Safety of Medication in Paediatrics

KRISTINA STAR
Abstract

Background: In paediatrics, the limited documentation to guide medication, the lack of suitable dosage forms, and the continuous development in childhood present a scenario where safety of medication is a particular challenge.

Aim: To explore reported adverse drug reactions (ADRs) and the challenges in prescribing and administering medicines in paediatrics, in order to identify and suggest areas needing international surveillance within medication safety and improvement in the clinical setting.

Methods: Four exploratory studies were conducted. Worldwide reporting of suspected ADRs (individual case safety reports, ICSR) with ages 0-17 years were examined overall. Twenty published case reports and ICSRs for adolescents, who developed a rare and incompletely documented ADR (rhabdomyolysis) during antipsychotic medicine use, were analysed in-depth. Prescribed doses of anti-inflammatory medicines were studied in a UK electronic health record database. Transcribed focus group interviews with 20 registered nurses from four paediatric wards in Sweden were analysed for factors that may promote or hinder safe medication practices. Descriptive statistics, multiple regression, and content analyses were used.

Results: Although, skin reactions and anti-infective medicines were most frequently reported, and more reported in paediatric patients than in adults, medication errors and adverse reactions related to psychostimulant medicines were reported with increased frequency during 2005 to February 2010. The in-depth case analysis emphasised the need for increased vigilance following changes in patients’ medicine regimens, and indicated that ICSRs could contribute with clinically valuable information. Prescribed dose variations were associated with type of dosage form. Tablets and capsules were prescribed with a higher dose than liquid dosage forms. Six themes emerged from the interviews: preparation and administration was complex; medication errors caused considerable psychological burden; support from nurse colleagues was highly valued; unfamiliar medication was challenging; clear dose instructions were important; nurses handling medications needed to be accorded higher priority.

Conclusions: Age-specific screening of ICSRs and the use of ICSRs to enhance knowledge of ADRs and medication errors need to be developed. Access to age-appropriate dosage forms is important when prescribing medicines to children. To improve medication safety practices in paediatric care, interdisciplinary collaborations across hospitals on national or even global levels are needed.

Keywords: paediatrics, adverse drug reaction, drug-related problem, medication error, patient safety, individual case safety reports, pharmacovigilance, medication, nurses, health care personnel, dosage form, NSAID, dosing, prescription, antipsychotic medicines, postmarketing surveillance

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To all who seek better use of medicines for children
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
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<tr>
<td>ADE</td>
<td>Adverse Drug Event</td>
</tr>
<tr>
<td>ADHD</td>
<td>Attention Deficit Hyperactivity Disorder</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical, Therapeutic, Chemical classification</td>
</tr>
<tr>
<td>BNFC</td>
<td>British National Formulary for Children</td>
</tr>
<tr>
<td>CIOMS</td>
<td>Council for International Organisations of Medical Sciences</td>
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<tr>
<td>DDD</td>
<td>Defined Daily Dose</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use</td>
</tr>
<tr>
<td>ICSR</td>
<td>Individual Case Safety Report</td>
</tr>
<tr>
<td>IMS</td>
<td>Intercontinental Medical Statistics</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
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<tr>
<td>MPA</td>
<td>Medicines Product Agency</td>
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<tr>
<td>NCC MERP</td>
<td>National Coordinating Council for Medication Error Reporting</td>
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<tr>
<td>NHS</td>
<td>National Health Service</td>
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<tr>
<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drugs</td>
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<tr>
<td>PVC</td>
<td>Pharmacovigilance Centre</td>
</tr>
<tr>
<td>PDD</td>
<td>Prescribed Daily Dose</td>
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<tr>
<td>rPDD</td>
<td>Relative Prescribed Daily Dose</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitors</td>
</tr>
<tr>
<td>UMC</td>
<td>Uppsala Monitoring Centre</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
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<tr>
<td>US</td>
<td>United States</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WHO-ART</td>
<td>World Health Organization Adverse Reaction Terminology</td>
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</table>
Definitions of key concepts

**Patient safety**
“Freedom for a patient from unnecessary harm or potential harm associated with healthcare.”[1] (p. 8)

**Pharmacovigilance**
“The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.”[2] (p. 7)

**Adverse drug reaction**
“An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alternation of the dosage regimen, or withdrawal of the product.”[3] (p. 1255)

**Medication error**
“A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.”[4] (National Coordinating Council for Medication Error Reporting)
Preface

Medicines can be life saving. Health care would not be what it is without vaccines, antibiotics, antihypertensive medicines, antiretroviral medicines and antiepileptic medicines. Medications are first and foremost beneficial, but they come with a risk. The adverse effects of some medicines are common, such as hair loss following chemotherapy. For other medicines the adverse reactions are rare and unexpected, such as serious skin reactions following antiepileptic medicines.

Coming from the chaotic and unpredictable work of a nurse at infectious diseases wards in Sweden and the United States (US) to the structured and highly regulated world of the pharmaceutical industry, and a period at the Swedish Medical Products Agency (MPA), I began working for the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC) in 2003. After a few years of working with detection of previously unknown adverse drug reactions (ADRs) reported globally, I started to question the effectiveness of our current routines. In particular, I noticed that problems specific for children were rarely highlighted. Why were medication problems in children not being identified to a higher extent? Are problems specific for children hidden by the multitude of reports for adults in the WHO database? How many ADRs and what type of ADRs have been reported for children? What are the specifics of prescribing and administering medicines for children that can influence the type of reports sent? What challenges to safe medication practices do clinicians face?
Background

Historical events important for safety of medication, affecting paediatric patients

Inspired by Clavenna et al.\[^5\]\ and by Choonara et al.,\[^6\]\ this thesis begins with an account of historical events that will serve as a reminder of the many aspects that encompass medication safety in paediatric care.

In 1937, sulphanilamide elixir (an antimicrobial agent) containing the solvent diethylene glycol caused over 100 patients’ deaths in the US, of which many were children.\[^7\]\ As a consequence, the mandate of the US Food and Drug Administration (FDA) was widened to enforce regulations for pharmaceutical development. Diethylene glycol is a solvent used in antifreeze preparations and wallpaper strippers and can cause multiorgan failure with acute renal failure if ingested.\[^8\]\ Diethylene glycol continues to cause outbreaks of deaths in children treated with paracetamol or cough syrups with the added solvent, as in South Africa in 1967,\[^9\]\ Nigeria in 1990,\[^10\]\ Bangladesh in 1990,\[^11\]\ India in 1998,\[^12\]\ and Nigeria again in 2008.\[^13\]\ In these cases, diethylene glycol was inadvertently or deliberately added as a solvent.

In 1956, Silverman et al. studied the effect of two anti-bacterial medicines in pre-mature infants and found that the rate of kernicterus (brain damage by excessive bilirubin in brain tissue) and the incidence of fatal outcomes was significantly higher in the group receiving penicillin and sulphisoxazole than the babies receiving oxytetracycline.\[^14\]\ Pre-mature infants commonly have increased serum bilirubin. Sulphonamide displaced bilirubin from its protein binding site, thereby causing kernicterus.\[^15\]\

In 1959, Sutherland noted that three newborns had died from high doses of chloramphenicol.\[^14\]\ The syndrome was called grey baby syndrome (vomiting, diarrhoea, flaccidity, hypothermia, ashen-grey colour).\[^15\]\ Newborn infants accumulate very high concentrations of chloramphenicol in tissue because their hepatic conjugation has low activity.\[^15\]\ When the recommended dose of chloramphenicol was reduced, the medicine could continue to be given to babies with serious infections, such as meningitis.

In 1961, skeletal malformations was detected in babies of mothers having taken thalidomide for insomnia or nausea during pregnancy.\[^16\]\ Thalidomide was withdrawn from the market. The thalidomide tragedy resulted in more strict requirements for pre-marketing studies as well as the introduction of
post-marketing surveillance. Thalidomide is still being used in some parts of the world for leprosy and also for multiple myeloma. A recent study noted that thalidomide-induced congenital malformations have increased in Brazil, which may be correlated with a greater availability of thalidomide in the country.\footnote{17}

In 1979, valproic acid was first reported with hepatotoxicity,\footnote{18} leading to fatal outcomes in many children, particularly infants less than 3-years old.\footnote{19} The knowledge of valproate-induced hepatotoxicity in children lead to changes in prescribing habits, which reduced the problem.\footnote{20}

In 1980, a dose-related association between salicylate and Reye’s syndrome (hepatotoxicity) was highlighted.\footnote{21} Salicylates ceased to be used in children and the incidence of Reye’s syndrome in children declined.

In 2004, the US FDA called for an increased awareness that antidepressant use resulted in a higher risk of suicide in the young.\footnote{22}

In 2006, the US Institute for Safe Medication Practice issued a report on deaths of premature infants following administration of 1000-fold higher doses of heparin than was intended.\footnote{23} The reasons for the errors were several: the label on the vial was not checked before administration; automated medicine-dispensing cabinets were incorrectly filled; and similar labels and vial sizes for different heparin strengths were used.

In 2007, the US FDA notified the manufacturers to include a warning of cardiovascular risks with Attention Deficit Hyperactivity Disorder (ADHD) medicines in their product information.\footnote{24}

In 2010, increased reporting of narcolepsy in children following Pandemrix vaccination in Scandinavian countries was noted. The association was recently confirmed by a published study from Finland.\footnote{25}

This background describes instances of patient safety problems and highlights the challenges and difficulties of medication therapy in children. Several of the medicines in the above examples were probably not primarily developed for use in children. Studies on paediatric patients describe that:

- 49% of the prescriptions for hospitalised paediatric patients are given without supporting documentation for their use in paediatric patients (Swedish study).\footnote{26}
- 11% of in-patient children experience an ADR (review of studies).\footnote{5}
- Medication errors with a potential for harm has a 3 times higher rate in paediatric hospital care than in adult care.\footnote{27}
- 22-27% of medicines indicated for paediatric patients lack age-appropriate dosage forms (Australian study).\footnote{28}
- The continuous development during childhood complicates pharmacotherapy and particularly the selection of a suitable dose and dosage formulation.\footnote{29}

Children are vulnerable to ADRs, dosing and administration problems, which are the focus of this thesis.
Introduction

Scope of this thesis

The overall aim of this thesis is to explore the nature of reported ADRs and the challenges in prescribing and administering medicines for paediatric patients. The enhanced understanding of ADRs and these medication practices will be used to identify and suggest areas needing special international surveillance within medication safety and improvement in the clinical setting.

ADRs reported for paediatric patients worldwide are reviewed overall as well as a specific problem in-depth. The studies exemplify prescribing difficulties for general practitioners (GP) and challenges in medication practices for nurses in paediatric care. The studies are based on one global database of suspected ADRs, one national electronic health record database and on interviews with nurses from two hospitals in one country. The studies cover aspects of both commonly and rarely used medicines, and both serious and common ADRs in all paediatric age groups, from neonates to adolescents. The studies in brief are:

I  an overall review of ADRs reported for children worldwide,
II  an in-depth evaluation of a rare, serious, intrinsic, and incompletely documented ADR,
III  an analysis of variations in prescribed doses for commonly used medicines in children based on data from the United Kingdom (UK),
IV  interviews with nurses in Sweden on what factors facilitate and hinder safe administration of medicines in paediatrics.

Study I found that medication errors and related terms indicating administration and dosing difficulties had commonly been reported in the younger age groups during recent years, hence, the focus on dosing in Study III and on administration in Study IV. Study II was performed to investigate the clinical circumstances around a serious ADR and to study whether reports of suspected ADRs would contribute valuable clinical information to enhance the understanding of ADRs. Study IV captures challenges in safe medication practices in paediatric care, covering problems highlighted in Studies I, II and III.
Challenges in medication of paediatric patients

Lack of pre-marketing clinical studies and documentation for medication in paediatric patients

Medicines available on the market have not always been tested in the child population, or passed pre-clinical studies on age-specific animal models. Nonetheless, these medicines sometimes need to be used in paediatric patients. This use is called ‘off-label’ and has been defined as prescriptions or use “outside the terms of product license.” Examples of off-label use are when prescriptions refer to other doses, indications or ages than those described in the product license. The use of medicines not licensed for use in children has been denoted ‘unlicensed use’ for example when a tablet is a crushed to provide a suspension. The definitions of off-label and unlicensed use have varied in the published literature.

In a recent published review, off-label prescriptions ranges between 18 to 65% of the prescriptions in hospitals, and 11 to 31% in primary care. The wide ranges are a result of how off-label use was defined in different studies, as well as the variation of type of hospital wards included in these studies. Studies on neonatal wards tend to have a higher proportion of off-label use than wards for older children. In one study in Swedish hospitals, nearly half of all prescriptions for paediatric patients (49%) were given without supporting documentation for their use in paediatric patients (off-label, unlicensed, extemporaneously prepared medicines). The rate in neonatal care was 69%.

The consequence of this situation is that health care professionals are drawing upon their own previous experience, other expert opinion or pharmacological inference when prescribing or administering medicines. The prescriber is restricted to absent or sparse information on age-specific dosages or descriptions of ADRs. The most common facet of off-label prescribing is deviation from the recommended dose in the product label. Lower than recommended doses for antibiotic prescriptions were commonly seen in off-label studies in primary care, which in theory could facilitate antimicrobial resistance in the population. To overcome the limited access of dose information in the United Kingdom (UK), the British National Formulary for Children (BNFC) has been developed to provide practical information on medicine use in children based on emerging evidence, best-practice guidelines and clinical expert advice.

