Reported Adverse Drug Events in Pediatric Inpatients in Public Hospitals in Denmark

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M. Sc. thesis

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Heiðrós Tinna Hannesdóttir

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ABSTRACT

Reported Adverse Drug Events in Pediatric Inpatients in Public Hospitals in Denmark

Aim: The aim of this study is to identify ADEs involving pediatric inpatients under 18 years old in public hospitals in Denmark.

Methods: This retrospective study reviewed ADEs reported to the DPSD using content analysis. ADEs were collected, coded by category and then analyzed and presented according to the medication process stages relating to the prescribing, dispensing and administration of a drug. The ADEs were further categorized into the type of ADE and compared across the patient's age, severity of event, and type of drug involved. PRR was calculated for the most frequent types of events.

Results: Extracted ADEs numbered 1926 of which 314 were categorized in this study according to the medication process stages. The ADEs occurred most often at the time of dispensing of a drug 45.8% (121) followed by prescribing 38.6% (102) and administration 15.5% (41) where most of the ADEs reached the patient 86.4% (228). There were 8.6% (27) ADEs that lacked information and 7.3% (23) that did not concern this study. The most common types of ADEs were wrong dose 40.2% (106), wrong time 17.4% (46) and wrong drug 13.3% (35). According to PRR calculations wrong dose at the time of prescribing was the most frequent in comparison to type of ADEs in all other medication process stages. Patients included in the ADEs were 40.2% (106) in the age group of 0-1 years old and 72.2% of the ADEs were evaluated as no harm to the patient. Antiinfectives for systemic use (ATC group: J) 35.2% (74) and drugs for the nervous system 31.4% (66) were the most common types of drugs involved in ADEs.

Conclusion: This study indicates that implementation of further interventions are needed to prevent ADEs from occurring within the health care system. The results strongly suggest that standardized methods and definitions are needed for better comparison between studies.

ÁGRIP

Skráð lyfjaatvik hjá börnum á opinberum sjúkrahúsum í Danmörku

Markmið: Markmið þessarar rannsóknarinnar var að greina lyfjaatvik hjá börnum undir 18 ára í opinberum sjúkrahúsum í Danmörku.

Efni og aðferðir: Þessi afturrýna rannsókn skoðaði skráð lyfjaatvik í DPSD með innihaldsgreiningu (e. content analysis). Lyfjaatvikunum var safnað, þau kóðuð og síðan greind eftir því hvar þau lágu í lyfjagjafaferlinu; við ávísun, tiltekt eða gjöf lyfs. Lyfjaatvikin voru greind áfram í gerð lyfjaatviks og borin saman við aldur skjólstæðings, alvarleika lyfjaatviks og gerð lyfsins í atvikinu. PRR var reiknað fyrir algengustu gerðir af lyfjaatvikum.

Niðurstöður: Fjöldi lyfjaatvika voru 1926 og þar af voru 314 flokkuð í þessari rannsókn eftir því hvar þau lágu í lyfjagjafaferlinu. Lyfjaatvikin áttu sér oftast stað við tiltekt lyfs 45.8% (121), þar á eftir við ávísun lyfs 38.6% (102) og síðast við gjöf lyfsins 15.5% (41) þar sem að flest atvikin náðu til sjúklingsins 86.4% (228). Það voru 8.6% (27) lyfjaatvik þar sem upplýsingar voru ekki tiltækar og 7.3% (23) sem tengdust ekki rannsókninni og ekki skoðuð frekar. Algengustu gerðir lyfjaatvika voru rangur skammtur 40.2% (106), röng tímasetning 17.4% (46) og rangt lyf 13.3% (35). Samkvæmt PRR útreikningum var rangur lyfjaskammtur við ávísun lyfs algengast í samanburði við gerð lyfjaatvika allra annarra lyfjagjafaferla. Skjólstæðingar í lyfjaatvikunum voru 40.2% (106) á aldrinum 0-1 árs og 72.2% lyfjaatvika voru metin skaðlaus. Sýkingalyf til altækrar notkunar (e. systematic use) (ATC flokkun: J) 35.2% (74) og lyf fyrir taugakerfið 31.4% (66) voru algengustu gerðir lyfja í lyfjaatvikunum.

Ályktanir: Þessi rannsókn gefur til kynna að þörf er á frekari inngripum til þess að koma í veg fyrir lyfjaatvik innan heilbrigðiskerfisins. Niðurstöður benda sterklega á að þörf sé á samræmdum aðferðum og skilgreiningum til betri samanburða milli rannsókna.

