erinevad oluliselt täiskasvanutest organismi koostise (rasvade ja veesisaldus) ning ravimeid metaboliseerivate ensüümide aktiivsuse poolest, mis mõjutab nii aktiivsete toimeainete kui ka ravimites olevate abiainete farmakokineetilist profiili (Bartelink *et al.* 2006). Seetõttu ei ole enamasti ka võimalik täiskasvanutel tehtud uuringutest tuletada, kuidas ravim laste organismis imendub, jaotub, metaboliseerub või eritub.

Kliiniliste uuringute puudumisel pärinevad andmed ravimi annuste kohta lastel sageli arstide kliinilisest kogemusest või üksikutest ravijuhtudest (Ceci *et al.* 2006). Seetõttu on ravimite annustamise soovitused erinevates ravimiinfo allikates väga erinevad. Lastele ravimite annustamise informatsiooni erinevusi pole seni süstemaatiliselt uuritud.

Ravimvormide koostises kasutatakse tuhandeid erinevaid abiaineid, mis moodustavad keskmiselt 90% ravimvormi massist (Haywood & Glass 2011). Ideaalis peaks abiaine olema farmakoloogiliselt inaktiivne, mitte-toksiline ja mitte omama koostoimeid toimeainete või teiste abiainetega. Paraku on selliseid abiaineid tegelikkuses vähe, ning abiainete ohutus on viimasel ajal lastearstide ja eelkõige neonatoloogide jaoks järjest teravamalt tähtsustatud (Hall *et al.* 2004). Abiainetega seonduv on võrreldes toimeaineid puudutavate seadustega olnud vähem reguleeritud ning lastel nende ohutust reeglina kliiniliselt hinnatud ei ole. Siiski on täiskasvanutele ohutud abiained põhjustanud lastele manustamisel traagilisi tagajärgi. Näiteks säilitusainena kasutatavat bensüülalkoholi on seostatud enneaegsetel vastsündinutel tekkinud intravaskulaarse hemorraagia ja surmajuhtumitega (Hiller *et al.* 1986).

Hetkeseisuga on abiainete tegelik toksilisus vastsündinutele siiski täpselt teadmata. Ka ei olnud seni täpselt teada, kui paljude erinevate abiainetega vast-

sündinud ravi käigus kokku puutuvad või kui suur osa vastsündinutel kasutatud ravimitest sisaldab neile potentsiaalselt toksilisi abiaineid.

**Uurimistöö eesmärgid**

Uurimistöö peamisteks eesmärkideks oli kirjeldada ja analüüsida laste farmakoteraapiat, hinnata OL/UL ravimite kasutuse määra ning seda, millisel määral puutuvad vastsündinud haiglaravi jooksul kokku ravimites olevate abinetega ning kui suur osa nendest abiainetest võivad olla neile toksilised.

Konkreetsed eesmärgid:

1. Kirjeldada Eesti laste ambulatoorset ravimikasutust ning vastsündinute ravi haiglas;
2. Võrrelda ambulatoorset antibiootikumide määramist Eesti ja Rootsi lastele;
3. Hinnata lastele määratud ravimite ravimiomaduste kokkuvõtetes olevat infot selle kohta, kas ravim on lastel kasutamiseks näidustatud;
4. Tuvastada laste ja vastsündinute farmakoteraapias need kitsaskohad, kus ravimeid kasutatakse kõige rohkem, kuid samas ametlik pediaatriline info kõige sagedamini puudub;
5. Võrrelda lapsi ja vastsündinuid puudutava info olemasolu ravimiomaduste kokkuvõttes ja teistes sageli kasutatavates ravimiinfo allikates nagu Briti Rahvuslik Formular (ingl. *British National Formulary*, BNF) ja Thomson Micromedex andmebaasis;
6. Luua Eesti vastsündinutele haiglaravi jooksul ravimite koostises manustatud abiainete põhjal klassifikatsioon lähtuvalt abiainete võimalikust toksilisusest;
7. Kirjeldada potentsiaalselt toksiliste abiainete esinemist vastsündinutel kasutatud ravimites;
8. Kirjeldada hospitaliseeritud vastsündinute kokkupuudet neile potentsiaalselt toksiliste abiainetega.

**Patsiendid ja metoodika**

Käesolev uurimus sisaldab kahte andmebaasidele põhinevat ja ühte prospektiivset vaatlusuuringut ning viimase põhjal tehtud *Post-hoc* analüüsi.

Eesti lastele ambulatoorselt määratud retseptiravimite kasutuse ja OL/UL ravimikasutuse määra uuring põhineb ajavahemikul 1.01.2007–31.12.2007 kuni 19a isikutele välja kirjutatud retseptidel Eesti Haigekassa Retseptiravimite andmebaasist.

Vastsündinute ravimikasutuse ja OL/UL ravimikasutuse määra uurimiseks dokumenteerisime prospektiivselt ajavahemikel 01.02–01.08.2008 Tartu Ülikooli Kliinikumi ja 01.02–01.08.2009 Tallinna Lastehaigla neonatoloogia osakonda hospitaliseeritud kuni 29 päevaste vastsündinute ravimikasutuse.

Vastsündinute ravimikasutuse uuringu andmete põhjal hindasime ka vastsündinute kokkupuudet neile potentsiaalselt toksiliste abiainetega. Selleks tuvastasime ravimiomaduste kokkuvõttest või pakendi infolehelt ravimite koostises olevad abiained ning jaotasime nad kirjandusallikate alusel võimaliku toksilisuse alusel meie enda loodud klassifikatsiooni järgi rühmadesse.

Eesti ja Rootsi laste antibiootikumikasutust võrdlev uuring põhines ajavahemikul 1.01.2007 – 31.12.2007 mõlema riigi lastele ambulatoorselt välja kirjutatud retseptide analüüsil, mis pärinesid Eesti Haigekassa Retseptiravimite andmebaasist ja Rootsi Retseptiravimite andmebaasist.