The problem of off-label prescribing and unlicensed use of medicines has been used as an argument to raise the need for more clinical studies to be conducted in paediatric populations. Several regulatory initiatives have been taken to change the situation (e.g., in the US in 1997 and in EU in 2007) by encouraging pharmaceutical manufacturers to perform clinical studies with the incentive of prolonging their patents.
more and better labelling of products for paediatric patients. WHO has focused on working towards better access to medicines for children in resource-limited countries and providing formulations of medicines suitable for children.\[^{46}\]

Lack of age-suitable dosage forms

Another consequence of using medicines without paediatric marketing approval is that age-suitable dosage forms can be lacking. The administration of a correct dose is dependent on the availability of pre-clinically tested age-suitable dosage forms. The dosage form should ensure optimal uptake in the body, as well as correct measurement and intake of the dose during administration to the patient. Lack of suitable formulations for the growing child with various needs during different developmental stages constitutes a challenge.\[^{47, 48}\] Tablets and capsules, the most commonly used dosage forms for adults, and preferred by manufacturers, are cheaper to produce and easier to store than liquid formulations which are preferred for younger children. Liquid formulations can be more complex to develop and may require solvents and surfactant excipients for solubility, and preservatives for stability. The unpleasant taste of a liquid formulation must also be successfully masked adding to a more complex product development.\[^{48}\] Solid dosage forms suitable for paediatric patients have been developed, such as powders and granules mixed with fluid, and orodispersible tablets meant to melt on the tongue.

Age-appropriate dosage forms are not always available, even when the medicine is indicated for children: an Australian study found that 22-27% of medicines indicated for paediatric patients lacked such dosage forms.\[^{28}\] In the absence of age-appropriate dosage forms, tablets are crushed and mixed with liquids, or capsule-content is mixed with food for individual dose administrations, increasing the risk of an incorrect dose being administered. The lack of adequate dosage forms, lead to the use of extemporaneous preparations produced by pharmacists. The Dutch formulary includes standardized formulations that can be used by pharmacists for extemporaneous preparations,\[^{49}\] which are more reliable than ad hoc approaches.

Developmental influences on medicine use in paediatric patients

In addition to the lack of medicines developed specifically for paediatric patients, the stages of physiological and psychological development during childhood complicate pharmacotherapy.\[^{29}\] Children differ biologically not only from adults but also within their own age group. Widely recommended dosing formulae are often weight/body-size based, requiring calculation of the dose for each individual prescription or administration. Weight, body-
surface area, organ and enzyme maturity change immensely during childhood.[29] An adolescent can weigh more than 100 kg, which is 200 times more than the weight of a premature baby of 0.5 kg. The underlying disease and gender can also result in biological differences in children of the same age.

Pathophysiology relevant for medication in paediatric patients
Most changes in medicine disposition (absorption, distribution, metabolism and excretion) occur before two years of age. A summary of the specific considerations of pathophysiology with relevance for pharmacotherapy for this paediatric age group is given in Table 1.[6, 29, 50-53]

Table 1. Considerations of medicine use in patients < 2 years old [6, 29, 50-53]

<table>
<thead>
<tr>
<th>Characteristics of paediatric patients &lt; 2 years old</th>
<th>Consequences</th>
</tr>
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<tbody>
<tr>
<td><strong>MEDICINE ABSORPTION</strong></td>
<td></td>
</tr>
<tr>
<td><em>Gastro-intestinal</em></td>
<td></td>
</tr>
<tr>
<td>Full term neonates: gastric pH fluctuates from low to high levels during day one, is elevated from day 2 and decreases to adult values between 20 and 30 months of age.</td>
<td>Oral acid-labile medicines such as β-lactam antibiotics require lower doses as they are absorbed to a greater extent, whilst weak-acid-medicines such as phenobarbital and phenytoin require higher doses as they are absorbed to a lesser extent.</td>
</tr>
<tr>
<td>Neonates and young infants: irregular gastric emptying time and reduces intestinal motility</td>
<td>Rate of absorption erratic or reduced.</td>
</tr>
<tr>
<td>Infants: increased intestinal motility.</td>
<td>Maximal plasma level time is variable.</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
</tr>
<tr>
<td>Neonatal, infants and children: greater cutaneous perfusion and hydration of epidermis plus increased ratio of total body surface area to body mass compared to adults.</td>
<td>Increased systemic exposure with potential for toxic effects. Small areas of exposure to skin can cause toxicity, e.g. corticosteroids, antiseptics.</td>
</tr>
<tr>
<td><strong>Muscle</strong></td>
<td></td>
</tr>
<tr>
<td>Neonates: reduced skeletal muscle mass and blood flow and immature muscle contractions.</td>
<td>Slower and unpredictable absorption from intramuscular injections.</td>
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### Considerations of medicine use in patients < 2 years old

**Characteristics of paediatric patients**

<table>
<thead>
<tr>
<th><strong>&lt; 2 years old</strong></th>
<th><strong>Consequences</strong></th>
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<tbody>
<tr>
<td><strong>MEDICINE DISTRIBUTION</strong></td>
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</table>

#### Body composition

Neonates and young infants: larger extracellular and total-body water spaces, and higher ratio of water to lipid in adipose stores. Lower plasma medicine concentrations with weight based dosing. Volume of distribution changed for some medicines.

#### Plasma protein

Most changes occur during first year of life: fewer drug-binding proteins and reduced binding affinity of the proteins. Serum bilirubin is increased (metabolism underdeveloped). Increased and variable free fraction of highly protein bound medicines. Sulphonamides (highly protein bound) can displace bilirubin from its protein binding site causing kernicterus (unbound bilirubin crosses immature blood-brain barrier).

#### Blood-brain barrier

The blood-brain barrier is immature in neonates. Medicines can penetrate to the central nervous system and cause toxic effects.

**MEDICINE METABOLISM**

Neonatal period: most enzymatic metabolic activity of medicines, mainly in the liver, is reduced. During childhood: some enzyme activity may exceed adult levels to decline to adult values after end of puberty. Consequences for dosing and dose intervals. For example, reduced clearance of midazolam in infants (1-2 years). Paracetamol and morphine are eliminated by glucuronidation. Half-life for paracetamol is not affected because of compensatory sulphation, which is not the case for morphine resulting in a longer half-life.

Glucuronidation is reduced. **MEDICINE EXCRETION**

In particularly preterm infants and newborns, the renal function is reduced. Glomerular filtration rate increases during the first 2 weeks of life and reaches adult activity by 8-12 months of age. Active/passive medicine excretion is reduced, which has consequences for dosing and intervals.

## By the age of 2 years, medicine absorption is similar to the adult pattern, except for a slight increase of the gastric emptying time and intestinal motility. The renal medicine clearance is at or near normal adult values. The activity of medicine metabolizing enzymes exceeds adult values during early childhood, requiring higher weight-based doses for some medicines to reach effect.

Adolescence is associated with a significant reduction of the total body fat, 50% for males and 28-25% for females, production of sex hormones, and rapid growth. The hormonal systems which particularly influence the physical changes seen in adolescents are the hypothalamic-pituitary-gonadal
axis, the hypothalamic-pituitary-adrenal axis, and the growth hormone axis.\textsuperscript{[55]} When puberty begins, the activity of medicine metabolizing enzymes starts to decrease, to reach adult capacity at the end of puberty.\textsuperscript{[56]} A temporal relationship has been demonstrated between variations in clearance of medicines eliminated via the liver and different stages of sexual maturity or changes in body size and composition. Many medicines used for diseases common during adolescence (depression, diabetes and epilepsy) are cleared by hepatic metabolizing enzymes. Therefore, doses used before puberty for chronic illnesses might become too high or too low once the patient enters adolescence, causing signs of toxicity or lack of effect in these patients.\textsuperscript{[56]}

**Psychosocial development relevant for medication in paediatric patients**

Not only biological changes but also psychosocial development has a bearing on the safety of medication in children at different ages. Children develop from being fully dependent on a caregiver/parent to being independent, *Figure 1*. Successful monitoring of ADRs will depend on how well an individual is able to communicate. A small child only has limited opportunities to communicate sufferings through crying or behavioural changes.\textsuperscript{[57]} Growing independence in a young person, who is not fully mature, can result in non-adherence to medications.\textsuperscript{[58]} To motivate a young person to take medicines for a chronic disease can be particularly difficult with rates of adherence among adolescents ranging between 10 and 89\%.\textsuperscript{[58]} Adolescents, who are seeking an identity, might be resistant to incorporating their chronic disease into the self.\textsuperscript{[58]} The importance of appearance for a teenager can hinder adherence to taking medications that cause for example acne or other skin-related ADRs.\textsuperscript{[58]} Easy access to medicines can be dangerous for a teenager on the verge of suicide.\textsuperscript{[59]}

*Figure 1.* Psychosocial development, moving from complete dependence on caregiver/parent to independence during childhood, relevant for medication in paediatric patients

Pharmacological therapy for paediatric patients is particular because of the child’s dependency on a parent or caregiver. An experimental study found that the perception of risk from a medicine varied among the participants
depending on whether the risk concerned themselves or a young child.\textsuperscript{[60]} The participants perceived the risk to be higher if the medicine was to be given to a child. However, the type of medication must be considered in this context, since the acceptance of negative effects would probably increase with therapy given for life-threatening diseases, as opposed to vaccination of an otherwise healthy child.

The limited guidance on medication therapy in paediatric patients and the lack of suitable dose formulations for certain ages and medicines, and the variations in body size and organ development throughout childhood presents a complex starting point for prescribing and administering medicines to children. Another aspect is that the development of a child can be affected by pharmacological therapy, which might not be apparent until adulthood.\textsuperscript{[61]} An example of this is chronic asthma treatment with corticosteroids and its effects on growth.\textsuperscript{[62]}

These conditions portray a scenario where patient and medication safety is particularly important.

**Patient and medication safety**

The work towards preventing patients from harm is included within the scope of patient safety, which has been defined as:

“Freedom, for a patient, from unnecessary harm or potential harm associated with healthcare.”\textsuperscript{[4]} (p. 8)

The patient safety concept is very broad and this thesis will focus on medication safety, which is about guarding patients from harm or potential harm from medicines. The following definition of pharmacovigilance spotlights the scope of this thesis:

“The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.”\textsuperscript{[2]} (p. 7)
Medicine-related problems include any problem found in connection with the use of medicines, encompassing:

- ADRs, be it a medicine’s direct pharmacological adverse effect or a patient’s unanticipated response to a medicine.\textsuperscript{[3]}
- Medicine/food/alcohol interactions.\textsuperscript{[63]}
- Lack of effect,\textsuperscript{[63]} i.e.,
  - the intended effect of a medicine fails an individual patient despite using a recommended dose,
  - too low doses are prescribed or chosen by the patient,
  - a pharmaceutical product does not meet quality specifications.
- Dependence and addiction.\textsuperscript{[63]}
- Accidental or intentional overdose.\textsuperscript{[63]}
- Non-adherence to product labelling, such as for off-label use of medicines.\textsuperscript{[65, 66]}
- Medication errors (failure in treatment that leads to or potentially could lead to harm).\textsuperscript{[64, 67, 68]}

Many stakeholders are actively involved in trying to improve medication safety; WHO World Alliance for Patient Safety, the International Medication Safety Network, national patient safety organisations, WHO Medicines Safety Programme, the WHO Collaborating Centre for International Drug Monitoring.\textsuperscript{[69]} Regulatory bodies, such as the Swedish MPA, the European Medicines Agency (EMA) and the US FDA stipulate regulations for the pharmaceutical industry regarding for example post-marketing surveillance. Other active members within the field are academic research centres, health care personnel, patient organisations and patients themselves, raising actions needed to accomplish safe medication use.

Medication errors

Medication errors are common when prescribing and administering medicines for paediatric patients.\textsuperscript{[27, 70, 71]} Most medication errors can be prevented and much of the effort within patient safety is focused on prevention of harm. Medication errors most often do not cause harm to the patient, although when they do they can cause detrimental effects for health care because of cost and loss of credibility, for the health care professionals involved, and not least for the individual patient.\textsuperscript{[72]} A medication error is often thought of as a problem caused by health care professionals but can equally be due to system errors.\textsuperscript{[73]} The underlying cause of these errors can be a sub-optimal medication device or a deficient product label, both of which are the responsibility of the manufacturer.\textsuperscript{[74]}
There is a need for a deeper understanding of medication errors, particularly of administration errors in the paediatric setting. Part of this thesis therefore investigated factors that influence safe transcribing, dispensing, administration and monitoring of medicines by nurses working on different paediatric wards.

**Definition of medication error**

The World Alliance for Patient Safety has worked on defining and grouping patient safety concepts to harmonise classifications within patient safety. In a technical report, nine previously published definitions of a medication error were listed. The following definition was chosen for this thesis because it is one of the few that involves regulatory agencies and the pharmaceutical industry, which cannot be kept outside the domain of medication errors:

The below definition is used by the National Coordinating Council for Medication Error Reporting (NCC MERP) in the US. Nations define medication error and related terms in different ways.

“A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.” (NCC MERP)

Medication errors can be classified according to severity of outcome (NCC MERP), see Table 2.