ABBREVIATIONS

ADE	Adverse Drug Event
DPSD	Dansk Patient Sikkerheds Database
EPM	Electronic Patient Medication
NAPRC	National Agency for Patients' Rights and Complaints
PRR	Proportional Reporting Ratio
SOP	Standard Operating Procedure

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1 INTRODUCTION

1.1 The Medication Process

Medical care is a complex process that consists of the decisions and actions of many individuals e.g. physicians, nurses, patient, relatives, pharmacists and other health care workers. The medication process in Denmark can be divided into the following stages prescribing, dispensing and administration of a drug (figure 1) (Andersen, 2006). During the whole process an electronic patient medication (EPM) system is often used. EPM consists of records of a drug that the patient should receive. The physician prescribes a drug and a nurse or other authorized health care worker uses this information from the EPM to determine when the drug should be dispensed and administered, leaving their signature both after dispensing and again after administering. When a patient is hospitalized their former medication list should be registered into the EPM. This information is either received from the patient, health authority or home care. The EPM should also contain information regarding the patient's allergies to certain drugs and other information about the medication use of the patient. This information should be completely up to date (Andersen, 2008).

It can be the same nurse or health care worker with dispensing authorization or two different health care workers who dispense and administer a drug order (Andersen, 2006). The nurse is only allowed to change the prescription after approval from a physician (Sundhedsstyrelsen, 2006).

There is always a risk that some of these health care professionals mentioned above make a mistake. This mistake can, however, be spotted by another health care professional before reaching the patient indicating that harmful adverse drug events are the result of multiple failures in the medication process (Walsh et al., 2005). If everything in this process is made without error and reaches the patient then a perfect medication use process has been completed.

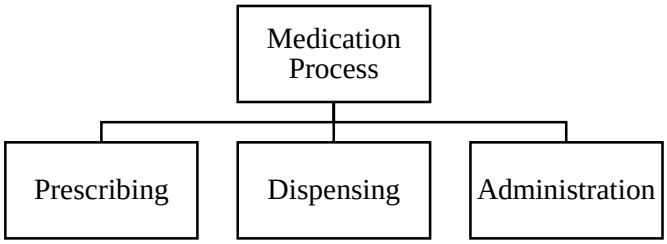

Figure 1. The medication process devides into three main process stages from when a drug is prescribed until reaching the patient.

1.1.1 Prescribing

Prescribing of a drug consists of identifying the patient, a decision to treat with a drug, the choice of a formulation, dose and duration of treatment and ordering of the drug from a list of drugs. It also concerns keeping records and providing the patient and caregiver with important information, making sure the patient understands (Andersen, 2006; Lægemiddelstyrelsen, 2004). The prescription is sent electronically to the medication room where the drug can be dispensed. Before prescribing a drug the physician has to be aware of any contraindications, allergy or interactions with other drugs, food or disease (Lægemiddelstyrelsen, 2004). It is required that the prescribing is made in a certain manner to ensure that the dispensing and administration can be made correctly (Sundhedsstyrelsen, 2006).

1.1.2 Dispensing

Dispensing of a drug is the measurement and laying out of a drug. For example, the portioning out of drugs or mixing and dilution of drugs for any kind of an injection. In Denmark drugs are often kept in a medication room or medication cabinet and dispensed by nurses (Ministeriet for Sundhed og Forebyggelse, 2009). A medication room or a cabinet is stocked by the staff from a hospital pharmacy. The pharmaceutical staff orders, delivers and stores the drugs in each medication room or cabinet, but there is normally one medication room or cabinet in each ward of a hospital (Lægemiddelstyrelsen, 2004). There are two kinds of dispensing, either when drugs are dispensed and administered in one

session or when drugs are dispensed in medication boxes and administered according to a certain time schedule (Andersen, 2006). The process of dispensing in a Danish hospital involves a nurse receiving a prescription from a physician and the prescribed drugs are found and prepared for administration. The nurse prepares the drugs to be given to a patient, according to the prescription (Sundhedsstyrelsen, 2006). Dispensing of a drug is documented through an electronic system or in a paper medication schedule and it should be in relation to the prescription. Only nurses or other health care workers with authorized license to dispense a drug are allowed to make changes to a prescription, and only after approval from a physician (Sundhedsstyrelsen, 2006; Lægemiddelstyrelsen, 2004).

1.1.3 Administration

Administration of a drug pertains to bringing a medicine to a patient and making sure that the patient receives and consumes the prescribed drug on time (Andersen, 2006). The medication administration process enhances patient safety by confirming the five “rights” of administration; right patient, drug, dose, route and time; and ensuring that others, most often nurses, follow medication use and equipment use protocols (Koppel et al., 2008).

Administration of a drug is documented through an electronic system or in a paper medication schedule and it should be in relation to the prescription (Andersen, 2008). It also depends on patient compliance if the patient is willing to take the drugs or not (Lægemiddelstyrelsen, 2004; Andersen, 2006).

1.2 Adverse Drug Events

1.2.1 Definition

The Danish Health and Medicines Authority define an adverse drug event (ADE) as a known or unknown event or error occurring in connection with health care activities or in connection with the information about medicines. That event or incident leads to or could lead to harm or no harm to the patient. The harm in question is in no relation to the illness of the patient (Sundhedsstyrelsen, 2014). An adverse drug event can be classified as one that reaches patient or a *near-*

miss event. A near-miss event is a potentially harmful error that does not reach the patient. That is an event that occurs before reaching the patient and is intercepted and corrected without causing observable harm to the patient (Kringelbach, 2001). ADE is not the same as an adverse drug reaction which can be defined as a routine side effects emerging while treating a patient with the certain drug while an ADE can occur as a result of human mistakes or system flaws (Walsh et al., 2005; Stucky, 2003).

