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OFF-LABEL DRUG USE, MEDICATION ERRORS AND ADVERSE DRUG EVENTS – AMONG SWEDISH PEDIATRIC INPATIENTS

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Till Maria, Doris och Alfred

”Ett fel närmare rätt”

[Den Svenska Björnstammen]

ABSTRACT

Background: In pediatrics, treatment with drugs is an important and fully integrated part of everyday medical practice. However, authorized drugs specified to be used in children are often lacking which leads to off-label use, i.e. outside of approved product monographs. Another challenge is medication errors (ME) which is an important cause of adverse drug events (ADE) in hospitalized children. The consequences and effects of these conditions are largely unknown. Studies within the field of pediatric, and especially neonatal, drug safety are lacking. Unsafe drug use may be an important and unrecognized contributor to suboptimal health in this vulnerable group with limited capacity for drug metabolism and excretion.

Aim: The general aim of the thesis was to explore the magnitude of drug safety issues within Swedish pediatric inpatients. More specifically we aimed to investigate; I. National extent of off-label drug-use, II. Contents in national ME incident reports, III. Type of ADEs in a pediatric inpatient setting and IV. The views of pediatricians on a clinical decision support system (CDSS) to aid in prescribing drugs.

Methods: In the four papers we used different study approaches. In paper I we performed a descriptive cross-sectional study based on collection of drug charts during two time-points. In paper II we used an analytic cross-sectional register-based study on Lex Maria incident reports and complaints from the Health and Social Care Inspectorate. In paper III we carried out a cohort study using a chart review with a pediatric trigger tool covering 600 admissions stratified in four different units, and in paper IV we used qualitative semi-structured interviews with pediatricians.

Results: Paper I showed that half of all drug orders received by pediatric inpatients was outside approved product monographs, extemporaneously prepared or unlicensed. In paper II the ME reports indicated frequent occurrence of substances from three previously known high-alert lists with specified error characteristics among the different drug handling processes. In paper III we showed that skin/tissue/vascular harm, omission of analgesic drug therapy and hospital acquired infections are the most abundant ADEs as identified by an extended set of medical record triggers. In paper IV the CDSS-experiences of pediatricians emerged into six categories being: use, benefit, confidence, situations of disregards, misgivings/risks and development potential.

Conclusions: Paper I found a similar situation in Sweden regarding off-label and unlicensed drug use as in many other countries. Paper II found that the existing high-alert lists are relevant for pediatric inpatients and suggested the use of process dependent high-alert lists. Paper III found that ADEs are common in pediatric inpatients and that the incidence varied with ADE-type, depending on ward and time after admission. In paper IV the experiences of pediatricians after the implementation of a CDSS gave insights on usability and the need for future developments.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following publications, which will be referred to in the text by their roman numbers.

I. Kimland E, **Nydert P**, Odlind V, Böttiger Y, Lindemalm S.
Paediatric drug use with focus on off-label prescriptions at Swedish hospitals – a nationwide study
Acta Paediatr. 2012;101:772-8

II. **Nydert P**, Kumlien A, Norman M, Lindemalm S.
Cross-sectional study identifying high-alert substances in medication error reporting among Swedish pediatric inpatients
Acta Paediatr. 2020; [Epub ahead of print] doi:10.1111/apa.15273

III. **Nydert P**, Unbeck M, Pukk Härenstam K, Norman M, Lindemalm S.
Drug use and type of adverse drug events – identified by a trigger tool in different units in a Swedish pediatric hospital
Drug, Healthcare and Patient Safety 2020;12:31-40

IV. **Nydert P**, Vég A, Bastholm-Rahmner P, Lindemalm S.
Pediatricians' understanding and experiences of an electronic clinical-decision-support-system
Online J Public Health Inform. 2017;9(3):e200

CONTENTS

LIST OF ABBREVIATIONS

ADE	Adverse drug event
AE	Adverse event
ADR	Adverse drug reaction
ATC	Anatomic therapeutic chemical classification system
CDSS	Clinical decision support system
CI	Confidence interval
DDA	Number of days a dose was administrated for each substance by route
DRP	Drug-related problem
EMA	European medicines agency
EMR	Electronic medical record
ePed	Evidence- and experience based pediatric drug information system
HAMEC	Harm associated with medication error classification
HFMEA	Health-care version of the failure mode effects analysis
ICD	International classification of diseases
IQR	Interquartile range
IVO	The health and social care inspectorate
LF	The Swedish pharmaceutical insurance [Läkemedelsförsäkringen]
LOS	Length-of-stay
LÖF	Insures publicly financed health care providers [Landstingens ömsesidiga försäkringsbolag]
ME	Medication error
MPA	Medical products agency
NCC MERP	National coordinating council for medication error reporting and prevention
pADE	Preventable adverse drug event
PDCO	Pediatric committee
PIP	Pediatric investigation plan
RCA	Root-cause analysis
SRQR	The standards for reporting qualitative research
STROBE	Strengthening the reporting of observational studies in epidemiology
US	United States
WHO	World health organization

1 INTRODUCTION

Many have experiences with regards to patient safety, affecting dear-ones or ourselves as care-givers or patients. For me, a first-hand experience took place in the beginning of my adolescents. I was on a continuous treatment with oral corticosteroids due to a chronic inflammation in my right eye that blurred the vision. Of course, I remember the *adverse drug reactions* in my teens with the moon face and buffalo hump and the bitter taste of the ten prednisolone tablets a day. Meanwhile, the physicians worried over the systemic treatment affecting my growth and searched for alternatives. A Finish physician based in Helsinki had started with an *off-label* treatment injecting corticosteroid locally close to the eye (periocular). My parents arranged for a second opinion and we were lucky to get the opportunity to go to Finland. The first injection in Helsinki was scary but went well. Later, our local ophthalmologist was set to administer the rest of the monthly injections. He was probably terrified, because I was. Each time the syringe came close to my eye we took turns in calling it off, and we had to do the procedure several times until the injections could be carried out. But something went wrong. I guess the injection went into another compartment because suddenly I went completely blind on both of my eyes. I cried, and the physician screamed to the nurse "What was it in that syringe?". Luckily my normal vision came back after an hour or so, and no mix-up or other known *medication error* that caused the temporary *adverse drug event* could be identified. The physician decided, with our consent, to go back to the oral treatment with the known risk profile.

The field of patient safety is multifaceted and for research there is "*so many unanswered questions on patient safety, it is difficult for researchers to know where to start"* as described by Bates (1). The starting point for this thesis was the possibility given by the research school in clinical epidemiology, introducing a deeper understanding of statistics in health-care and how to handle the large amount of information that is entered daily into our electronic medical records (EMR). However, behind the numbers that are presented in this thesis there are patients and health-care staff with unique problems and situations. Articles describing the specific patient perspective are sparse with some exceptions (2-4). Among Swedish pediatric inpatients, two devastating mix-ups happened in Sweden during the 00s; one between different strengths of lidocaine and another in our hospital between isotonic and concentrated sodium chloride which both led to legal cases which have been reported elsewhere in detail (5,6). Those events came to form the way the pediatric drug therapy group at Karolinska University Hospital approach their work by building a system with a memory. At the time, patient safety was a topic starting to be recognized and reports as *To err is human* (7) and the pioneer work carried out by the Institute of Medication Safety Practice (ISMP) within drug safety was leading the way (8).

So, to build a system with a memory based on the known Swedish off-label prescriptions, errors and events within pediatrics became an idea that was developed together with several colleagues and professions. This idea later became the knowledge management system for evidence- and experience based pediatric drug information system called ePed (9). And to better understand the epidemiology of the drug-usage, -errors and -events, this thesis was initiated.

2 BACKGROUND

This background, or literature overview, is written as an introduction to the field of off-label drug use, medication errors (ME) and adverse drug events (ADE) among pediatric inpatients.

2.1 THE PEDIATRIC POPULATION

"Children are not small adults, but adults are large children" Lindemalm (10)

Today in Sweden 2 million inhabitants are children in the age-group 0-17 years which is approximately 20% of the population. 115 000 newborn infants are born each year and almost 7 000 are born preterm (before 37 completed weeks of gestation) (11).

The development of infant care during the last century has had a remarkable impact on the pediatric population with a decrease in infant mortality from 10 to 0.25% in Sweden (12). This achievement is multifactorial with high impact of vaccinations, antibiotics and the development of a social welfare state. In perspective, child mortality below five years of age was in 2002 more than 10% in over 40 countries and the major initiatives to establish better health-care and research for children in these countries are fundamental (13).

A primary determinant of health in the pediatric population is growth and it can be classified into four phases: intrauterine, infancy, childhood and puberty with a dependency of nutrition during infancy, growth hormone during childhood and sex steroids and growth hormone during puberty (12). Detecting abnormalities in growth is important for early intervention. As pediatric growth is not linear, drug dosing guidelines have tried to establish better understanding of the basal metabolic rate in relation to, for example body weight or surface area. Different scaling factors have been in use but have rarely been successful in the neonatal population or as a universal scaling factor for all drugs (14,15).

Regarding neonatal care in Sweden, 3.3 out of 1 000 infants are born extremely preterm (gestational age $\leq$27 weeks) and nowadays, the majority survives but 55% suffer severe neonatal morbidity (16). At an age of 2.5 years (corrected age i.e., chronological age reduced by the number of weeks the child was born before 40 weeks of gestation) 69% survived of whom 73% had mild or no disability (17). This population has a great need of drug treatment in the neonatal period but clinical studies on all aspects of drug treatment within this field are lacking. Retinopathy of prematurity, necrotizing enterocolitis, sepsis, bronchopulmonary dysplasia and intracranial hemorrhage are all major morbidities in preterm infants but the full significance of drugs for these and other conditions during the neonatal period is largely unknown.

When treating neonates, infants, children and adolescents with drugs, they should not be regarded as small adults. Their development with regards to maturation of organs as liver,

kidney, brain, lymph, genitals and the metabolic capacity over age makes it more difficult to assess and evaluate the pharmacokinetic changes (18). The need for understanding those changes are important. The risk of conducting inappropriate research in children has led to ethical guidance withholding proper clinical trials in this population. To understand the best interest of the child, both in the short and long perspective, is a major principle in the Convention on the Rights of a Child from 1989 (19). This could be difficult to determine without research and follow up studies and we need to rethink the research strategy in order to provide better use of drugs in the pediatric population (20).

2.2 PATIENT SAFETY

"Safety is a characteristic of systems and not of their components. Safety is an emergent property of systems" Cook (7)

First, do not harm. Even if the exact wording probably wasn't stated by Hippocrates it is still part of the guiding oath sworn by students entering medicine (21). During the eighteen- and nineteen-centuries, the modern medicine was born with the new possibilities to examine diseases in clinics. Partly leaving the discourses of the patients behind when shifting towards describing diseases with methods that could identify what was previously hidden for the eye. It was a paradigm shift where the power of knowledge about diseases was redefined and relocated to the hospitals (22). The field of medicine has since made incredible contributions to humanity and shifted towards a holistic and multidisciplinary approach, but sometimes the structure of health-care has come to be part of a silencing culture and practicing of guilt in errors committed, as shown in a Swedish context by Ödegård et al. (6). They analyzed four well-known lethal cases, two of them occurred in neonatal care. The book concludes that you must see the responsibility of the system and not put the blame on a single individual that never intended to do harm. Internationally, the publication *To Err is Human* (7), has been a stepping-stone in the research of finding better system and management approaches to acknowledge the patient safety aspects. Many layers interact within patient safety and the simplified Swiss cheese model visualize how hazards can penetrate most layers if they have large or small holes like slices of cheese. The layers include not only technical and human factors, but also organizational processes, safety cultures, regulations, economic and political issues (23). The definition of patient safety in the Swedish law states *"protection against health-care related harm"* (24). The World Health Organization (WHO) defines patient safety in more detail as *"the absence of preventable harm to a patient during the process of health-care and reduction of risk of unnecessary harm associated with health-care to an acceptable minimum"* where the acceptable minimum is defined as *"the collective notions of given current knowledge, resources available and the context in which care was delivered weighed against the risk of non-treatment or other treatment"* (25). An important goal, as stated in the national support for patient safety, is learning from adverse events (AE) to prevent similar events from happening again (26).

In general, work with high level of agreement and with certain outcomes can be described as simple or up to some degree – complicated. But in systems like health-care it quickly becomes complex (27) . For example, the care-processes handles both planned and unplanned events and needs to be in place perpetually. Hospitals are designed to take care of this complexity, but e.g. staffing challenges and poorly introduced changes put pressure on established systems. For children, the variability in patient characteristics and the fact that they have the larger life-span ahead of them put higher demands on risk-management. In addition, a difference in symptoms compared to adults have impact on patient safety if prioritizations are misplaced (28). Pediatric competence is therefore of importance. In 2017, Sweden had 823 licensed pediatricians and 2 400 specialized nurses in child care (29). Together with colleagues they took care of 81 000 pediatric inpatients with 465 000 days (consulting the National Board of Health and Welfare database for children 0-19 years receiving inpatient care). At the moment no specialization into pediatric pharmacy exists in Sweden, as developed in the United States (US) (30). But approximately 20-30 pharmacist in Sweden work with inpatient pediatric care. As more professions enters a field and when higher specialization is required to take on the complexity, leadership with knowledge into patient safety is crucial (6). Preferably with the possibility to include a focus on drug therapy as 27% of the pediatric patient safety incident reports received by the Health and Social Care Inspectorate (IVO) in 2019 were drug related (31).

2.3 PHARMACOEPIDEMIOLOGY AND PHARMACOVIGILANCE

"It is interesting that most of the errors relate to historical developments in medicine and might not have happened in another era" Robertson (32)

The pharmaceutical industry has developed an impressive flora of treatment options helping in the diagnosis, treatment and prevention of diseases. At the same time, important steps have been taken towards safer drugs, often based on tragical events in pediatrics such as the "sulphanilamide-disaster" (33). In the US during the end of the 1930s toxicity studies were not regulatory demanded which made a company place a sulphanilamide-elixir on the market with diethylene glycol as the drug vehicle. Diethylene glycol was chosen due to its solving capacity and sweet taste but is toxic when ingested, which led to the death of 107 persons, mainly children. The event called for new regulations and one-year later the *1938 Food, Drug and Cosmetic Act* was released which helped US to avoid the sequent thalidomide-disaster (33). This disaster was discovered in 1961 by an Australian physician connecting the congenital malformations with thalidomide, a drug marketed as safe during pregnancy (34). Over 10 000 children were born with this malformation in countries that lacked proper pharmaceutical regulations (35). Neonatology, caring for the most vulnerable patients, has always been at risk for unwanted pharmacological effects. Three articles by Robertson have outlined several historical events in neonatology e.g. chloramphenicol causing gray-baby syndrome in the 1950s and the preservative benzyl alcohol in arterial flush lines causing gasping-syndrome in the 1980s (32,36,37). Star and Choonara described in a similar way historical events in pediatrics like Reye's syndrome by salicylates (38). Those and several other events have shaped

the field of drug safety within pharmacoepidemiology, defined as *"the study of the utilization and effects of drugs in large numbers of people"*(39). One of the purposes of the field is to fill the gap that the randomized controlled trials in the pre-market process cannot handle. This is a relatively new discipline, focusing on methods in drug efficiency and safety, with a need to evolve into patient safety studies regarding drug therapy (40,41). Unique to the field of pharmacoepidemiology is the discipline of pharmacovigilance, which is defined as *"the process and science of monitoring the safety of medicines and taking action to reduce the risks and increase the benefits of medicines"* (42). Traditionally, pharmacovigilance has investigated the unpreventable events of the drug itself, e.g. adverse drug reactions (ADR), or processes more in control by the pharmaceutical industry. At the same time, patient safety terminology has focused on the preventable events caused by MEs, or processes more in control by health-care facilities. Today pharmacovigilance has moved toward the area of patient safety by new regulatory directives within the European Union to include reporting of ME (43). Case-control and cohort studies have also been undertaken to fill this regulatory gap (40). One of the large problems in those patient safety studies is the difficulty to compare results due to several reasons, e.g. how to reproduce study data, how to understand of denominators and how to standardize the classification of severity (44). This will be discussed later in more detail.

2.4 OFF-LABEL DRUG USE

"It is important to recognize that health professionals dealing with children use unlicensed and off-label medicines because they have no other alternative" Choonara (45)

The use of drugs outside of marketing authorizations did not, of course, exist until regulations were in place. For many countries this date to the time of the thalidomide-disaster (described above). But even after regulations came into place, drugs have rarely been registered for pediatric use (46). Partly due to ethical considerations and constraints of the pharmaceutical industry. So, when those drugs reach the market with obvious pediatric applications, it pushes forward the ethical considerations to the prescribers (47). This dilemma is cumbersome with the need to e.g. extrapolate pharmacological details from adult data, bearing in mind the different developmental phases of the child. And even if pediatric evidence is provided, the dosage forms and preservatives used do not always meet the full criteria for proper handling (48,49). Aiming to change this situation, the Pediatric Regulation came into force in Europe 2007, stating a mandatory Pediatric Investigation Plan (PIP) when applying for market authorization of new drugs (50). The regulation also established the Pediatric Committee (PDCO) and had several other implications, including demands on national inventories targeting the use of drugs that lacked pediatric details in their product monographs (51), described as below (*Figure 1*).