## Peamised tulemused

**Ambulatoorne retseptiravimite kasutus**

Eesti lastele kirjutati välja 2007. aastal 467 334 retsepti 851 ravimpreparaadile ja 309 toimeainele. Keskmiselt määrati 1,7 retsepti lapse kohta. Alla kuue aastastele lastele määrati kaks korda rohkem retseptiravimeid (2,5 retsepti lapse kohta) kui ülejäänud vanuserühmadele. Kõige sagedamini määrati süsteemseid antibakteriaalseid ravimeid, hingamisteedesse toimivaid ning dermatoloogilisi ravimeid. Kolmveerand retseptidest (77%) kuulus neisse kolme ravimirühma. Kolmandik (31%) retseptidest oli OL, neist enamuse (29%) puhul polnud lapsi ravimiomaduste kokkuvõttes mainitud ning 2% retseptidest (106 erinevat toimeainet) olid vastunäidustatud. 42% vastunäidustatud ravimitest ei olnud lastele sobivad suure kõrvaltoimete riski tõttu. Kõige suurem OL ravimite osakaal oli urogenitaalsüsteemi ravimite hulgas (97%), järgnesid dermatoloogilised (74%) ja kardiovaskulaarsüsteemi ravimid (61%).

Ambulatoorne UL ravimite kasutus oli harv, vaid 0.05% retseptidest 6 ravimile.

Kasutatud ravimite kohta erines pediaatriline info erinevates allikates kõige suuremal määral kesknärvisüsteemi ravimite ja antibiootikumide osas.

**Eesti ja Rootsi laste ambulatoorne antibiootikumikasutus**

Eesti lastele kirjutati 2007. aastal ambulatoorselt välja poole rohkem antibiootikumi retsepte kui Rootsi lastele, vastavalt 616 vs. 353 retsepti 1000 lapse kohta. Eestis määrati 22 ja Rootsis 50 erinevat antibiootikumi, kuid 90% retseptidest olid mõlemas riigis välja kirjutatud kaheksale toimeainele. Kõige sagedamini manustatud antibiootikumide grupp oli penitsilliinid (74% kõigist retseptidest Rootsis ja 49% Eestis). Eestis määrati sagedamini laia toimespektriga penitsilliine nagu amoksitsilliini ja selle kombinatsiooni beta-laktamaasi inhibiitoriga, samas Rootsis olid pooled retseptid kitsa toimespektriga fenoksümetüülpenitsilliinile.

**Vastsündinute ravimikasutus haiglas**

Kõigist 490st uuringuperioodil hospitaliseeritud vastsündinust said ravimeid 71%. Neile määrati 1981 korral 115 erinevat ravimit. Keskmiselt sai iga vastsündinu 4 erinevat ravimit. Kõige sagedamini kasutati antibakteriaalseid, kardiovaskulaarsüsteemi ja kesknärvisüsteemi ravimeid. Kõik ravitud vastsündinud said vähemalt ühte ravimit, millel puudub müügiluba või ametlik näidustus vastsündinutel kasutamiseks. Mitte ühelgi kasutatud meeleelundite, skeletilihassüsteemi, seedekulgla ja ainevahetuse, urogenitaalsüsteemi haiguste ravimil ja suguhormoonil polnud SPCs infot vastsündinutel kasutamiseks.

Vastsündinute ravimiseks vajalik info erines infoallikates oluliselt. Kõige suurem erinevus esines ajalisi vastsündinuid puudutavas informatsioonis – määratud ravimitest 67%-l oli info olemas BNFCs, 38% Micromedexi andmebaasis ja vaid 24% Eesti SPCs.

### Vastsündinute kokkupuude ravimites olevate potentsiaalselt toksiliste abiainetega

Enamus kasutatud ravimitest (87%; 93/107) sisaldas vähemalt ühte abiainet. Kokku said vastsündinud ravimitega 123 erinevat abiainet. Kolmandik (42/123) abiainetest klassifitseeriti potentsiaalselt ohututeks, teine kolmandik (47/123) potentsiaalselt vastsündinutele toksiliseks. Viimati mainitud kategooria sisaldas ka kaheksat juba teadaolevalt vastsündinutele toksilist abiainet – parabeene, sahhariin naatriumi, naatriumbensoaati, bensüülalkoholi, bensalkooniumkloriidi, propüleenglükooli, polüsorbaat 80 ja etanooli. Ülejäänud 34 abiaine kohta ei leidunud kasutatud kirjandusallikates ohutusalast infot või ei olnud abiaine kirjeldus ravimiomaduste kokkuvõttes piisav kirjanduseotsingu tegemiseks.

Ravitud vastsündinutest 97% (339/348) said ravimite koostises vähemalt ühe potentsiaalselt toksilise abiaine ja 88% said vähemalt ühe teadaolevalt toksilise abiaine. Kasutatud ravimitest 68% sisaldasid vähemalt ühte potentsiaalselt toksilist ning 31% teadaolevalt toksilist abiainet.

### Järeldused

I Eesti lastele ja vastsündinutele määratakse ambulatoorselt ja ka haiglas suurel hulgal OL ravimeid. Et laste farmakoteraapiat ratsionaalsemaks muuta, on vaja diagnoosidega lingitud farmakoepidemioloogilisi uuringuid sagedamini lastele määratud ravimirühmades.

II Eesti ja Rootsi laste ambulatoorne ravimikasutus erineb olulisel määral nii kvantitatiivselt kui kvalitatiivselt. Eesti lastele määratakse antibiootikume sagedamini ning kasutatakse ka laiema toimespektriga ravimeid kui Rootsi lastele. See viitab Rootsis toimivale riiklikule strateegiale sarnase tegevuse vajalikkusele Eestis, et ennetada antibiootikumide väärkasutust. Ravimikasutuse auditid peaksid keskenduma antibiootikumide ratsionaalsele kasutusele ning tõenduspõhiste ravijuhiste järgimisele.

III OL/UL ravimikasutuse osakaal on Eestis sarnaselt Lääne-Euroopas tehtud uuringutega kõrge. Võrreldes süsteemselt manustatud ravimitega, on nahale manustatavate ravimid sagedamini OL. OL retseptide osakaal on suurem ka alla 2 a lastel võrreldes vanemate lastega. Seetõttu tuleks nooremaid lapsi ning nahale manustatavaid ravimeid esile tõsta lastel enim uurimist vajavate ravimite nimekirjas.

IV UL retseptide osakaal oli ambulatoorsetest retseptidest väike. Seevastu hospitaliseeritud vastsündinutele määratud ravimitest 25% ja määramiskordadest 22% olid UL. See näitab vastsündinute ravimiseks vajalike

ravimite kohaliku ja ka Euroopa tsentraalse müügiloa puudumist ning vajadust ametliku sekkumise järele.