In this thesis an error of prescribing is when a drug is prescribed erroneously (e.g. wrong dose, route of administration, drug or time). An error of dispensing is when a drug is not dispensed according to the prescription. An error of administration is when the right drug is administered wrong or administered to the wrongly patient.

1.2.2 Adverse Drug Events in Children

So far, most studies which examine ADEs concern adult patients. However, ADEs are a significant problem in pediatric practice, but pediatric patients are up to three times more sensitive towards potentially dangerous ADEs than adults and potential ADEs may be more common in pediatrics (Holdsworth et al., 2003; Wong et al., 2008). Drugs are often not available in pediatric dosages and therefore manipulations of drugs are often the only solution for dispensing a drug to a pediatric patient (Kaushal et al., 2001; Walsh et al., 2005; National Institute for Health Research, n.d.). The risk is often because of the need for extra complex calculations to determine the dose (Smith, 2004). Those factors can lead to calculation errors by the prescriber, pharmacist, nurse or caregiver (Paediatrics, 2003). Additives in some products may be harmful and not licensed for use in children and are therefore to be considered specially before prescribing (Smith, 2004). Other causes include lack of available dosage forms and appropriate concentrations for administration to children, need for precise dose measurements and appropriate drug. Doses of drugs in children should be obtained from a pediatric dosage handbook and should not be extrapolated from the adult dose (Paediatrics, 2003).

Weight is one of the most widely used indicator of growth for children, but height and head circumference is important as well for children up to two years

old. In addition, assessment of hearing, vision, motor development and speech are performed at the child health clinics and play a vital role in the national childhood immunization program (Paediatrics, 2003).

1.2.3 Frequency of ADEs

According to The Institute of Medicine report *To Err Is Human: Building a Safer Health System,* there are an estimated 44000-98000 deaths each year in the United States because of medical error (Kaushal et al., 2001; Kohn et al., 2000). A review of studies from 1995-1999 by the US Pharmacopeia demonstrated medication error resulting in harm or death where some errors had significantly increased rate amongst children (31.0%) compared to adults (13.0%) (Cowley et al., 2001). Not all errors are reported and the most common reason is that physicians and nurses are unsure about what is considered a medical error (Walsh et al., 2005). Rates of errors vary between studies depending on the definitions used and setting investigated (Ghaleb et al., 2010).

The first published study to investigate medication errors in pediatrics was in 1983 when 217 drug administrations were observed with the error rate of 5.5%, but the type of study was not mentioned so it is difficult to evaluate these results (Ghaleb et al., 2006). Since then there have been numbers of studies concerning pediatric inpatients worldwide, but none in Denmark. However, studies concerning ADEs in adult patients in Denmark have been performed.

1.2.3.1 Frequency of ADEs in Adult Patients in Denmark

In Denmark a cross-sectional study in adult inpatients from 2010 was performed by using three different methods; direct observation, chart reviews and unannounced control visits in three psychiatric wards in Aalborg University Hospital collecting dispensed drugs. There were 189 ADEs detected; 5.3% (10) prescribing, 9.5% (18) dispensing and 75.1% (142) administration ADEs. The most common types of errors were 95.0% (135) lack of identity control when the identity of patient was not established before administration. Other errors were omission of “when needed” dosing (PRN), omission of dose and omission of drug. There were 8.0% serious and fatal ADEs. Most common drugs involved were psycholeptic drugs (ATC code: N05) (Soerensen, 2013).

Another cross-sectional study in adult inpatients (18 years old and over) was performed in Denmark. This study used three different methods; direct observation, chart reviews and unannounced control visits in randomly selected medical and surgical wards in Aarhus University Hospital collecting dispensed drugs in 2003. There were 355 ADEs detected as defined; these related to prescribing 47.0% (167), dispensing 6.2% (22) and administration 46.7% (166). The same study also reviewed discharge summaries and transcription ADEs that totalled 710. The most common types of ADEs were 14.1% lack of identity control, 11.7% lack of drug formulation in the medical record (they are often correct but these actions are beyond nurses authority and could ultimately result in fatal consequences for the patient) and 4.0% omission of drug/dose. The most common drugs were involved antiinfectives for systemic use, cardiovascular system drugs and nervous system drugs (Lisby et al., 2005).

1.2.3.2 Frequency of ADEs in Pediatric inpatients outside of Denmark

Studies conducted on children outside Denmark show various types of ADEs. According to a study review by Walsh et al., prescribing errors accounted for 3.0-79.0%, dispensing errors for 4.0-30.0% and administration errors for 4.0-60.0% of pediatric patient medication errors. Within prescribing, two studies observed 29.0 and 9.3 near-miss events per 1000 patient-days respectively compared to 6.6 and 7.5 events per 1000 patient-days which reached the patient. Near-miss events at the time of dispensing and administration ranged from 4.0-42.0% of all near-miss events in the studies conducted. That review included two prospective chart reviews from 2001 and 2003 including inpatient children. The most common errors in both studies at the time of prescribing were wrong dose. In those studies and two incident reports from 1989 the most common dispensing errors were wrong drug, wrong dose and wrong preparation. From several incident reports the most common errors for administration were wrong time, wrong rate and wrong dose (Walsh et al., 2005).