<table>
<thead>
<tr>
<th>Type of error</th>
<th>Category</th>
<th>Severity of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Error</td>
<td>A</td>
<td>Events had the capacity to cause error</td>
</tr>
<tr>
<td>Error, No harm</td>
<td>B</td>
<td>Error did not reach patient</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Error reached patient, but no harm caused</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>Error reached patient, monitoring of patient needed</td>
</tr>
<tr>
<td>Error, Harm*</td>
<td>E</td>
<td>Required intervention</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>Required hospitalization</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>Permanent patient harm</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>Required intervention to sustain life</td>
</tr>
<tr>
<td>Error, Death*</td>
<td>I</td>
<td>Patient died</td>
</tr>
</tbody>
</table>

*Medication error may have contributed to harm/death

Within patient safety, injury resulting from the use of a medicine or by its pharmacological action are often defined as adverse drug events (ADE), and more specifically as “an injury resulting from medical intervention related to
Within pharmacovigilance, ADEs or adverse events (AEs), terms which have become synonymous, signify events not necessarily related to medication use and primarily collected in pre-marketing clinical studies and cohort event monitoring. However, a “patient safety ADE” is usually associated with an adverse clinical effect related to a medication error and would therefore not mean the same as an AE in clinical studies. Within the context of this thesis, ADE will not be used, since this terminology overlap creates confusion in pharmacovigilance.

An ADR has been distinguished from an ADE by stating that ADRs are not preventable. This is somewhat arbitrary and even misleading, since the whole aim of pharmacovigilance is to prevent patients from harm by collecting detailed ADR information during post-marketing use. The knowledge collected on ADRs can lead to changes in the recommendations for its use, preventing susceptible patients from further harm. The need to differentiate between preventable ADEs and ADRs (or non-preventable ADEs) partly originates from the reporters need to know whether a report should be sent to the regulatory medicines agency or to the national patient safety organisation. Not all countries have a separate national patient safety alliance organisation, and efforts are currently made to include medication error reporting within the scope of pharmacovigilance. Another reason for introducing ADE was that the original ADR definition from 1972 did not include ADRs resulting from use of medicines outside “normal” doses.

**The extent of medication errors in paediatric patients**

In a US chart review on paediatric wards, 5.7% (616/10778) of all medication orders involved medication errors, 1.1% (n=115) of the orders had errors with significant potential for harm and 0.24% (n=26) resulted in harm, of which 5 were preventable. The study found that the rate of medication errors with potential for injury was three times higher within paediatric health care than in a separate corresponding hospital study on adults. One prospective study in the UK showed an overall incidence of 13% for prescribing errors and 19% for administration errors in the studied paediatric inpatients. The most common findings were incomplete prescriptions and errors occurring during medication preparation.

**Adverse drug reactions**

When a medication is introduced on the market, there is incomplete knowledge of its ADR profile. The medicines have most often been tested in a limited number of patients (<5000). The studies are restricted in time to short exposure durations and follow-up. The studies are also run with strict inclusion and exclusion criteria. Patients with certain diseases or medications, or ages, as for example children, are usually not included in the pre-marketing studies. This background makes reporting of suspected ADRs
by health care personnel and patients particularly important, to gain further information of ADRs in the post-marketing phase.

**Definition of adverse drug reaction**

The most cited definition of an ADR is the WHO definition from 1972:

"A response to a medicine which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."[80] (WHO, 1972)

The definition includes both the pharmacological effect of a medicine and the unanticipated reaction of a patient to a medicine. ADR and adverse drug effect are usually used interchangeably, where the adverse effect focuses on the pharmacological action and adverse reaction on the patient reaction.[3, 63]

The above definition excludes accidental or deliberate overdose: nor is harm resulting from sub-optimal use of medicines included in the definition. However, the term ADR has been used historically in pharmacovigilance in a way that includes patient harm resulting from pharmacological action of a medicine, a patient’s reaction, and medication errors. ADR in this thesis will be used to describe patient harm independent of the underlying cause, as suggested by Edwards and Aronson.[3]

“An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alternation of the dosage regimen, or withdrawal of the product.”[3] (p.1255)

The above definition corresponds with the EMA’s definition for regulatory purposes, which explicitly encompasses reactions from misuse, abuse and medication errors as follows:

“An adverse drug reaction (also known as a side effect) is defined as a response to a medicinal product which is noxious and unintended. This can be through the normal use of the medicine but also as a result of misuse (situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information), abuse (persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects) or medication error.”[81] (p.6)

**The extent of adverse drug reactions in paediatric patients**

In a review of six prospective studies in paediatric patients published between 2001 and 2007, 1.8% of the admissions to hospitals were due to ADRs, 10.9% of in-patient children, and 1.0% of outpatient children experienced ADRs.[5] In another review of 102 observational studies of
ADRs in paediatric patients (with no restriction of year of published article), the pooled incidence estimate was 2.9% (range 0.4% to 10.3%) for ADRs resulting in hospital admission (based on 30 studies with this information); and ranged between 0.6 and 16.8% for ADRs occurring during hospital stay (based on 36 studies with this information, no pooled estimate were computed because of too wide range of results).\(^{[82]}\) The difficulty in pooling data from studies to determine ADR rates is a result of the heterogeneity in study settings, study designs, and paediatric ages included. One conclusion that however could be drawn from this review is that the incidence rate overall is higher in in-patients compared with the rate in outpatients and the rate of ADRs causing admission to hospital.\(^{[5, 82]}\) The reason for the higher rate of ADRs in in-patients is probably the higher possibility of receiving multiple medicines in hospitals, which is a risk factor for acquiring ADRs.\(^{[83]}\)

In a recent UK prospective observational study, the reason for the acute admission to hospital of 178 out of 6,821 children was assessed to be caused by an ADR, an estimated incidence of 2.9 per 100 admissions.\(^{[84]}\) Among the children with ADRs in that study, 17.7% had been prescribed medicines in the community and the remainder in hospital. The authors assessed that one fifth of these ADRs could have been avoided. Almost half of the ADRs in this study were for oncology patients. The ensuing health care cost\(^{[84]}\) and suffering for these children and their families is a great burden for society and the individual, especially as some ADRs can be prevented.

Detecting the previously unknown and incompletely documented

The main purpose of collecting suspected ADR reports is to detect the previously unknown and incompletely documented problems, which is a core activity within pharmacovigilance.\(^{[85]}\)

**Collections of suspected adverse drug reaction reports**

As a result of the thalidomide tragedy in the beginning of 1960s, individual national pharmacovigilance centres (PVC) began to collect individual case safety reports (ICSRs) of suspected ADRs (also called spontaneous reports). In 1968, ten countries joined to collaborate in the collection of ICSRs by developing common processes and dictionaries.\(^{[86]}\) The first members were Australia, Canada, Czechoslovakia, Netherlands, New Zealand, Ireland, Germany, Sweden, UK, and US.\(^{[86]}\) As of February 2013, the WHO Medicines Safety Programme consists of 111 collaborating PVCs.\(^{[69]}\)

The PVCs are responsible for maintaining their own registry of ICSRs and for monitoring safety of medicines in their nation. The information on the ICSRs is collected in generic data fields, with the focus on making it possible to assess causality between a medicine and a reported reaction. The majority of PVCs collect ICSR information according to the International Conference of Harmonization (ICH) format, including: 1) patient
characteristics, 2) reaction(s), 3) tests and procedures, 4) medicine(s), 5) a case narrative. The ICSRs can be sent to the PVC directly from health care professionals and patients or via the nation’s regional centres (often closely connected to hospitals) or via product manufacturers. The PVCs operate under diverse procedures that can change over time resulting in heterogeneous collections of reports. Mandatory and/or voluntary reporting can be stipulated according to different criteria by the PVCs. Some PVCs allow only certain types of reporters, such as physicians, and others permit pharmacists, other health care professionals and patients to contribute with reports. PVCs can also differ in what types of reports they collect, such as medication errors, lack of effect, substandard medicines (quality issues) and other reports of medicine-related patient harm.

Some PVCs collect only ADRs with at least a possibility of a causal relationship between the medicine and reported event, and others, such as the US FDA, collect “…any adverse event associated with the use of a medicine in humans, whether or not considered drug related…” Each nation’s Ministry of Health appoint a PVC to be responsible for contact with WHO concerning safety of medicines. The PVC can be part of the national governmental medical products agency (MPA), such as the MPA in Sweden, or independent foundations, such as the Netherlands Pharmacovigilance Centre, Lareb.

Processing individual case safety reports nationally

The reported medical terms on the ICSRs are coded at the PVC according to the WHO Adverse Reaction Terminology (WHO-ART) or the Medical Dictionary for Regulatory Activities (MedDRA). Both terminologies are hierarchical; WHO-ART has four levels and MedDRA five. When the medical event is coded, the lowest level term is used to match the reported term as closely as possible. To make analyses on the highest level, the system organ classes of the terminology are used and in analyses on a more specific level, the preferred terms are used, which group synonymous or similar lowest level terms. Some PVCs classify the ICSRs according to the strength of association (described more in detail below). The PVCs transfer ICSRs in structured report files to international compilations of ICSRs, such as the EudraVigilance, the EMA’s database with ICSRs from countries within the European Union, and the WHO global ICSR database, VigiBase.

Processing individual case safety reports globally

VigiBase is maintained by the WHO Collaborating Centre for International Drug Monitoring, the UMC, in Sweden. The minimum requirement for a report to be valid in VigiBase is that it must include at least: a country code, unique case identification, a reaction and a medicine. When the reports are entered in VigiBase, the medicinal products listed on the reports are encoded to the WHO Drug Dictionary, which groups all medicinal products with
the same substance to a common preferred base level in a hierarchy integrating the WHO Anatomical Therapeutic Chemical (ATC) classification. ADR information can be retrieved by using either the WHO-ART or MedDRA. The PVCs can access VigiBase data via a common search interface, and data are also accessible for other stakeholders under certain conditions.

Causality assessment of suspected adverse drug reactions

Many PVCs and pharmaceutical manufacturers perform causality assessments on the ICSRs when received, i.e. determine the likelihood of a medicine’s causal effect on an event. However, some PVCs restrict their causality assessment to reports under special investigation. The following questions are central to the evaluation of case causality assessment:

a. Did the event re-occur at re-exposure of the medicine (rechallenge)?

b. Did the event abate when the medicine was withdrawn or dose was decreased (dechallenge)?

c. Did the event occur with a reasonable time relationship to medicine intake?

d. Is the underlying disease or other medicines more likely to be the cause of the event?

e. Is there a plausible mechanism to explain the event being caused by the medicine?

The completeness of information on the report predicts how well the above questions can be answered. Rechallenge and dechallenge are not feasible for irreversible events such as for fatal reactions or congenital abnormalities. There have been many attempts to grade the strengths of, or estimate the probability of a causal relationship of suspected ADR reports. Various algorithms have been developed that classify the assessment into different causality categories such as certain, probable, possible, and unlikely. Bradford Hill suggested a set of considerations to use when deciding the likely causation of an association.

Causality assessment based on clinical judgement has been criticized for both the disagreements between different assessors and the inconsistencies in individual assessors’ reports. It has been suggested that due to lack of consistency and reproducibility of the different methods, they are of limited scientific value. It should also be noted that causality assessment between a medicine and an event can change over time when more data are collected and further knowledge of risk groups or pharmacological mechanisms is obtained. Nevertheless assessments of the number and content of ICSRs and subsequently various data mining observational studies do allow for concerns of reporters to register as early warnings of possible harm from medicines.
Definition of signal

The detection of previously unknown and incompletely documented ADRs has been denoted ‘signal detection’. A “signal” has been defined by the Council for International Organisations of Medical Sciences (CIOMS) Working group VIII - Practical Aspects of Signal Detection in Pharmacovigilance, as follows:

“Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.” (p. 14)

A signal is a potential causal association between an intervention and an event that needs further investigation to be confirmed.

Detecting emerging signals

Signals are detected by global/national PVCs and the pharmaceutical industry in a similar way to how clinicians discover suspected ADRs. The clinicians monitor for unexpected signs or patterns in a patient or a group of patients and the global/national PVCs/industry screen for unexpected signs in collections of data that warrant further investigation. Before describing the processes of signal detection within global and national pharmacovigilance, the origin of this activity will be presented briefly.

In 1961, McBride wrote to the Lancet of his concern of seeing unexpectedly more babies born with serious and specific abnormalities delivered by mothers having taking thalidomide during their pregnancy. He wrote:

“Have any of your readers seen similar abnormalities in babies delivered of women who have taken this medicine during pregnancy?” (p. 1358)

McBride’s action is a good illustration of what signal detection entails. It starts with a concern or a suspicion that a medicine could be associated with an event, the event being out of the ordinary in relation to the patient population or an individual patient. McBride considered the underlying disease; congenital abnormalities are expected to a certain extent, but not as many as he had lately seen. He also considered the specific pattern of how the congenital abnormalities were presented in these babies, most with their bone development being affected. Then he asked, if anyone else had seen the same thing? Signal detection starts with a suspicion of a possible causal relationship, which is then communicated. It is important to note that a signal is not yet verified, it is a hypothesis that needs further investigation. It is a communication of a question. Traditionally, discussions and evaluations of signals were held behind closed doors within the pharmacovigilance...
community and communicated to clinicians only when the signal had been verified. Today, some regulatory bodies and the industry are open about signals already before they are verified or supported by other investigation. In the Netherlands for example, signals are accessible on the homepage of the Netherlands Pharmacovigilance Centre Lareb.[99]

Global and national PVCs perform activities to detect signals and the pharmaceutical industry work according to regulatory stipulations. [100] Many recent regulatory developments within the area originate from the aftermath of the rofecoxib withdrawal in 2004. The association between rofecoxib and cardiovascular disorders was first highlighted in ICSRs by the PVC in the Netherlands (Lareb). [101] The manufacturer detected an increased risk of myocardial infarction in rofecoxib long-term users in a post-marketing randomized clinical study and decided to withdraw the medicine. [102] Most verified signals do not lead to withdrawal of a medicine but to added warnings and precautions for use, dose recommendation changes or further descriptions of ADRs.