V Ravim klassifitseeriti OL ravimiks kõige sagedamini seetõttu, et ravimiomaduste kokkuvõttes puudus info kasutamise kohta lapsel või vastsündinul. Spetsiifilistest ravimiinfo käsiraamatutes nagu Briti Rahvuslik Formular Lastele või andmebaasides nagu Micromedex on oluliselt rohkem pediaatrilist infot kui ametlikus ravimiomaduste kokkuvõttes. Kuna paljude OL ravimite kohta on olemas piisavalt kliinilist informatsiooni lastel kasutamise kohta, oleks vajalik vaid nende ravimite ravimiomaduste kokkuvõtete värskendamine. Kui ravimit ei soovitata lastel kasutada, siis tuleb selle põhjus ravimiomaduste kokkuvõttes välja tuua, et teavitada ravimi tarvitajaid ja määrajaid võimalikest ravimi kasutamisega seotud ohtudest lastel või ebaefektiivsest toimest.

VI Kolmandik hospitaliseeritud vastsündinutele ravimitega manustatud abiainetest klassifitseeriti vastsündinutele potentsiaalselt ohtlikeks, kuid neist vaid kaheksat on varem vastsündinutele ohtlikuks liigitatud. Hetkel on vajadus valideeritud klassifikatsiooni järele, mille alusel saaks abiaineid ohtlikkuse järgi jaotada.

VII Praktiliselt kõik ravimeid saanud vastsündinud said uuringuperioodil ravimeid, mis sisaldasid vähemalt ühte neile potentsiaalselt ohtlikku abiainet. Kuna avaldatud informatsioon abiainete kohta on vähene, on äärmiselt oluline ravimites olevate abiainete põhjalik toksikoloogiline hindamine lähtuvalt nende potentsiaalsest toksilisusest vastsündinutele. Abiainetest tulenevad potentsiaalsed ohud vastsündinutele ning ka abiainete kvantitatiivsed kogused ravimis tuleb teha apteekritele ja vastsündinuid ravivatele arstidele kättesaadavaks, et oleks võimalik valida vastsündinule sobivaimaid ja ohutumaid ravimeid.

# ACKNOWLEDGEMENTS

This study was carried out at the Institute of Microbiology of the University of Tartu and the data were collected in the neonatal units of Tallinn Children's Hospital and Tartu University Hospital.

I wish to express my sincere and deepest gratitude to:

- Prof. Irja Lutsar, the supervisor of this thesis, for being the perfect supervisor and for sharing with me her experience in the fields of science. I appreciate all her contribution of time, good ideas and logical way of thinking to make my PhD experience productive and stimulating. I am also thankful for the example she has provided as a successful scientist and a good person.
- Prof. Jörg Breitkreutz for being the opponent of this thesis.
- Prof. Jyrki Heinamäki and Dr. Kersti Oselin for reviewing the thesis.
- Dr. Heili Varendi, Dr. Tuuli Metsvaht, Dr. Mark A. Turner, Utpal Shah and Kaisa Naelapää for their invaluable contribution to my thesis.
- Heti Pisarev for helping me operatively with the medical statistics.
- Kaarin Jõgi, Dr. Ruth Käär and Triin Leinemann for their cooperation and support in data collection.
- Dr. Alar Irs, my first mentor and a dear friend, for guiding my first steps in the field of research and introducing me the concept of "educated guess", for the constructive discussions and for reading the dissertation.
- Dr. Mai Blöndal, a dear friend and a co-student who has stood with me in all of the ups and downs of the PhD studies and always helped me to find the way through the administrative paperwork.
- Dr. Maksim Zagura, Dr. Martin Serg and Dr. Erik Salum, co-students and friends for the cheerful lunch-brakes in the hospital. The group has been a source of friendship as well as good advice.
- Mari Kand, Marika Saar, Irja Uiboleht, Malle Määrmann and all other dear colleagues at the hospital pharmacy for their friendship and support and for providing the relaxed working athmosphere.
- Patrick Moynagh for his time, interest and helpful comments in reviewing the dissertation.
- Irja Roots for helping me with the thesis formatting.
- Kristel Kalda for constant friendship and proof-reading my thesis summary in Estonian.
- My greatest gratitude goes to my family for love and for affording me the personal background that has supported me throughout this work – my grandmother, Vaike, Elen and last but not least my husband Juhan and our son Ruuben for the inspiration but also for the understanding and patience.

# PUBLICATIONS

# CURRICULUM VITAE


| | |
|---|---|
| Name: | Jana Lass |
| Born: | 30.10.1979 |
| Citizenship: | Estonia |
| Address: | Tartu University Hospital, Pharmacy Department<br>L. Puusepa 8, Tartu 51014, Estonia |
| Telephone: | +372 5331 8333 |
| E-mail: | jana.lass@kliinikum.ee |


**Education:**

| | |
|---|---|
| 1986–1998 | Secondary School No 46, Tallinn, Estonia |
| 1998–2003 | Faculty of Medicine, Pharmacy Department, University of Tartu |
| 2004–2006 | Queens University Belfast, MSc in Clinical Pharmacy |
| 2008–2012 | PhD student, Faculty of Medicine, University of Tartu |

**Professional employment:**

| | |
|---|---|
| 2001–2004 | Pharmacist, community pharmacy, Tallinn, Estonia |
| 2004–2007 | Pharmacist, North Estonia Medical Centre, Pharmacy department, Tallinn, Estonia |
| 2007– | Clinical pharmacist, Tartu University Hospital, Pharmacy department, Tartu, Estonia |

**Academic interests:**

Research fields: paediatric pharmacoepidemiology, acute pain management, treatment of mental illnesses

**Memberships:**

Estonian Society of Hospital Pharmacists
European Society of Clinical Pharmacy

**List of publications:**


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

Lass J, Irs A, Pisarev H, Leineman T, Lutsar I. Off-label use of prescription medicines in children in outpatient setting in Estonia is common. Pharmacoepidemiol Drug Safety 2011;20(5):478–481

Lass J, Käär R, Jõgi K, Varendi H, Metsvaht T, Lutsar I. Drug utilisation pattern and off-label use of medicines in Estonian neonatal units. Eur J Clin Pharmacol 2011;67(12):1263–1271

Raudsepp D, Lass J, Saar M, Kuld L, Irs A. Ravimite koos- või kõrvaltoimed erakorralise meditsiini osakonda pöördumise põhjusena – prospektiivne vaatlusuuring. Eesti Arst 2011;3:122–128

Lass J, Valk H, Toome V, Baburin A, Ringmets I, Marandi T. Operatsioonijärgse valuravi juhendi mõju hindamine. Eesti Arst 2011;6:263–269