A systematic review of studies and a review of local reporting of ADEs was published in Australia. Those reviews were performed to build up an evidence-based practice guideline to reduce errors within pediatric intensive

care units. They showed results from 2008-2009 in pediatric (younger than 16 years old) intensive care units. Some studies listed the frequency ADEs, but they varied between 22.7-40.0% (Ullman et al., 2013).

A two-stage medical record review at eight academic pediatric centers and 14 community hospitals in Canada studied adverse events from 2008-2009 for 18 years old and under. A total of 3669 children were admitted to hospital during the study period and the rate of adverse events was 6.5% (237) whereas drug-related adverse events was 13.5% (32) of all other events within academic and community hospitals in Canada (Matlow et al., 2012).

In London, a prospective review of drug charts in 11 different wards for prescribing and prospective observation for administration in 10 different wards was performed. The data derived from 2004-2005 and included pediatric inpatients from five hospitals. Adverse event reports were collected for each ward studied. There were 391 prescribing ADEs concerning incomplete prescription 41.2%, wrong use of abbreviations 24.0% and wrong dose 11.3%. There were 429 administration ADEs and the most common type of ADEs were 20.7% incorrect preparation, 19.8% wrong rate of intravenous administration and 18.7% wrong time (Ghaleb et al., 2010).

An analysis was performed of cardiovascular ADE reports from 2003-2004 for pediatrics (younger than 18 years) of 616 subscribing hospitals in the USA. The analysis was based on US Pharmacopeia MEDMARx database which is a national, voluntary, internet-accessible, error-reporting system. The total number of ADEs was 821 and most common ADEs during administration was 28.0% improper dosing, 17.9% omission of drug and 17.8% wrong time. The most common drug group involved were diuretics and 50.0% of ADEs occurred in 0-1 years old patients (Alexander et al., 2009).

A prospective direct-observation study was performed in France at four clinical units in a pediatric teaching hospital and the observation took place in 2002-2003. Twelve observers accompanied nurses giving medications and witnessed the preparation and administration of all drugs to all patients. The mean age was 0.8-56.1 months. There were 47.0% opportunities for errors occurring for 1-2 years old. There were 538 ADEs observed concerning 36.0%

wrong time, 19.0% wrong route of administration and 15.0% wrong dose. Most common drugs involved were cardiovascular drugs (Prot et al., 2005).

A systematic review of studies relating to medication errors occurring for pediatric inpatients was found in the databases MEDLINE, EMBASE, Pharm-line, International Pharmaceutical Abstracts, Cumulative Index to Nursing and Allied Health Literature and British Nursing Index. The majority of studies found were conducted in the USA or Canada, but five were from UK, three from France, one from Switzerland, one in Australia and one in India. In total 1772 studies were found from the years 1969 to April 2006, but only 32 of the studies reviewed the incidence of medication errors (the definition for medication varied between studies of nine different definitions) leaving the year range decreased from between 1983 to April 2006. Three methods were used to detect medication errors in the studies: spontaneous reporting (n=10), medication order/ chart review (n=14) or observation (n=8). Prescribing errors varied between 0.45 and 30.1 errors per 100 orders and reported drug administration error rates varied between 0.6% and 27.0%. Some studies cannot be compared as they used different denominators. Some reported the error rate per patient day, others per day and yet others reported only the number of medication errors identified. The most common errors were wrong dose, reported as the most common error in 10 studies (often 10 times the dose), wrong drug in eight studies and wrong route of administration in three studies. The most common drug groups included were antibiotics and sedatives (Ghaleb et al., 2006).

An overview of studies of ADEs in pediatric inpatients published within the last 10 years (2005-2015) showed various numbers of ADEs within the medication process and the studies used different methods and definitions. Of those studies which covered the whole medication process prescribing and administration seemed to be most frequent. However, errors at the point of administration are not likely to be detected and are much more likely to reach the patient than at other stages of the medication process (Leape et al., 1995; Kopp et al., 2006). The most common type of ADEs were linked to variations of drug dose while wrong time, wrong route of administration and lack of identity control were also prominent. Other studies than those mentioned above showed wrong dose frequency as 12.9-47.0% of reports (Ferranti et al., 2008; Cowley et al., 2001).