Sources of signals
The sources of signals can be controlled, randomized clinical studies, observational studies, cohort event monitoring, individual case safety reporting systems, and case reports or series of reports in publications. [103] One single well-described case can even constitute a signal: when a patient re-experiences a reaction after re-exposure to a medicine, or presents with a rare and serious event that is highly attributable to medicine exposure (e.g. toxic epidermal necrolysis). [104]

Signal detection process – an example
Signals can also be detected in accumulations of reports at national PVCs and in global databases such as in VigiBase. The great continuous influx of reports to VigiBase (~500 000 per year) has led to the necessity of developing methods and processes for signal detection at the UMC. [37, 105-113] Every quarter, problems highlighted on newly received reports are selected focusing on: medicine and ADR combinations reported disproportionally more frequently relative to the general reporting in VigiBase [105, 110] with:

- newly marketed substances and serious adverse reactions, or
- medicine and ADR combinations reported disproportionally more compared with the previous quarter.

The selected problems are assessed to determine whether they are previously unknown, according to existing product information. The plausibility of the medicine’s pharmacological effect on the event is considered, as well as the clinical characteristics of the event; is it rare or common, serious or trivial or
a typical ADR? Thereafter, the reports are assessed in-depth to consider the likelihood of a causal association. The evidence for and against a signal is then considered using Bradford Hill criteria as a basis. Meyboom et al. wrote there need to be:

“...a delicate weighing of the credibility of the signal, its importance for individual users and in the public health perspective, of the measures needed, and of the consequences if the signal proves false.” (p. 463)

If the review supports a ‘signal’ that should be communicated, the case evaluations (signals) with reasoning behind the decision are circulated to the collaborating PVCs via a document named ‘WHO Signal’. From February 2012, these signals are also publically available in the WHO Pharmaceuticals Newsletter.

The time period from an early suspicion of a medicine-induced reaction and a signal until the establishment of a fully described and understood ADR can be long. Some ADRs listed in the product label can be highly uncertain and incomplete, needing further scientific evaluation. To affirm a signal, observational or clinical studies need to be conducted. For rare and serious reactions, case series analyses might be the only source of evidence.

**Signal detection in data on paediatric patients – need for development**

In a retrospective review of VigiBase signals from 1998 to 2008 issued by the UMC, only 4% concerned paediatric patients (internal UMC evaluation), of which several had not been detected via the regular signal detection processes. One of the signals found between 1998 and 2008 concerned babies born with neonatal withdrawal syndrome following mother exposure of selective serotonin reuptake inhibitors (SSRI). Another signal detected during the time period was for serious cardiac effects after atomoxetine use. Atomoxetine was at the time a new medicine indicated for ADHD. The signal, issued in November 2005, described 26 cases reported with cardiac arrest, ventricular tachycardia, or QT prolongation. Cardiac effects, such as increased blood pressure and heart rate, were known for atomoxetine. In 16 of the cases, the patient recovered when the medicine was stopped. QT interval prolongation was later added to the label for atomoxetine, where the WHO signal possibly was one puzzle piece to induce change.

Several of the signals for children had been initiated and detected outside the UMC’s regular pre-defined processes for detecting signals. Possible reasons for the low proportion of UMC signals concerning children could be that certain medicines are excluded in the current UMC process, such as old medicines and known problems for adults. However,
• old medicines are commonly used in paediatric patients (whether or not they are licensed for use in this population),
• known ADRs in adults might be unknown or incompletely documented for paediatric patients, who also could be presented with a completely different risk-benefit profile.

The above describes limitations in the recognition of important problems in paediatric patients and has spurred us to investigate the possibility to develop processes for highlighting signals specific for this population. In preparing for this work, this thesis was undertaken to enhance our understanding of safety of medication in paediatric patients.
Rational for the studies in this thesis

- Several studies have reviewed national reporting patterns of suspected ADRs in children. [118-128] In planning for routine screening of ADRs reported for paediatric patients, the worldwide reporting pattern was explored to gain knowledge on the characteristics of reports across nations in paediatric age groups.

- There is limited knowledge of how serious and rare ADRs present themselves clinically in children. Antipsychotic medicines are increasingly prescribed for children and adolescents. [129] In a screening of recent VigiBase reports (1995 to 2010) classified by age groups as further described in Table 4, rhabdomyolysis was reported disproportionally more frequently with olanzapine (antipsychotic substance) in the adolescent age group relative to the background of all reports for adolescents. Antipsychotic-induced rhabdomyolysis (skeletal muscle destruction resulting in muscle constituents into plasma, which can be toxic to the kidneys) [130] is a rare ADR and not well described for children in the absence of neuroleptic malignant syndrome (a known ADR to antipsychotic medicines). There was also a need to explore whether ICSRs can be used to gain further clinically useful knowledge about rare ADRs in paediatric patients.

- The limited documented basis for dosing in growing children makes prescribing a challenge. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are commonly used in children (particularly ibuprofen) for pain, fever and anti-inflammatory purposes (including juvenile idiopathic arthritis). Despite the common use of NSAIDs in children, there is limited published research on what real-life doses are prescribed in this population.

- This study was conducted to give an account of the challenges in preparing and administering medicines to children. Nurses play a crucial role in being able to detect and prevent administration errors of medicines, but research describing paediatric nurses’ own views in their context of medication practice is limited.
Overall and specific aims

The overall aim of this thesis is to explore the nature of reported ADRs and the challenges in prescribing and administering medicines for paediatric patients. The enhanced understanding of ADRs and these medication practices will be used to identify and suggest areas needing special international surveillance within medication safety and improvement in the clinical setting.

Study I
The first aim of this study was to characterize and contrast child reports against adult reports in an overall medicine and adverse reaction review. The second aim was to highlight increases in the reporting of specific adverse reactions during recent years, subdivided by age group.

Study II
The aim of this study was to investigate the clinical circumstances surrounding the diagnosis of rhabdomyolysis in children and adolescents treated with antipsychotic medicines. ICSRs of suspected ADRs were critically reviewed to evaluate how clinically useful they can be in a case series analysis.

Study III
The aim of this study was to investigate if variations in NSAID doses prescribed to children could be explained by patient age, indication for use, dosage form, type of NSAID, or year of prescription.

Study IV
The aim of this study was to explore nurses’ experiences of handling medications in paediatric clinical practice, with a focus on factors that hinder and facilitate safe medication practices.
Materials and methods

The studies in this thesis had exploratory study designs. Table 3 gives an overview of the data sources, participants and data analyses used in the studies.

Table 3. Data sources, participants and data analyses used in this thesis

<table>
<thead>
<tr>
<th>Study</th>
<th>Data sources</th>
<th>Participants</th>
<th>Data analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>VigiBase (overall)</td>
<td>Ages ≤17 years Global coverage</td>
<td>Descriptive statistics</td>
</tr>
<tr>
<td>II</td>
<td>VigiBase (in-depth)</td>
<td>Ages ≤17 years Global coverage</td>
<td>Descriptive statistics</td>
</tr>
<tr>
<td></td>
<td>Literature cases</td>
<td></td>
<td>Disproportionality analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Content analysis</td>
</tr>
<tr>
<td>III</td>
<td>IMS Health Disease Analyzer</td>
<td>Ages 2 to 11 years United Kingdom</td>
<td>Multiple linear regression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Descriptive statistics</td>
</tr>
<tr>
<td>IV</td>
<td>Focus group interviews</td>
<td>Swedish registered nurses from neonatal, acute medical, oncology, psychiatric wards</td>
<td>Content analysis</td>
</tr>
</tbody>
</table>

Materials

VigiBase (Studies I and II)

Studies I and II used VigiBase data\(^{[90]}\) compiled up to February 2010 at which time almost 5 million ICSRs had been accumulated since 1968. New ICSRs are continuously entered in VigiBase and at the end of 2012 the database contained 7.8 million reports. Studies I and II were restricted to reports where age had been specified. Reports recorded with vaccines, classified as vaccines subordinated to the WHO ATC classification code J07,\(^{[91]}\) were excluded in Study I. Possible duplicate reports were excluded by using a previously published pre-defined algorithm applied on the complete VigiBase dataset in Studies I and II.\(^{[131]}\)

Duplications of reports can occur when different reporters submit reports on the same case. A pre-defined algorithm has therefore been developed and can be applied on VigiBase. The method for identification of duplications is built to find similarities between database records relating to the same event.\(^{[131]}\) Each ICSR is compared against other ICSRs with at least one medicine in common and at least one reported adverse reaction from the
same system organ class. For each pair of reports, a total match score is computed. Each individual report field considered receives a sub-score, which are summarised in a total match score. When the information matches, positive sub-scores are generated and mismatches generate negative sub-scores. Missing data for either report gives sub-score 0.

Study II was restricted to reports recorded with the MedDRA preferred term ‘Rhabdomyolysis’ reported with an antipsychotic medicine as defined by the WHO ATC classification code N05A (antipsychotics). Few reports are available in VigiBase with a narrative; therefore the national PVC that contributed the reports evaluated in Study II were requested to send the de-identified original files with narratives for the purposes of the study, which is routinely done when in-depth analysis of specific problems are performed.

Published case reports (Study II)
In Study II, published case reports of children with antipsychotic medicines and rhabdomyolysis, in the absence of neuroleptic malignant syndrome, were searched for in multiple databases and used in the case series evaluation. Abstracts from 1970 to May 2010 were retrieved and screened using pre-defined search terms as defined in Study II.

IMS Health Disease Analyzer (Study III)
In Study III data from The Intercontinental Medical Statistics (IMS) Health Disease Analyzer was used, which is an electronic health record database in the UK.[132] In the UK, the majority of the GPs use computerized recording of clinical data. Almost the entire UK population is registered with a GP, who has the responsibility for their patients’ primary care and specialist referrals. The IMS Health Disease Analyzer database in the UK includes de-identified electronic health records from more than 500 GPs in the UK, broadly representative of the UK population.[133, 134] The prescriptions in the computer system allow linkage to diagnoses for which the medicine is issued. To code the clinical data, the GPs use Read codes, first developed in early 1980s by Dr James Read, a general medical practitioner from the UK.

NSAID prescriptions recorded from 1988 until the end of 2005 were retrieved from the IMS Health Disease Analyzer. NSAID substances within the European Pharmaceutical Marketing Research Association (EphMRA) anatomical classification M01A1 (Anti-rheumatics, non-steroidal plain) were studied.

As for any observational dataset, errors in data can occur; however, data inaccuracies in the UK IMS Disease Analyzer are kept to an absolute minimum by extensive ongoing quality assurance work; one example of this quality assurance is outlined by De Lusignan et al.[133]
Focus group interviews (Study IV)

Data for Study IV was collected through focus group interviews. Registered nurses from neonatal, acute medical, psychiatric and oncology wards were recruited to represent medication practices for various types of medicines and caring for children of different ages and with a range of diseases. Twenty nurses (17 females and 3 males) with a median age of 39.5 years and with a median nursing work experience of 7 years participated in the interviews. Thirteen of the 20 nurses had specialist training in paediatric, oncology, midwifery, intensive care, or psychiatry nursing. Five focus group interviews representing each ward were conducted. The neonatal ward was represented by two groups, one of which consisted of experienced nurses and the other of new nurses.

Focus group interviews were suitable since the aim of Study IV was to gather thoughts, experiences and viewpoints of medication practices in paediatric care. Data collection through focus groups is characterized by having a clear research purpose in contrast to discussion groups for other purposes, such discussions aimed to make decisions. The researcher uses the interaction and discussion in the group to generate data and broadly directs the dialogue according to his/her purposes. To affirm openness in the focus groups in Study IV, the participants in each of the five groups were asked not to speak about the content of the discussion outside the interview session. The moderator used a prepared interview guide and started each session by defining the scope of medication practices and thereafter asked an introductory question about how much time was spent on handling medications in their daily work, to help the participants focus on the subject of discussion. Thereafter, the following questions were covered: a) What would you say is special about handling medications on your ward and with the children in your care? b) What experiences do you have of factors that facilitate safe medication practice? c) What experiences do you have of factors that hinder safe medication practice? In some of the interviews, when question b had been posed, the conversation naturally continued to cover question c without it being asked. During the interview, probing questions could be asked, for example to be more specific about certain situations, or types of medicines, or patients referred to in the discussion. The moderator ended all interviews with: ‘What important aspects have we not yet captured concerning safe medication practice?’ The interviews were recorded and transcribed, which constituted the data source in this study.
Age categories (Studies I, II, III)

The age groups used in this thesis were based on a guidance for clinical investigation of medicinal products in the paediatric population by the International Conference on Harmonisation (ICH) and are displayed in Table 4.\textsuperscript{[51]} The ages in Table 4 refers to completed days, months, and years (e.g. 11 years means until the end of the 11th year). This classification was chosen because it considers the overall developmental biology and pharmacology during childhood. One limitation in the classification is the wide age span from 2 to 11 years of age. Even if organs, important for pharmacology, are more or less mature at 2 years of age, the body size, and social and psychological maturity differs immensely between a 2-year-old and an 11-year-old child. Overall, it was decided to avoid modification of a classification that is internationally agreed upon and overall relevant for pharmacology. In Study II, the age groups for children and adolescents were merged in the disproportionality analysis. In Study III, the 2 to 11 year age group was broken down to four age groups, which was considered important when investigating trends in the prescribed doses.