Lass J Männik A, Bell JS. Pharmacotherapy of first episode psychosis in Estonia: comparison with national and international treatment guidelines. Clin Pharm Ther. 2008;33(2):16

# ELULOOKIRJELDUS


Nimi: Jana Lass
Sünd. 30.10.1979
Kodakondsus: eesti
Aadress: Tartu Ülikooli Kliinikum, apteek
L. Puusepa 8, Tartu 51014, Eesti Vabariik
Telefon: 5331 8333
E-post: jana.lass@kliinikum.ee


**Haridus:**

| | |
|---|---|
| 1986–1998 | 46. Keskkool, Tallinn |
| 1998–2003 | Tartu Ülikool, Arstiteaduskond, Farmaatsia instituut |
| 2004–2006 | Queens University Belfast, MSc kliinilises farmaatsias |
| 2008–2012 | Doktoriõpe, Tartu Ülikooli arstiteaduskond |

**Teenistuskäik:**

| | |
|---|---|
| 2001–2004 | Jaemüügi apteek, proviisor |
| 2004–2007 | Põhja Eesti Regionaalhaigla, haiglaapteek, proviisor |
| 2007– | Tartu Ülikooli Kliinikumi apteek, kliiniline proviisor |

**Teadustegevus:**
Uurimisvaldkonnad: laste ravimikasutus, ägeda valu ravi, skisofreenia ravi

**Kuuluvus erialaseltsidesse:**
Eesti Haiglaapteekrite Selts, juhatuse liige
European Society of Clinical Pharmacy

**Publikatsioonid:**


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

Lass J, Irs A, Pisarev H, Leineman T, Lutsar I. Off-label use of prescription medicines in children in outpatient setting in Estonia is common. Pharmacoepidemiol Drug Safety 2011;20(5):478–481

Lass J, Käär R, Jõgi K, Varendi H, Metsvaht T, Lutsar I. Drug utilisation pattern and off-label use of medicines in Estonian neonatal units. Eur J Clin Pharmacol 2011;67(12):1263–1271

Raudsepp D, Lass J, Saar M, Kuld L, Irs A. Ravimite koos- või kõrvaltoimed erakorralise meditsiini osakonda pöördumise põhjusena – prospektiivne vaatlusuuring. Eesti Arst 2011;3:122–128

Lass J, Valk H, Toome V, Baburin A, Ringmets I, Marandi T. Operatsioonijärgse valuravi juhendi mõju hindamine. Eesti Arst 2011;6:263–269

Lass J Männik A, Bell JS. Pharmacotherapy of first episode psychosis in Estonia: comparison with national and international treatment guidelines. Clin Pharm Ther. 2008;33(2):165–73

# DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS

1. **Heidi-Ingrid Maaroos.** The natural course of gastric ulcer in connection with chronic gastritis and *Helicobacter pylori*. Tartu, 1991.
2. **Mihkel Zilmer.** Na-pump in normal and tumorous brain tissues: Structural, functional and tumorigenesis aspects. Tartu, 1991.
3. **Eero Vasar.** Role of cholecystokinin receptors in the regulation of behaviour and in the action of haloperidol and diazepam. Tartu, 1992.
4. **Tiina Talvik.** Hypoxic-ischaemic brain damage in neonates (clinical, biochemical and brain computed tomographical investigation). Tartu, 1992.
5. **Ants Peetsalu.** Vagotomy in duodenal ulcer disease: A study of gastric acidity, serum pepsinogen I, gastric mucosal histology and *Helicobacter pylori*. Tartu, 1992.
6. **Marika Mikelsaar.** Evaluation of the gastrointestinal microbial ecosystem in health and disease. Tartu, 1992.
7. **Hele Everaus.** Immuno-hormonal interactions in chronic lymphocytic leukaemia and multiple myeloma. Tartu, 1993.
8. **Ruth Mikelsaar.** Etiological factors of diseases in genetically consulted children and newborn screening: dissertation for the commencement of the degree of doctor of medical sciences. Tartu, 1993.
9. **Agu Tamm.** On metabolic action of intestinal microflora: clinical aspects. Tartu, 1993.
10. **Katrin Gross.** Multiple sclerosis in South-Estonia (epidemiological and computed tomographical investigations). Tartu, 1993.
11. **Oivi Uibo.** Childhood coeliac disease in Estonia: occurrence, screening, diagnosis and clinical characterization. Tartu, 1994.
12. **Viiu Tuulik.** The functional disorders of central nervous system of chemistry workers. Tartu, 1994.
13. **Margus Viigimaa.** Primary haemostasis, antiaggregative and anticoagulant treatment of acute myocardial infarction. Tartu, 1994.
14. **Rein Kolk.** Atrial versus ventricular pacing in patients with sick sinus syndrome. Tartu, 1994.
15. **Toomas Podar.** Incidence of childhood onset type 1 diabetes mellitus in Estonia. Tartu, 1994.
16. **Kiira Subi.** The laboratory surveillance of the acute respiratory viral infections in Estonia. Tartu, 1995.
17. **Irja Lutsar.** Infections of the central nervous system in children (epidemiologic, diagnostic and therapeutic aspects, long term outcome). Tartu, 1995.
18. **Aavo Lang.** The role of dopamine, 5-hydroxytryptamine, sigma and NMDA receptors in the action of antipsychotic drugs. Tartu, 1995.
19. **Andrus Arak.** Factors influencing the survival of patients after radical surgery for gastric cancer. Tartu, 1996.