1.3 Pharmacokinetic and Pharmacodynamics of Children

Growth and development are important indicators for a child and vary between gender and age ranges where 0-2 years covers the growth spurt, 2-11 years old the gradual growth phase and 12-18 years puberty and the adolescent growth spurt (Paediatrics, 2003). Children's absorption, distribution, drug metabolism and renal excretion are different from adults (Smith, 2004; Paediatrics, 2003). Therefore it is important not to treat children as small adults. Changes in the absorption rate appear to be less important when compared to the age-related differences of drug distribution and excretion. For distribution of a drug, for example, the total body water and extracellular fluid volume decrease with age, resulting in larger doses of water-soluble drugs required in younger children than in the older ones to achieve similar plasma concentration. For drug metabolism, at birth the majority of enzyme systems responsible for drug metabolism are either absent or present in reduced amounts compared with adult values. In 1-9 year old children, metabolic clearance of most drugs is shown to be greater than in adults, requiring higher dosage than adults to achieve similar plasma concentration. For renal excretion the immaturity of the kidneys at birth limits renal excretory capacity, but after eight months the renal excretion of drugs is comparable with that observed in older children and adults. In addition to age-related changes, nutritional status and disease states can influence drug handling (Paediatrics, 2003).

1.4 Public Hospitals in Denmark

The first public hospital in Denmark was opened in 1757 and currently there are 53 public hospitals operating in Denmark with 106870 health care workers when last updated in March 2014 (Danske regioner, 2014d; Gyldendal, 2012). Danish hospitals are among the most efficient hospitals in the world and take care of 2.4 million patients each year (Danske Regioner, 2011). According to the Statistic bank of Denmark on average 642607 patients were hospitalized each year from 2010-2013 (Danmarks Statistiks, n.d.a). However, the average

number of hospitalizations each year from 2010-2013 were 1309317 of which 17.1% (224409) were children between the ages of 0-19 years old (Danmarks Statistiks, n.d.b).

Denmark is divided into five regions; the Capital, Zealand, Southern Denmark, Central Denmark and North Denmark (Danske Regioner, 2014c). Within each region are numbers of operating hospitals, but the regions' main responsibility is for health care (Danske Regioner, 2014a). The regions are financed through contributions from the state and the municipalities, including rate payments. Health care is financed through state block grants, state activity related subsidies, and basic as well as activity related contributions from the municipalities (Danske Regioner, 2014b). Each region has a regional risk management board that receives all complex and comprehensive tasks that need a decentralized solution within health care (Danske Regioner, 2014a). Within each hospital there is a risk manager responsible for the reports of adverse drug events occurring within the hospital that they would send to the regional risk management board of the region where the hospital is located (Patientombuddet, n.d.a).

1.5 Dansk Patient Sikkerheds Database (DPSD)

Dansk Patient Sikkerheds Database (DPSD) is a national database in Denmark established the 1st of January 2004. It gathers all reported ADEs from all health services in Denmark into one database in the form of free text (Sundhedsstyrelsen, 2006). From 2004-2014 741183 ADEs were reported to the DPSD (Patientombuddet, 2014; Patientombuddet, 2015b).

1.5.1 Reporting of ADEs to the DPSD

The reporting of ADEs occurs electronically through the National Agency for Patients' Rights and Complaints' (NAPRC) website which is the institution responsible for collecting reports of ADEs and analyzing and disseminating the information to improve patient safety (Patientombuddet, 2015a). Reported ADEs from public hospitals are first handled by risk managers in each hospital where the ADE occurred. The reports are examined in order to see what

happened, why it happened and how such an ADE could possibly be prevented. After anonymizing the ADE the risk manager sends it to the regional risk manager board of the involving hospital. When the region has finalized it, they send it to NAPRC where it is recorded into DPSD (Sundhedsstyrelsen, 2006; Patientombuddet, n.d.a; Danske Regioner, 2014c; Danske Regioner, 2014a). Information about the person who reported or any other personalized information is also removed before storage in DPSD (Patientombuddet, 2015a).

Since the establishment of DPSD health care workers at Danish public hospitals have been required to report an ADE they witness no later than seven days after the ADE was observed. Since 1st of September 2011 patients and relatives have also been able to report an ADE into the database anonymously (Sundhedsstyrelsen, 2006; Lov om patientsikkerhed i sundhedsvæsenet nr 913/2010 as amended; Patientombuddet, 2015a). An evaluation of DPSD from 2006 showed that 30.0% of health care workers at public hospitals in Denmark were aware of ADEs that were not reported. The quality of reported ADEs was also deemed to be poor as a learning tool (Sundhedsstyrelsen, 2006).

When someone reports an ADE they are required to fill in information regarding the location, date and severity of the ADE, name the event and give a free text description of what happened along with the consequences for the patient and suggestions for prevention. Other information is optional such as patients' sex, age, name or ID number. The severity levels from NAPRC are no harm, mild, moderate, serious and mortal. The definitions for *No harm* - no injury to the patient; *mild* - if the patient was injured, but with no need of increased treatment; *moderate* - temporal injury to the patient that requires a longer hospitalization; *serious* - permanent injury that requires longer hospitalization or injuries that requires lifesaving treatment; *mortal* - the patient died (Patientombuddet, n.d.b).