Table 4. Paediatric age groups suggested by the International Conference of Harmonisation (ICH) and those used in this thesis

<table>
<thead>
<tr>
<th>ICH classification</th>
<th>ICH age range</th>
<th>Age range in thesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm newborn infants</td>
<td>Undetermined in VigiBase</td>
<td></td>
</tr>
<tr>
<td>Term newborn infants</td>
<td>0 to 27 days</td>
<td>0 to 27 days</td>
</tr>
<tr>
<td>(denoted neonates in thesis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infants and toddlers</td>
<td>28 days to 23 months</td>
<td>28 days to 23 months</td>
</tr>
<tr>
<td>Children</td>
<td>2 to 11 years</td>
<td>2 to 11 years</td>
</tr>
<tr>
<td>Adolescents</td>
<td>12 to 16-18 years,</td>
<td>12 to 17 years</td>
</tr>
<tr>
<td></td>
<td>depending on region</td>
<td></td>
</tr>
</tbody>
</table>

\begin{itemize}
  \item In Study I, globally reported patients aged 0 to 17 years were included in the overall review of ICSRs. A separate analysis was made for the paediatric age groups specified in Table 4.
  \item In Study II, reports recorded in the range of ages 2 to 17 years with rhabdomyolysis and antipsychotic medicines were retrieved from VigiBase and from the published literature.
  \item In Study III, NSAID prescriptions for ages 2 to 11 years were retrieved from the IMS Health Disease Analyzer. In parts of the analysis, the children were divided into four age groups as follows: 2-3, 4-5, 6-8 and 9-11 year olds.
\end{itemize}
Statistical analyses (Studies I, II, III)

In Studies I to III, descriptive statistics was used. In addition, in Study II disproportionality analysis was used and Study III multiple linear regression, described as follows.

Disproportionality analysis (Study II)

The lack of a denominator (number of worldwide users of specific products are unknown) and the underreporting of ICSRs (only around 6% of ADRs are reported to a PVC[^137]) have led to the use of disproportionality analyses using the general reporting pattern in VigiBase as a reference.[^105, 110] To get a sense of how commonly rhabdomyolysis was reported with antipsychotic medicines in children and adolescents (2 to 17 years) and in reports for adults (≥18 years), disproportionality analyses were used in Study II.

The measure of disproportionality is given with an observed-to-expected ratio, based on the reporting of a specific medicine with a certain ADR in VigiBase. Shrinkage observed-to-expected ratios on a logarithmic scale are calculated and given as the ‘Information Component’ (IC).[^105, 110] The following formula is applied to generate the IC:[^110]

\[
IC = \log_2 \frac{O + 0.5}{E + 0.5}
\]

The O (observed value) is the number of reports recorded with a specific medicine (e.g, any antipsychotic substance) and ADR (rhabdomyolysis). The E (expected) number of reports is computed as the product of the total number of reports of the medicine (any antipsychotic) and the total number of reports with the specific term (rhabdomyolysis), divided by the total number of reports in the dataset or subset defined (reports with ages 2 to 17 years and ages ≥ 18 years, respectively). The ‘0.5’ in the formula signifies the shrinkage of the observed-to-expected ratio, which reduces the IC from fluctuating when numbers are low. The IC is given with its 95% credibility interval. A positive lower limit of the credibility interval (IC025) signifies that the medicine and ADR combination is reported more frequently than expected based on the overall reporting in the dataset or subset defined.

Multiple linear regression (Study III)

Multiple linear regression was used in Study III to analyse several variables simultaneously so as to potentially explain what variables influenced the prescribed dose of an NSAID. A relative prescribed daily dose (rPDD) was computed based on the prescribed daily dose in the patient record relative to the daily assumed average maintenance dose for an adult weighing 70 kg for
the different NSAID substances. The reason for using the rPDD was to be able to group and compare the different NSAID substances in the analysis. The optimal analysis would have been to relate the dose to the child’s own weight but this was not possible because of limited recorded data on weight at the time of prescription in the dataset used in this analysis.

The outcome variable in the multiple linear regression analysis was the rPDD and the explanatory variables: age (years), time of prescription (years), dosage form, individual NSAID substance, indication (related or not to juvenile idiopathic arthritis). We hypothesized that higher doses might be prescribed for juvenile idiopathic arthritis; therefore indication was included in the regression analysis.

Content analyses (Studies II, IV)
The content analysis of the cases in Study II was conducted according the structure in a guideline for submitting adverse events for publications by Kelly et al. The analysis involved summarizing the information on the retrieved VigiBase and published case reports into clinical areas relevant in case series analyses of ADR reports.

A qualitative method was used in Study IV. Qualitative methods originate from the social and human sciences. The method is appropriate when aiming to increase the understanding of the nature or meaning of a phenomenon by interpreting people’s own experiences of the event. In Study IV, the purpose was to represent nurses’ perceptions of medication practices in paediatric clinical practice, so we aimed to, as Sandelowski describes it, “offer a comprehensive summary of an event in the everyday terms of those events” that would closely represent the data collected without high abstraction of data. A systematic analysis is important in qualitative research to affirm its scientific value. The interview transcripts were analysed using qualitative content analysis with the help of structures and processes described by Graneheim and Lundman.

Ethical considerations
This thesis was performed according to the Declaration of Helsinki. The two databases used in Study I, II and III consisted of de-identified ICSRs and patient records. The data in Study I and III were used on a group level. In Study II, published case reports and de-identified original files were used, received routinely on request from the contributing national PVCs. A final draft of the manuscript of Study II was also reviewed by collaborating national pharmacovigilance centres contributing original files. To use the UK Disease Analyzer, IMS Health’s independent scientific and ethics
advisory committee reviewed and approved the protocol for Study III. Study IV was reviewed by the Regional Ethics Review Board in Uppsala, Sweden (Dnr 2011/198). According to Swedish law 2003:460, this study required no formal ethics approval.
Results

Main findings

**Study I:** Only 7.7% of the ICSRs in VigiBase were reported for children (vaccine reports were excluded from the analysis). Skin reactions (35%) and anti-infective medicines (33%) were most frequently reported for paediatric patients. These reactions and medicines were proportionally more reported in paediatric patients than in reports for adults. A higher proportion of reports concerned paediatric patients in Latin America, Africa and Asia (14-15%) than in reports from the rest of the world (7%). Between January 2005 and February 2010, events related to medication errors and ADHD medicines were reported with an increased frequency compared with the reporting between 1995 and 1999.

**Study II:** 20 reports with antipsychotic medicines and rhabdomyolysis, in the absence of neuroleptic malignant syndrome, were evaluated. Symptoms preceding rhabdomyolysis, included various types of muscle pains, abdominal pain, dark urine and general weakness. Onset of rhabdomyolysis was in several cases triggered by changes in the patient’s medication or by known risk factors of the diagnosis. The study indicated that a case series analysis of ICSRs can add clinical value to known single medicine-ADR relationships.

**Study III:** 21,473 prescribed doses for NSAID substances were evaluated. The prescribed doses varied substantially with dosage form. Tablets and capsules were prescribed with a higher dose than liquid dosage forms. The difference was most noticeable for preschool children.

**Study IV:** Six themes emerged from the interviews of 20 nurses in paediatric care: preparation and administration was complex; medication errors or near misses caused considerable psychological burden; support from nurse colleagues was highly valued; unfamiliar medication was challenging; clear dose instructions and routines were important; nurses handling of medicines needed to be accorded higher priority.
Review of reported adverse drug reactions (Study I)

Overall reporting in VigiBase

Reporting over time
A total of 268,145 (7.7%) ICSRs entered in VigiBase between 1968 and February 2010 concerned paediatric patients with ages 0-17 years (reports with vaccines were excluded). The number of reports entered in VigiBase by year is displayed in Figure 2. The number of reports entered in VigiBase by year is displayed in Figure 2. Reports for paediatric patients are entered in VigiBase with a consistent proportional frequency across the years.

Age and sex distribution
For ages 0-17 years, males constituted 53% of all reports with recorded patient sex. The number of reports by age in years and by patient sex is given in Figure 3. For ages 18 years and above, the corresponding proportion of males was 39%.

Figure 2. Number of reports entered in VigiBase by year for ages 0-17 years (children) and ≥ 18 years (adults). Reports excluded from the count: vaccine reports, duplicate reports, and reports with age not specified.
Figure 3. Number of reports in VigiBase by age (in years) and by patient sex. Reports excluded from the count: vaccine reports, duplicate reports, and reports with age not specified.

**Reporting by geographical region**

The proportion of reports for ages 0-17 years within each geographic region (Latin America, Africa, Asia, North America, Oceania and Europe) is given in Figure 4.

![Graph showing reports by age and sex](image)

**Figure 4.** Percentage of reports for paediatric patients within each geographical region

**Most frequently reported adverse reactions**

The five most frequently reported adverse reactions grouped by system organ class for paediatric patients are displayed in Table 5 (percentages for adult patients are given as a reference).
Table 5. The five most frequently reported adverse reactions by system organ class for the paediatric patients (percentages for adult patients are given as a reference)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>0-17 years</th>
<th>≥18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin disorders</td>
<td>35%</td>
<td>23%</td>
</tr>
<tr>
<td>General disorders</td>
<td>20%</td>
<td>23%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>19%</td>
<td>20%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>15%</td>
<td>19%</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>11%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Percentage is based on the number of reports within the MedDRA system organ class divided by the total number of reports in the age group (n=268,145 for children, n=3,204,038 for adults). The percentages do not add up, since one report can be recorded with more than one adverse reaction and thereby be represented in more than one system organ class.

Examples of ‘General disorders’ in Table 5, are fever, face oedema and drug ineffective (lack of effect from a medicine). Skin reactions were reported proportionally more in paediatric patients than in reports for adults.

The specific skin reactions reported more commonly for paediatric patients contrasted with reports for adults are displayed in Table 6.

Table 6. Skin reactions reported more frequently for paediatric patients (0-17 years) contrasted with reports for adults (≥18 years)

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>0-17 years</th>
<th>%</th>
<th>≥18 years</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria</td>
<td>21891</td>
<td>8.2%</td>
<td>116149</td>
<td>3.6%</td>
</tr>
<tr>
<td>Rash</td>
<td>25379</td>
<td>9.5%</td>
<td>176869</td>
<td>5.5%</td>
</tr>
<tr>
<td>Rash maculo-papular</td>
<td>10428</td>
<td>3.9%</td>
<td>57335</td>
<td>1.8%</td>
</tr>
<tr>
<td>Rash erythematous</td>
<td>10137</td>
<td>3.8%</td>
<td>65709</td>
<td>2.1%</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>2851</td>
<td>1.1%</td>
<td>10291</td>
<td>0.3%</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>2403</td>
<td>0.9%</td>
<td>11763</td>
<td>0.4%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13321</td>
<td>5.0%</td>
<td>148503</td>
<td>4.6%</td>
</tr>
<tr>
<td>Periorbital oedema</td>
<td>1651</td>
<td>0.6%</td>
<td>10314</td>
<td>0.3%</td>
</tr>
<tr>
<td>Erythema</td>
<td>2598</td>
<td>1.0%</td>
<td>22846</td>
<td>0.7%</td>
</tr>
<tr>
<td>Angioedema</td>
<td>3484</td>
<td>1.3%</td>
<td>33672</td>
<td>1.1%</td>
</tr>
<tr>
<td>Skin discolouration</td>
<td>843</td>
<td>0.3%</td>
<td>7126</td>
<td>0.2%</td>
</tr>
<tr>
<td>Rash macular</td>
<td>495</td>
<td>0.2%</td>
<td>2998</td>
<td>0.1%</td>
</tr>
<tr>
<td>Skin striae</td>
<td>226</td>
<td>0.1%</td>
<td>270</td>
<td>0.0%</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>1719</td>
<td>0.6%</td>
<td>18720</td>
<td>0.6%</td>
</tr>
<tr>
<td>Rash papular</td>
<td>416</td>
<td>0.2%</td>
<td>3227</td>
<td>0.1%</td>
</tr>
<tr>
<td>Toxic epidermal necrolysis</td>
<td>535</td>
<td>0.2%</td>
<td>4775</td>
<td>0.1%</td>
</tr>
<tr>
<td>Petechiae</td>
<td>348</td>
<td>0.1%</td>
<td>2578</td>
<td>0.1%</td>
</tr>
<tr>
<td>Acne</td>
<td>589</td>
<td>0.2%</td>
<td>5502</td>
<td>0.2%</td>
</tr>
<tr>
<td>Purpura</td>
<td>1449</td>
<td>0.5%</td>
<td>15783</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Percentage is based on the number of reports with the adverse reaction (MedDRA preferred term) divided by the total number of reports in the age group (n=268,145 for children, n=3,204,038 for adults). The table is sorted according to the greatest difference in percentage units between paediatric patients and adults. Adverse reactions with at least a difference of 0.05 in percentage units between the paediatric and adult reports are listed. The figures do not add up because one report can be recorded with more than one adverse reaction.
Most frequently reported medicines

The five most frequently reported medicines by the WHO ATC classification for paediatric patients are displayed in Table 7 (percentages for adult patients are given as a reference).