20. **Tõnis Karki.** Quantitative composition of the human lactoflora and method for its examination. Tartu, 1996.
21. **Reet Mändar.** Vaginal microflora during pregnancy and its transmission to newborn. Tartu, 1996.
22. **Triin Remmel.** Primary biliary cirrhosis in Estonia: epidemiology, clinical characterization and prognostication of the course of the disease. Tartu, 1996.
23. **Toomas Kivastik.** Mechanisms of drug addiction: focus on positive reinforcing properties of morphine. Tartu, 1996.
24. **Paavo Pokk.** Stress due to sleep deprivation: focus on $GABA_A$ receptor-chloride ionophore complex. Tartu, 1996.
25. **Kristina Allikmets.** Renin system activity in essential hypertension. Associations with atherothrombogenic cardiovascular risk factors and with the efficacy of calcium antagonist treatment. Tartu, 1996.
26. **Triin Parik.** Oxidative stress in essential hypertension: Associations with metabolic disturbances and the effects of calcium antagonist treatment. Tartu, 1996.
27. **Svetlana Päi.** Factors promoting heterogeneity of the course of rheumatoid arthritis. Tartu, 1997.
28. **Maarike Sallo.** Studies on habitual physical activity and aerobic fitness in 4 to 10 years old children. Tartu, 1997.
29. **Paul Naaber.** *Clostridium difficile* infection and intestinal microbial ecology. Tartu, 1997.
30. **Rein Pähkla.** Studies in pinoline pharmacology. Tartu, 1997.
31. **Andrus Juhan Voitk.** Outpatient laparoscopic cholecystectomy. Tartu, 1997.
32. **Joel Starkopf.** Oxidative stress and ischaemia-reperfusion of the heart. Tartu, 1997.
33. **Janika Kõrv.** Incidence, case-fatality and outcome of stroke. Tartu, 1998.
34. **Ülla Linnamägi.** Changes in local cerebral blood flow and lipid peroxidation following lead exposure in experiment. Tartu, 1998.
35. **Ave Minajeva.** Sarcoplasmic reticulum function: comparison of atrial and ventricular myocardium. Tartu, 1998.
36. **Oleg Milenin.** Reconstruction of cervical part of esophagus by revascularised ileal autografts in dogs. A new complex multistage method. Tartu, 1998.
37. **Sergei Pakriev.** Prevalence of depression, harmful use of alcohol and alcohol dependence among rural population in Udmurtia. Tartu, 1998.
38. **Allen Kaasik.** Thyroid hormone control over β-adrenergic signalling system in rat atria. Tartu, 1998.
39. **Vallo Matto.** Pharmacological studies on anxiogenic and antiaggressive properties of antidepressants. Tartu, 1998.
40. **Maire Vasar.** Allergic diseases and bronchial hyperreactivity in Estonian children in relation to environmental influences. Tartu, 1998.

41. **Kaja Julge.** Humoral immune responses to allergens in early childhood. Tartu, 1998.
42. **Heli Grünberg.** The cardiovascular risk of Estonian schoolchildren. A cross-sectional study of 9-, 12- and 15-year-old children. Tartu, 1998.
43. **Epp Sepp.** Formation of intestinal microbial ecosystem in children. Tartu, 1998.
44. **Mai Ots.** Characteristics of the progression of human and experimental glomerulopathies. Tartu, 1998.
45. **Tiina Ristimäe.** Heart rate variability in patients with coronary artery disease. Tartu, 1998.
46. **Leho Kõiv.** Reaction of the sympatho-adrenal and hypothalamo-pituitary-adrenocortical system in the acute stage of head injury. Tartu, 1998.
47. **Bela Adojaan.** Immune and genetic factors of childhood onset IDDM in Estonia. An epidemiological study. Tartu, 1999.
48. **Jakov Shlik.** Psychophysiological effects of cholecystokinin in humans. Tartu, 1999.
49. **Kai Kisand.** Autoantibodies against dehydrogenases of α-ketoacids. Tartu, 1999.
50. **Toomas Marandi.** Drug treatment of depression in Estonia. Tartu, 1999.
51. **Ants Kask.** Behavioural studies on neuropeptide Y. Tartu, 1999.
52. **Ello-Rahel Karelson.** Modulation of adenylate cyclase activity in the rat hippocampus by neuropeptide galanin and its chimeric analogs. Tartu, 1999.
53. **Tanel Laisaar.** Treatment of pleural empyema — special reference to intrapleural therapy with streptokinase and surgical treatment modalities. Tartu, 1999.
54. **Eve Pihl.** Cardiovascular risk factors in middle-aged former athletes. Tartu, 1999.
55. **Katrin Õunap.** Phenylketonuria in Estonia: incidence, newborn screening, diagnosis, clinical characterization and genotype/phenotype correlation. Tartu, 1999.
56. **Siiri Kõljalg.** *Acinetobacter* – an important nosocomial pathogen. Tartu, 1999.
57. **Helle Karro.** Reproductive health and pregnancy outcome in Estonia: association with different factors. Tartu, 1999.
58. **Heili Varendi.** Behavioral effects observed in human newborns during exposure to naturally occurring odors. Tartu, 1999.
59. **Anneli Beilmann.** Epidemiology of epilepsy in children and adolescents in Estonia. Prevalence, incidence, and clinical characteristics. Tartu, 1999.
60. **Vallo Volke.** Pharmacological and biochemical studies on nitric oxide in the regulation of behaviour. Tartu, 1999.
61. **Pilvi Ilves.** Hypoxic-ischaemic encephalopathy in asphyxiated term infants. A prospective clinical, biochemical, ultrasonographical study. Tartu, 1999.
62. **Anti Kalda.** Oxygen-glucose deprivation-induced neuronal death and its pharmacological prevention in cerebellar granule cells. Tartu, 1999.

63. **Eve-Irene Lepist.** Oral peptide prodrugs – studies on stability and absorption. Tartu, 2000.
64. **Jana Kivastik.** Lung function in Estonian schoolchildren: relationship with anthropometric indices and respiratory symptomas, reference values for dynamic spirometry. Tartu, 2000.
65. **Karin Kull.** Inflammatory bowel disease: an immunogenetic study. Tartu, 2000.
66. **Kaire Innos.** Epidemiological resources in Estonia: data sources, their quality and feasibility of cohort studies. Tartu, 2000.
67. **Tamara Vorobjova.** Immune response to *Helicobacter pylori* and its association with dynamics of chronic gastritis and epithelial cell turnover in antrum and corpus. Tartu, 2001.
68. **Ruth Kalda.** Structure and outcome of family practice quality in the changing health care system of Estonia. Tartu, 2001.
69. **Annika Krüüner.** *Mycobacterium tuberculosis* – spread and drug resistance in Estonia. Tartu, 2001.
70. **Marlit Veldi.** Obstructive Sleep Apnoea: Computerized Endopharyngeal Myotonometry of the Soft Palate and Lingual Musculature. Tartu, 2001.
71. **Anneli Uusküla.** Epidemiology of sexually transmitted diseases in Estonia in 1990–2000. Tartu, 2001.
72. **Ade Kallas.** Characterization of antibodies to coagulation factor VIII. Tartu, 2002.
73. **Heidi Annuk.** Selection of medicinal plants and intestinal lactobacilli as antimicrobil components for functional foods. Tartu, 2002.
74. **Aet Lukmann**. Early rehabilitation of patients with ischaemic heart disease after surgical revascularization of the myocardium: assessment of health-related quality of life, cardiopulmonary reserve and oxidative stress. A clinical study. Tartu, 2002.
75. **Maigi Eisen.** Pathogenesis of Contact Dermatitis: participation of Oxidative Stress. A clinical – biochemical study. Tartu, 2002.
76. **Piret Hussar.** Histology of the post-traumatic bone repair in rats. Elaboration and use of a new standardized experimental model – bicortical perforation of tibia compared to internal fracture and resection osteotomy. Tartu, 2002.
77. **Tõnu Rätsep.** Aneurysmal subarachnoid haemorrhage: Noninvasive monitoring of cerebral haemodynamics. Tartu, 2002.
78. **Marju Herodes.** Quality of life of people with epilepsy in Estonia. Tartu, 2003.
79. **Katre Maasalu.** Changes in bone quality due to age and genetic disorders and their clinical expressions in Estonia. Tartu, 2003.
80. **Toomas Sillakivi.** Perforated peptic ulcer in Estonia: epidemiology, risk factors and relations with *Helicobacter pylori*. Tartu, 2003.
81. **Leena Puksa.** Late responses in motor nerve conduction studies. F and A waves in normal subjects and patients with neuropathies. Tartu, 2003.