1.6 Proportional Reporting Ratio

Proportional Reporting Ratio (PRR) involves calculation of the proportions of a specific type of ADE according to medication process stages of interest where the comparator is all other medication process stages in the database, where the PRR, in a two by two table (see table 2) is calculated as following equation (Evans et al., 2001):

$$PRR = \frac{\frac{a}{a+c}}{\frac{b}{b+d}}$$

The expected null (no difference) value for a PRR is 1.0 and the values generated are measures related to strength of the association (Evans et al., 2001). If PRR is higher than 1.0 it indicates that more reports of the type of ADE for the particular medication process stage of interest than other processes in the database (Brinker et al., 2013). PRR is a frequently used measure that indicates whether there is a signal in ADR reporting for drugs. According to this methodology, judgement about whether or not there is a signal, and its strength, is made on the basis of PRR, chi-square and the absolute number of reports. A fictive example of such calculation is given in table 3. Here the PRR equals 1.61 with chi-squared 6.50 and p-value 0.01. This indicates that the type of ADE *wrong dose* generates slightly (1.6 times) more reports in the process of prescribing than other processes in the database. In other words the chi-squared test indicates that the ratio of wrong dose within prescribing is not equal to the ratio of all other type of ADEs within all other medication processes. The strength of the statistical association is not high.

Table 1. Calculation of PRRs.

	Medication process stage of interest	**All other medication process stages**
Type of ADE of interest	a	b
All other types of ADEs	c	d

Table 2. Fictive example of a PRR calculation.

	Prescribing	All other processes
Wrong dose	30	70
All other types of ADEs	55	250
Total	85	320

PRR = 30/85 divided by 70/320 = 1.61. Chi-squared (1 degree of freedom) 6.50. P-value 0.01.

1.7 The Future of Patient Safety

It is impossible to eliminate all ADEs from a modern health care system, although there are a number of interventions that could have beneficial impact within the health care system. Too often, serious mistakes occur which could have been prevented (Donaldson, 2000).

The reporting and prevention of medication errors is important. There are two chief causes for the occurrence of errors in medicating patients, a human error and a system error. The more common and easier explanation is to blame the person who made the error. This approach focuses on the person rather than the circumstances. For example, the perceived lack of attention, obliviousness or carelessness of health care workers. This kind of approach leads to insecurity for the staff and could possibly lead to even more ADEs. The causes of medication errors are usually multifactorial and it is important that when investigating medication errors, particular focus should be placed on system changes (Paediatrics, 2003). It is still important however, to make sure that each health care professional is responsible for their own actions (Leval et al., 2000).

Other approaches are to view the error from the perspective of the system and look at the whole picture (Donaldson, 2000). While it is hard to change human beings, we can change the circumstances they work under in order to reduce ADEs (Reason, 2000). When serious errors occur it is not important to

know who made the mistake, but knowing why and how the protocol failed. The same kind of circumstances can lead to the same mistakes over and over again, no matter which person was involved (Donaldson, 2000). One way is to learn from other high risk industries' experiences such as commercial aviation and nuclear power through open communications about errors (Walsh et al., 2005; Smith, 2004; Kopp et al., 2006). For error prevention, detection is the first step in handling and resolving issues and is just as important as error prevention. Understanding errors and why they occur is probably the most cost-efficient way, in the long term, to improve safety in health care. (Leval et al., 2000).

Since there is already plentiful knowledge of how common ADEs occur in pediatrics and how children are different from adults, pediatricians and other health care workers should acknowledge the risk in children's medication use and encourage safer child health care systems at all levels to improve child health care (Walsh et al., 2005). Although a number of studies have reported the prevalence of ADEs in hospitalized children no such studies have been performed in Denmark.

2 AIMS

The aim of this study is to identify adverse drug events that are reported in the *Danish Patient Safety Database* (DPSD). The ADEs involved inpatients under the age of 18 years in public hospitals in Denmark. These were analyzed in relation to:

- Type
- Frequency
- Age of patient involved
- Severity
- Type of drug involved

2.1 Research Questions

- What types of ADEs are reported to the DPSD?
    - Do they reach the patient?
    - Are they near-miss events that were discovered before reaching the patient?
- At which medication process stage and with what frequency do these reported ADEs occur?
    - Is it during prescribing when a physician prescribes a drug?
    - Is it during dispensing when a nurse prepares a drug?
    - Is it during administration when a nurse administers a drug?
    - What characterizes the reported ADEs?
- Which patient age group has the highest frequency of reported ADEs?
- How serious are the reported ADEs in relation to patient safety?
    - Do any of the ADEs result in the death of the patient involved?
- Which types of drugs (ATC code classification) are frequently involved in ADEs?

3 METHODS

3.1 **Design**

This retrospective study categorized reviewed ADEs reported to the DPSD through content analysis.

3.2 **Setting**

The reported ADEs from the DPSD concerned patients younger than 18 years old hospitalized at pediatric wards in Denmark. The categorization involved ADEs reported and finalized from January 1st 2010 to December 31st 2014. The categorization of the ADEs took place at the NAPRC in Copenhagen from 23rd of February until 9th of March, including the 27th of March 2015, which involved 11 weekdays during the time when staff was present. The categorization had to take place at the NAPRC as the reported ADEs could potentially contain confidential information which are not allowed to be removed from NAPRC.

3.3 **Data Analysis**

The procedure of content analysis is when data is collected, coded by category and then the coded data are analyzed and presented (Bowling, 2009; Pope et al., 2006; Mayring, 2000). This method of analysis was chosen since collected data included text based reports.