Table 7. The five most frequently reported medicines by Anatomical Therapeutic Chemical classification (class of medicines) for paediatric patients (percentages for adult patients are given as a reference)

<table>
<thead>
<tr>
<th>Class of medicines</th>
<th>0-17 years</th>
<th>≥18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinfectives for systemic use</td>
<td>33%</td>
<td>15%</td>
</tr>
<tr>
<td>Nervous System</td>
<td>28%</td>
<td>25%</td>
</tr>
<tr>
<td>Dermatologicals</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>Alimentary tract and metabolism</td>
<td>10%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Percentage is based on the number of reports within the WHO Anatomical Therapeutic Chemical classification divided by the total number of reports in the age group (n=268,145 for children, n=3,204,038 for adults). The percentages do not add up, since one report can be recorded with more than one medicine and thereby be represented in more than one class of medicine.

Reporting during recent years

The ten most frequently reported adverse reactions for paediatric patients (0-17 years) before and after 2005 are displayed in Table 8.

Table 8. The ten most frequently reported adverse reactions before and after 2005 for ages 0-17 years

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>17452</td>
<td>Rash</td>
<td>7927</td>
</tr>
<tr>
<td>Urticaria</td>
<td>15694</td>
<td>Urticaria</td>
<td>6197</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8709</td>
<td>Vomiting</td>
<td>4989</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8667</td>
<td>Pruritus</td>
<td>4612</td>
</tr>
<tr>
<td>Rash maculo-papular</td>
<td>7508</td>
<td>Pyrexia</td>
<td>3057</td>
</tr>
<tr>
<td>Rash erythematous</td>
<td>7480</td>
<td>Rash maculo-papular</td>
<td>2920</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7169</td>
<td>Nausea</td>
<td>2900</td>
</tr>
<tr>
<td>Convulsion</td>
<td>4715</td>
<td>Drug ineffective</td>
<td>2686</td>
</tr>
<tr>
<td>Headache</td>
<td>4399</td>
<td>Rash erythematous</td>
<td>2657</td>
</tr>
<tr>
<td>Nausea</td>
<td>4034</td>
<td>Headache</td>
<td>2595</td>
</tr>
</tbody>
</table>

The figures do not add up, since one report can be recorded with more than one adverse reaction. The adverse reactions reported before 2005, which were not listed among the ten most frequently reported adverse reactions after 2005, are given in italics. The adverse reactions reported after 2005, which were not listed among the ten most frequently reported adverse reactions before 2005, are given in bolded text.
In Table 9, the ten adverse reactions reported with a greater frequency during recent years are listed for each age group (reactions reported in 2005 to February 2010 are contrasted with reports during 1995 to 1999).

Table 9. *Adverse reactions by age group reported with a greater frequency during recent years (2005 - February 2010) contrasted with reporting during 1995-1999*

<table>
<thead>
<tr>
<th>0-27 days</th>
<th>28 days to 23 months</th>
<th>2 to 11 years</th>
<th>12 to 17 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature baby</td>
<td>Erythema</td>
<td>Drug ineffective</td>
<td>Drug ineffective</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Pruritus</td>
<td>Erythema</td>
<td>Suicidal ideation</td>
</tr>
<tr>
<td>Neonatal disorder</td>
<td>Irritability</td>
<td>Decreased appetite</td>
<td>Suicide attempt</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Medication error</td>
<td>Psychomotor hyperactivity</td>
<td>Completed suicide</td>
</tr>
<tr>
<td>Blood lactic acid increased</td>
<td>Drug ineffective</td>
<td>Abdominal pain upper</td>
<td>Depression</td>
</tr>
<tr>
<td>Foetal growth retardation</td>
<td>Accidental overdose</td>
<td>Aggression</td>
<td>Erythema</td>
</tr>
<tr>
<td>Medication error</td>
<td>Drug toxicity</td>
<td>Somnolence</td>
<td>Nausea</td>
</tr>
<tr>
<td>Hypertriglyceridaemia</td>
<td>Lethargy</td>
<td>Crying</td>
<td>Intentional overdose</td>
</tr>
<tr>
<td>Feeding disorder neonatal</td>
<td>Eyelid oedema</td>
<td>Suicidal ideation</td>
<td>Loss of consciousness</td>
</tr>
<tr>
<td>Anaemia macrocytic</td>
<td>Respiratory arrest</td>
<td>Medication error</td>
<td>Feeling abnormal</td>
</tr>
</tbody>
</table>

The adverse reactions listed in each age group are sorted according to the greatest differences in percentage units between two time periods (January 2005 to February 2010 versus January 1995 to December 1999). Percentages were calculated based on the number of reports with the adverse reaction in the time period and age group divided by the total number of reports in the time period and age group. The percentages for each reaction during 2005 to February 2010 were then contrasted with the percentages during 1995 to 1999. The adverse reactions listed for ages 0-27 days can refer to foetal medicine exposure or medicine exposure of neonate.
Medication error and related terms had been reported with a greater frequency during recent years. The five most frequently reported medicines with these terms for ages 0-17 years are listed in Table 10.

Table 10. The five most frequently reported medicines by medication error and related terms for ages 0-17 years during recent years (January 2005 - February 2010)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranitidine</td>
<td>67</td>
<td>Paracetamol</td>
<td>64</td>
<td>Paracetamol</td>
<td>68</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>64</td>
<td>Oxycodone</td>
<td>50</td>
<td>Diphenhydramine</td>
<td>32</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>37</td>
<td>Atomoxetine</td>
<td>42</td>
<td>Dextromethorphan</td>
<td>30</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>28</td>
<td>Ibuprofen</td>
<td>40</td>
<td>Pseudoephedrine</td>
<td>27</td>
</tr>
<tr>
<td>Budesonide and Lamotrigine</td>
<td>25</td>
<td>Morphine</td>
<td>29</td>
<td>Methadone</td>
<td>25</td>
</tr>
</tbody>
</table>

The figures do not add up, since one report can be recorded with more than one medicine.

The majority of terms reported more frequently during recent years (compared with the earlier time period) for the 2 to 11 year olds, in addition to many of the events reported for the adolescents, were related to centrally acting sympathomimetics (medicines used for ADHD). Drug ineffective was most commonly reported with atomoxetine and methylphenidate (both used for ADHD). The term drug ineffective could be used when the intended effect of a medicine fails an individual patient. Atomoxetine and methylphenidate have moved up to be represented among the ten most frequently reported medicines for the paediatric patients over the years. Table 11 displays the most frequently reported medicines before and after 2005 for ages 0-17 years.

Table 11. The ten most frequently reported medicines before and after 2005 for ages 0-17 years

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefaclor</td>
<td>6900</td>
<td>Atomoxetine</td>
<td>6405</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>6504</td>
<td>Amoxicillin</td>
<td>3519</td>
</tr>
<tr>
<td>Sulfamethoxazole/Trimethoprim</td>
<td>5223</td>
<td>Ibuprofen</td>
<td>2304</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>4882</td>
<td>Methylphenidate</td>
<td>2057</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>4321</td>
<td>Paracetamol</td>
<td>1887</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>3803</td>
<td>Sulfamethoxazole/Trimethoprim</td>
<td>1674</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>3569</td>
<td>Oseltamivir</td>
<td>1657</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>3552</td>
<td>Lamotrigine</td>
<td>1498</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>3180</td>
<td>Isotretinoin</td>
<td>1476</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>2381</td>
<td>Montelukast</td>
<td>1423</td>
</tr>
</tbody>
</table>

The figures do not add up, since one report can be recorded with more than one medicine. The top reported medicines reported before 2005, which were not listed among the top ten reported medicines after 2005 are given in italics. The medicines reported after 2005, which were not listed among the top ten reported medicines before 2005 are given in bolded text.
Figure 5 displays the cumulative reporting by year of entry in VigiBase for the ten most frequently reported medicines for paediatric patients accumulated from 1968 to February 2010.

**Figure 5.** Cumulative reporting by year of entry in VigiBase (start 1968) for the ten most frequently reported medicines in paediatric patients (0-17 years) in February 2010
In-depth evaluation of a serious adverse reaction (Study II)

Twenty reports with rhabdomyolysis suspected to be induced by antipsychotic medicines were retrieved from VigiBase and the published literature. Reports with rhabdomyolysis in the absence of neuroleptic malignant syndrome were evaluated in more depth. Table 12 presents the characteristics of the twenty cases.

Table 12. Summary of reports for children and adolescents with rhabdomyolysis (in the absence of neuroleptic malignant syndrome) reported with antipsychotic medicines

<table>
<thead>
<tr>
<th>Report variable</th>
<th>Case summary results</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. reports</td>
<td>20</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>14.5 years (6 to 17)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>16/4</td>
</tr>
<tr>
<td>Suspected antipsychotic medicine</td>
<td>Olanzapine, risperidone, haloperidol, paliperidone, quetiapine, clozapine, cyamemazine, aripiprazole</td>
</tr>
<tr>
<td>Examples of reported indication for antipsychotic medicine</td>
<td>Bipolar disorder, schizophrenia, obsessive compulsive disorder</td>
</tr>
<tr>
<td>Symptoms prior to rhabdomyolysis diagnosis</td>
<td>Abdominal and muscle pain (extremities, facial, back); weakness and walking problems; dark urine; diaphoresis; vomiting</td>
</tr>
<tr>
<td>Time from start of medicine to onset of rhabdomyolysis</td>
<td>At varying times within 2 months after medicine start</td>
</tr>
<tr>
<td>Possible additional triggering factors for rhabdomyolysis</td>
<td>Intramuscular injection, other antipsychotic medicines added, dose increase, seizure, strenuous physical activity</td>
</tr>
<tr>
<td>Dose</td>
<td>Five patients were recorded with daily doses in the higher range of what is recommended</td>
</tr>
<tr>
<td>Co-reported renal problems</td>
<td>Two patients were recorded with acute renal failure and one patient with renal insufficiency</td>
</tr>
<tr>
<td>Outcome</td>
<td>16 patients recovered/were recovering on the day of report. Four reports included limited information on outcome.</td>
</tr>
</tbody>
</table>

In VigiBase, rhabdomyolysis (in the absence of NMS) was reported disproportionally more with olanzapine compared with all reports for children and any antipsychotic medicine.

Two published cases among the 20 cases were especially noteworthy regarding the delayed detection of the ADR. One 13-year-old boy started to experience weakness, sore throat, abdominal cramping, muscle pain and
diaphoresis after treatment with olanzapine, which progressed to inability to take part of activities whilst in residential care.\cite{145} The residential care staff interpreted his behaviour as disobedience and he received more medications. The boy became progressively worse during 3 weeks and was admitted to hospital where he was diagnosed with olanzapine-induced rhabdomyolysis. The other example is for a 6-year-old boy, whose mother had noted that the boy had dark urine off and on for 2 months after starting haloperidol treatment.\cite{146} The boy was subsequently examined and diagnosed with rhabdomyolysis.

In Study II, we found that ICSRs could contribute valuable information to describe the clinical circumstances surrounding rhabdomyolysis in children and adolescents. However, access to case narratives was crucial to capture information about the circumstances around the event, laboratory values, and treatment of the reaction. Medical history and underlying risk factors were sparsely recorded on the ICSRs.

The importance of age-suitable dosage form for prescribing (Study III)

A total of 21,473 prescriptions with NSAIDs were studied for children between 2 and 11 years, of which 50% were prescriptions for boys. The number of prescribed NSAID substances by dosage form evaluated in Study III is presented in Table 13.

Table 13. Number of prescribed NSAID substances by dosage form included in Study III

<table>
<thead>
<tr>
<th>Substance</th>
<th>Dosage form</th>
<th>No. Prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>Tablet or Capsule</td>
<td>2201</td>
</tr>
<tr>
<td></td>
<td>Liquid</td>
<td>18652</td>
</tr>
<tr>
<td></td>
<td>Granules</td>
<td>2</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Tablet or Capsule</td>
<td>227</td>
</tr>
<tr>
<td></td>
<td>Suppository</td>
<td>23</td>
</tr>
<tr>
<td>Indometacin</td>
<td>Tablet or Capsule</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Liquid</td>
<td>7</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>Tablet or Capsule</td>
<td>162</td>
</tr>
<tr>
<td></td>
<td>Liquid</td>
<td>79</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Tablet or Capsule</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Liquid</td>
<td>40</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Tablet or Capsule</td>
<td>24</td>
</tr>
</tbody>
</table>

The major finding of the multiple linear regression analysis was that the rPDD varied considerably with the prescribed dosage form. Tablets or capsules were prescribed with higher doses than liquid dosage forms with a mean adjusted difference in rPDD of 0.17 in the ibuprofen group and 0.75 in
the other NSAIDs analysed as one group. In mg, the rPDD of 0.17 for ibuprofen corresponds to a difference of 204 mg and an rPDD of 0.75 corresponds to 75 mg diclofenac or indometacin; 750 mg mafenamic acid; 375 mg naproxen; and 15 mg piroxicam. The difference between doses of tablets or capsules and liquid dosage forms was particularly noticeable in preschool children.