82. **Krista Lõivukene**. *Helicobacter pylori* in gastric microbial ecology and its antimicrobial susceptibility pattern. Tartu, 2003.
83. **Helgi Kolk.** Dyspepsia and *Helicobacter pylori* infection: the diagnostic value of symptoms, treatment and follow-up of patients referred for upper gastrointestinal endoscopy by family physicians. Tartu, 2003.
84. **Helena Soomer.** Validation of identification and age estimation methods in forensic odontology. Tartu, 2003.
85. **Kersti Oselin.** Studies on the human MDR1, MRP1, and MRP2 ABC transporters: functional relevance of the genetic polymorphisms in the *MDR1* and *MRP1* gene. Tartu, 2003.
86. **Jaan Soplepmann.** Peptic ulcer haemorrhage in Estonia: epidemiology, prognostic factors, treatment and outcome. Tartu, 2003.
87. **Margot Peetsalu.** Long-term follow-up after vagotomy in duodenal ulcer disease: recurrent ulcer, changes in the function, morphology and *Helicobacter pylori* colonisation of the gastric mucosa. Tartu, 2003.
88. **Kersti Klaamas.** Humoral immune response to *Helicobacter pylori* a study of host-dependent and microbial factors. Tartu, 2003.
89. **Pille Taba.** Epidemiology of Parkinson's disease in Tartu, Estonia. Prevalence, incidence, clinical characteristics, and pharmacoepidemiology. Tartu, 2003.
90. **Alar Veraksitš**. Characterization of behavioural and biochemical phenotype of cholecystokinin-2 receptor deficient mice: changes in the function of the dopamine and endopioidergic system. Tartu, 2003.
91. **Ingrid Kalev.** CC-chemokine receptor 5 (CCR5) gene polymorphism in Estonians and in patients with Type I and Type II diabetes mellitus. Tartu, 2003.
92. **Lumme Kadaja.** Molecular approach to the regulation of mitochondrial function in oxidative muscle cells. Tartu, 2003.
93. **Aive Liigant**. Epidemiology of primary central nervous system tumours in Estonia from 1986 to 1996. Clinical characteristics, incidence, survival and prognostic factors. Tartu, 2004.
94. **Andres, Kulla.** Molecular characteristics of mesenchymal stroma in human astrocytic gliomas. Tartu, 2004.
95. **Mari Järvelaid.** Health damaging risk behaviours in adolescence. Tartu, 2004.
96. **Ülle Pechter.** Progression prevention strategies in chronic renal failure and hypertension. An experimental and clinical study. Tartu, 2004.
97. **Gunnar Tasa.** Polymorphic glutathione S-transferases – biology and role in modifying genetic susceptibility to senile cataract and primary open angle glaucoma. Tartu, 2004.
98. **Tuuli Käämbre.** Intracellular energetic unit: structural and functional aspects. Tartu, 2004.

99. **Vitali Vassiljev.** Influence of nitric oxide syntase inhibitors on the effects of ethanol after acute and chronic ethanol administration and withdrawal. Tartu, 2004.
100. **Aune Rehema.** Assessment of nonhaem ferrous iron and glutathione redox ratio as markers of pathogeneticity of oxidative stress in different clinical groups. Tartu, 2004.
101. **Evelin Seppet.** Interaction of mitochondria and ATPases in oxidative muscle cells in normal and pathological conditions. Tartu, 2004.
102. **Eduard Maron.** Serotonin function in panic disorder: from clinical experiments to brain imaging and genetics. Tartu, 2004.
103. **Marje Oona.** *Helicobacter pylori* infection in children: epidemiological and therapeutic aspects. Tartu, 2004.
104. **Kersti Kokk.** Regulation of active and passive molecular transport in the testis. Tartu, 2005.
105. **Vladimir Järv.** Cross-sectional imaging for pretreatment evaluation and follow-up of pelvic malignant tumours. Tartu, 2005.
106. **Andre Õun.** Epidemiology of adult epilepsy in Tartu, Estonia. Incidence, prevalence and medical treatment. Tartu, 2005.
107. **Piibe Muda.** Homocysteine and hypertension: associations between homocysteine and essential hypertension in treated and untreated hypertensive patients with and without coronary artery disease. Tartu, 2005.
108. **Külli Kingo.** The interleukin-10 family cytokines gene polymorphisms in plaque psoriasis. Tartu, 2005.
109. **Mati Merila.** Anatomy and clinical relevance of the glenohumeral joint capsule and ligaments. Tartu, 2005.
110. **Epp Songisepp**. Evaluation of technological and functional properties of the new probiotic *Lactobacillus fermentum* ME-3. Tartu, 2005.
111. **Tiia Ainla.** Acute myocardial infarction in Estonia: clinical characteristics, management and outcome. Tartu, 2005.
112. **Andres Sell.** Determining the minimum local anaesthetic requirements for hip replacement surgery under spinal anaesthesia – a study employing a spinal catheter. Tartu, 2005.
113. **Tiia Tamme.** Epidemiology of odontogenic tumours in Estonia. Pathogenesis and clinical behaviour of ameloblastoma. Tartu, 2005.
114. **Triine Annus**. Allergy in Estonian schoolchildren: time trends and characteristics. Tartu, 2005.
115. **Tiia Voor.** Microorganisms in infancy and development of allergy: comparison of Estonian and Swedish children. Tartu, 2005.
116. **Priit Kasenõmm.** Indicators for tonsillectomy in adults with recurrent tonsillitis – clinical, microbiological and pathomorphological investigations. Tartu, 2005.
117. **Eva Zusinaite.** Hepatitis C virus: genotype identification and interactions between viral proteases. Tartu, 2005.