3.3.1 Data Extraction

To identify ADEs a search in the DPSD was conducted by a consultant from NAPRC.All ADEs for patients 18 years old and younger were extracted. Only events that contained information about the age of the patient were included in the search. A report of each ADE was constructed from the search and information regarding the following subjects were retrieved from the DPSD. Examples of retrieved ADEs are shown in appendix 1.

3.3.2 Data Cleaning

When working at the NAPRC the data had to be cleaned to fit the aims of the study before starting the categorization of the data. First, duplicates had to be removed. Secondly, a few reports had to be removed which did not concern the study as they did not concern the medication process. Thirdly, there were ADEs that did not occur at public hospitals, but in private hospitals, dentists, home care and other places. Fourthly, one ADE was removed that occurred in the year of 2015. There were also ADEs that were reported as if they had occurred 1910-1914, but since DPSD did not exist then it was assumed to be a typographical error and the date of the ADEs were changed into 2010-2014 respectively. Lastly, ADEs were removed that contained patients at 18 years of age, since these patients are not defined as children. The ADEs were given a randomized queue number after data cleaning and categorized in that randomized order. This was to ensure the data was analyzed in case only a sample of ADEs could be categorized.

3.3.3 Preparation for categorization

The researcher had the opportunity to practice categorizing skills before arriving at the NAPRC by categorizing three different cases with a few examples of reports and received feedback from a supervisor. A coding table (see appendix 2) of categorizations and a standard operating procedure (SOP) (see appendix 3) was constructed before arriving at the NAPRC to increase the validity of the categorization process. The coding table was constructed based on studies that consisted of Danish guidance on medication management and different articles concerning categorization of ADEs (Sundhedsstyrelsen, 2006; Andersen, 2006; Barker et al., 2002; Benjamin and Pendrak, 2003; Beso et al., 2005; Nielsen and Hellebek, 2009; ASHP, 2014; National Coordinating Council, 2015; National Institute for Health Research, n.d.; Vantard et al., 2015; Prot-Labarthe et al., 2013; Fernández-Llamazares et al., 2013; Coombes et al., 2009; Berman, 2004; American Pharmacists Association, 2007; Saghafi and Zargarzadeh, 2014; Fahimi et al., 2008; Levin et al., 2012).

3.3.4 Categorization

An example of how a category was found is shown in appendix 1. First, each ADE was categorized into *type of incident*, concerning whether the ADE reached the patient or if it was a near-miss event. Secondly, the ADEs were categorized into the medication process stage that represented whether the ADE occurred at the time of prescribing, dispensing or administration as listed in figure 2. There were a few ADEs that did not concern the study and others that lacked information. ADEs that did not concern the study occurred during monitoring, at the hospital pharmacy, pharmacological production, or other locations not concerning the included medication process stages. However, since they concerned medication in some way they appeared at this stage of the categorization and therefore were not removed earlier. If there was doubt about categorizing a medication process stage as either dispensing or administration, most often the researcher decided to categorize the event as dispensing when the patient was not supposed to have a drug administered as the drug should not have been dispensed. Thirdly, the ADEs were categorized into proper *types of ADE* and *sub-type of ADE* as listed in appendix 2. The type

Figure 2. ADEs of the medication process stages. ADEs can happen at these stages of the medication process

of ADE reflected what actually occurred or the obvious mistake made at the time of an ADE and the sub-type of ADE is a further clarification of the type of ADE. For example, if the type of ADE is wrong dose the sub-type of ADE could either be underdosage or overdosage. Another example could be when a physician prescribes a drug that was supposed to be discontinued. In this example the type of ADE would be categorized as wrong drug and the sub-type of ADE would be discontinued drug administered. Further definitions of each type of ADE are listed in table 1 along with supporting literature when applicable. While categorizing the ADEs, documentation in the form of a short explanation of why an ADE occurred (if reported) was made. Fourthly, the standard information was extracted such as severity, information of the drug involved, patient's age, gender and date of ADE.

Table 3. Type of ADE definitions.

Change prescription without approval: This occurs when a nurse makes changes in prescription without talking to the physician that prescribed the drug and administering the drug to a patient (1).
Double dosage: When prescribing, dispensing or administering a double amount of drug of what was expected. When prescribing it can occur because of an absent or wrong medication schedule. When dispensing and administration it can occur because no documentation from earlier administered drug is available (2; 3; 4; 5; 6).
Expired drug: When dispensing and/or administration of a drug that has expired or dispensing and/or administration of a drug with reduced duration after mixing or opening (5; 3).
Lacking patient information: When a physician prescribes a drug and does not document important information of a patient, e.g. weight and age (7).

Manipulation error:

A physical alteration while dispensing a drug for the purposes of extracting and administering the required proportion of the drug dose, but an error would for example be irresponsible mixing of a drug, splitting/crushing of a drug or removing important part of a drug (8; 5; 4).

No drug:

An event when there is either no drug prescribed, dispensed or administered. When prescribing it can occur if it was forgotten or because of electronic system error. When dispensing it can be because it was forgotten, the wrong medication schedule was read or omission of reading the medication schedule (9; 2; 10; 3; 4; 7).