- Off-label drugs - authorized drugs not used as stated in the product monographs
- Unlicensed drugs - authorized dispensing of drugs licensed in other countries
- Extemporaneously prepared drugs - authorized preparation in a pharmacy of drugs not on the national or international market

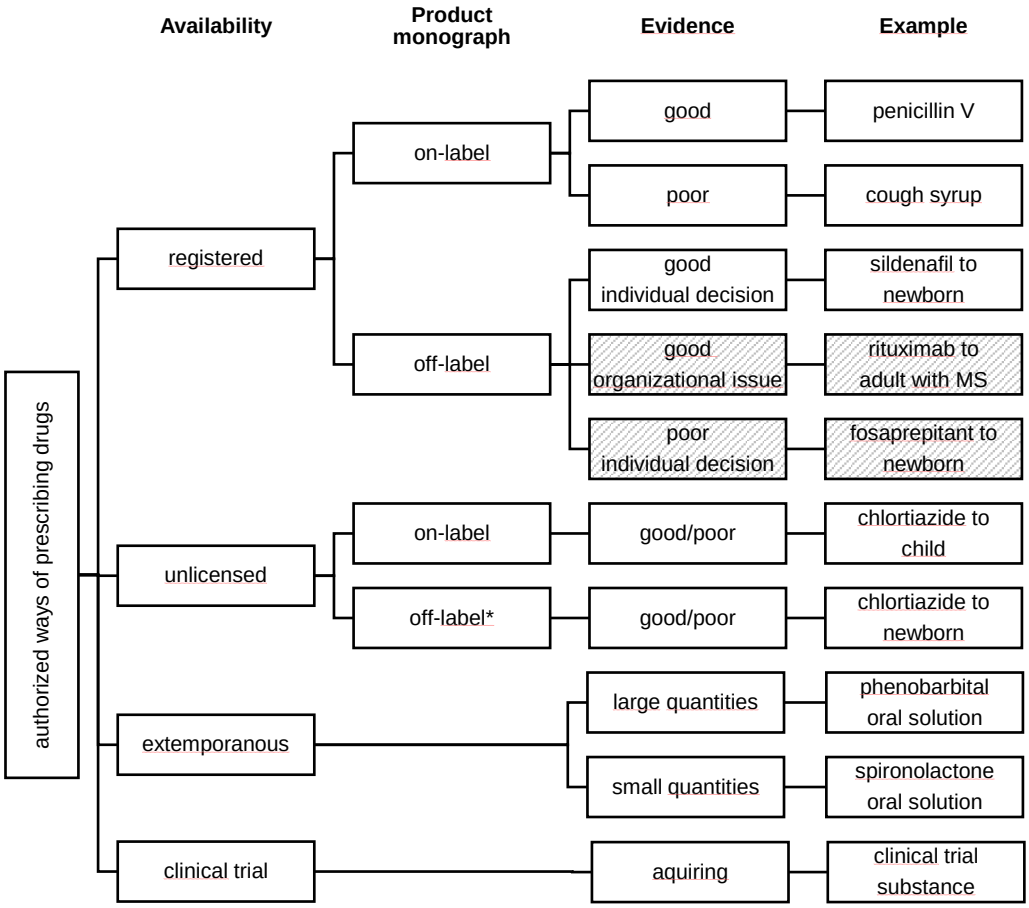


Figure 1 *Different status of drug orders. Grey boxes exemplify off-label with the need to investigate the status of the insurance policy, regarding the risk for not being refunded in the event of an ADRs. *Classified as unlicensed but can be off-label based on the original product monograph.*

Studies have shown a significantly higher off-label drug use among infants below 6 months of age than in older children (52,53). Some reports estimate that the majority of newborn infants receive at least one off-label or unlicensed drug during their hospital stay (54). A review compiling data from over 500 hospitalized newborn infants in six countries showed that 55-79% off-label and unlicensed drug orders were administered to 80-93% of the patients (52) and off-label drug use in neonatal units has been reported to vary largely from 12 to 79%, as seen in *Table 1* (53,55-66). Regarding the pediatric population, including neonates, a review has found hospital orders to contain 12-71% off-label and 0.2-48% unlicensed drugs with 42-100% patients with at least one off-label or unlicensed drug (67). The large differences in numbers is partly due to different criteria for off-label classification. Comparing the actual use to an approved monograph could for example identify off-label by indication, by pharmaceutical form, by route, dosage by age and/or if contraindicated as outlined by Neubert et al. (68).

Table 1 *Off-label use reported within neonatal units*

Author	Country	Year	Patients	Preterm	Orders	OL	UL	OL+UL
Conroy (57)	UK	1999	70	70%	455 orders	55%	10%	65%
Avenel (55)	France	2000	40	88%	257 orders	54%	10%	64%
Barr (56)	Israel	2002	105	NI	525 orders	59%	16%	75%
t'Jong (53)	Netherlands	2002	66	NI	621 orders	14%	62%	76%
O'Donnell (65)	Australia	2002	97	72%	1442 orders	47%	11%	58%
Dell'Aera (58)	Italy	2007	24	NI	176 orders	28%	12%	40%
Kumar (61)	US	2008	2 304	65%	61 iv drugs	-	-	45%
Lindell-Osuagwu (63)	Finland	2009	28	NI	54 orders	28%	17%	45%
Prandsetter (66)	Austria	2009	81	NI	748 orders	34%	18%	52%
Doherty (60)	Canada	2010	38	NI	268 orders	-	-	66/50/12%*
Neubert (64)	Germany	2010	183	69%	135 drugs	-	-	62%
Dessý (59)	Italy	2010	79	42%	88 orders	-	-	53%
Nguyen (69)	France	2011	65	85%	265 orders	29%	17%	46%
Lass (62)	Estonia	2011	348	NI	1 981 orders	-	-	76/62/33%*

*Depending on the source, not included (NI), off-label (OL), unlicensed (UL)

The ten-years report after the implementation of the pediatric regulation states that, 111 medicines, 156 indications and 43 pharmaceutical forms for use in children had been authorized, which is double compared to the reference period (70). The report concluded that it has been a major shift in awareness regarding pediatric clinical trials by stake-holders, but there is still a lot of work needed among old products. To address this lack of initiative, an expert group called "Safe and Timely Access to Medicines for Patients" is working with *repurposing*, a way to use independent research-data in the application process to help old drugs to get on-label status (71). So, as we wait for further market authorizations, a local dialogue can coordinate proper dosing guidelines, information about available products, dilutions and patient safety issues. In Sweden, the ePed-system is working towards a better dialogue among health-care regions in the safe handling of pediatric on- and off-label drugs (9). The need for coordination has also become visible in the digitalization of drug therapy whereas off-label, unlicensed and extemporaneously prepared drugs are not always present in the EMR. On a local level there are also demands to raise awareness of prescribing patterns regarding off-label. Above 70% of pediatric neurologists in US stated that they used newer agents for neonatal seizures without pediatric safety and efficacy data (72). We have previously shown that off-label ciprofloxacin tends to be prescribed to younger and younger patients over time (73) and that doses for omeprazole to neonates vary due to a lack of evidence (74). Another interesting example is Pandolfini et al. who found that on-label drug treatment for pharyngotonsillitis in children produced decreased adherence to guidelines rather than off-label treatment (75). This calls for a system approach on both off- and on-label drugs. A recent joint policy statement from the European Academy of Pediatrics and the European Society for Developmental Perinatal and Pediatric Pharmacology set out the following recommendations with regard to off-label prescribing in children (76).

- Information should be available
- Pediatric pharmacologists and pharmacists should be involved in decision making
- Enhanced safety monitoring should be advocated
- Patient and parents should be educated about off-label use of medicines

- Market holders should take appropriate measures where off-label use is common
- Research into off-label use should be stimulated
- Health authorities and insurances should reimburse evidence-based practice for off-label

In the article referred to above, Sweden is mentioned as one country that require informed consent when prescribing off-label, referring to the law of patients (77) and law of patient safety (24). Reading the law, it does not explicitly state how to handle off-label drugs. Rather should all work adhere to science and proven experience, and drug prescribing should be based on the physicians right of making individual decisions with the best intention for the patient (24). The care should also be planned together with the patient as much as possible, regardless of being off-label or not (77). The same is valid when patients needs to be informed, e.g. if expecting essential risks of complications or ADR. To deliver this information, it is crucial for the physician to have access to data relevant for the off-label prescribing. In addition, as stated in *Figure 1,* there are situations when the patient explicitly needs information about the off-label status. For example, the insurance system in Sweden might not cover harm by an off-label drug with poor evidence, nor harm by organized off-label prescribing when an on-label equivalent is available (78). In adult care, the organized off-label prescribing with rituximab in multiple sclerosis instead of a more expensive on-label equivalent, have been investigated (79). The idea was to test if the Medical Product Agency (MPA) could authorize well-established off-label use, which was discarded (79). At the same time, changes took place among the two major insurance companies handling harm by drugs and health-care.

- LF - the Swedish pharmaceutical insurance, conditional and voluntary for the pharmaceutical industries. Simplified description; it covers harm caused by the drug itself (80).
- LÖF - a nationwide Swedish insurance company with a statutory insure for publicly financed health-care providers. Simplified description; it covers harm caused by the health-care process (81).

Previously LF had signaled that they would not cover for the organizational prescribing of off-label drugs. Instead LÖF had to implement a new "off-label insurance" intended for the health-care providers, which ended up to be valid only for adult care (78). To my knowledge this is due to miscommunication which hopefully will change over time. An updated understanding of the above systems is of importance when investigating the definition of off-label and the distinction from MEs (which will be discussed in more detail in the next chapter). The balancing line between ME versus off-label is thin and both are sometimes seen by the pharmaceutical industry as deviations from the product monograph, and per se - off-label prescribing (82). But MEs are unintentional by nature and do not adhere to the off-label definition stated by the National Board of Health and Welfare as *"the intentional use of medicinal products for medical purposes that constitute a deviation from use according to the approved product monograph"* (83). This definition contrasts with the unintentional use when drugs are handled erroneously causing harm. It is no statutory requirement for the

pharmaceutical industry or health-care provider to include off-label without harm in their pharmacovigilance reporting to the agencies (84). For harm by drug, a strong consensus exists that all ADR by on- and off-label drugs should be reported. *Table 2* illustrate the regulatory perspective by the pharmaceutical industry, the usage perspective by the patient responsible physician in health-care and liability issues in the case of harm (85).

Table 2 *Simplified distinction of off-label between the regulation, the use of drugs and liability issues.*

Type	Regulation	Usage	Liability
System	Pharmaceutical industry	Health-care	Insurance
Body	Medical product agency	National board of health and welfare	Ministry of finance
Guiding regulation	European/National	National	National
Process	Drug distribution	Drug handling	Compensation
Simplified off-label definition	Usage not stated in product monograph.	Evidence- and experience-based, intentional deviation from product monograph	Organizational or individual prescriber decision
Mission	Safe and single market for medicinal products	Relation between practitioner and patient.	Assures the responsibility of the health-care regions (LÖF) and the pharmaceutical industry (LF)
Harm by intentional use	Addressing filed report by pharmacovigilance	File report of harm by drug (adverse drug reaction)	Addressed by LF or LÖF
Harm by unintentional use	*	File report of harm by process (medication error)*	Addressed by LÖF

*Handling of medication error is discussed in detail in next chapter

However, we should not dispute whether a treatment is off-label or not, but whether it is evidence based with reliable guidelines. For example, cough syrups are registered from six months of age despite poor evidence, with scientific recommendations not to be used below the age of six years (86). It is important to distinguish between poor and good evidence-based off-label prescribing (*Figure 1*) where the former should as far as possible be removed from recommendations or carried out in proper clinical trials and always with consent (87).

2.5 MEDICATION ERRORS AND ADVERSE DRUG EVENTS

2.5.1 Definition of medication errors

"Errors and violations are commonplace, banal even. They are much a part of the human condition as breathing, eating, sleeping and dying" Reason (23)

A simple computerized program can contain a defect caused by an error in programming. The defect can be identified and fixed before carrying out the error by the receiver, causing a failure. As the health-care system is complex, the way to identify, change or eliminate system-defects is harder. So, if we cannot easily detect the root-cause of an error in a complex system, the risk is high in blaming the individual that unfortunately experienced it. In addition, the medical profession of today is well-trained in the sense of individual responsibility for the patient. This training will also feed the belief that you are personally responsible for any error that occur.

This “blame and train” culture introduces the risk of covering up mistakes rather than reporting them, missing out the possibility to learn from and understand system causes of an error (88).

Medication errors can occur anywhere in the process of drug handling, i.e. prescribing, dispensing, storing, preparing or administrating a drug. Several definitions exist in patient safety terminology (89). Pintor-Mármol et al. studied 147 articles with 60 terms related to medicines in patient safety research and found 189 different definitions (90). Lisby et al. investigated different definitions of ME and included 45 studies in which they found 26 different wordings where 17 used the definition by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP), an independent body composed of several US organizations (91). They define ME as *“A ME 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”* (92). The NCC MERP organization have created an outcome-based classification system of ME described in *Table 3.*

In Sweden the National Board of Health and Welfare have a similar, but shorter, definition with the addition that the ME is unintended (93). This is also stated by the European Medicines Agency (EMA) as *“an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient”* (94). A guideline by EMA to assist in the recording, coding, reporting and assessing of MEs has been released where they clearly distinguished ME from off-label use (95). The guide also outlines the terms in proximity of ME, as potential ME i.e. the recognition of circumstances that could have led to a ME which may or may not involve a patient (95,96). Other related terms as, intercepted ME, when errors are carried out but discovered before it reaches the patient are outlined in *Table 3* with relations to the NCC MERP classification.

Table 3 *NCC MERP classification, an outcome-based definition of ME together with an adaptation of the EMA guide on coding of medication errors (95,97).*

NCC MERP		EMA	
Class	**Description**	**Action**	**Outcome**
A	circumstances or events that have the capacity to cause error	No ME Risk/Potential ME	No harm
B	an error that occurred but did not reach the patient.	Intercepted ME (before reaching the patient)	Potential harm Near miss/Close call
C	an error that reached the patient but did not cause patient harm.	ME (reaching the patient)	Potential harm No harm
D	an error that reached the patient and required monitoring to confirm that it resulted in no harm and/or required intervention to preclude harm.		
E	an error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention.	ME (reaching the patient)	Harm (ADE*)
F	an error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention or prolonged hospitalization.		
G	an error that may have contributed to or resulted in permanent patient harm.		
H	an error that required interventions necessary to sustain life.		
I	an error that may have contributed to or resulted in the patient's death.		

Medication errors are, as above, described from their clinical consequences and the NCC MERP system have been criticized for lacking a possibility to grade potential harm by ME. Another scale called the Harm Associated with Medication Error Classification (HAMEC) has been published for those purposes, e.g. coding potential severity of NCC MERP class B events (98). In addition, the documentation of the contributing factors as the contextual, modal and physiological details are recommended to better analyze the event (96,99). More specifically 1) Contextual details regards setting, patient risk factors, ameliorating factors etc., 2) Modal details regards the way the error occurred and 3) Details on psychological or human behavior can be divided into, 3a) Mistakes that regards error in planning, i.e. rule- or knowledge-based errors and 3b) Skill-based error that regards errors in action when correctly planned, i.e. slips and lapses (23). Finally, even before identifying an error for the first time, the error could have been known for a long time without proper handling and being introduced by the system itself, placing the ME in a relation to the managing system (100).

2.5.2 Definition adverse drug events

"A clear theme is that safety bodies prefer ADEs, whereas regulatory agencies use the term ADRs" Falconer (101)

The unintended harm originating from a drug is usually defined as an ADE. Adverse drug events are further categorized into preventable or non-preventable events where a preventable-ADE (pADE) is harm caused by a ME and a non-pADE is harm occurring with appropriate use of medication, also known as ADR (102). But today, a Swedish definition of ADE is lacking. Mainly due to a disagreement since ADE has its base in the patient safety sector and ADR in the regulatory sector (101). The regulatory bodies of MPA and EMA define an ADR as *"a response to a medicinal product which is noxious and unintended"* (94,103). As the

definition has changed, previously it stated that an ADR only occurred when the drug has an appropriate use, all ADEs can now be defined as ADRs. In other words, even preventable events caused by ME would be defined as ADR. This has an impact on the way all ME-related incident reports should be handled. Previously only ADRs were reported to the MPA if they were a reaction to common usage of drugs. Today, in the eyes of the EMA, even MEs should be reported, preferably by the national responsible organization forwarding relevant incident reports to the MPA. The MPA then must make sure that the information ends up in the European database for pharmacovigilance, EudraVigilance (95).

In this thesis we will respect the definition stated by EMA but continue to use the term ADE for both pADE, originating from MEs, and non-pADEs (or ADR) originating from the drug itself. In *Figure 2* the graphical relationship between ME and ADE is presented.

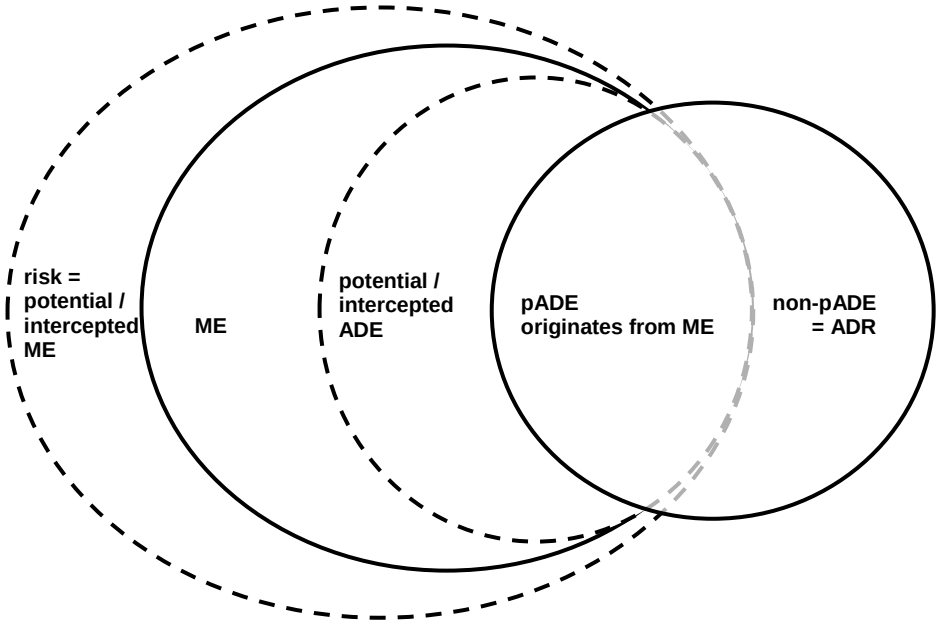


Figure 2 *Relationships between Medication Errors (ME), Adverse Drug Events (ADE) and Adverse Drug Reactions (ADR). Modified from Morimoto et al. 2004.*

The relationship can be exemplified by a case, where an AE occurs as a rash. If the rash was unexpectedly caused by a drug, it would be a non-pADE (ADR). If the patient had a known allergy to the drug with previous history of rashes, the event would classify as a pADE. The error causing the pADE could be described as a miss in consulting the medical history together with contributing factors such as error in planning, short staffing and an acute situation.

The severity of ADE can be judged by different scales as category E-I of the NCC MERP index or the five-level HAMEC-scale (97,98). For ADR e.g. Hartwig et al. used a seven-level severity scale (104). Adverse drug events should also be defined by its causal relationship and the preventability, which we will discuss in the following chapters.

2.5.3 Intentional overdose, misuse and abuse

"Several studies have demonstrated that adolescent substance abuse is a serious and growing problem" Faggiano (104)

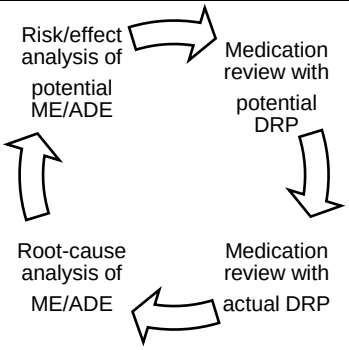
An increasing substance abuse is reported among adolescents (104). The safety information, as stated in the European directive, shall also be collected in the joint pharmacovigilance databases regarding intentional overdoses, misuse, abuse and suspected adverse reactions associated with occupational exposure (105). But intentional overdose, misuse or abuse are not the objectives of this study.