Complexities of preparing and administering medicines (Study IV)

The twenty nurses working within paediatric care gave examples of the complexity in preparing and administering medicines to paediatric patients, with dosing needing to be adjusted to each individual child. A nurse in paediatric medication care emerged as someone who had to take the responsibility for inadequate decisions made in the long chain of activities in the medication delivery process.

Six themes evolved from the interviews:

- The complexity specific for nurses working on paediatric wards is a hindrance to safe medication practices.
- Nurses’ concerns about medication errors cause a considerable psychological burden.
- The individual nurse works hard for safe medication practices and values support from other nurse colleagues.
- Circumstances out of the ordinary are perceived as critical challenges for maintaining patient safety (for example unfamiliar medicine and emergency situations).
- Nurses value clear instructions, guidelines and routines but these are often missing, variable or changeable.
- Management, other medical professionals, the pharmacy, the pharmaceutical industry and informatics support need to respond to the requirements of the nurses’ working situation to improve safe medication practices.

Clear dose instructions to prepare and administer medicines were not always easily available. The nurses gave examples of computerized physician order entry systems that were insufficient for recordings of paediatric dosing; generic products, temporarily replacing a branded product used on the ward, that differed in shelf life and even strength, making them incompatible with current standardised dose instructions; and delayed administration of medicines due to long and complicated product descriptions that needed to be searched in order to find instructions relevant specifically for nurses.
Discussion

The most striking discovery in Study I was the increase of reports relating to medication errors, and the dominance of reports for ADHD medicines received during recent years. In Study II stressed the need for increased monitoring of any unexpected symptom following initiation of a medicine, and involving parents, patients and other care givers. Study II also found that ICSRs could contribute with clinically valuable information of the circumstances around the onset of the rare adverse reaction evaluated. The results in Study III emphasised the need to further develop age-suitable dosage forms of medicines. Study IV described that nurses were often left to solve the inadequacies of pharmacological treatment in paediatric care.

Areas of special focus to be considered in signal detection

The significant patterns of reports for paediatric patients seen in Study I, considering the group as a whole compared with adult reports, and also the specific pattern reported for each child age group, suggest the importance of performing age group specific signal detection in VigiBase as a complement to screening the complete database. The use of paediatric age groups as a reference when generating disproportionality measures should also be assessed as an additional step to routine screening. In planning for signal detection in data for paediatric patients, consideration should be given to focussing on reports from emerging PVCs with higher proportional reporting for paediatric patients (Study I), although this reporting pattern could be related to the different age distributions in these parts of the world.

Skin reactions, such as rash and urticaria, were commonly reported for the paediatric patients in Study I, which has been noted in many other studies in paediatrics reviewing reported ADRs. Specific serious skin reactions, such as erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in VigiBase proportionally more in reports for paediatric patients than in reports for adults. Serious skin reactions might be recognized as induced by a medicine and lead to reporting to a higher extent for children than for adults. Medicines with a higher risk of serious skin reactions could also be used or initiated more frequently in children than in adults, such as anti-infective sulphonamides, phenobarbital, carbamazepine and lamotrigine. Serious skin reactions should be considered for special review in VigiBase.
The increased reporting of ADHD medicines seen in Study I, especially for atomoxetine, could be because the medicine is newly marketed and therefore intensely monitored. However, compared with montelukast, which also is a fairly newly marketed medicine and is used for common diagnoses in children - allergy and asthma, the increase was considerably more. The increased reporting for atomoxetine could result from US FDA warnings about an increased risk of suicidal thinking in 2005,[150] and a possible risk of cardiovascular and psychiatric ADRs in 2007.[151] In addition, the increased prescribing of ADHD medicines seen during recent years could have stimulated reporting.[152] Parents might have a low tolerance of ADRs for these medicines and report ADRs to a higher extent when the medicine does not meet their expectations.

Frequently reported events for the ADHD medicines were: aggravated or added psychiatric symptoms, such as psychomotor hyperactivity, aggression, and drug ineffective. These events may indicate unexpected treatment failure. Therapeutic ineffectiveness could result from the use of suboptimal doses or from off-label indications.[63] Medicines developed specifically for paediatric patients might be ‘over prescribed’ for other diagnoses. ADHD medicines could be prescribed for a depressed youth (in the limited choice of anti-depressants specifically available for children), resulting in reports of lack of effect or suicide-related events. In this context, it is worth mentioning that all children with ADHD do not respond to the therapy. In a cross-over study, the response rate was 56% for methylphenidate and 45% for atomoxetine.[153] Around 40% of the non-responders in the two treatment groups, did respond to treatment when they were switched to the other medicine.[153]

The increase in reporting for females during adolescence has been noted in earlier reviews of VigiBase.[154, 155] The disproportionate patient sex distribution, where adult females represent around 60% of the reports in VigiBase, is consistent across nations and over time. It is interesting that the predominance of female reports starts during puberty when the biological diversion of the sexes occurs. This suggests that biological differences could make females more susceptible to ADRs.[156, 157] It may be important to consider both the stage in puberty and patient sex when prescribing medicines for adolescents.[56] Near adult appearances in adolescents might be deceptive and lead to thinking that dosing could equal that in adult treatment. It could be worth emphasising that children, including adolescents, are not little adults.

Sources of information of rare adverse drug reactions
Study II illustrated that ICSRs, in addition to published case reports, can contribute with clinically valuable information to increase our understanding of an ADR. VigiBase contains de-identified information primarily in
structured format. If the fields are filled in correctly, a very informative report can be retrieved. However, much information on ICSRs is recorded as a free text narrative, which is most often available only at the national PVC. In many cases these “narratives” generate a fuller picture of the situation (Study II). ADR narratives are accessible for about 11% of the VigiBase reports for UMC internal use. There is a long history of sharing narratives by physicians in published case reports but the publication process can result in delayed publicly-available information. Therefore, access to ICSRs outside the regulatory realm could potentially benefit the paediatric health care community. However, the reports need to be of good quality. When ICSRs are well documented, a more comprehensive description of ADRs can be communicated to health care personnel, parents and patients. The description could cover, preceding signs or symptoms of the ADR, when in time the event is most likely to occur from medicine start to ADR onset, and if there are patient risk groups/factors needing particular caution. The need for good quality reports applies particularly to ADRs where the causal relationship is under assessment, such as for signals. If signals were to be communicated to health care personnel more actively and with more information than today, the uncertainty of the link between the medicine and event would need to be clarified and reasoning around the issue transparent.

Capturing early symptoms to prevent serious consequences

The uncertainty of prescribing and administering medicines within paediatric care requires increased watchfulness of emerging ADRs or medication errors in connection to medication use, and especially during dose regimen changes as was seen in Study II. Even seemingly non-serious ADRs such as unexpected abdominal pain should be followed up during medicine use (Study II). Constipation is another example that might seem like a non-serious ADR but that can develop into being so severe as to require hospitalization. With any unexpected symptom in a paediatric patient, the possibility of a medicine-related problem should at least be considered. The vigilance should not be restricted to the prescriber but involve other health care professionals, parents, other care givers, and for the older children, the patients themselves, who should be informed to monitor for possible ADRs. This requires an open mind by health care personnel and parents/care givers. Unexpected signs or symptoms do not necessarily relate to an ADR but could be associated with the underlying disease, or to the normal developmental changes of the growing child, and might be difficult to distinguish from an ADR. However, the parent should be encouraged to discuss any changes in the child with the clinician. Nurses interviewed in Study IV highlighted the importance of being perceptive to comments from nurse assistants, parents or children themselves as valuable forewarnings of
medication errors. The same thinking could be applied to watch for early symptoms and signs preceding ADRs in a patient (Study II).

In order for parents and children to be aware of the possibility of ADRs, they need information. Clinicians’ communication about problems with medicines can be poor, as described in a recent interview study of parents to children with ADRs, although parents to children with cancer were generally satisfied with the information they received about ADRs. ADRs are common within oncology and clinicians might be more used to dealing with problems of medicines, resulting in better communication. In the interviews of oncology nurses in Study IV, it was very apparent that ADRs were integral to the clinical picture of their patients. There is such a fine balance between the non-toxic and toxic effects of cancer treatment that accounting for ADRs in treatment was a natural part of care. It might also be easier for oncologists to describe risks of cancer treatment in light of the often life-saving cancer treatment. Information about uncertain and rare ADRs might be much more difficult to communicate to parents, especially when there is a risk that the patient might not comply with the dose regimen because of fear of ADRs. Further investigation is needed to evaluate how to best communicate possible ADRs to parents of children on medication therapy, or children old enough to be involved in the risk-benefit discussion concerning their medicines.

Vigilance in prescribing and administering medicines

Situations that require increased vigilance are when suboptimal dose formulations are used, such as using tablets and capsules in young children. The type of dosage form seems important not only to enhance uptake and administration of a medicine but also to prescribe an appropriate dose, as highlighted in Study III. Non-suitable dosage forms prescribed for a child should be followed up by increased monitoring. Is the child able to take the medicine? Is the parent or nurse able to administer the correct dose? Should the pharmacist be contacted to prepare an extemporaneous formulation? In Study IV, the interviewed nurses’ gave examples of crushing tablets according to her/his best knowledge, or left with an uncertainty of whether the very small amount of medicine administered via a narrow gastric tube had reached the patient. Increased effort is needed to follow-up on the nurses’ and parents’ medicine administration and the ability for the child to take the medicine to pinpoint particular medicines, dosage forms or administration devices that need to be modified to better suit the child population.

The nurses in Study IV identified factors that both hindered and helped them to maintain safe medication practice. They acknowledged situations where they felt they should be extra vigilant for errors, such as when giving an unfamiliar medicine for the first time. The nurses had developed solutions
suited for their ward to prevent mistakes. However in one example, a ward used only red cups for inhalation liquids, whereas a nurse coming from a different hospital was used to having morphine in red cups. Safety strategies are developed but need to be evaluated, and the work would benefit from a national collaboration to achieve consistency and prevent double-work.

**Patient safety and pharmacovigilance**

This thesis investigated problems relating to ADRs and medication errors. These problems are most often evaluated and dealt with within two different paradigms, of which one consists of regulators and manufacturers working for safety of medicinal products, and the other, the national or regional health care organisation working for safety of patients in health care facilities. Both systems depend on health care professionals to report medication errors/ADRs. In neither system of compiled reports is it possible to know the extent of a problem accurately. In addition, both systems suffer from under-reporting.[137, 164] Within the medication error area, the prevention of a problem is emphasized and therefore the focus is to determine the root-cause of an error (seek to understand the underlying and contextual cause of the medication error),[165] thus to know what improvements in health care systems should be made. The primary aim of ADR reporting is to detect and understand new ADRs not identified in the pre-marketing clinical studies. Therefore, the focus is very much on determining whether the pharmaceutical substance is the cause of the reported event (causality assessment). The collection of ADRs is usually based on a global collaboration and medication errors are most often collected regionally/nationally. The two systems could be developed and improved in light of each other. The pharmacovigilance definition emphasizes prevention but in the collection of details around an ADR this aim is not visible since the collected information concerns patient demographics, details of the medicine and adverse reaction and very limited information is given on the circumstances around the event.[166] It is both feasible and essential to start collecting information specifically related to preventability,[79, 167] so that systematic errors can be rectified by regulators, pharmaceutical companies and health care organizations working together. In 2007, the World Alliance for Patient Safety in collaboration with the UMC and the Moroccan PVC started a pilot project to investigate the role of the PVC in collecting reports relating to medication errors.[79] The WHO, the Moroccan PVC, the UK National Patient Safety Agency and the UMC are currently leading a project on how the role of a PVC can be expanded to identify and analyse medication error reports to impact changes in health care.[168]

Spontaneous ADR reporting systems might be particularly important to capture medication errors occurring in the out-patient setting as indicated by an evaluation of medication error reports in the New Zealand
pharmacovigilance database.\textsuperscript{167} Specific medication errors, relating to use of error prone products in sub-populations, such as children, might not be acknowledged as a significant problem at a national level but instead be more easily detected in a global collection of medication errors. An example of a medication error detected in VigiBase and communicated as a WHO Signal was the maladministration of a vaccine against rotavirus to prevent gastroenteritis in infants.\textsuperscript{169} There are two products of this vaccine on the market and both should be given orally. One vaccine is administered with a dosage tube and the other with a syringe (no needle). The latter was shown to be a more error prone administration device, since it caused the vaccine to be administered intramuscularly instead of orally. After marketing, the manufacturer of this product has been involved in trying to improve both product information and device, but the error continued to occur. This medication error, executed by health care professionals, could probably have been prevented by having a less ambivalent administration device. Only a few cases of this problem had been reported in each of five countries thereby making them less likely to be captured nationally. This example showed that global collection of reports can be useful in the detection of an error-prone administration device. However, it is unknown whether the communication of that signal reached health care organisations, since the distribution of the WHO Signal document at the time was restricted to national PVCs within the WHO Medicines Safety Programme. The national PVCs decide how or if signals should be communicated further.