118. **Piret Kõll.** Oral lactoflora in chronic periodontitis and periodontal health. Tartu, 2006.
119. **Tiina Stelmach.** Epidemiology of cerebral palsy and unfavourable neurodevelopmental outcome in child population of Tartu city and county, Estonia Prevalence, clinical features and risk factors. Tartu, 2006.
120. **Katrin Pudersell.** Tropane alkaloid production and riboflavine excretion in the field and tissue cultures of henbane (*Hyoscyamus niger* L.). Tartu, 2006.
121. **Külli Jaako.** Studies on the role of neurogenesis in brain plasticity. Tartu, 2006.
122. **Aare Märtson.** Lower limb lengthening: experimental studies of bone regeneration and long-term clinical results. Tartu, 2006.
123. **Heli Tähepõld.** Patient consultation in family medicine. Tartu, 2006.
124. **Stanislav Liskmann.** Peri-implant disease: pathogenesis, diagnosis and treatment in view of both inflammation and oxidative stress profiling. Tartu, 2006.
125. **Ruth Rudissaar.** Neuropharmacology of atypical antipsychotics and an animal model of psychosis. Tartu, 2006.
126. **Helena Andreson.** Diversity of *Helicobacter pylori* genotypes in Estonian patients with chronic inflammatory gastric diseases. Tartu, 2006.
127. **Katrin Pruus.** Mechanism of action of antidepressants: aspects of serotoninergic system and its interaction with glutamate. Tartu, 2006.
128. **Priit Põder.** Clinical and experimental investigation: relationship of ischaemia/reperfusion injury with oxidative stress in abdominal aortic aneurysm repair and in extracranial brain artery endarterectomy and possibilities of protection against ischaemia using a glutathione analogue in a rat model of global brain ischaemia. Tartu, 2006.
129. **Marika Tammaru.** Patient-reported outcome measurement in rheumatoid arthritis. Tartu, 2006.
130. **Tiia Reimand.** Down syndrome in Estonia. Tartu, 2006.
131. **Diva Eensoo.** Risk-taking in traffic and Markers of Risk-Taking Behaviour in Schoolchildren and Car Drivers. Tartu, 2007.
132. **Riina Vibo.** The third stroke registry in Tartu, Estonia from 2001 to 2003: incidence, case-fatality, risk factors and long-term outcome. Tartu, 2007.
133. **Chris Pruunsild.** Juvenile idiopathic arthritis in children in Estonia. Tartu, 2007.
134. **Eve Õiglane-Šlik.** Angelman and Prader-Willi syndromes in Estonia. Tartu, 2007.
135. **Kadri Haller.** Antibodies to follicle stimulating hormone. Significance in female infertility. Tartu, 2007.
136. **Pille Ööpik.** Management of depression in family medicine. Tartu, 2007.
137. **Jaak Kals.** Endothelial function and arterial stiffness in patients with atherosclerosis and in healthy subjects. Tartu, 2007.

138. **Priit Kampus.** Impact of inflammation, oxidative stress and age on arterial stiffness and carotid artery intima-media thickness. Tartu, 2007.
139. **Margus Punab.** Male fertility and its risk factors in Estonia. Tartu, 2007.
140. **Alar Toom**. Heterotopic ossification after total hip arthroplasty: clinical and pathogenetic investigation. Tartu, 2007.
141. **Lea Pehme.** Epidemiology of tuberculosis in Estonia 1991–2003 with special regard to extrapulmonary tuberculosis and delay in diagnosis of pulmonary tuberculosis. Tartu, 2007.
142. **Juri Karjagin.** The pharmacokinetics of metronidazole and meropenem in septic shock. Tartu, 2007.
143. **Inga Talvik.** Inflicted traumatic brain injury shaken baby syndrome in Estonia – epidemiology and outcome. Tartu, 2007.
144. **Tarvo Rajasalu.** Autoimmune diabetes: an immunological study of type 1 diabetes in humans and in a model of experimental diabetes (in RIP-B7.1 mice). Tartu, 2007.
145. **Inga Karu.** Ischaemia-reperfusion injury of the heart during coronary surgery: a clinical study investigating the effect of hyperoxia. Tartu, 2007.
146. **Peeter Padrik.** Renal cell carcinoma: Changes in natural history and treatment of metastatic disease. Tartu, 2007.
147. **Neve Vendt**. Iron deficiency and iron deficiency anaemia in infants aged 9 to 12 months in Estonia. Tartu, 2008.
148. **Lenne-Triin Heidmets.** The effects of neurotoxins on brain plasticity: focus on neural Cell Adhesion Molecule. Tartu, 2008.
149. **Paul Korrovits.** Asymptomatic inflammatory prostatitis: prevalence, etiological factors, diagnostic tools. Tartu, 2008.
150. **Annika Reintam.** Gastrointestinal failure in intensive care patients. Tartu, 2008.
151. **Kristiina Roots.** Cationic regulation of Na-pump in the normal, Alzheimer's and $CCK_2$ receptor-deficient brain. Tartu, 2008.
152. **Helen Puusepp.** The genetic causes of mental retardation in Estonia: fragile X syndrome and creatine transporter defect. Tartu, 2009.
153. **Kristiina Rull.** Human chorionic gonadotropin beta genes and recurrent miscarriage: expression and variation study. Tartu, 2009.
154. **Margus Eimre.** Organization of energy transfer and feedback regulation in oxidative muscle cells. Tartu, 2009.
155. **Maire Link.** Transcription factors FoxP3 and AIRE: autoantibody associations. Tartu, 2009.
156. **Kai Haldre.** Sexual health and behaviour of young women in Estonia. Tartu, 2009.
157. **Kaur Liivak.** Classical form of congenital adrenal hyperplasia due to 21-hydroxylase deficiency in Estonia: incidence, genotype and phenotype with special attention to short-term growth and 24-hour blood pressure. Tartu, 2009.