2.5.4 The relation to drug related problems

"A drug related problem exists when a patient experiences or is likely to experience either a disease or symptom having an actual or suspected relationship with drug therapy." Hepler and Strand (106)

The work with terms like ME and ADE in patient safety usually adheres to processes of minimizing harm by finding system related causes. But, when working in the direct patient care, drug-related problem (DRP) is the common term for data collected. Within pediatrics, DRPs have been identified in medication reviews (107) and medication reconciliations (108,109). We have previously investigated the relationship between the way of documenting drug-related patient safety initiatives and medication reviews as illustrated in *Table 4* (110). It is an obvious overlap of the ME/ADE and DRP terminology and an overview has summarized the use of the different terms in pediatric studies (111). Usually DRPs are seen as an umbrella-term for the subset of events leading to ME/ADE, promoting DRP as a possibility to better include the potential MEs (112) and issues like lack of indication of a drug (101). On the other hand Nebecker et al. have shown the overlap in terminology by following a single patient case, describing how ME/ADE could be used in documenting the patient-centered care (89). Medication reviews can also be used to scan for potential ME/ADE which was used by Kaushal as an observational method compared to just rely on incident reporting (113). Historically, the DRP-term is in close connection to the principles of pharmaceutical care developed and defined by Helper and Strand as *"an event or circumstance involving drug therapy that actually or potentially interferes with the patient experiencing an optimum outcome of medical care"* (106,114). A system developed for the classification of DRP exist from the Pharmaceutical Care Network Europe (115).

Table 4 *Comparison between system centered and patient centered processes for evaluation of drug events*

Process Evaluation	**System centered**	**Patient centered**
Evaluating outcome	Root-cause analysis of ME/ADE	Actual DRP by retrospective medication review
Evaluating potential outcome	Risk/Effect analysis (HFMEA) of potential ME/ADE	Potential DRP by prospective medication review
Main type of failures identified	Latent	Active
Terms used	ME/ADE	DRP
Documentation	Incident reports	Note in patient chart
Examples	*Potential ME/ADE:* We have seen troughs of vancomycin out of range. How can we optimize the dosing schedule?	*Prospective DRP:* The vancomycin trough of the patient is too low. We need to adjust the next dose.
	ME/ADE: Why was the order of morphine misinterpreted? How can we avoid reoccurrence?	*Retrospective DRP:* A too large dose of morphine in an acute situation required the administration of naloxone. Patient is stabilized and adequately monitored.
Relationship		

2.5.5 Drug causality

"No cause is self-sufficient" Rothman (116)

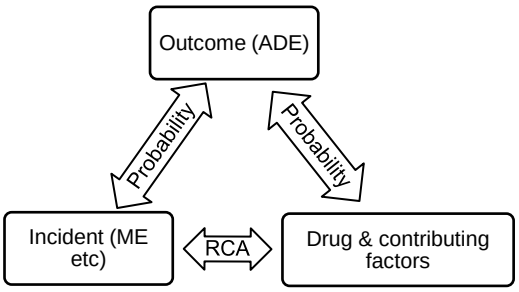
Causality related to drug therapy is commonly used in pharmacoepidemiology and pharmacovigilance. The field is complex and has developed several methods for causality assessment where the WHO Uppsala Monitoring Center and the Naranjo probability scales are the most used (117), even in the evaluation of intoxication events due to ME (118). In pediatrics, a modified Naranjo scale has been developed in the ADR in children program (119). Most methods have criteria's based on a paper by Bradford Hill who published seven statements that you need to consider before interpreting an association as a causation; strength, consistency, specificity, temporality, biological gradient, plausibility and coherence (120). The probability scales are especially useful in estimating the causality in incident reports, reporting the relationship as certain, probable, possible, coincidental or doubtful. Alternatively, ADRs can be identified on a larger scale by algorithms using databases with incident reports to find the causation by drugs. The algorithms are however not fully reliable for several reasons, e.g. as shown by Mascolo, that none of the present algorithms include contribution from ME (43). This is cumbersome, bearing in mind that ME are thought to have a relation to the outcome in about half of all the cases (121). A French pharmacovigilance-study among neonates, found that one report out of five was ME related (122). Overdose is however a situation managed by

some of the algorithms (43). In overdose cases, the primary effect is enhanced by an ME but carried out by the drug itself. On the other hand, some drugs involved in ME are secondary to the incident as described in *Table 5*. The relation to a drug is central in the definition of an ADE or ME. If the relation to a drug is just suspected terms like DRP or AE are preferable. For example, in clinical trials when a non-evaluated relationship between a drug and an event is identified, the term AE is used until a causal relationship is defined (123). To define the relationship a multicausal model was postulated by Rothman where no cause is self-sufficient (116) and causation is always in risk of biases and confounding. Contributing factors such as drug interactions should be considered alongside contingent factors, e.g. the individual metabolizing capacity (121). The probable causative factors can also be further divided on health determination, e.g. distal (structural), intermediary (behavioral) or proximal (biological) factors (124). Adding an understanding of ME in the probability assessments of AE would be a way to lower the risk of confounding by unintended incidents in drug handling. In lethal cases, the autopsy report should include an investigation to understand if an unintended ME or ADR where present to better establish a causal relationship (125).

Table 5 *The probability of the drug being the primary or secondary cause of adverse outcome, i.e. was the harm carried out by the drug itself or by another incident. Illustrated by different situations. The cause of an incident could be evaluated by a root-cause analysis (RCA). The contribution factors state just a few examples.*

Contribution factors, examples	Incident	Outcome	Drug cause probability
Paracetamol, misinterpreted verbal order communication	Unrecognized overdose	Liver failure	Primary: Drug caused the harm - enhanced by incident
Paracetamol, poor infusion pump training	Intercepted wrong rate in infusion pump	Antidote given	Primary: Drug caused the harm - enhanced until intercepted incident
Paracetamol, unknown allergy	-	Rash	Primary: Drug caused the harm
Paracetamol, NaCl syringes look-a-likes	Mix-up and secondary omission	Insufficiently treated pain	Secondary: Other source of harm, the drug part of the incident
Paracetamol, poor aseptic technique	Microbiological growth	Sepsis	Secondary: Other source of harm, the drug part of the incident
Paracetamol, intravenous access not cared for	Misplaced infusion line with subcutaneous infusion	Discomfort at site	Secondary: Other source of harm, the drug part of the incident

Relation:



2.5.6 Detection

"Computerized detection will probably soon replace the all-manual approach, although substantial refinement of it is needed." Morimoto (126)

Detection is dependent on the methods used and we have previously observed an underreporting of ADEs with incident reports compared to methods as for example triggers and chart reviews (127). The chart review is usually referred to as the gold standard for detection of AE (128) and even more information could be collected by direct observational studies (129,130). Some of those detection methods used in pediatrics are discussed below with an overview in *Table 6*, adapted from Montesi et al. (131).

Table 6 *Examples of detection methods for ME and ADE. *Methods used in this thesis.*

Method	Mandated in Sweden	Main usage	Main advantage and limitation	Main type of failures	Main finding	Activity needed
National ADR reports	Yes	Practice	Defined process but poor reporting	Latent	ADR	Regulatory pharmacovigilance
*National severe reports (Lex Maria)	Yes	Practice	Defined process but fear of blame	Active/Latent	ME/ADE	Root-cause analysis
*Local incident reports	Yes	Practice	Simple but variable quality	Active/Latent	ME/ADE	Incident handling group
Administrative data	No	Practice	Simple but lack clinical data	Active/Latent	ADE	ICD-10 coding
*Clinical decision support systems	System dependent	Practice	Real-time but risk of warning fatigue	Active	DRP/ME	Software maintenance
*High-alert drugs	No	Practice	Focus on high-risk ME but poor practice	Active	ME	High-alert drug list
Drug chart review	≥75 years, ≥5 drugs	Practice	Gold standard but need reviewer training	Active	DRP/ME /ADE	Reviewers
*Triggers	No	Research	Simple but can generate false positive	Active	ADE	Reviewers
Direct observation	No	Research	Accurate but need observer training	Active/Latent	ME	Observers
*Personnel and patient perspective	No	Research	New insights but not standardized	Active/Latent	DRP/ME /ADE	Interviewers
Mixed-model	No	Research	Strengthen validity but need several methods	Active/Latent	ME/ADE	Several methods
Audit (clinical)	No	Audit	System based but need continuous work	Latent	Risk	Plan/Do/Study/Act
HFMEA	No	Audit	Proactive but is rarely used	Latent	Risk	Failure modes and effects analysis

ICD - International classification of diseases

2.5.6.1 National ADR reports

Detection of ADR is done through pharmacovigilance monitoring as described in earlier chapters. It is dependent on reporting from health-care staff and the public, and there is a known underreporting of ADR. Less than 10% of all serious ADR identified at a local hospital were sent in and reported to the authorities (132). A simple calculation done in the US divided the number of reported ADRs with the number of physicians in 1997 and found out that a physician reported an ADR once every 336 years. For pharmacists the number was once every 26 years (133).

2.5.6.2 National and local incident reports

The detection of ME and ADE is usually done by so called voluntary reports. But as stated in the Swedish patient safety law those reports are actually mandatory for health-care personnel when observing AEs and potential AEs (24). Even if reporting is fundamental for patient safety the mandatory system is somewhat problematic. Reporting needs to be non-punitive and confidential and voluntary reporting provide more useful information than mandatory reporting with the possibility to get the full story (134). In this thesis we will describe the reporting from health-care personnel as incident reports. Incident reports are usually investigated by root-cause analysis (RCA) where Ishikawa- or fishbone diagram is a basic tool to graphically display the multifactorial causality (135). Published examples of RCA in pediatric drug handling are sparse but Morse at al demonstrated a 90% success carrying forward actions from 20 serious ADE with approximately 4 action plans per RCA using an associated implementation plan (136). In Sweden there is also an electronic system for RCA (137). When compared to other detection methods, incident reporting identify few ME but is effective in capturing severe ADE (130). Manias et al. retrospectively studied the incident reports in an Australian pediatric hospital with 3 340 reports for five years (0.56% per admission) and found that parents and patients alerted health-care staff about ME in 15% of the cases (138).

2.5.6.3 Administrative databases

Since most ways of detecting MEs and ADEs are time-consuming, methods have been tried for automatization. For example, 85% of the ICD-10 codes used for the detection of ADEs, in the form of ADR (Y40-Y59) and ADE due to ME regarding accidental overdoses (X40-X49), did catch harm when compared to a manual chart review process in an Australian pediatric hospital (139). Using similar codes from the ICD-9 system (E930-949 and E850-858) in different populations, showed that elderly people were more at risk of ADR compared to children under 18 years who were more in risk of accidental overdoses (140).

2.5.6.4 Clinical Decision Support Systems

Computerized drug order entry has reduced several MEs originating from transcribing and misreading. But the EMRs have also introduced new types of errors, e.g. dosing errors when choosing the wrong unit (e.g. mg and mL). In 2005 Han et al. published a study which showed an increased mortality after the introduction of an EMR in a pediatric hospital (141). Later, Brenner et al. evaluated the safety of 69 studies in the implementation of EMR or Clinical Decision Support Systems (CDSS) showed the Han study to be the only negative, while the majority (62%) had non-significant or mixed findings and 36% found beneficial outcomes (142). Clinical Decision Support Systems have been introduced as one way to help the EMR to detect ME in real time. One often used CDSS in pediatrics is the dose-alert check to detect under- and overdoses (143,144). The dose-alert system investigated in this study, was at the time based on a voluntary dose-calculating weight needed for the dose-alert to warn for wrong single and daily dose in mg/kg or mg/patient in certain age- and weight-spans for each included

substance and route (9). Primarily high-alert substances from previously known miscalculations were included in the dose-range check.

2.5.6.5 High-Alert Drugs

Some drugs and drug-classes are more frequently occurring in incident reports and are regarded as high-alert *(Table 7)*. They are defined as *"Drugs that bear a heightened risk of causing significant patient harm when they are used in error. Although mistakes may or may not be more common with these medications, the consequences of an error are clearly more devastating to patients"* (8). These drugs usually have a pharmacological profile with narrow therapeutic windows (e.g. digoxin) or are in risk of events when used erroneously (e.g. wrong route). Knowledge about high-alert drugs can help to detect and build tools to prevent severe ADE. Such knowledge can also help in the teaching at universities and in practice (145,146).

Table 7 *Number of drugs, drug-classes, processes in pediatric high-alert drug list.*

Study	Published	Country	Drugs	Drug-classes	Processes	Comment
Bataille (147)	2015	France	17	-	53	Selected by committee
Colquhoun (148)	2009	Canada	5	-	-	Top 5 from reports
Dos Santos (149)	2012	Brazil	12	21	-	Use of ISMP classification
Franke (150)	2009	US	43	19	19	Survey in PICU
ISMP (151)	2018	US	12	21	-	Literature, reports, experts
Labib (145)	2018	Turkey	12	21	-	Use of ISMP classification
Maaskant (152)	2013	International	14	4	-	Delphi process
Melo (153)	2014	Brazil	21	-	-	From prescriptions in ED
NHS, Never Event (154)	2018	UK	4	-	1	General, not only pediatric
NSW, A PINCH (155)	2020	Australia	2	4	-	General, not only pediatric
Santell (156)	2005	US	9	-	19	From MedMarx register
Sinha (157)	2007	Australia	10	1	10	Review
Stavroudis (158)	2010	US	12	21	-	Use of ISMP classification
WHO (159)	2019	International	-	6	9	General, not only pediatric

ISMP - Institute for Safe Medication Practices, ED - Emergency Department, WHO - World Health Organization, PICU - Pediatric Intensive Care Units, NHS - National Health Service, NSW - New South Wales, MedMarx - United States Pharmacopeia incident reporting system.

2.5.6.6 Drug chart reviews

For retrospective chart reviews a suggested methodology exists for researchers (160,161) as for prospective chart reviews (113). In practice, chart reviews usually include ward rounds and interviews with patient and parents to enhance the finding of DRP (162,163). When performing a chart review the term DRP is most often used to collect drug related issues, including off-label use, MEs and ADEs. To achieve a correct drug chart, a medication reconciliation can be carried out, which have been started to be recognized in pediatrics (108). In Sweden, medication reconciliation in the daily clinical work is mandatory for inpatients over 75 years with more than five drugs, but also for patients with or in suspicion of DRPs (164). If problems still exist after a medication reconciliation, an advanced drug chart review should be offered. In pediatric research, drug chart reviews have been used to detect ME and ADE. Kaushal have suggested a methodology for research into retrospective chart reviews for ADE and ME (113). The research group by Kaushal have also published a well cited article using a prospective drug chart review identifying a three times higher rate of potential ADEs than in adult practice (165).

Holdsworth et al. have also used the methodology finding most common ME in the under-dosing of children, particularly in pain treatment (166).

2.5.6.7 Trigger tool

Two major trigger-tool instruments exist, the Harvard Medical Practice Study and Global Trigger Tool (167). In this thesis we have focused on the Global Trigger Tool by the Institute for Healthcare Improvement. The tool was developed for adults measuring ADE by using a set of drug-focused triggers (168). For example, the finding of naloxone use could be a trigger for an overdose of opioids. Further development of the trigger-based record review methodology for the identification of the overall AEs in pediatric care has been carried out (169-172). With regards of ADE specific triggers in pediatrics, Takata et al. performed a multicenter study reviewing 960 charts and 2 388 triggers and 107 unique ADEs (173). The most common ADEs were pruritis and nausea and opioids and antibiotics were more often involved in ADEs. Criticism of the tool in identifying ADE includes poor identification of harm when compared to methods as chart reviews and incident reports (174). Triggers do not identify ME as well as chart reviews combined with incident report analysis (174). Older automated detection system had poor algorithms for detecting ADEs (175,176) where e.g. Kilbridge et al. used specified pediatric rules to automatically detect ADEs with a positive predictive value of 13% (identifying 160 ADE from 1 226 alerts), manly focusing on laboratory values and drug levels out of range (177). The trigger tool is otherwise beneficial for tracking changes over time. For example, the trigger tool has been used to monitor joint patient safety initiatives over time in 12 included pediatric hospitals e.g. the implementation of standardization of order sets and high-alert drug lists. An overall reduction (42%) in ADE was seen but mainly in six hospitals, six did not change (178).

2.5.6.8 Direct observation

The direct observation method has been useful in pediatrics to understand the manipulation of drugs and techniques used to administer drugs to children (179). The method have also been used in simulation facilities for medication room training among pediatric professions to raise awareness about common ME (180). The direct observation technique is superior to incident reports and chart reviews to identify MEs during administration (181).

2.5.6.9 Personnel and patient perspective

Few studies have investigated the patient perspective of AE. Harrison et al. reviewed the problem and found the most common AE described to be drug related (4). Many of the events were classified as ADRs, which are seldom preventable. The patients were often distressed by the events and felt that they had much to offer regarding prevention and detection of AEs (4). The power of the patient perspective regarding patient safety is enormous and the core understanding of this field of research is well described in the story of Kelsey and her difficult journey through the health-care system (2). Studies have confirmed that children can self-report ADE from the age of 8 years and tools are developed as the "Pediatric Patient-Reported Outcome Version of the Common Terminology Criteria for Adverse Events" (182). It is also

shown that when allowing patient to report incidents, new previous unrecognized AEs were identified (183).

2.5.6.10 Mixed model

The use of several different methods for detection of harmful MEs has been proven to be more reliable than single methods (174,184,185). For example, direct observation combined with clinical audit and focus groups identified four themes for pediatric nurse's perception on ME, including the understanding of ME, stress, environment and compliance with policies (186).

2.5.6.11 Clinical audit

Clinical audit is defined as, *"Aspects of the structure, processes, and outcomes of care are selected and systematically evaluated against explicit criteria. Where indicated, changes are implemented at an individual, team, or service level and further monitoring is used to confirm improvement in healthcare delivery"* (187). An audit can be carried out in several ways, where one of the most common is the Plan-Do-Study-Act cycle (188). One important and growing type of audit is the model of antibiotic stewardship, which have been applicated in pediatrics with goals to reduce unnecessary utilization and prevent resistance (189,190). Other examples in pediatric drug safety with published audits are, the use of safe abbreviations (191,192), drug calculations (193) and tools for self-audit of safe compounding at wards (194).

2.5.6.12 Failure Modes and Effects Analysis

To perform a risk analysis, a modified health-care version of the Failure Mode Effects Analysis (HFMEA), developed by US Department of Veterans Affairs, can be used (195). For example, the tool has been used in a neonatal unit in New Zeeland showing high risks in ordering and administration of drugs to neonates (196).