Information channels between organisations working with safety of medicines and health care, including patients, need to be investigated and improved. Quality reports from health care on problems relating to medicines is the start of a communication loop, with the circle closed when clinically useful information has been contributed to health care and patients. This improvement might be particularly important within paediatric health care, since its activities can fall outside the responsibility of the regulatory authorities and manufacturers.

\section*{Methodological considerations}

\subsection*{Individual case safety reports (Studies I and II)}

The number of ICSRs given in Studies I and II of accumulated ICSRs does not correspond to the general occurrence of the problem in a population but represents \textit{reporting} of ADRs. Compilations of ICSRs lack denominator information, particularly of worldwide medicine use. Sales data for individual medicines can be acquired from individual analyses, but to obtain such data for all products in VigiBase is impractical. Even if medicine use data was available, a population-based frequency of ADRs would not be
correct because of the existence of underreporting of ADRs. The reporting depends on the ADR being recognized by the patient and/or health care professional and the report being sent to the national PVC: thus ADRs are very likely to be underreported.\textsuperscript{137, 170} Only about 6\% of ADRs are reported to the pharmacovigilance collection systems.\textsuperscript{137} The most common reasons for underreporting, as described in a literature review of 45 studies where the authors used categories of physicians’ attitudes towards not reporting as previously described by Inman\textsuperscript{171} were: ignorance of the requirement of reporting (95\% of the studies); hesitancy to report only suspicions (72\%); lethargy or procrastination, lack of interest or time (77\%); indifference and insecurity or impossible to know if an ADR occurred (67\%); complacency or thinking that only safe medicines are marketed (47\%); and fear of litigation (24\%).\textsuperscript{172} The lack of a denominator for the reports in VigiBase and the existence of underreporting have lead to the use of disproportionality measures where a group of reports with a specific medicine and ADR are contrasted to the general reporting pattern in the database (described in detail in the ‘Materials and methods’ section’).\textsuperscript{105, 110}

The information collected on ICSRs is not adjusted to specific diseases, medicines or groups of patients; therefore data that is important specifically for the analysis of reports on paediatric patients can be limited. By reviewing only the coded terms for the youngest age group in VigiBase (Study I), it was not always possible to determine if the event was related to exposure to medicines via placenta or exposure in a neonate. Another limitation was that an age referring to a premature baby could not be determined by reviewing only the age field. To give clarity to these uncertainties, a case by case evaluation would be needed to review the free-text, or even the list of events where terms such as ‘Premature baby’ and ‘Foetal exposure during pregnancy’ can be coded.

The evaluation in Study II was dependent on quality information on individual reports. Information on ICSRs can be missing. The reporter may leave specific information unrecorded because of time constraints, forgetfulness, or the impression that specific details are unimportant to the case. Information can also be filled in erroneously. Continuous efforts are being made to increase the quality of reports within the pharmacovigilance system and VigiBase.\textsuperscript{131, 173, 174}

An additional constraint when using ICSRs in research is the heterogeneity of data, particularly in quantitative analyses. The collected information on the ICSRs can vary across regions and concern suspected ADRs with varying strengths of causal relationship to the medicine. The quality and level of information varies from report to report. Reporting can also vary over time and increase following attention to problems from the public media, or because of intense monitoring when the medicine is recently marketed or being withdrawn because of a safety issue.\textsuperscript{175}
In spite of various shortcomings in the spontaneous reporting of ADRs, they constitute a valuable source for hypothesis generation of potential safety problems and contribute to the further characterisation of ADRs. Rare ADRs seldom present themselves in pre-marketing studies (hence risk management planning and the intensive monitoring for previously unknown ADRs at the time of marketing of a new medicine) or not even in large collections of electronic health records. For some reactions and populations, ICSRs could be the only source of information available to give further information about an ADR. The strength of VigiBase is its worldwide coverage of reports, which enables detection of rare reactions or reactions occurring only in subpopulations. The database can be used to study problems that take place in any clinical setting (hospital or outpatient), that are caused by any type of medicine (prescription, off-label, misuse, non-prescription, including herbal medicines), that are produced by any manufacturer, that are reported by any health professional or patient, and that take place in any of 111 countries around the world. The database undergoes continuing development and testing and has been used for over 40 years to detect emerging medicine safety problems.

Electronic health records (Study III)

Study III included prescriptions restricted to 1988 to 2005; hence further development of formulations might exist. In the electronic health records used in the NSAID dose study, it is neither possible to ascertain whether the patient actually took the prescribed dose of the medicine nor to verify potential recording errors. A limitation of Study III was that patient weight at time of prescription and indication of use were not always specified in order to determine if the prescribed dose for the individual patient was too high or low. The general patterns for the prescribed doses by age groups were instead the focus in this study.

Multiple linear regression analysis was used to investigate what variables influenced the prescribed dose in Study III. As with most observational data of this kind, an assumption of normality will to some degree be incorrect. However, multiple linear regression is one of the core tools when analyzing several potential explanatory variables simultaneously. Because of its usefulness, we opted to use this method, knowing that certain assumptions are likely to be violated, which could affect estimates. At the same time we have clearly disclosed the implicit assumptions needed for this methodology. Therefore it is reassuring that all stratified non-parametric graphical analyses that we present as a complement to the regression unanimously support our main message: there is a consistent pattern of higher doses in tablet prescriptions than in liquid prescriptions. The question of the exact magnitude of the difference then becomes secondary, and the small biases
that are likely to be present in the regression estimates are negligible with respect to the overall conclusion.

Focus group interviews (Study IV)
The analysed interview material in Study IV was extensive. To conform to the word limitation of the journal where it was submitted, the supportive quotes within each theme were placed in an appendix. We intentionally chose to publish in a biomedical journal to reach a wide range of health care professionals working in paediatric medication practices.

Nurses from neonatal care represented two focus groups in Study IV, possibly influencing the results towards medication practices specific for very young children. The situation for nurses working in paediatric oncology and psychiatric care might benefit from being reviewed in a separate study to describe more in-depth the specifics of their medication practices.

To perform focus groups with participants from the same ward can mean that they do not mention topics which they take for granted. The interviewer therefore asked the participants to expand on comments that were raised. A group of colleagues knowing each other might not willingly share mistakes, since it could result in later consequences. This did not seem to be a considerable problem in the groups interviewed, since personal mistakes were shared in all groups.

Four of the five interviews were performed with only one interviewer, which limited the possibility to visually observe the group dynamic in more detail. However, it was possible to register nuances and feelings from the recorded interviews. In addition, the groups were small, including only 3 to 5 participants, and it was reasonable to manage with one moderator.

Study IV was the only study in this thesis that focused on a specific health care discipline. Nurses in paediatric care were interviewed because descriptions of their particular challenges in medication practice have had limited coverage in biomedical journals. Nurses were included also because they are less represented within pharmacovigilance. Nurses can contribute knowledge particularly concerning medication administration and highlight where changes are needed to improve safe medication practices.
Conclusions

• In planning for signal detection processes for paediatric patients using VigiBase, particular consideration should be given to: serious skin reactions; events related to medication errors; psychotropic medicines; and problems from emerging pharmacovigilance centres (Study I).

• Study II indicated that it is possible to learn about the circumstances around the event in ICSRs to get clues on whether and how the event could be prevented in future. Evaluations of ICSRs have the potential to be used beyond causality assessment (is the medicine the cause or not?). Efforts are needed to increase the quality and the accessibility of de-identified detailed clinical information globally.

• Prescribers of medicines to paediatric patients should be aware that absence of age-suitable dosage forms can influence how accurate the prescribed dose will be (Study III).

• Involve paediatric nurses at an early stage when structural changes are planned on the ward, such as introducing computerized order entry systems or generic products (Study IV).

• Involve paediatric nurses to review and test administration devices, packaging, labelling, and instructions for administration in the product information (Study IV).

• Facilitate national collaboration between hospitals caring for paediatric patients, involving all health care personnel (physicians, nurses and pharmacists), to advance best medication safety practices (Study IV).
Future development and research

• Separate processes need to be developed to screen for age-specific adverse reactions in paediatric patients.
• Further research is needed to know how to best inform parents about highly uncertain ADRs to avoid non-adherence and medicine scares.
• Studies are needed on how to best educate parents and older children to monitor for ADRs.
• Continue the on-going work by regulators to increase the number of clinical studies in children with the purpose of enhancing the evidence for the suitability and the documentation of medicines specific for paediatric patients. Hopefully the resulting information will be adjusted to parents/care givers actually administering the medicine and to clinicians – who often work in fast-paced and short-staffed environments.
• Continue to develop age-suitable formulations for paediatric patients.
• Develop strategies for improved information channels between health care and medicines safety organisations.
Svensk sammanfattning (Swedish Summary)

**Bakgrund:** Läkemedel som enbart är studerade på vuxna kan ibland behöva användas till barn. Nästan hälften av alla läkemedelsföreskrivningar till barn saknar fullgod anvisning om dosering, kontraindikationer och biverkningar. När ett läkemedel primärt är framtaget för vuxna kan det sakna lämplig administrationsform avsett för barn. Mot denna bakgrund torde läkemedelssäkerhet vara särskilt viktig inom barnsjukvården.

**Syfte:** Denna avhandling ämnar undersöka internationellt rapporterade biverkningar för barn, både övergripande och i ett specifikt fall, samt belysa vilka utmaningar som förskrivning och administrering av läkemedel till dessa patienter utgör. Den utökade kunskapen syftar till att identifiera och föreslå områden som kan behöva särskild biverkningsövervakning på internationell nivå, samt som kan behöva utvecklas i klinisk verksamhet.

**Metoder:** Fyra explorativa studier genomfördes. En övergripande analys av biverkningsrapporter från WHOs globala biverkningsdatabas (VigiBase) på barn (0 till 17 år) utfördes (rapporter gällande vacciner var exkluderade). En fallserie med tjugo publicerade fallrapporter och biverkningsrapporter för barn och ungdomar med antipsykotikabehandling som utvecklat rabdomyolys, en sällsynt och ofullständigt beskriven biverkan bland barn, beskrevs ingående. Förskrivna doser av antiinflammatoriska läkemedel undersöktes i en engelsk patientjournaldatabas för att utröna vad som påverkade dosvariationer. Transkriberade fokusgruppintervjuer med 20 sjuksköterskor från fyra barnavdelningar i Sverige analyserades med avseende på vilka faktorer som kan främja eller hindra en patientsäker läkemedelshantering. De fyra studierna analyserades med beskrivande statistik, multipel regression, och innehållsanalys.

**Resultat:** Av rapporterna i VigiBase gällde 7.7% misstänkta biverkningar på barn. Hudreaktioner och infektionsläkemedel var mest frekvent rapporterade för barn. Dessa biverkningar och mediciner var proportionellt mer rapporterade bland barn i jämförelse med rapporter bland vuxna. Felmedicinering och liknande händelser samt biverkningar för psykostimulantia var rapporterade med ökad frekvens under senare år (january 2005 till februari 2010). Felmedicinering gällde ofta yngre barn och rapporter på psykostimulantia gällde de äldre. Fallserieanalysen av rapporter
med antipsykotikainducerad rabdomyolys betonade behovet av ökad vaksamhet hos förskrivare, förälder eller annan vårdgivare vid förändringar av barnens medicinering, såsom ökad dos, tillagda eller utbytta läkemedel. Fallserieanalysen visade även att biverkningrapporter kunde bidra med kliniskt värdefull kunskap om, i detta fall, en ovanlig biverkan. Dosvariationer bland förskrivningar av antiinflammatoriska läkemedel var associerade med den förskrivna administreringsformen. Tablett och kapslar var förskrivna med högre doser än förskrivningar med flytande administreringsform. Skillnaden var särskilt stor bland förskolebarn. Sex teman framkom ur sjuksköterskornas intervjuer och sammanfattas som att: beredning och administrering var ett komplicerat moment som måste anpassas efter varje enskilt barn; felmedicinering eller ’nästan fel’ orsakade stor psykologisk börda; stöd från sjuksköterskokollegor värderades högt i säkerhetsarbetet; läkemedel eller situationer utöver det vanliga upplevdes som riskfyllda; tydliga dosinstruktioner och rutiner var viktiga; sjuksköterskors läkemedelshantering borde ges högre prioritet.

Slutsatser: De specifika mönster som identifierades bland rapporter på barn, jämfört med rapporter på vuxna och även mönster som framträde inom olika åldersgrupper för barn ger underlag för att läkemedelsövervakning bland globalt insamlade biverkningsrapporter specifikt på barn behövs. För att utöka kunskapen om biverkningar hos barn där begränsad dokumentation föreligger föreslås att väldokumenterade biverkningssyntaxer kan pröva att användas för att inhämta kliniskt värdefull information. Tillgång till åldersanpassad administreringsform är viktig för att kunna förskriva en lämplig dos till barn. För att främja en patientsäker läkemedelshantering inom barnsjukvården föreslås att resurser till en nationell koordinering av kunskap vad gäller barn och läkemedel upprättas som innefattar representanter från all hälso- och sjukvårdspersonal som arbetar med barn.
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