158. **Kersti Ehrlich.** Antioxidative glutathione analogues (UPF peptides) – molecular design, structure-activity relationships and testing the protective properties. Tartu, 2009.
159. **Anneli Rätsep.** Type 2 diabetes care in family medicine. Tartu, 2009.
160. **Silver Türk.** Etiopathogenetic aspects of chronic prostatitis: role of mycoplasmas, coryneform bacteria and oxidative stress. Tartu, 2009.
161. **Kaire Heilman.** Risk markers for cardiovascular disease and low bone mineral density in children with type 1 diabetes. Tartu, 2009.
162. **Kristi Rüütel.** HIV-epidemic in Estonia: injecting drug use and quality of life of people living with HIV. Tartu, 2009.
163. **Triin Eller.** Immune markers in major depression and in antidepressive treatment. Tartu, 2009.
164. **Siim Suutre.** The role of TGF-β isoforms and osteoprogenitor cells in the pathogenesis of heterotopic ossification. An experimental and clinical study of hip arthroplasty. Tartu, 2010.
165. **Kai Kliiman.** Highly drug-resistant tuberculosis in Estonia: Risk factors and predictors of poor treatment outcome. Tartu, 2010.
166. **Inga Villa.** Cardiovascular health-related nutrition, physical activity and fitness in Estonia. Tartu, 2010.
167. **Tõnis Org.** Molecular function of the first PHD finger domain of Autoimmune Regulator protein. Tartu, 2010.
168. **Tuuli Metsvaht.** Optimal antibacterial therapy of neonates at risk of early onset sepsis. Tartu, 2010.
169. **Jaanus Kahu.** Kidney transplantation: Studies on donor risk factors and mycophenolate mofetil. Tartu, 2010.
170. **Koit Reimand.** Autoimmunity in reproductive failure: A study on associated autoantibodies and autoantigens. Tartu, 2010.
171. **Mart Kull.** Impact of vitamin D and hypolactasia on bone mineral density: a population based study in Estonia. Tartu, 2010.
172. **Rael Laugesaar.** Stroke in children – epidemiology and risk factors. Tartu, 2010.
173. **Mark Braschinsky.** Epidemiology and quality of life issues of hereditary spastic paraplegia in Estonia and implemention of genetic analysis in everyday neurologic practice. Tartu, 2010.
174. **Kadri Suija.** Major depression in family medicine: associated factors, recurrence and possible intervention. Tartu, 2010.
175. **Jarno Habicht.** Health care utilisation in Estonia: socioeconomic determinants and financial burden of out-of-pocket payments. Tartu, 2010.
176. **Kristi Abram.** The prevalence and risk factors of rosacea. Subjective disease perception of rosacea patients. Tartu, 2010.
177. **Malle Kuum.** Mitochondrial and endoplasmic reticulum cation fluxes: Novel roles in cellular physiology. Tartu, 2010.
178. **Rita Teek.** The genetic causes of early onset hearing loss in Estonian children. Tartu, 2010.

179. **Daisy Volmer.** The development of community pharmacy services in Estonia – public and professional perceptions 1993–2006. Tartu, 2010.
180. **Jelena Lissitsina.** Cytogenetic causes in male infertility. Tartu, 2011.
181. **Delia Lepik.** Comparison of gunshot injuries caused from Tokarev, Makarov and Glock 19 pistols at different firing distances. Tartu, 2011.
182. **Ene-Renate Pähkla**. Factors related to the efficiency of treatment of advanced periodontitis. Tartu, 2011.
183. **Maarja Krass.** L-Arginine pathways and antidepressant action. Tartu, 2011.
184. **Taavi Lai.** Population health measures to support evidence-based health policy in Estonia. Tartu, 2011.
185. **Tiit Salum.** Similarity and difference of temperature-dependence of the brain sodium pump in normal, different neuropathological, and aberrant conditions and its possible reasons. Tartu, 2011.
186. **Tõnu Vooder**. Molecular differences and similarities between histological subtypes of non-small cell lung cancer. Tartu, 2011.
187. **Jelena Štšepetova.** The characterisation of intestinal lactic acid bacteria using bacteriological, biochemical and molecular approaches. Tartu, 2011.
188. **Radko Avi.** Natural polymorphisms and transmitted drug resistance in Estonian HIV-1 CRF06_cpx and its recombinant viruses. Tartu, 2011, 116 p.
189. **Edward Laane**. Multiparameter flow cytometry in haematological malignancies. Tartu, 2011, 152 p.
190. **Triin Jagomägi.** A study of the genetic etiology of nonsyndromic cleft lip and palate. Tartu, 2011, 158 p.
191. **Ivo Laidmäe.** Fibrin glue of fish (*Salmo salar*) origin: immunological study and development of new pharmaceutical preparation. Tartu, 2012, 150 p.
192. **Ülle Parm.** Early mucosal colonisation and its role in prediction of invasive infection in neonates at risk of early onset sepsis. Tartu, 2012, 168 p.
193. **Kaupo Teesalu.** Autoantibodies against desmin and transglutaminase 2 in celiac disease: diagnostic and functional significance. Tartu, 2012, 142 p.
194. **Maksim Zagura**. Biochemical, functional and structural profiling of arterial damage in atherosclerosis. Tartu, 2012, 162 p.
195. **Vivian Kont.** Autoimmune regulator: characterization of thymic gene regulation and promoter methylation. Tartu, 2012, 134 p.
196. **Pirje Hütt.** Functional properties, persistence, safety and efficacy of potential probiotic lactobacilli. Tartu, 2012, 246 p.
197. **Innar Tõru.** Serotonergic modulation of CCK-4- induced panic. Tartu, 2012, 132 p.
198. **Sigrid Vorobjov.** Drug use, related risk behaviour and harm reduction interventions utilization among injecting drug users in Estonia: implications for drug policy. Tartu, 2012, 120 p.

199. **Martin Serg.** Therapeutic aspects of central haemodynamics, arterial stiffness and oxidative stress in hypertension. Tartu, 2012, 156 p.
200. **Jaanika Kumm.** Molecular markers of articular tissues in early knee osteoarthritis: a population-based longitudinal study in middle-aged subjects. Tartu, 2012, 159 p.
201. **Kertu Rünkorg.** Functional changes of dopamine, endopioid and endocannabinoid systems in CCK2 receptor deficient mice. Tartu, 2012, 125 p.
202. **Mai Blöndal.** Changes in the baseline characteristics, management and outcomes of acute myocardial infarction in Estonia. Tartu, 2012, 127 p.