2.5.7 Prevalence and incidence

"Medication errors are the most common preventable cause of undesired adverse events in medication practice and present a major public health burden" Goedecke (96)

Prevalence is defined as the proportion of a population who have a condition during a specified time, and incidence is the proportion of a population who develop a condition over time. In the drug safety literature incident is the most commonly term used. Talking about incidence and prevalence in pediatric drug safety you usually start by mentioning a well cited study by Kaushal et al. in 2001 showing an incident of 2.4 ADE and 10 potential ADE and 55 ME per 100 admissions after a prospective chart review (165). The potential ADE rate was estimated to be three times higher than in adult care reports. Other examples of reports with different detection methods are displayed in *Table 8*. But comparing findings of ME and ADE with other hospitals is problematic. A statement from NCC MERP concludes that the use of ME rates to compare health-care organizations are of no value (197). Reasons for this are attributed to differences in culture of reporting, definition of ME, patient populations and detection systems.

They also state that there is no acceptable incidence rate for ME and the health-care organizations should use the information to improve their drug use process. Even so, meta-analyses have been used to measure the ME rates among pediatric patients. In 2014, Koumpagioti et al. identified 25 articles that met the inclusion criteria and found prescribing error per medication order to be 17.5% (95% CI 10.8-27) and administrations errors per administrations to be 31.6% (95% CI 14.8-55) (198). The incident of errors in prescribing have also been studied in a review from Lewis et al. in 2009 with ME (IQR) in prescribing 4% (2-17) of the orders, 52% (8-227) of the admissions or 2.4% (0.6-21.2) of the length of stay (LOS), showing dosing errors and omissions as the most common error (199). In an early review by Miller et al. 2007, they included 31 articles and identified ME in prescribing 3-37%, dispensing 5-58% and administration 72-75% (200). In a series of more recent reviews in 2019, Gates et al. included 56 papers differentiated by pediatric ward type and use of EMR with findings of higher occurrence of ME in intensive care units and a tendency to lower rates among hospitals using EMR (201). The same group also investigated dosing errors as the most common ME in pediatrics with the finding of one dosing error per 20 drug orders with a lower but not definitive number of MEs in EMR-systems (129). Finally, they investigated the incidence of pADE showing a range of 0-17 pADE per 1000 LOS in general wards but up to 29 pADE per 1000 LOS in intensive care units, where most of the harm was minor (202). They also refer to a study from Kunac showing the highest rates with 35 pADE per 1000 LOS and 74 potential ADE per 1000 LOS (203). The same group later described 12.9 ADE per 100 admissions or 22.1 ADE per 1000 LOS by a mixed model (185).

Also, in 2019 Alghamdi et al. investigated 35 studies for inclusion in a recent review regarding ME and pADE. Rate of ME in pediatric intensive care units was 14.6 per 100 medication orders or 6.4-9.1 per 1000 days and in neonatal intensive care units 5.5-77.9 per 100 medication orders or 4-35.1 per 1000 days, identifying a need to focus on dosing errors (204). A gentler take on all this has been done by Ghaleb and Wong in 2006 when they reported the findings of MEs in 12 different studies without aggregation concluding problems with different denominators and definitions of ME (205). Their findings can be summarized by saying that ME is not uncommon in pediatrics. As mentioned previously, a review by Lisby et al. in 2010 investigated the large variation in definitions of ME which also identified a large span in ME incidence of 2-75% (91). So, studies regarding incidence and prevalence data in patient safety should be interpreted carefully.

Table 8 *Extract of published incidences of ME and ADE in pediatric inpatient with N admissions and X, representing ADE, AE or ME. Sorted by X and design. Year related to the year of the publication.*

Year	Author	Design	Patients	N	X	X/1000 LOS	X/100 N	X with N /100 N	Ref
2019	Scripcaru	Administrative data	PH	9320076	ADE	-	1.5	-	(140)
2008	Ligi	Incident reports	N	388	ADE	-	4.9	-	(206)
2016	Dedefo	Mixed model	PH	233	ADE	17	7.3	-	(162)
2009	Kunac	Mixed model	W, N	495	ADE	22.1	12.9	-	(185)
2001	Kaushal	Prospective chart review	W, N, P	1120	ADE	6.6	2.3	-	(165)
2003	Holdsworth	Prospective chart review	W, N	1197	ADE	7.5	6.0	-	(166)
2003	King	Retrospective cohort	W, S	36103	ADE	0.1	0.05	-	(207)
2011	Burch	Trigger	R	59	ADE	~10	29	24	(208)
2008	Takata	Trigger	12 PH	960	ADE	15.7	11.1	7.3	(173)
2012	Matlow	Trigger	PH	1692	ADE	-	-	1.5	(209)
2014	Call	Trigger	O	390	ADE	-	8.5	-	(210)
2015	Maaskant	Trigger	W, O	369	ADE	10	5.1	4.9	(174)
2018	Silva	Trigger	PH	240	ADE	20.3	25.8	18.7	(211)
2012	Kirkendall	Trigger	PH	240	AE	76.3	36.7	25.8	(212)
2006	Sharek	Trigger	N	749	AE	32	74	-	(213)
2018	Stockwell	Trigger	16 PH	3790	AE	19	10.9	8.0	(214)
2000	Ross	Incident report	W, N, P	112536	ME	0.51	0.15	-	(215)
1989	Raju	Incident report	N, P	2147	ME	8.8	14.7	-	(216)
2018	Manias	Incident report	PH	~596000	ME	5.73	0.56	-.	(138)
2016	Dedefo	Mixed model	PH	233	ME	514	220	-	(162)
2001	Kaushal	Prospective chart review	W, N, P	1120	ME	157	55	-	(165)
2019	Alghamdi	Review	P	-	ME	6.4-9.1	50 (24-75)	-	(201)
2019	Alghamdi	Review	N	-	ME	4-35.1	26.4	-	(201)

N - Neonatal, O - Oncology, P - Pediatric intensive care, PH - Pediatric hospital, R - Rehab, S - Surgical, W - General ward

2.5.8 Prevention

"Medication errors occur across the entire spectrum of prescribing, dispensing, and administering, are common, and have a myriad of non-evidence based potential reduction strategies" Miller (200)

The Cochrane Collaboration have published a review on interventions to reduce ME that could be prevented in pediatric hospitals (217). Maaskant et al. studied 5 185 publications before November 2014, of which 28 were studied more thoroughly, and only 7 were included to assess the effectiveness of different interventions with the goal of reducing ME and preventable ADE (pADE), *Table 9*. Five different types of interventions were found in these studies. 1) Participation of clinical pharmacist, 2) The use of an EMR, 3) The use of bar codes, 4) Structured order sets and, 5) Implementation of checklists. No meta-analysis was done because of the differences between the studies.

Kaushal showed that the use of a trained clinical pharmacist at fulltime gave significant effect on severe ME in children in the intensive care setting but not for part-time at a general ward (218). The possibility for significant effect was larger in the intensive care setting as the ME rate was 3-4 times higher compared with the general wards. Anyhow, Zhang et al. showed positive effect of clinical pharmacists on compliance and LOS for children in China with

respiratory disease in general wards (219). The introduction of an EMR gave in the two included studies varied results, both showed a reduced incidence of ME, but no effect on injuries (207,220). One of the studies reported by King in 2003, also showed an increased incidence of potential ADEs. However, King's study lacked the presence of CDSS as weight-based dosing and a dose range check. In addition, they found 804 ME and only 18 ADE over six years among 36 103 discharges. They confess to have low numbers due to a passive reporting system and did not include the more drug-intense clinics in the study (207).

The use of bar codes for pharmaceutical and patient monitoring in a neonatal unit yielded significant results on ME as well as the structured prescription sheet that helped with drug prescriptions (221). The use of checklists for prescriptions of pediatrics rounds gave only impact on technical errors (222).

Other compilations, which have been more inclusive, evaluated the effect of less stringent interventions, e.g. Rinke et al. who evaluated 63 studies on preventative measurements for ME, mainly EMR and CDSS (223). Bannan et al. reviewed studies set to reduce prescribing and administration errors in pediatrics by bundle interventions, both at a professional and organizational level (224). Both reviews show benefit from additional methods but are also critical with regards of the lack of well performed studies. More robust studies are needed to better evaluate the impact of different interventions, knowing that patient safety research cannot always use a full randomized controlled trial system. This should be high on the research agenda, since we know that children are more vulnerable to these MEs, such as pharmaceutical miscalculations.

Table 9 *Seven studies included in the Cochrane review on interventions to reduce ME*

Study	Published	Country	Category	Type	Ward
King (207)	2003	Canada	EMR	CBA	Pediatric
Kozer (225)	2005	Canada	Structured order sets	RCT	Pediatric Emergency
Kaushal (218)	2008	USA	Clinical Pharmacist	CBA	Pediatric, PICU
Morriss (221)	2009	USA	Bar codes	CBA	Neonatal
Lepee (222)	2012	UK	Check list	ITS	Pediatric
Zhang (219)	2012	China	Clinical Pharmacist	RCT	Pediatric
Walsh (220)	2008	USA	EMR	ITS	Pediatric, Neo, PICU

CBA - Controlled before after study, RCT - Randomized controlled trial, ITS - Interrupted time series study, EMR - Electronic medical record

In 1995 Leape said that the two most potentially powerful system changes are to make the pharmacist a member of the team and to introduce EMR (226). Fortescue et al. did a cohort investigating the potential of different prevention strategies in minimizing potential ADEs. They identified 1) EMR with CDSS, 2) Clinical pharmacists and 3) Improved communication to have the largest impact (227). Since good evidence-based studies are lacking it has been shown that most prevention advices within pediatric medication safety has been based on expert opinion (200). But a lot of suggestion for safe practice exist and is important reading to question your own practice, find areas of research or implement clinical audits to understand the impact on your local MEs and pADEs (228-232).

2.6 KNOWLEDGE MANAGEMENT SYSTEMS

Cass claims that we usually lack the evidence we need to state the case in patient safety. And even when we have evidence there are delays and resistance to change and finally, and most frustrating, is that locally implemented changes is hard to scale up. This is a huge challenge for the health system of today to reduce duplication of efforts and sharing (233). Wrigstad shows in his thesis that the handling of incident reports is carried out in the same way all over Sweden, but it seems like the investigation is more important than the result. The results usually refer to actions close in time and place of the event. This has a major risk for building a system without memory and without a wider learning from the event (234).

Knowledge management is the process of creating, sharing, using and managing the knowledge and information of an organization (235). Today, we use a simplified collaborative software with a version control to coordinate a knowledge management system for pediatric drug therapy called ePed (9). It has grown during a 15-years period from a regional practice database coordinating the drug therapies between four neonatal hospital units in the Stockholm Region to a national system including therapies for all children *(Figure 3)*. Since 2016 it has been partly integrated to the EMRs in Sweden provided by the Swedish Drug-Information Services (236). The system has the possibility to facilitate the collaborative editing of e.g. dilution schemes, dose-range check, dosing guidelines, best-practice for reconstitution etc. and can, if needed, both visualize, coordinate and accept regional differences were evidence for knowledge-based consensus is lacking. Two of several reasons for the differences are;

1) The different regional approaches to off-label drugs in lack of product monographs
2) The different regional approaches to prevent risk of ME and ADE.

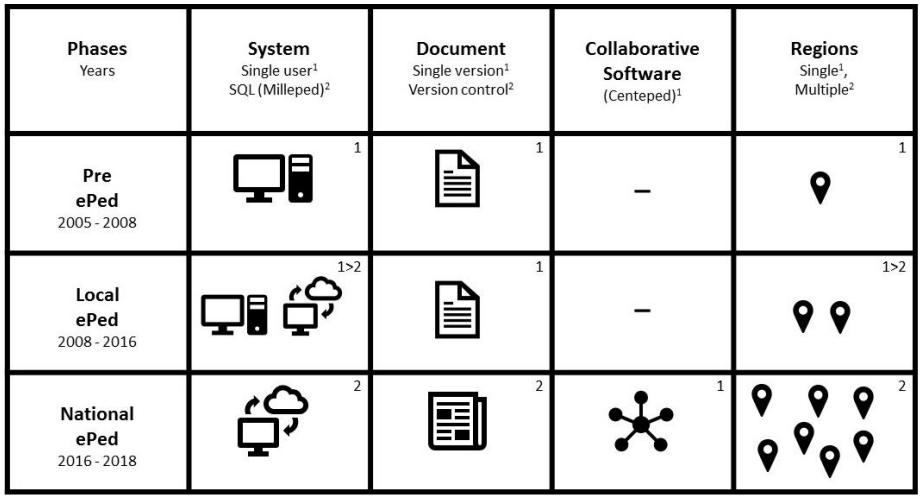


Figure 3 *ePed was initiated in 2008, for pediatric drug data curation. The workflow includes; collection of data in an SQL server system (Milleped) such as experience based, evidence based, input from clinicians and the regional collaboration network, new recommendations, data from known MEs, ADEs. All data is evaluated by the drug therapy group and consolidated and adapted to Swedish practice and published as drug instruction documents. From 2016, new or updated drug instructions are distributed nationally by a simplified collaborative software with version control (Centeped) if accepted by the participating regions.*

3 AIMS AND RESEARCH QUESTIONS

We hypothesized that off-label use and ME and ADE is common in pediatrics and that data from available drug records can help us to investigate the problem, find strategies to prevent and understand the impact of patient safety initiatives. The aims of this thesis are therefore to;

I. Estimate the prevalence of pediatric and neonatal drug use with focus on off-label
II. Investigate the characteristics of reported pediatric MEs and the prevalence of high-alert substances
III. Determine the incidence and type of ADE as identified by a pediatric trigger tool
IV. Explore pediatricians' experiences and views of a clinical decision support system

Our contribution will be to add to the understanding of the scope of the problem in a Swedish context using available drug and patient safety data in a field that lack of authorized drug data but is rich in clinical evidence and experience.

3.1 RESEARCH FRAMEWORK

The research framework is outlined in *Table 10*.

Table 10 *Overview of the research questions and overall research framework*

Domain	Research question	Article	Data source
Prevalence of off-label drug use	Estimate the use of off-label, unlicensed and extemporaneously prepared drugs among pediatric inpatients.	I	Prospective cross-sectional study, all Swedish hospitals for 2+2 days 2008
Prevalence and incidence of ME and ADE	Characterize national drug incident reports by process and identify the prevalence of high-alert substances by comparing three different high-alert lists. Investigate the use of high-alert substances in a pediatric university hospital population and its relation to local incident reports.	II	Retrospective analytical cross-sectional study of drug related incidents in pediatric inpatients nationally reported 2011-2017 and locally reported 2011+2017.
	Determine incidence and type of ADE among pediatric inpatients in relation to hospital unit and LOS.	III	Trigger-tool identified ADE in a cohort of 600 admission to four different pediatric units, 2010
Explore views and experiences of a system to detect ME in real-time, i.e. dosing errors	How do pediatricians understand and experience a decision support system for dose range-check and weight-based dose calculation?	IV	Semi-structured qualitative interviews with physicians, 2012

4 METHODS

The methodological aspects of the paper I-III are presented with subheadings as outlined by the statements published by the STROBE (strengthening the reporting of observational studies in epidemiology) initiative (237). Paper IV is presented as outlined by the standards for reporting qualitative research, SRQR (238).

4.1 PAPER I: CROSS-SECTIONAL STUDY TO FIND OFF-LABEL USE

Design: Descriptive cross-sectional or point-prevalence prospective study. The initiation of the study was based on article 42 from the Better Medicines for Children Act published by the European Union, stating that all members should "collect available data on all existing uses of medicinal products in the pediatric population" (50).

Setting: The study invited all Swedish pediatric hospitals (n=34) and included other hospitals with pediatric inpatients (n=7) that asked to be part of the study. It was carried out during 48 hours at two different time-points, in May and October 2008. The recruitment was carried out by invitation letters. Data collection was made by locally involved health-care personnel copying drug charts which were sent to the research group.

Participants: Drug orders from all pediatric inpatients (0-18 years) at the 41 included hospitals. Blood products and oxygen therapy were excluded.

Variables: The study investigated the exposure of drug orders that was prescribed off-label, extemporaneously or unlicensed. Covariates collected were age, gender, weight and cause of admittance. For all drugs the following details were recorded; indication, strength, dosage, form, route and estimated duration.

Data source and measurements: Transcribed copies of drug chart records were used as the data source. The data was entered into a study database designed with rules to identify extemporaneous (prepared in a pharmacy) or unlicensed (not authorized in Sweden) or off-label drug use. Off-label drug use was defined from seven categories; age, weight, complete absence of pediatric information, stated lack of pediatric clinical data, contraindicated, indications not stated, and route not stated in the authorized product monograph.

Bias: The paper-based model was in risk for selection bias due to incomplete drug chart collection. Therefore, the number of patients admitted during the two study periods was retrieved from the National Board of Health and Welfare showing 70% coverage. In addition, the two time-points were chosen to minimize the effect of season variations, e.g. prescribing of antihistamines during spring-time. The risk of off-label misclassification was handled with an independent check of 20% of the drug specific rules by a hospital pharmacist.

Study size: The study was aiming for the complete population; no power calculation was needed.

Quantitative variables: Number of prescriptions and patients were used as variables together with weight and age (in years) or age-group (neonates, infants, child, adolescent) as defined by EMA (239).

Statistical methods: Descriptive analysis of the proportion of off-label prescriptions over the total number of prescriptions and the number of patients with at least one off-label prescribed drug. Specific analysis of age, substance and drug class by ATC-code (anatomic therapeutic chemical classification system) was evaluated. The analysis was also carried out for extemporaneous and unlicensed drugs.

4.2 PAPER II: CROSS-SECTIONAL STUDY TO FIND HIGH-ALERT DRUGS

Design: Analytical retrospective cross-sectional study. The study was initiated by the project Best-Practice Reconstitution within the National Pharmaceutical Strategy to understand which drugs that carried a heightened risk of error (240).

Setting: The study data was retrieved from two different settings:

- *National reports:* All national Lex Maria incident reports and complaints filed to the Health and Social Care Inspectorate (IVO) during 2011-2017 in the study population of all Swedish pediatric inpatients.
- *Local reports:* All local reports registered in the Karolinska University Hospital incident database during the calendar years 2011 and 2017 in the study population of all inpatients of the local pediatric hospital.

Participants: All reports registered as ME-related were included if they had a description of the actual substance involved. Reports concerning outpatients were excluded.

Variables: The study investigated the exposure of reports involving substances on three published high-alert drug lists of variable length; short, medium and long (148,151,152). The number of reports and substance involved were collected in a study database together with:

- *National reports:* Data was collected regarding context (type, year, age-group, unit, transfer between units, region, route, potency of dose error) and modal details (where in the process the ME occurred). Including an estimated severity of harm as defined by the NCC MERP classification system.
- *Local reports:* Data contained information on the number of days a dose was administrated (DDA) for each substance.

Data source and measurements:

- *National reports:* The national reports denoted as drug-related and occurring in inpatient care were obtained as a list from the central IVO database and the anonymized reports were afterwards acquired from the six regional IVO centers.
- *Local reports:* Local reports were extracted from the hospital incident report database [HändelseVis], if classified as drug-related and occurring at the pediatric department. The number of doses administered was retrieved from the data storage of the two different EMR systems TakeCare (TakeCare, CompuGroup Medical Sweden, Uppsala, Sweden) and CCC (Centricity, GE Healthcare IT, IL, US).

Bias: The reports in the study have a risk for selection bias, as we know that incident reporting is generally poor. The reports also have a risk for misclassification as it is interpretations of written text. There is also a risk for confounding as the substance is not the sole reason for an ME to occur.

- *National reports:* Selection bias could occur, but an identification of the proportion of drug related incidents of the total number of incidents were similar in the two populations investigated (22% national and 28% local) and IVO state in 2019 that 27% of all their pediatric issues are drug related (31). In addition, a multivariate analysis was used to identify variables that were unevenly distributed between reported severity of harm. To minimize the risk of misclassification two independent persons reviewed the reports and disagreements were solved by discussion.
- *Local reports:* Selection bias was investigated by relating the number of local reports to the number of DDA to see correlations for volume. In addition, the number of Lex Maria-reports had comparable prevalence's in the two study populations, 2.5 (national) and 2.8 (local) per 10 000 patients, signaling that the number of serious events reported for other hospital admissions was similar.

Study size: The study was aiming for the complete number of reports; no power calculation was needed.

Quantitative variables: Number of reports, number of substances and DDA.

Statistical methods: Prevalence of the number of reports in the study population was reported for both populations. Proportion of reports for the different variables was calculated.

- *National reports:* Logistic regression for crude odds ratio (OR) was carried out for severe cases with NCC MERP G-I. A multivariate analysis was carried out with NCC MERP E-F as a base.
- *Local reports:* Sensitivity, specificity and positive predicted value were calculated based on the number of incidents and non-incidents in relation to DDA administrated, with the assumption that one incident report was caused by one DDA.

4.3 PAPER III: COHORT STUDY TO FIND TYPE OF HARM OVER TIME

Design: Retrospective cohort study, defining the start of the cohort as first day of the inpatient admission and ending the cohort with the last day of admission. The study was part of a larger initiative in Sweden to develop a national pediatric trigger tool (172).

Setting: The study was carried out 2010 at the pediatric department of Karolinska University Hospital in Stockholm, Sweden.

Participants: 600 admissions, with hospital stay lasting longer than 24 hours for patients under the age of 19 years, were randomly sampled into four blocks of 150 admissions each. The four-unit categories were: neonatology, surgery/orthopedics, medicine and emergency-medicine units.

Variables: The number and type of ADE and severity of ADE by NCC MERP was recorded as the outcome with the exposure of four different units over time. Co-variates regarding age, sex and number of DDA for each substance and route were recorded with type of drug, e.g. high-risk drug (151), intravenous irritating drug (241) and analgesics.

Data source and measurements: The data source was the EMR used in the study setting; TakeCare (TakeCare, CompuGroup Medical Sweden, Uppsala, Sweden) and CCC (Centricity, GE Healthcare IT, IL, US). The selected admissions in the EMR were reviewed in the first stage by trained registered nurses with a pediatric trigger tool (172) identifying potential AEs using 88 specific triggers (e.g. if naloxone was given, a morphine overdose could have occurred). All data was recorded in a study database. Every potential AE was reviewed separately by the physicians in the second review stage. To qualify as an AE, the physician had to assign the event a probability score of ≥4 on a 6-point Likert scale together with information on the severity of the AE harm by using a modification of the NCC MERP classification. Type of AE was recorded and classified as an ADE, using broad inclusion-criteria, both pADE and non-pADEs were included together with events caused by medication devices used for drug delivery. From the data storage of the EMR mentioned above, all drug orders for the included admissions were extracted and compiled by substance and route.

Bias: The study had a risk of selection bias. To minimize this, the random sample was extracted by an independent person not part of the clinical research group. The selected population represented 4.7% of the total population. Since the four groups were stratified in 150 admission each, it was possible to compare the units. But when investigating the whole hospital (all units together), the numbers needed to be weighted to minimize the effect of the neonatal-unit with longer LOS. The study was based on finding written or laboratory data by a standardized pediatric trigger-tool to minimize the risk of misclassification. Anyhow, the causal relation for a drug to be part of the ADE can be in risk of confounding in the broad definition of ADE used in this study. To minimize this, one registered nurse in the research group evaluated all findings which also was reevaluated with high reliability by a clinical pharmacologist. Another take on this was that we included an evaluation of the 17 “drug-focused” among the 88 triggers in the trigger tool, previously used in other studies to measure ADE (173).

Study size: The sample size of N=600 had a simplified calculation aiming for 10% (95% CI 7.6-12.4) admissions with an AE. This was based on best guess and data from e.g. the Swedish AE-study by Soop et al, which was relevant at the time of writing the study proposal (242).

Quantitative variables: Number of admissions, number of ADE, number of triggers, number of DDA, LOS as [date of discharge] - [date of admission] +1.

Statistical methods: Presenting ADE data in relation to time is difficult. Several denominators were used to simplify the evaluation and comparison, e.g. number of patients with at least one ADE (cumulative incidence), or different types of incident rates e.g. number of admissions with ADE divided by the time until first harm (also described as the proper incident rate and graphically presented in the paper by an inverted Kaplan-Meier), number of ADE/LOS, number of ADE/DDA, accumulated number of ADE/LOS. The neonatal unit was used as reference when calculating Risk-Ratio and Incidence-Risk-Ratio. The drug use statistics were only used to graphically relate to the extent of exposure for potential harm by drugs in the different populations.

4.4 PAPER IV: QUALITATIVE STUDY TO UNDERSTAND THE NEED OF THE PEDIATRICIAN

Qualitative approach and research paradigm: A qualitative approach was chosen to explore experiences, attitudes, thoughts and perceptions regarding the post-development of a clinical decision support system, CDSS (243). The research aimed to explore as many opinions as possible.

Researcher characteristics and reflexivity: The research group consisted of a pediatric pharmacist, a clinical pharmacologist and pediatrician and two behavioral scientists. The pediatric professionals were involved in developing the tool investigated, but the behavioral scientists were included from another organization. The behavioral scientists carried out the interviews with the informants. Both scientists had previous PhD-experience into research within the field of pharmacotherapy and qualitative studies (244,245).

Context: The CDSS investigated was part of the ePed system (9) and was integrated in the physicians EMR system. The CDSS checked for the correctness of a drug order by testing the dose towards a pre-defined range for a specific substance. The CDSS also demanded the insertion of a dose-calculating weight and the possibility to order the dose by weight-based dose calculation, e.g. 10 mg/kg generated 100 mg for a 10 kg dose-calculating weight.

Sampling strategy: The snowball strategy was used were the first informants mentioned another colleague to be included. This was carried on until saturation in information was reached (243).

Ethical issues pertaining to human subjects: No ethical permit was required but all participants gave informed consent.

Data collection methods: Pediatricians working at pediatric wards in the Stockholm County were interviewed during the year 2012. The interviews were carried out in the workplace of the informants and continued for 25-40 minutes. Each interview begun with information of the study and consent. The interviews were semi-structured. Questions were modified after response, but all interviews begun with questions regarding difficulties in the prescribing process. More specific questions followed regarding CDSS.

Data collection instruments and technologies: Audio files were recorded during the interview.

Units of study: Seventeen pediatricians participated as informants. They consisted of 4.9% of the pediatrician work-force in Stockholm County at the time. Sex was equally distributed as was primary type of care units. Most of the participants had a consultant role (65%).

Data processing: Interviews were transcribed verbatim into text.

Data analysis: The analysis went through several steps including reading and categorizing the data into sub-categories. A holistic approach was used to name each sub-category together with matching quotes.

Techniques to enhance trustworthiness: Two experienced researches did the data analysis. The program NVivo8 (QSR International, Australia) was used as a tool in the organization and categorization of data. The trustworthiness of the findings was discussed after analysis with the research group.

4.5 ETHICAL CONSIDERATIONS

Paper I-III were conducted with separate ethical permits from the Regional Ethical Review Board in Stockholm and the studies were performed accordingly. The ethical considerations addressed the use of patient specific data to find population-based exposures of off-label use, ME and ADE. All data in paper I and III was handled with personal identification numbers to avoid duplication and giving the possibility to connect data to medication history. After this was done all connection to patient data was removed and discarded. Paper II was performed without any personal identification numbers and all incident reports were retrieved with all patient data shielded. Paper IV was in no need of ethical permit, but it involved informed consent from the informants with the possibility to withdraw from the study at any time. All studies were approved by the head of the institution where they were conducted. Since the research was retrospective, the patient which data was used can unfortunately not take benefit from the individual findings. One of the benefits was the possibility to use the data to better understand and prevent future ADEs.

5 RESULTS

The results are described with the same tool used for the methodological aspects of paper I-III, outlined by the statements published by the STROBE initiative (237). Paper IV is presented as outlined by SRQR (238).

5.1 PAPER I: OFF-LABEL DRUG USE IN HALF OF THE PRESCRIPTIONS

Participants: Drug charts for 2 973 patients were retrieved and 2 947 (99%) of the patients were included for analysis.

Descriptive data: Most of the patients (33%) were under the age of 1 year with 54% boys. They were exposed to 11 294 prescriptions with known indication for 89% of the prescriptions, mainly pain (19%), infection (11%) and prematurity (9.8%). The drugs prescribed were mainly used for treatment (56%), followed by prevention (34%) and diagnosis (4.3%). The most common routes were oral (40%) and intravenous (35%). Forty-three percent had their prescription for more than one week, 22% for less than one week and 35% had single doses.

Outcome data: Seventy-one percent of the children received at least one drug off-label extemporaneously or unlicensed. Of the 744 authorized drugs, 41% was given off-label and of the 11 294 prescriptions, 34% was off-label. Absence of information was the most common cause for off-label classification (39%) followed by age (17%), indication (14%), route of administration (10%), stated lack of pediatric data (8.8%), weight (5.9%) and contraindication (4.6%). The proportion of causes varied by age-group. *Table 11* describe the most common substances prescribed off-label, extemporaneously or unlicensed.

Table 11 *Number of prescriptions with the most common substances prescribed*

ATC group	Drug	Type	N (%)
B	Carbohydrates	OL	479 (4.2)
B	Electrolytes without carbohydrates	OL	341 (3.0)
N	Paracetamol	OL	320 (2.8)
A	Multivitamins	UL	216 (1.9)
N	Morphine	EX	181 (1.6)
B	Sodium chloride	OL	113 (1.0)
V	Allergen extracts	UL	108 (1.0)
C	Epinephrine	OL	103 (0.9)
N	Morphine	OL	102 (0.9)
N	Midazolam	OL	87 (0.8)
N	Caffeine citrate	EX	86 (0.8)
J	Sulfamethoxazole/trimethoprim	OL	84 (0.7)
M	Diclofenac	OL	83 (0.7)
B	Heparin	OL	81 (0.7)
-	**All off-label**	**OL**	**3 879 (34)**
-	**All extemporaneous**	**EX**	**1 126 (10)**
-	**All unlicensed**	**UL**	**514 (4.6)**
-	**All types**	**OL+EX+UL**	**5 519 (49)**
-	**All prescriptions**	**-**	**11 294 (100)**

Off-label (OL), Extemporaneously (EX) or Unlicensed (UL).

Main results: 50% of all prescriptions were carried out off-label, extemporaneously or unlicensed, which equals 1.9 prescription per patient. The proportion of prescriptions of these classes varied by age-group, being 79% for neonates, 55% for infants, 47% for children and 34% for adolescents, or expressed as average number of prescriptions in *Table 12*.

Table 12 *Average number of patients, prescriptions and prescriptions per patient (95% CI) in each age-group being on-label or OL+UL+EX (off-label, extemporaneously or unlicensed)*

Age-group	N (%)	Prescriptions (%)	% of N with (OL+UL+EX)	Prescriptions (OL+UL+EX)	On-label
Neonate	476 (16)	1 875 (17)	87%	2.7 (2.5-3.0)	1.2 (1.1-1.3)
Infant	698 (24)	2 644 (23)	78%	2.1 (1.9-2.3)	1.7 (1.6-1.8)
Child	1 043 (35)	3 800 (34)	64%	1.7 (1.6-1.8)	1.9 (1.8-2.1)
Adolescent	730 (25)	2 975 (26)	56%	1.4 (1.2-1.5)	2.7 (2.5-2.9)
All	**2 947 (100)**	**11 294 (100)**	**71%**	**1.9 (1.8-2.0)**	**1.9 (1.9-2.0)**

Other analyses: Analysis of drug-class contribution to the off-label prescribing was also done, showing ATC-group N (nervous system drugs, 23% of prescriptions) with paracetamol as the most off-label prescribed substance (11% of prescriptions). In ATC-group B (blood and blood forming organs, 34% of prescriptions) the most abundant prescribing of off-label drugs occurred mainly due to absence of pediatric information (54% of the off-label classifications).

5.2 PAPER II: HIGH-ALERT DRUGS CAUSING SEVERE HARM

Participants: Two populations were used.

- *National reports:* 204 reports, classified as medication related among pediatric inpatients were retrieved and after exclusion 160 (78%) reports remained, 144 of 150 (96%) Lex Maria and 16 of 54 (30%) complaints. Most exclusions were carried out among the complaints due to; no inpatient care (12), duplicates (12) and insufficient data (10).
- *Local reports:* 1 221 incident reports classified as medication related among pediatric inpatient were retrieved and after exclusion 885 (72%) remained. Main exclusion being insufficient data on drug therapy (234), medicine technique (36) and no drug cause (35).

Descriptive data: Reports were categorized as described below for the two populations

- *National reports:* Context dependent variables showed 20-30 reports each year except in the first years which could be due to startup effect of the IVO process. Reports were mainly filed for the age group 0-6 years (127, 79%) from large hospital regions (108, 67%) and for drugs administrated by the intravenous route (105, 66%). Potency errors were made in 105 (66%) of the reports. The reports involved processes of prescribing (57, 36%), dispensing (45, 28%) and administration (58, 36%) which were evenly distributed. Wrong dose was most common in the process of prescribing (34, 21%).

Wrong concentration was most common in the process of dispensing (30, 19%). Different types of dosing errors (30, 19%), e.g. wrong rate (13, 8.1%) were most common in the process of administration together with identity errors (21, 13%). Other types of errors like omissions and monitoring errors were made primarily in prescribing (12, 7.5%) and administration (7, 4.4%).

- *Local reports:* Local reports were not described by context or modal details as above. Instead details regarding the population drug use was reported. 530 184 DDA was administered during the study period. Details on type of substances on a second-level ATC-code showed a correlation to numbers of incident reporting and number of DDA.

Outcome data: The two populations were investigated on the severity of harm by NCC MERP index.

- *National reports:* The prevalence of reports in the pediatric inpatient population were 2.5 per 10.000. Thirty-two (20%) of the reports were classified as no harm (NCC MERP A-D), 98 (61%) temporary harm (NCC MERP E-F) and 30 (19%) severe harm such as long-term harm, major interventions or death (NCC MERP G-I). A multivariate analysis showed that reports classified as no harm, were more frequent among complaints. Reports classified as severe harm were more frequent among older children >6 years, other type of modal events (not dosing or identity errors) and for substances on the high-alert lists.
- *Local reports:* The prevalence of the 14 reports that ended up as Lex Maria in the pediatric inpatient population were 2.8 per 10.000 admissions. But counting all 885 reports, the prevalence was 1.7 per 100 admission. The severity as expected for an incident reporting system for all types of incidents was much lower with 90% of the reports classified as NCC MERP A-D.

Main results: The two populations have main results with clinical patient safety implications of the high-alert lists.

- *National reports:* The substances from the three high-alert lists (short, medium and long list) were present in 17/35/47% of the national reports and were more frequently part of reports with severe harm. The processes of prescribing, dispensing and administration have different types of ME with need for different strategies.

Table 13 *The number of local reports with the number of DDA for each high-alert list. Showing the odds-ratio and a sensitivity analysis removing insulin (ATC group A10).*

High-alert list	N (%)	DDA (%)	Prevalence	OR (CI 95%)	Insulin excluded
Short	88 (10)	33 420 (6.3)	0.26%	1.6 (1.3-2.0)	1.4 (1.1-1.8)
Medium	249 (28)	68 247 (13)	0.36%	2.7 (2.3-3.1)	2.5 (2.1-2.9)
Long	294 (33)	95 049 (18)	0.31%	2.3 (2.0-2.6)	2.1 (1.8-2.4)
All	**885 (100)**	**530 184 (100)**	**0.17%**		

- *Local reports:* The substances on the high-alert lists have an odds-ratio of 1.6 (1.3-2.0) for the short to 2.7 (2.3-3.1) of the medium long list compared to non-alert substances to be part of an incident. Some drugs as immunosuppressants (L04) and especially insulin (A10) were overrepresented while a larger group was underrepresented as drugs for acid related disorders (A02) in incident reporting in relation to DDA *(Figure 4)*. A sensitivity analysis removing insulin showed similar numbers as presented in *Table 13*.

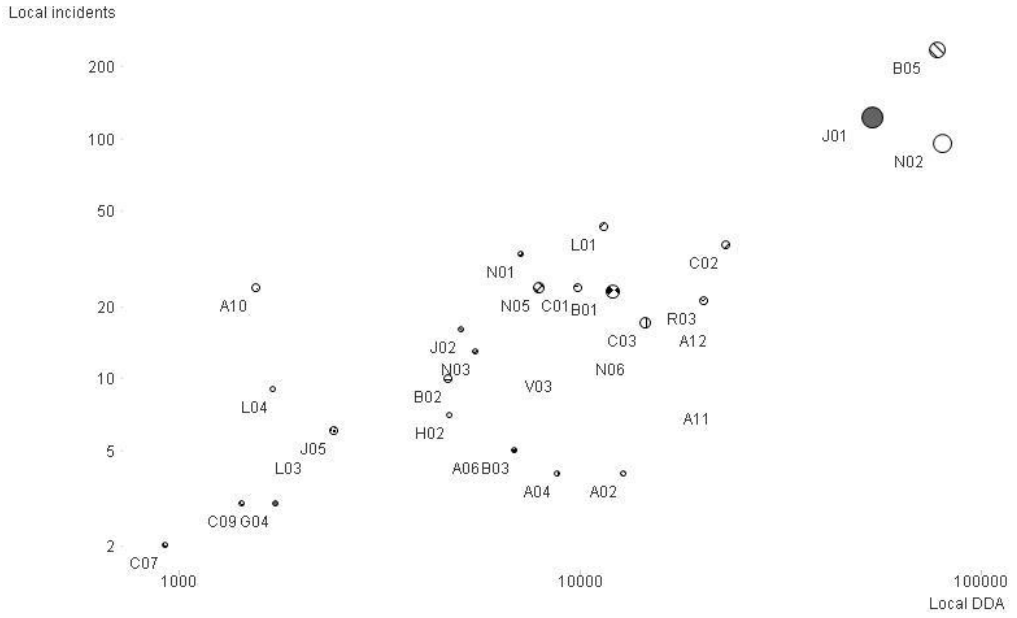


Figure 4 *Displayed are all medication groups related to local incident reports during calendar years 2011 and 2017 by second level ATC-code. The axis represents the logarithmic number of locally reported incidents (y-axis) and DDA (x-axis). The size of the bubbles represents the relative volume of national reported incidents 2011 to 2017. No bubbles in the upper right corner of the ATC-code means no recorded national incidents [with permission from the publisher]*.

Other analyses: Other analyses were done regarding the number of substances included.

- *National reports:* For the national reports we found 80 substances and the three high-alert lists identified 6.2/27/35% substances from the short/medium/long list. The process of prescription involved the highest number of all types of substances (57%). The process of dispensing involved the highest proportion of substances of the three high-alert lists, 14/34/55% of the substances. In the process of administration, the three high-alert lists identified 11/36/33% of the substances, showing no additional help from the longest high-alert list.
- *Local reports:* When the substances causing the most severe harm in the national reports were added to the medium-high-alert list, the list would cover 39% of all local reports, but with lower specificity.

5.3 PAPER III: DRUG-RELATED VASCULAR HARM PEAKS ON DAY FIVE

Participants: From a pediatric hospital population of 12 760 admissions we randomly sampled 600 (4.7%) admissions from four different types of units. 150 admissions from the neonatal units, 150 from the surgery/orthopedic units, 150 from the medicine units and 150 from the emergency-medicine units.

Descriptive data: The population characteristics varied between the four units. Median age was higher in the surgery/orthopedic units (7.4, IQR 10) and medicine units (5.6, IQR 9.7) compared to the emergency-medicine units (1.3, IQR 2.9) and the neonatal units caring for premature born children. The distribution of sex was even over the units with a slight overrepresentation of males (52% in the population). The LOS differed significantly for the neonatal units and the rest of the units, with a median LOS (IQR) of 12 (27) compared to 4 (2-3). The characteristics were comparable to the study population of the whole hospital except for an overrepresentation of longer LOS at the neonatal units.

Outcome data: The AE found by the trigger-tool and deemed as drug related (ADE) by the reviewing physician, were more present in the neonatal units as shown in *Figure 5*. The comparison between the units was better illustrated by the ADE per LOS showing only a significant difference for the emergency-medicine units from the other units. With regards of DDA this difference was visible but not significant. Regarding harm classified as NCC MERP ≥F the proportion was higher among ADEs from the medicine and emergency-medicine units. The cumulative incidence in the weighted population was 20 (17-24) per 100 admissions with ADE. Anyhow, if only using "drug focused triggers" without involvement of drug-devices, the cumulative incidence was 7.2 per 100 admissions.

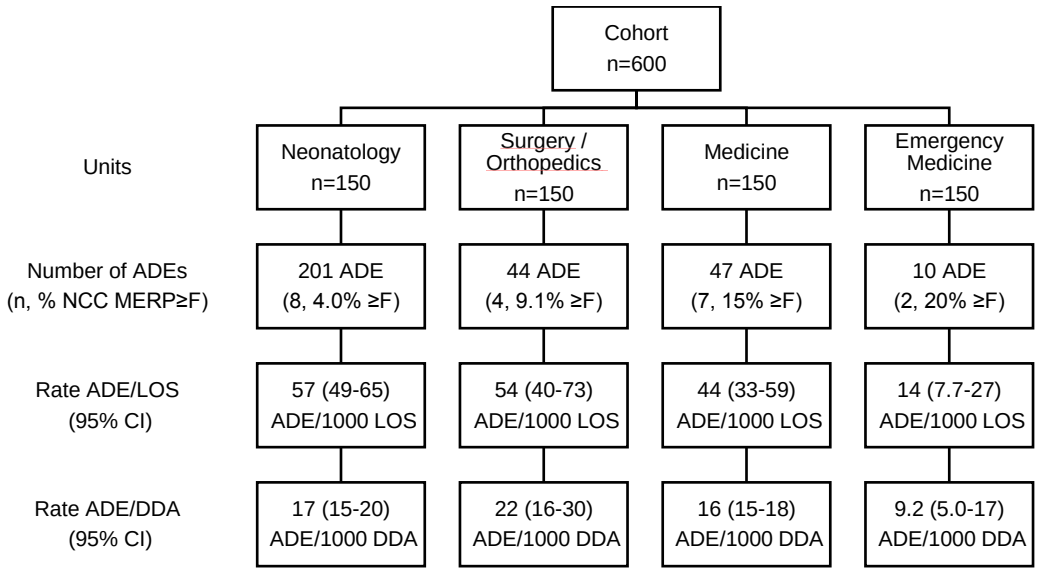


Figure 5 *All identified ADEs with rates for ADE/LOS and ADE/DDA stratified by unit category.*

Main results: The type of ADE variation over time can be displayed in different ways. In *Figure 6*, the type of harm is displayed in absolute numbers during different time intervals. 302 ADEs were identified with information on type of harm. Pain due to insufficient treatment (55, 18%) was mainly present during the first days at the surgical/orthopedic units. Skin, tissue or vascular harm (117, 39%) peaked at day five at the neonatal and medicine units. Hospital-acquired infections (39, 13%) were mainly seen at longer hospital stay *(Figure 6)*. Other type of ADE (92, 30%) peaked during the first days mainly due to insufficient treated hypoglycemia (12, 4.0%) during the first days in the neonatal units and consisted of a large flora of events. Among them the most serious events occurred, like bradycardia and allergic reaction affecting vital parameters (22, 7.3%). At day 20 the Kaplan-Meier curve were saturated indicating no new admissions with ADE in the population (data not shown here). The rate for LOS without ADE (95% CI) until median 25th percentile was 3 (3-3) days in the neonatal units, 4 (3-5) days in surgical/orthopedic, 5 (4-6) days in medicine units and 13 (9-17) days in emergency-medicine unit. Still patients previously harmed got exposed to additional ADEs later during their hospital stay.

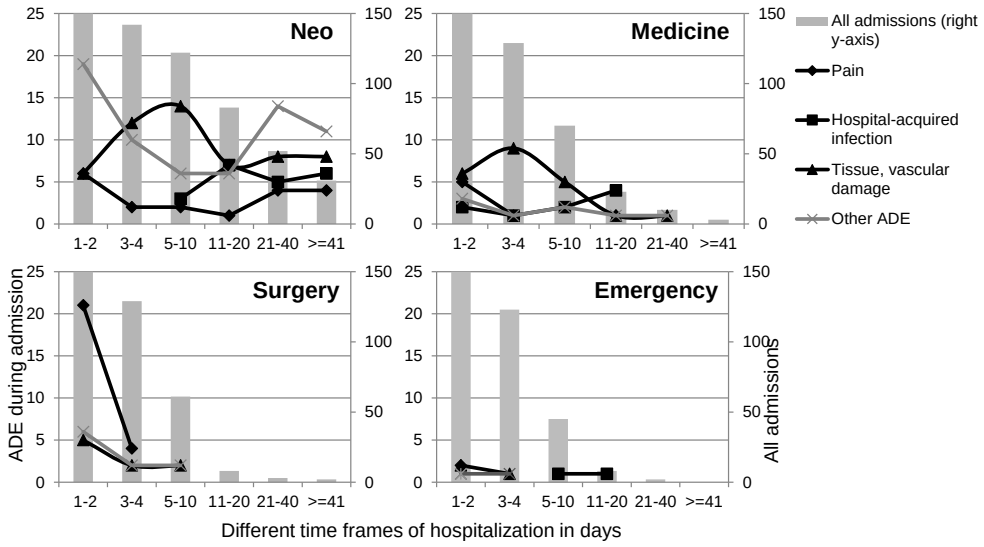


Figure 6 *Absolute number of ADE (y-axis) over LOS (x-axis) in six different time-intervals (with evenly distributed LOS) are displayed for each unit with lines indicating type of harm. Bars represents the number of admissions (second y-axis).*

Other analyses: No correlation between ADE and drug therapy was done due to risk of confounding and making correlations that the study was not set to answer. For this analysis we lacked e.g. data on which drugs the reviewing physician associated the harm to. Instead the number of DDA was presented to inform about the exposure of drug load. Of 17 794 DDA 64% was used at the neonatal units, 10% at the surgical/orthopedic units, 20% at the medicine units and 6.1% at the emergency-medicine units. High-alert drugs and vascular irritating drugs were mainly present at the neonatal ward, showing higher drug load with longer LOS. Intravenous route was also seen to decline over time in favor of the oral route.

5.4 PAPER IV: PEDIATRICIANS' NEEDS FOR CLINICAL DECISION SUPPORT DEVELOPMENT

Synthesis and interpretation: From the processing and analyzing of the interviews we ended up with six categories and fourteen subcategories *(Table 14)* describing the pediatricians' understandings, experiences and views of CDSS. The study also generated eleven suggestions for development as stated in the supplement of the paper.

Table 14 *Categories and subcategories identified*

Category	Subcategory
1. Use	• Use is influenced by clinical experience • Habit leads to increased use • Good that the CDSS is not compulsory
2. Benefit	• Prompts consideration • Help with calculations reduces errors • Greatest benefit in emergency care
3. Confidence in the weight-based dose calculation and dose-range check	• Use of a manual dose-range check • Double-checking the dosage
4. Situations in which the doctor disregards the weight-based dose calculation and/or the dose-range check	• When it is easy to work out the dosage using mental arithmetic • In case of special indications
5. Misgivings/risks	• False security and non-disease specific warnings • Human error is unavoidable • Wrong dose-calculating weight
6. Development potential	• Optional or compulsory - registering and signing for weight

Links to empirical data: Quotes were used to exemplify the categories and subcategories outlined in *Table 14*.

1. The CDSS was described as simple to use, *"It's straightforward. There's nothing difficult about it"* and *"The module works well"*. But the CDSS was also associated with a false sense of security. The informants expressed that with time and experience they came to trust the system more. The possibility to control the CDSS was appreciated. *"…It doesn't forbid me from using that dose."*
2. The views of the benefit from using the system varied, while some favored the possibility to calculate the dose by weight, some valued the dose-rang check. *" the dose-range check is of course one additional safety check that prevents you from making disastrous mistakes*". Those who had experienced a warning were positive about it. The warnings seemed to be most important in emergency care and for substances previously involved in disastrous miscalculations.
3. The physicians had confidence in the CDSS but usually did their own assessments and rechecked the dose as well. Sometimes the dose-range check gave information that was contradictory to other guidelines *"it calculates, not in accordance with the national dosing guidelines then, or I don't know"'*
4. In some situations, the physician disregarded the CDSS, e.g. when the dose is easy to calculate *"It depends on what kind of drug it is. Sometimes I don't use it, if it is*

something that is easy to work out per kilogram". Also, there were some occasions when the indication was rare and required a higher dose than normal, *"So sometimes we do prescribe dose levels other than what is normal. Definitely, there may well be an indication for which some other dose has to be given".*

5. For misgivings and risks, some physicians were thinking about the risk of turning into a "checklist-person" rather than using your own mind. But the risk of human error is always present *"the dose was right, but I didn't see that it said milliliters instead of milligrams"*. But again, the risk of entering the wrong weight would give the same error. "*So, there ought to be a reasonableness check on dosing weight as well".*
6. The informants also saw potential for development. The weight was central, and the informants discussed if it should be mandatory or not. For example, some suggested that the weight should be differentiated depending on the age as the need for the CDSS becomes less important for older children. Also, the weight entered into the system by the nurse, should be able to be used by the physician as a dose-calculating weight. *"Having to sign for the weight when the nurse has already taken a weight is an unnecessary step. Because that's something that I can't check"*

6 DISCUSSION

The reason for doing the study was to explore the magnitude and enhance the understanding of off-label drug use, MEs and ADEs among Swedish pediatric inpatients.

6.1 KEY FINDINGS

In paper I, we had three key findings. 1) The use of drugs outside an authorized product monograph was prominent among Swedish pediatric inpatients with half of the drug orders prescribed off-label, extemporaneously or unlicensed. 2) The exposure was related to age-groups, affecting mainly the neonatal population, which was found to have the largest need for regulatory solutions. 3) A list of all identified off-label, unlicensed and extemporaneous drugs was compiled for Sweden.

In paper II, we had five key findings. 1) 17/35/47% of the IVO registered national reports contained substances from the three high-alert lists investigated (a short/medium/long list). 2) The listed high-alert drugs were found in even higher proportions of reports with more severe harm (NCC MERP G-I) 3) The drug handling processes were in close relation to the modal type of the error, e.g. distribution did mainly relate to dosing errors due to wrong drug concentration. 4) The number of reports at a local university hospital did trend with the number of DDA for each second-level ATC-code. 5) The prevalence of the local reports among the number of DDA used was low (0.17%) but it was higher among the number of DDA generated by the high-alert list substances (0.26% short/0.36% medium/0.31% long).

In paper III, we had four key findings. 1) We identified a high incidence of ADEs. Partly because the term ADE was stretched to include harm due to devices used to deliver drugs identifying skin/tissue/vascular harm, hospital-acquired infections and insufficiently treated pain. 2) Most ADEs were minor harm, but more severe harm (NCC MERP ≥F) was anyhow seen weekly in the population studied. 3) The type of ADE varied with LOS and between units. 4) When comparing this study with other studies it was important to understand the broad inclusion of ADE and the denominators used.

In paper IV, we had three key findings. 1) Views of pediatricians of the CDSS they worked with were visualized in the post-developmental process of the CDSS trough six identified categories and fourteen subcategories together with a list of suggested changes. 2) The CDSS was an appreciated support, with opportunities for improvements. 3) The qualitative method was effective in identifying unfinished parts in the development of the CDSS.

6.2 INTERPRETATIONS AND RELATIONS TO PREVIOUS STUDIES

6.2.1 Paper I: The off-label drug use

Sweden has a similar off-label situation as reported from other countries. An early review from 2006 regarding studies from five neonatal intensive care units and 15 pediatric intensive care units and general wards showed 24-79% off-label and unlicensed orders with higher exposure (80-93%) of the neonates (52). Later reviews have confirmed those numbers but still within a wide range. For example, Magalhães et al. included 34 studies with 42-100% of the patients experiencing an off-label drug (67). The variation among the included studies was attributed to different definitions, were ours cohered to the most used definition proposed by Turner (246), which was later refined in a Delphi-process by Neubert (68). Balan et al. revisited the topic in 2018 and reviewed 101 off-label studies. They categorized the studies into different themes. Our study was categorized within "a combination of settings" and the off-label rate between those studies was found to be similar over all included years, 1996 to 2016 (46). Despite initiatives to enhance development of pediatric medicines, the off-label frequency over time do not change rapidly. This has also been shown in a recent Israeli study (247). They found that the change over a decade was non-existent, partly due to the high use of old substances. Those substances lack proper initiatives for industry to acquire approved pediatric indication, which is also seen in the ten-year report of the European pediatric initiative (70). Investigating the top substances prescribed off-label in our study *(Table 11)* we found two regulatory changes from 2008 until today. The first occurred with a multivitamin solution when the MPA changed the possibility to prescribe imported nutritional products for clinical indications as unlicensed drugs. This created problems for the families affected, since no other reimbursement-system took over the cost for those treatments. At the same time there were issues regarding the appropriate formulation and composition of the multivitamin product used. Both circumstances led to the transfer to an extemporaneously prepared multivitamin-product designed for neonatal care. Another example was the transfer of extemporaneously prepared caffeine citrate (in 10 mL injection flasks and 100 mL bottles for oral use) to the registered product Peyona (in 1 mL glass ampoules intended for both intravenous and oral use). Peyona was registered as an orphan drug in European Union in 2009 based on clinical documentation for the indication apnea of prematurity. Due to its remarkedly good effect on reducing the number of days on positive-pressure ventilation, health-economy studies showed that it could be sold at a very high price with cost-benefit (248). The market for a pediatric drug was identified and the old extemporaneously prepared drug could be replaced by a drug with the long-awaited product monograph. But despite the authorization of Peyona, some hospitals still continued to use the preserved extemporaneously prepared oral solution of caffeine citrate to avoid the excessive cost of approximately 20 Euro/ampoule (249). As described in the background of this thesis, this would be an example of "organizational off-label prescribing" or off-label prescribing due to economical purposes, where the patient would be at risk of not being insured in the case of an ADR. But as well as the need for better and safer medicines in pediatric care, the costs for orphan-drugs are noticeable and need to be questioned (250).

An international definition of off-label use is still lacking, but it is important to distinguish between the regulatory and the scientific need of such. The regulatory aspects focus on regional demands while scientific aspects are expressed mainly to be able to compare data. When comparing data, most studies identified off-label use by age or dose (46). In our study the most common off-label situation was the total absence of pediatric data, e.g. fluid therapy. But it could be argued that it is not off-label, since fluid therapy should be individualized based on nutritional requirements and ordered from nutritional and fluid guidelines. Anyhow, those drugs should not be on the top priority list for regulatory action, but rather be decided if they are to be defined as off-label, for better comparison between future off-label studies.

6.2.2 Paper II: Medication errors and high-alert substances

We found a prevalence of national incident reports to be 2.5 reports per 10.000 hospital admissions. It is well known that incident reports generate an underestimation of the actual MEs, but also that they have the possibility to identify more severe events (130). In a newly released report by IVO, it was stated that ME was the most common type of Lex Maria incident report in pediatrics (31). In our study of Lex Maria reports regarding children we included complaints filed by parents or patients. The reporting by parents and patients have previously been shown to identify additional MEs (251). By a multivariate analysis we found that those complaints were more often leading to no-harm, and that severe reports (NCC MERP G-I) were more often reported as events concerning older children and ME-types like, e.g. omission-, monitoring- and wrong technique-errors. One explanation could be that ME-types not causing a severe effect might be harder to detect, e.g. omissions. Alternatively, it is because dosing- or identity-errors were more commonly reported among younger children. Otherwise the modal characteristics of the ME-types were dependent on the drug handling process. Dose errors occurred primarily in prescribing, wrong concentration during dispensing and wrong rate during administration. The pattern was quite the same in a Danish pediatric inpatient study investigating the national incident reports. They found 487 ME during five-years which is far more than our 160 reports in seven-years, which could be due to the Danish anonymized reporting system (252).

Björkstén et al. investigated 585 reports between 1996-2006 when the system was handled by the national board of health and welfare in Sweden (253). They focused on ME and malpractice cases among nurses and the material included 43 children. In the total population they found wrong dose (41%), wrong patient (13%) and omission of drug (12%). The Swedish malpractice-study went further and classified the reports based on system and individual contributing factors where slips and lapses where more common than knowledge and rule-based errors. System errors were most commonly described as “role overload”, “unclear communication of orders” and “lack of, or access to guidelines” (253).

To help in the detection of errors with the risk of severe outcome, certain high-alert drugs can be pointed out as error-prone or with a narrow therapeutic window. The three high-alert lists

investigated in this study had differences in length. Logically it would result in different number of reports detected, which it did. As suspected, substances on all the three lists were also more prevalent among severe cases compared to non-alert substances. A significant overrepresentation of high-alert drugs was also seen for the long list in a US study on neonatal incident reports (158). A higher occurrence of reports related to the high-alert lists was also identified at our local university hospital. Some drugs, like insulin had low usage but was present in many reports. One patient-safety initiative carried out with insulin during this time was changing the strengths used at the neonatal ward from 0.1 and 1 E/mL to 0.2 and 1 E/mL. The events with insulin did over the two years studied decrease from 17 (2011) to 7 (2017). Insulin is one of the well-defined high-alert substances, together with morphine, fentanyl and potassium. Those drugs would preferably be suggested for any short list.

Another way of defining a high-alert list would be to focus on the usability. For example, the A-PINCH list abbreviated the first letter of the high-alert drugs to remind the user about the risk of Anti-infective, Potassium, Insulin, Narcotics, Chemotherapeutics and Heparin (155). The Never-Event list by the National Health Service in England combined only their top high-alert substances with processes including: mis-selection of high strength potassium solutions, overdose of insulin due to abbreviations or incorrect device, overdose of methotrexate in non-cancer treatments, mis-selection during sedation of high strength midazolam and any wrong route administrations (154). In paper II we suggested a practical approach, creating different high-alert lists based on process in the Swedish context. This was due to our finding that the process was related to the number of substances and ME-types.

Prescribing did mainly cause dosing errors of many substances. Since an electronic tool is available for dose-range check at most pediatric hospitals, those identified substances should all be included with suitable ranges to avoid warning fatigue.

Dispensing was closely related to wrong concentration errors and substances on the long list. The high-alert list should trigger risk-assessments of substances with identified risk of look-a-like or sound-a-like problems before they enter the medication room. A suggestion exists for this practice in a resolution stated by the Committee of Ministers in the European Union (254) and a model for the Swedish context has been developed (255).

Administration was involved in many different ME-types and with substances primarily from the short or medium list. Therefore, initiatives should suggest a short list combined with ME-types. The short list would be suitable when reaching out to the large community of nurses and in the development of training activities based on previous published experiences (145,146).

In addition, local hospitals have a need to include “jokers” or substances that carry specific problems in their population due to local treatment strategies (147). The way high-alert lists have been used clinically in other pediatric hospitals vary in the literature. For example, standard concentrations have been implemented for high-alert drugs (256). Double-checking has been suggested for high-alert drugs (witness the process, independently check calculations, check preparation, check identity, verify route) (257), but evidence is poor (258). An

observational study introduced a three-step intervention program releasing part of information regarding safe handling and known error prone drugs, starting with a handout of known errors, followed by educations and a comprehensive book with detailed information. This reduced the ME-rate from 88 to 49% of patients experiencing any error (259). But despite good efforts in reducing the number of events with high-alert drugs they keep on returning as illustrated with heparin, a drug with many available concentrations and a narrow therapeutic window (260). The case reveals both individual and system failures as, difficulty of interpreting a label with many zeros and look-a-like vials. The article concludes by encouraging everybody to review their medication processes.

6.2.3 Paper III: An extended view on adverse drug events

Paper III was based on data from a validation-study of a Swedish pediatric trigger-tool (172). Previous results from the validation showed a positive predictive value of 22.9% for the 88 triggers investigated (of which 17 were drug-focused). In addition, 34% of the 600 of the admissions were found to have an AE even if in the study-protocol aimed for 10% AE. One reason for the notable three-fold difference from the expected, was the variable and sparse data available at the time of setting the study base-line (173,213,261,262). Later, studies have shown higher, but still variable incidences as shown in *Table 15*, which both displays incidences of AE and ADE.

Our presented ADE-study included all AE from the validation-study classified as drug related (62% of the AE). This proportion was in line with Kirkendall who identified that 68% of the AE had an overlap with ADE (212). However, all other previous studies have used a strict criterion when identifying ADE, with up to 18 "drug-focused triggers" showing a direct causality to the drug. Our study differs by using a wider definition of ADE, allowing for the drug itself not to be the source of harm, e.g. omissions, infections and skin/tissue/vascular harm due to devices used for drug treatment. So, instead of saying – those AEs were classified as ADEs because they were found by a "drug-focused trigger" – we allowed the reviewing physician to evaluate and document a potential relationship to drug-therapy based on the type of AE. With this methodology it could be argued that those ADEs should be defined as AEs due to a vague causality. On the other hand, by using the term ADE we visualize the need for health-care staff, like pharmacists and physicians who work mainly with the drug itself, that they need to assist in the drug safety of intravenous access and omissions. Hopefully, the study will raise questions as; How can safer reconstitution change the risk of infections? Can the drug be switched to oral therapy? How do we lower the risk for cutaneous harm? How do we monitor the risk of omissions? In our study, skin/tissue/vascular harm, hospital-acquired infections and insufficiently treated pain were the most frequently occurring in the pediatric population. This have partly been stated in several other articles. For example, a large part, 11% of the AE, in the Kirkendall study was caused by health-acquired infections and the article discussed the lack of triggers to document the frequent occurrence of peripheral catheter related events (212). In a neonatal population studied by Sharek et al, they identified AE by vascular (15% of AE) or

infection related harm (28% of AE) to be the most prevalent causes (213). Similar data of harm by hospital-acquired infections (14% of AE) and vascular harm (19% of AE), have been shown by Stockwell in their mixed pediatric population (214). Noteworthy was that none of those studies included insufficiently treated pain. However, Maaskant et al. used a trigger-tool where insufficiently treated pain and nausea/vomiting were the only triggers identifying ADEs (174). Holdsworth et al. carried out prospective chart reviews with the help of clinical pharmacists identifying six ADE and eight potential ADEs per 100 admissions in a pediatric intensive care unit and at a general pediatric ward, with insufficiently treated pain being the most common ME (166).

Table 15 *Comparison between trigger-tool studies in pediatrics (investigating AE and/or ADE). Year relates to the year the data was collected.* [1-3]*Data compared in paper III with different denominators.*

Year	Author	Patients	T	N (harmed)	X type (% NCCMERP≥F)	X /1000 LOS	X /100 N	N with X /100 N	Ref
2005 -08	Burch	Rehabilitation	15	59 (14)	17 ADE (5.9%)	~10	29	24	(208)
2002	Takata	12 Hospitals	15	960 (70)	107 ADE (3%)	15.7	11.1	7.3[1]	(173)
2008	Matlow	Academic center	47 12	1692 (172) 1692 (25)	210 AE (-) - ADE	- -	12.4 -	10.2 1.5	(209)
2014	Call	Oncology	6	390 (-)	33 ADE (18%)	-	8.5	-	(210)
2013	Maaskant	3 Wards+Oncology	17	369 (18)	19 ADE (9%)	10	5.1	4.9	(174)
2014	Silva	Teaching hospital	17	240 (45)	62 ADE (0%)	20.3	25.8	18.7	(211)
2009	Kirkendall	Academic center	53 18	240 (62) 240 (-)	88 AE (24%) 60 ADE (-)	76.3 -	36.7 25	25.8 -	(212)
2004 -05	Sharek	Neonatal	17	749 (-)	554 AE (40%)	32	74	-	(213)
2007 -12	Stockwell	All Teaching Non-teaching Chronically ill	27	3790 (303) 1910 (-) 1880 (-) -	414 AE (47%) - AE (~46%) - AE (~60%) - AE (-)	19 27.2 5.1 33.9	10.9 21.1[2] 2.0 30.5[3]	8.0 - - -	(214)
2010	Nydert	All (non-weighted) All (weighted) Neonatal Surgery/orthopedic Medicine Emergency-medic. All drug-focused	88 88 88 88 88 88 17	600 (129) 600 (121) 150 (53) 150 (39) 150 (29) 150 (8) 600 (35)	302 ADE (7%) 250 ADE (8%) 201 ADE (4%) 44 ADE (9.1%) 47 ADE (15%) 10 ADE (20%) 43 ADE (4.6%)	49.5 47.4 56.9 54.2 44.1 14.3 7.0	50.3 41.7 134 29.3 31.3 6.7 7.2[1]	21.5 20.2[2] 35.3[3] 26.0 19.3 5.3 5.8	Paper III

T - Triggers, N - Number of admissions, X - type of harm, V - vascular harm, H - Hospital acquired Infection, P - Insufficiently treated pain.

Another way of comparing the studies would be to investigate the severity of the events. For example, Ligi et al. did an incident report study in a neonatal population which found 25.6 AE per 1000 LOS, identifying mainly cutaneous injuries (35% of AE), but when looking into seriousness, those were usually minor, as were drug-focused injuries (7.1% of AE) compared to the more serious hospital-acquired infections (23% of AE) and respiratory events (9.7% of AE) (206). The NCC MERP classification system of events recorded as NCC MERP ≥F tended to be proportionally higher in studies that reported low incidences. In our study, the units with fewer events had proportionally more serious events. The overall low proportion of serious

events in our study, could also be an effect of the numerous, but less harmful skin, tissue or vascular events.

In our paper we stressed the importance of the denominator in AE/ADE studies. Anyhow, some uncertainties regarding denominators are seen in our own published paper. The data marked with the same uppercase numbers in *Table 15* were used as a comparison with each other, although they have different denominators. Accidently, the "ADE per 100 patients" in the study was compared with "admissions with >1 ADE per 100 admissions". The main conclusions by this incorrect comparison will not change but it is obvious that we have found a lot more ADE in our population than AE in the Stockwell AE-study. One explanation for the difference between the studies can be found in the number of triggers used for detection. One way to eliminate this difference would be to only include the ADE caused by the so called "drug-focused triggers". We can see that we have found slightly less events; 7.2 ADE per 100 admissions which should be compared to 11.1 ADE per 100 admissions in the Takata study (173). But as Burch et al. showed in a pediatric rehabilitation hospital, these numbers could be hard to predict since Takata truncated their study after 30 days, which gave them a lower ADE per admission (208).

To minimize those problems, the cohort study format allowed us to follow the admissions over time. The appearance of different types of ADEs shifted depending on unit at LOS. Today, we are not aware of other studies in this field that have done similar investigations. Length of stay is otherwise hard to handle as a confounder and to understand the impact of incidences over time. The study did show time-dependence of insufficiently treated pain at the first days at the surgical ward, a peak of skin/tissue/vascular harm at day five mainly in the medicine and neonatal units and hospital-acquired infections both for admissions to the medicine units from day one and for the neonates at day ten. For other events the most serious were affecting vital parameters and occurred e.g. during intubation. After birth, insufficiently treated hypoglycemia among newborns were common. Seeing the large differences over time, it feels hard to group all the incidences. In retrospect it would have been easier to just focus on one type of harm e.g. vascular harm as outcome and looked at different characteristics and used type of drugs as exposure.

In our study we used the number of DDA only to visualize the extent of drug load in each unit. For example, the days of intravenous irritating drugs or high-alert drugs (i.e. the long list used in paper II) have an exposure of similar number of patients but due to longer LOS, the drug load among the neonatal units were much higher. Regarding intravenous irritating drugs, the threshold for including drugs on the list was low, e.g. esomeprazol was included since the product monograph stated a slight tissue-inflammatory effect. A better alternative would have been using lists of drugs with a more vesicant effect which cause blistering and can result in tissue necrosis (263). Finally, skin/tissue/vascular harm even if classified as "AE" or "extended ADE" or "ADE" needs our full attention and there is a lot of things to learn about caring for vascular access in relation to drug therapy. Some of the lessons learnt in neonatology has been summarized in an article by Sherwin et al. (264)

6.2.4 Paper IV: The experiences of a dose-range check system

Today, the usage of EMRs is common practice when prescribing and administrating drugs in pediatric settings. Most of the systems have been in place for around ten years or so, and CDSS have been implemented to handle parts of the challenges in pediatric prescribing. However, CDSS is expensive to implement and need demands from the public, profession or the authorities to succeed.

The reason for the development of a dose-alert in our hospital was due to public and professional demands after several MEs with 10-fold dosing errors (265). This type of computerized error was known by the American Academy of Pediatrics and they had released recommendations in 2003 to advise on usage of dose-range check system (266). Clinical Decision Support Systems with a dose calculating weight and a dose-range check have since then been shown to lower the risk of dosing errors in pediatric settings (267-269). Since 2017, it is also a common advice to use child-specific CDSS for prescribing, as stated in the Swedish regulation on drug handling (164).

At the time of the interviews with the informants, the EMR had been in place in our hospital for around three years and the CDSS for almost one year. An understanding of the system had begun to settle but it had clear potential for development. The view of the informants on the usability of the system illustrated an easy-to-use system, but with a need to allow for some time before fully relying on its functionality. The benefits of reducing dosing errors were obvious to the informants, with the largest potential seen in acute care. However, during acute care the computerized system is not always at hand. An article by Hoyle et al. used simulated dosing errors situations in the acute-care setting, still showing ten-potency errors after the implementation of new paper-based dose-schemes, implicating the need for clinical audits with constant improvement (270).

It was unexpected that no informants talked about warning-fatigue. This is one of the most common themes in other CDSS-studies (144,271-273). On the other hand, the informants in our study discussed their confidence in the system and stated that they tended to do their own reasonable check as well. And, when prescribing for unusual diagnosis they were aware of the need to go outside of the soft-stop boundaries. To have this possibility, were by the informants seen an advantage. But as discussed by Payne, the system of today have already served its time and we need to look forward (274). Better connection to other health data could refine the alerts based on labs and dosing history to deliver an updated system (274). Stultz, did describe the same needs, but he also discusses what could be done here and now. Customization is recommended, not only relying on large databases, working in combination with dose-alerts and order sentences in the local EMR (272). One risk with local configuration is shown by Chaparro who used the Leapfrog evaluation tool (275) to test EMR and CDSS in 41 pediatric hospitals. The CDSS detected on average 62% of the simulated ME-cases, mainly drug-allergy and dose-range alerts, but within a wide range (23-91%), indicating inequality between the implementations of the different hospitals (276). A similar finding by Fox et al. showed that

90.7% of all simulated erroneous orders could be prescribed due to configuration issues, and the results varied even if the hospitals had the same EMR (277).

Soon the next generation EMRs are knocking on the door. The possibility to investigate the usability of those systems is important. Today other tools exist for evaluating CDSS, for example the Grading and Assessment of Predictive Tools (278) or the System Usability Scale, e.g. used for the evaluation of dosing recommendation in pediatrics (279). They are easier to quantify but cannot fully replace the qualitative study. Ash et al. did a qualitative study in 2007 identifying that the home-grown CDSS had more discussions about content rather than presentation of content and vice versa for commercial systems (280). Saying, that if a clinician understood the system, they could better contribute to the system and the content. Some of the informants in our study, addressed a notion of not knowing how the system calculates, which would be crucial for further success of the system. Ash et al. further analyzed their material and explored the risk of overdependence on the CDSS and the need for robust systems and backups and trainings in situations when you need to work without computers (281). This was also expressed in our study, that we might risk the independent thinking. Others express that the dose-range check did not help them to think, rather being there as a safe-guard. Finally, the contribution of the suggested development list has been a valuable resource allowing for both updating the local dose-range check with better usability of the body-weights already in the system, and in the national roll-out for allowing for a weight-range check to minimize the risk of entering the wrong dose-calculating weight.

6.3 METHODOLOGICAL CONSIDERATIONS, STRENGTHS AND LIMITATIONS

In the work with the thesis we have used several different methods in four different populations. We have collected paper journals, used databases and data from EMRs and national registers. The trigger-tool methods have been tested and semi-structured interviews have been carried out. The variation of methods and different population is the strength of this thesis. The limitations are primarily found in the interpretations of the definitions and the known difficulties in the generalizability of off-label, ME and ADE data (282).

6.3.1.1 Definitions: Off-label, medication errors and adverse drug events

The terms off-label, ME and ADE are related as described in the background but have in this thesis been separated into three different publications. Off-label use have in previous studies been vaguely linked to an enhanced ADR reporting. Cuzzolin et al, did compile early studies of ADR and off-label drug-use, identifying three articles showing one-third or half of the drugs causing ADR when prescribed off-label (52). More recent studies by Bellis and Pratico, have in smaller populations identified a higher occurrence of ADR for patients with off-label drugs (283,284).

The incident reports described in paper II could benefit from a deeper perspective of the ADE-types but also from a wider contribution of psychological and systemic factors causing the ME,

not just focusing on the actual drug and drug handling process. The same is true for the trigger-study in paper III where a categorization of the associated ME would have enhanced the understanding of the causality of an event. However, the trigger tool methodology had only access to the patient chart which do not include all necessary information to fully describe a ME. One strength in paper II-III is the use of the well described NCC MERP classification system for harm (97). However, paper III lacks a statement on preventable events (pADE). The pADE data was collected but not published, showing that 83% of the ADEs was deemed as preventable, if scored ≥4 on a 6-point Likert scale. This lack of specificity, together with our broad take on ADE made us loose part of the generalizability (285). Maybe, a new term as DRAE (Drug Related Adverse Event) would enhance the possibility to communicate our finding to the drug safety community.

The definition of high-alert substances is known to vary between hospitals, being a combination of the most frequent drugs in incidents, drugs with narrow therapeutic windows and drugs with a known risk-profile. In paper II the issue of definition was handled by investigating different lists. As a result, the study could partly be defined as a diagnostic study exploring the sensitivity and specificity of the high-alert lists to identify reports.

For generalizability, a lot of the research in paper I-III are in the hand of the definitions. The use of interrater reliability is important which have been evaluated for ADE in pediatrics (286). There is a risk of information bias with regards to severity and causality in paper I-III. The two-rater system used is well accepted but it should be recognized that the reviewers are part of the same research group with similar ideas of off-label, ME and ADE. Finally, Hibbert et al. showed a five-fold difference (7-51 per 100 admissions) in identifying AE by the trigger tool, indicating a problem with reliability (282).

6.3.1.2 Days a Dose was Administrated

In pediatrics the term Daily Defined Doses (DDD) is hard to use. The DDD is provided by the WHO Collaborating Centre for Drug Statistics Methodology (287) and states an ordinary adult daily dose e.g. benzylpenicillin has a DDD of 3.6 g. This can be used to estimate the number of adult doses contained in a drug package. When using data from EMRs it's not necessary to use the term DDD since all data is available for each admission.

In paper II-III, EMR-data was used to capture the number of DDA. It is the number of days a dose was administrated for each substance by route. It is partly used to be able to handle continuous drug infusions which are registered in the EMR as a given dose each 15 minutes. The downside is that the DDA underestimates the risk of drugs being given several times each day. The advantage is a measurement of the daily exposure of risk.

At the investigated hospital several different EMR-systems were in use at the time for the studies. The main EMR were TakeCare (TakeCare, CompuGroup Medical Sweden) for general care and CCC (Centricity, GE Healthcare IT, IL, US) for intensive care. The drug-data for paper II and III was retrieved from the clinical data warehouse of the two systems. However, the oncology ward ordered their chemotherapy through the Cytodos (CSAM Health AS,

Norway) system and in the operating room they still ordered their drugs in paper journals. To include the data from the Cytodos system for paper II we estimated one dose per order retrieved from the pharmacy. So, in our pediatric hospital we have at least four systems for ordering drugs. This needs to be kept in mind when comparing different hospital data, as the full prescribing information is not always retrievable. Especially for continuous infusion therapies which are not always feasible to order safely in the TakeCare system, which means that some drugs are taken out of the EMR to be ordered separately on paper. For example, midazolam and morphine continuous infusions carried out at the general ward are "invisible" in the data retrieval and this could have effect on the high-risk drugs investigated in paper II, with suspected lower DDA estimates. In addition, the EMRs have "electronically unfinished" infusions still running in the systems that needs to be removed. So, infusions that had not been manually registered as completed in the EMR (3%), or could not be verified as administered, or appeared as duplicates were excluded.

The two main EMR systems were also based on different configurations which complicated the combination of data. This is cumbersome in pediatrics due to the high usage of drugs without identification numbers e.g. extemporaneously prepared drugs and drug-order sets written to enhance safety in the prescribing process, e g. Benzylpenicillin was not ordered as; 1 g powder for injection of one vial with NPLid 19490518000018; rather as Benzylpenicillin 100 mg/mL solution for injection 0.3 mL. This requires a key to link those together, for this we used the id provided by the ePed-system.

The definition of a drug was also needed to be kept in mind. Especially for children where a lot of nutritionals and supplements were registered as drugs or prepared extemporaneously as drugs. In paper III, drugs that were administered during the late phase of neonatal care consisted mainly of oral vitamins and minerals. In addition, more products are registered as "medical devices" bypassing the regulatory process by the MPA and entering the pediatric hospital without drug status. Some severe ADE have occurred with those products in our and other hospitals e.g. wrong dilution of rehydration fluids leading to cerebral hemorrhage (288-290).

6.3.1.3 Populations

In paper I the population studied was the number of drug orders. The method used, a point-prevalence study was selected to be able to retrieve and analyze prescriptions in the year 2008 when paper-based orders was the dominant way of documentation. The study is one of the largest off-label publications and is part of several review (46,67,247).

In paper II the population studied was the actual incident reports. Even if we collected all retrievable Lex Maria and complaints to IVO we know that we lack a lot of national data. During the process of the study we learnt that MEs reported by the pharmacies are sent to the MPA and are not seen in the IVO-data, if not reported by the hospital. Patient and parental complaints reported to a county-based board for patients are also lacking, as are the numerous ME filed in each hospital and events collected in Nitha (137). We also lack the ADR data. In Helsinki, Finland they used data from both ADR and ME reports to compile their high-alert

drug list and found that the lists differ with neoplastic and immunomodulating drugs being more common among ADRs and drugs for the nervous system were more common among MEs (291). But even if national data is lacking, patient safety research do state that we already know what to focus on; international high-alert lists are relevant for our practice and we now need to investigate measures to prevent MEs.

In paper III the population studied was a cohort of 600 randomly sampled inpatients. The population was well defined and stratified into four units which allowed for comparison between the units. However, if the data would to be generalized for the whole hospital, the numbers needed to be weighted due to the large impact of the neonatal population in LOS.

In paper IV the study population was included until data reached saturation. This study did only investigate the understanding and expectations of the pediatrician. In a Swedish context other drug-related interviews with other pediatric professions have been carried out. For example, Star interviewed 20 Swedish nurses on the experiences in drug handling in pediatrics (292). Six themes were stated in this study; 1) Complexity as a hindrance for safety practice, 2) ME cause a psychological burden, 3) Hard work, 4) Situations out of the ordinary is challenging to maintain safety, 5) Clear guidelines are valued, 6) Other professions need to step up to improve the safety situation. Concluding with the need to work together between the hospitals to share best practices.

6.4 PRACTICAL APPLICATIONS

The practical applications are summarized based on the findings from paper I-IV.

6.4.1 International level

- Paper I was used as part of the Swedish contribution to address article 42 of the Pediatric Regulation (50), informing EMA about the need for better medicines for children in Sweden. It is a continuous need to support the MPA in their work at PDCO and the future research by the pharmaceutical industry to find new drugs in pediatrics.
- Paper III expanded the views on ADE.
- Paper IV can be of value when international EMR vendors are entering the Swedish market to understand the pediatrician's views on the implementation of a new CDSS.

6.4.2 National level

- Paper I showed a prominent off-label prescribing. Today, physicians can prescribe off-label since they have the right of making individual decisions with the best intention for the patient (24). However, organizational off-label prescribing is only reimbursed by an insurance available for adults (LÖF). Additional alternatives should therefore be investigated, e.g. the Netherlands, were professional bodies need to develop protocols and standards before organizational off-label prescribing can take place (85).
- Paper II have presented ME-data that, if brought to the attention of the marketing authorization holders, needs to be reported to EudraVigilance. Today, MEs should be reported, preferably by the national responsible organization (IVO) forwarding relevant incident reports to the MPA who take the report to EudraVigilance (95). This is not in place today and needs to be discussed between IVO and MPA. In addition, how off-label use today should be communicated to the MPA and the market holder needs to be clarified.
- Paper II have compared the findings with a higher reporting rate of national incident reports in Denmark. A discussion on voluntary reporting with IVO should be initiated (134).
- Paper II suggested implementation of high-alert lists based on process;
    - Implement all substances with dose errors in the ePed dose-range check
    - Include all drug dispensing and reconstitution errors based on wrong concentration errors in the ePed "Best Practice Reconstitution tool" to be used in risk-assessments of a designated person as outlined by EDQM (254,255).
    - Start promoting the short list for the administration process within the ePed-collaboration, to be used in training and practice.
    - Discuss with IVO how to uphold and refine the high-alert lists
- Paper III show high rates of ADE. The insurance companies (LF and LÖF) and IVO should be contacted to discuss prevention strategies and their views on harm, being or not being drug related.

- Paper IV has suggestions on the development of dose-alert systems and dose-calculating weight which was responded to by the National Board of Health and Welfare in 2017 with the update of the new regulation on drug handling. Recommendation of those functionalities in IT solutions for pediatrics are now part of the regulation. (164).

6.4.3 Regional level

- Continue working with the MEs identified in paper II together with the regional ePed editors to compile and distribute good examples of best practices, dose ranges and drug instructions from different regions.
- The implementation of a designated person, to monitor safe reconstitution was suggested in paper III. The role is outlined by EDQM and needs to be handled by the national system for knowledge management in health care at the Swedish Association of Local Authorities and Regions (293).
- Several regions are implementing new EMRs. The list of developmental issues for CDSS in paper IV is still relevant and should be addressed for new CDSS. Kahn and Abrahamson outlined the future direction in understanding the safety benefits from technological achievements finding child specific platforms rather than tailoring the adult versions (294).

6.4.4 Hospital level

- The off-label situation illustrated in paper I have started to change. When drugs for pediatrics are approved with age-appropriate formulation, the cost for those drugs will probably increase. A pediatric formulary and horizon scanning for new pediatric drugs would be beneficial.
- Paper II suggest, as other publications, an underreporting of MEs. Discuss the possibilities for having a Medication Safety Officer on pediatric department level as for example outlined in England (295).
- In paper II transfer between units and hospitals is frequently reported as an ME. Continue using ePed and local order sets to standardize dilutions, units or measurements to minimize the risk when transferring patients between wards or hospitals as discussed by Grissinger (296).
- Paper III identified hospital-acquired infection as one of the leading ADEs. The contribution is most likely due to the handling of the vascular access device, but in the ongoing efforts on the hospital level, target should also be on drug contribution due to poor aseptic handling during reconstitution or non-validated hang-times.
- This thesis focuses on drugs. But the interconnections within the whole hospital system are vast and complex and needs to be understood for enhanced pediatric safety, as discussed by Cheung et al. (297).

6.4.5 Ward level

- When prescribing, dispensing and administrating the numerous off-label, unlicensed and extemporaneously prepared drugs shown in paper I, information needs to be in place and updated regularly based on a system with a memory.
- Paper II suggest, as other publications, an underreporting of MEs. We need to continue to create a safety climate to enhance reporting without fear of litigation and making systems that can handle the known errors and understand the workplace conditions and the effect of human factors affecting our daily practice.
- Educate on the short high-alert list suggested in paper II, and discuss the need for local "jokers", i.e. substances that are high-alert at your local ward. The list of "jokers" needs to be responsive since sudden drug-shortages can change the high-alert scenario quite rapidly.
- The ADE shown in paper III is probably well known for the health-care staff at the four included units. By recognizing insufficiently treated pain, skin/tissue/vascular harm and hospital-acquired infections as drug related, additional perspectives on finding interventions for those events can be found in the drug handling process, e.g. easier to use pre-order sets, safer intravenous drug therapy and reconstitutions.
- Paper IV was done several year ago. Pediatricians and other health-care staff needs to continue to place new demands on the EMR for continuous development.

7 CONCLUSIONS

These are the brief conclusions of the four papers in this thesis.

- The amount of off-label, unlicensed and extemporaneously prepared drug therapy among hospitalized children, infants and neonates in Sweden is prominent. This illustrate a need for joint efforts from the pharmaceutical industry and the pediatric profession to find and display evidence-based information and better medicines for children.
- High-alert drug lists are established tools in other countries and recommended by patient safety organizations. Several different lists exist with variable length. Substances from all lists studied have been identified to different degrees in national and local incident reports. We suggest using different high-alert lists depending on process (prescribing, dispensing, administration) and evaluate the impact of the implementation.
- Adverse drug events change over time and by pediatric unit. Our broad inclusion of harm due to drugs and medical devices used in drug delivery, identified insufficiently treated pain peaking already in the first days, skin, tissue or vascular harm peaking at the end of the first week and hospital-acquired infections peaking in later admission days. Professionals working within the field of pediatric drug therapy should, depending on ward type and time of admission, consider interventions to minimize the risk of omissions of analgesics and unsafe intravenous drug therapy.
- The experiences and understanding of a CDSS with a dose-range check and weight-based dose calculation among pediatricians described a benefit for the system but with a need for development. When new systems are entering the Swedish market, the views of the prescribers in the current system should be considered.

8 FUTURE RESEARCH

These are the ideas for future research, based on the four papers in this thesis. The ideas are also based on the need for good-quality studies for intervention in pediatrics to reduce ME, e.g. Miller et al., reviewed reduction strategies for ME and found that most prevention advices within pediatric medication safety is based on expert opinion (200). Bannan et al. reviewed in bundle interventions to reduce ME in pediatric inpatients and found only low quality before/after studies (224). Maaskant found in 2015 seven studies to include in a Cochrane review of interventions to reduce MEs (217). Hence, there is room for improvement.

- Create a collaboration with organizations handling pediatric ME incident reports, e.g. hospitals, EudraVigilance, LÖF, LF, MPA, IVO, Nitha, ePed, the county-based board for patients, WHO Uppsala Monitoring Center and other stake-holders.
- Create a randomized-control trial where patients are selected to have 24-48 hours hang-time or 12-24 hours hang-time. Measure harm by intravenous-venous access and hospital-acquired infection with focus on safe reconstitution. One arm should include a designated person to guarantee safe reconstitution.
- Create research possibilities to find information from patients and parents with experiences from ME and ADE to get their views on better medicines for children.
- Perform methodological studies to compare different tools with regards of causality. Create simulated cases that can be used to test tools and new EMRs
- Investigate the willingness-to-pay for the new drug products based on former extemporaneously prepared drugs and new orphan-drugs.
- Perform ecological studies together with other international pediatric hospitals with regards of common ME like 10 potency errors, searching for risk-modifying factors.
- Repeat the off-label and the interview-study with pediatricians and other health-care personnel.
- Investigate the impact of double-control on the correct dilution of high-alert drugs by measuring the concentration after reconstitution.
- Investigate the impact of the implemented dose-range check over time.

9 POPULÄRVETENSKAPLIG SAMMANFATTNING

Bakgrund: När läkemedel utvecklats har läkemedelsföretagen traditionellt valt att inte testa dem på barn. Det gör att det ofta saknas data hur läkemedel fungerar på barn. Men då behovet av läkemedel också finns hos barn, har barnläkare lärt sig att hantera förskrivning av det som kallas *off-label*, eller ”läkemedel utanför godkänd produktresumé” – dvs. då det saknas information i FASS. Med tiden har det istället byggts upp en klinisk erfarenhet och till stor del även publicerad evidens.

År 2007 kom en reglering från den Europeiska unionen som gav en möjlighet att ändra på detta. Läkemedelsföretagen fick bättre möjligheter att få ersättning för sina läkemedel, men också krav, om de såg till att tänka på barnperspektivet innan läkemedlet kom till apoteken. Dessutom har ett system som kallas ePed utvecklats i Sverige för att samla på och sprida information om läkemedel till barn på sjukhus.

En sak som kan drabba barn annorlunda än vuxna är biverkningar. Biverkningar är skador som beror på läkemedlet självt. Dessutom kan barn, liksom vuxna, som vårdas på sjukhus drabbas av vårdskada. Sådana skador kan exempelvis bero på en felaktig läkemedelshantering (*”medication error”*; ME). När en skada som beror på biverkan eller ME inträffar kallas den för en läkemedelsrelaterad skada (*”adverse drug event”*; ADE). Vårdpersonal rapporterar ME till lokala avvikelsehanteringssystem. Avvikelser som leder till allvarlig eller risk för allvarlig ADE skickas av vårdgivaren till Inspektionen för vård och omsorg (IVO) som en Lex Maria anmälan. Som anhörig eller patient kan man också skicka klagomål till IVO.

Flera åtgärder har testats för att minska risken för ME som leder till ADE. En sådan är övergången från pappersjournaler på sjukhus till elektroniska journaler (EMR). Det har varit problematiskt att de EMR som finns inte har varit utvecklade för barn utan istället har anpassats för barn, egentligen precis som vid förskrivning av *off-label* läkemedel. Ett sätt att råda bot på det har varit att ta in kliniska beslutsstöd (*”clinical decision support systems”;* CDSS). Framförallt gäller det möjligheten att kunna dosera i mg/kg till barn med beräkningshjälp och kunna få hjälp av gränser som känner av och varnar när man doserar för högt eller för lågt, en sk rimlighetskontroll (”*dose-range check”*).

Syfte: Detta avhandlingsprojekt syftar till att studera:

- Förekomsten av *off-label* förskrivning av läkemedel till barn som vårdas på sjukhus.
- Gå igenom Lex Maria och klagomål gällande barn på sjukhus för att se vilka läkemedel och ME-processer som är vanligast förekommande samt om de överensstämmer med de högriskläkemedel som definierats i andra länder.
- Studera hur ADE drabbar barn som ligger inne på sjukhus över tid och på olika avdelningar.
- Intervjua barnläkare för att få reda på deras erfarenheter kring ett CDSS som implementerats för att ge ökat stöd i dosering av läkemedel till barn.

Metoder: I avhandlingsarbetet användes följande datakällor och metoder

- Alla barnsjukhus i Sverige bjöds in att delta i stuien för att under 2+2 dagar (vår och höst) 2008 samla in alla läkemedelsordinationer som gjordes till barn. Ordinationerna skickades sedan för att utifrån FASS granskas om det där fanns information om hur läkemedlet ges till barn.
- Alla Lex Maria och klagomål som gällde barn och läkemdel under tiden 2011-2017 erhölls från IVO. Dessutom erhölls data från ett lokalt universitetssjukhus om alla avvikelser för kalenderåren 2011 och 2017 som registrerats gällade läkemedel och barn.
- Sexhundra sjukhusinläggningar följdes över tid år 2010 på fyra avdelningar med olika specialiteter (förtidigt födda, kirurgi, medicin, akutmedicin). Ett verktyg med 88 olika markörer användes för att identifiera händelser utifrån journaltext. En läkare bedömde sedan om det var en ADE.
- En intervjustudie genomfördes med barnläkare 2012. De fick svara på frågor rörande framförallt rimlighetskontrollen. När de som intervjuade förstod att de hörde samma saker från flera barnläkare utan att ny information tillkom beömdes datainsamlingen som färdig. Det inträffade efter att 17 barnläkare intervjuats.

Resultat: Följande fynd påträffades i de fyra studierna.

- Hälften av alla 11 294 insamlade ordinationer till 2 947 barn var givna *off-label.*
- Efter genomgång av de rapporter som erhölls från IVO studerade vi 160 stycken. Vi testade sedan tre olika listor med kända högriskläkemedel, en kort, en medellång och en lång lista avseende antal substanser på listorna, 17/35/47% av rapporterna innehöll högriskläkemedel beroende på lista. De mer allvarliga rapporterna inkluderade fler högriskläkemedel. Det verkade också som att läkemedel som användes ofta på det lokala barnsjukhuset, förekom oftare i rapporterna och att de olika läkemedelshanteringsprocesserna; ordination, orndingställande och administrering orsakar olika ME.
- Det var vanligt med ADE i den studerade populationen. Två av tio inlagda barn erhöll någon typ av skada, det flesta skadorna var övergående och inte allvarliga. Det var framförallt skador på hud, vävnad eller kärl pga den infart som användes för att ge läkemedlet. Även smärta pga för lite smärtläkemedel och vårdrelaterade infektioner var vanliga.
- Vid intervjuerna med läkarna sammanställdes svaren i följande sex kategorier; användning, nytta, förtroende, åsidosättande, tvivel och risker samt utvecklingspotential.

Slutsats: Vårdskador som orsakas av ME och ger ADE är vanliga hos barn. De flesta är övergående, men bland de skador av allvarligare karaktär finns det vissa läkemedel som är mer vanligt förekommande. Högrisklistor, CDSS och bättre information om läkemedel som ges till barn är åtgärder som bör studeras vidare för att se om det kan minska risken för ME.

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