Wrong dose:

When prescribing this can occur because of calculation error, disregarding written instructions, bad/wrong instructions of usage or electronic system error. When dispensing it can occur because of look- or sound-a-like, omission of reading the medication schedule or confusion with other drug prescribed (10; 3; 8).

Wrong drug:

Either prescribing a wrong drug by prescription of another active substance, by disregard of contraindication or late discontinuation. It could also occur while dispensing while picking up a wrong drug because of look- or sound-a-like, omission of reading the medication schedule/prescription or because of wrong placed drug (10; 3; 5).

Wrong formulation:

Either prescribing a wrong formulation or while dispensing while picking up a wrong formulation because of look-a-like, sound-a-like or disregard of reading the prescription (2).

Wrong patient:

When prescribing, administering or dispensing a drug to a wrong patient because of look-a-like patients, sound-a-like names or missing patient identification (9; 10; 3; 5).

Wrong route of administration: When prescribing a drug this can occur because of writing bad or wrong instructions on how to administer a drug or when administering a drug either by wrong injection, choosing left instead of right or not following the instructions of administration of the drug into the body properly (11; 5; 10; 9).
Wrong technique: When administering a drug by erroneous method, for example, choosing the wrong rate for injection, wrong volume or not turning on injection pump (5; 2; 10).
Wrong time: When prescribing a drug this can occur because of bad or wrong instructions regarding usage of time to administer, the late prescribing of a drug or early discontinuation. When dispensing or administering a drug this can occur early or late compared to the instructions of the prescribed drug (10; 11; 3; 5; 2; 4).

1) Sundhedsstyrelsen, 2006; 2) Barker et al., 2002; 3) Beso et al., 2005; 4) ASHP, 2014; 5) National Coordinating Council, 2015; 6) Coombes et al., 2009; 7) Vantard et al., 2015; 8) National Institute for Health Research, n.d.; 9) Andersen, 2006; 10) Benjamin and Pendrak, 2003; 11) Saghafi and Zargarzadeh, 2014

The definitions of the levels of severity were explained in the introduction. The ADEs were evaluated by the person reporting the event into no harm, mild, moderate, serious or mortal. ADEs that were categorized as serious were specially extracted and are explained further in the results.

Information about the drug involved was the brand name, active substance and ATC code of the drug as classified by WHO (Norwegian Institute of Public Health, 2015). However, the emphasis was put on the ATC code. It was categorized if it was the drug prescribed or administered, so both drugs involved were documented. Sometimes the ATC code was not reported, then the website pro.medicin.dk was used for searching for the right ATC code (Dansk Lægemiddel Information, n.d.).

The age of the patient was analyzed and divided into age groups as 0-1 years old, 2-11 years old and 12-17 years old (Paediatrics, 2003).

Some ADEs lacked information and were not possible to categorize fully. If the ADE included information relating to the main aim of the study they were included, but if they did not they were excluded. The ADEs lacking information that were excluded from the study did not include information of which type of incident, medication process stage and/or type of ADE. Those ADEs lacking information that were not excluded from the study lacked information regarding the sub-type of ADE or explanation of why an ADE happened. The categories that lacked part of information but were categorized partly are listed in appendix 6.

3.3.5 Analysis of Categorized Data

After categorization the data was brought out of the NAPRC for further analysis. The frequency of type of incident (either an ADE reached the patient or not) and type of ADE were analyzed according to medication process stages. Comparison of ADEs was done as percentages, PRR, p-values and Pearson's chi-square test.

3.3.5.1 Statistical Analysis

Pearson's chi-squared test was used to evaluate the type of incident as if the distribution of ADEs was equal within the medication process stages, whether if it was a near-miss or if it reached the patient.

PRR was calculated for the most common types of ADEs for all three medication process stages to see if there were any ADEs that occurred more often in comparison with the other medication process stages (clean PRR). PRR was calculated in the same way including ADEs that had some missing information. Measures of statistical association for PRR were calculated using a Pearson's chi-squared test with one degree of freedom to test whether if the ratio of a certain type of ADE within a certain medication process stage is equal to the ratio of all other type of ADEs within all other medication processes.

3.4 Programs

Microsoft® Excel 2013 for windows 7 (Edition 64-bit) was used for all categorization of the ADEs facilitated through the Coding Table. Each column in Excel had its own heading relating to what was extracted from each ADE report according to the aims and research questions of the study (See headings of categorization in appendix 1).

3.5 Permissions

An application was sent to NAPRC for permission to access the database. It was granted as shown in appendix 4.

4 RESULTS

In total 17173 ADEs were retrieved from the DPSD, 42.9% (7375) were duplicates and were removed, leaving 9798 ADEs. ADEs which did not concern the study aims such as ADEs concerning patients aged over 17 years, other locations than public hospitals and ADEs occurring before and after 2010-2014 were removed, leaving 1926 ADEs. These ADEs were assigned random number and 16.3% were categorized. Out of those ADEs there were 7.3% (23)

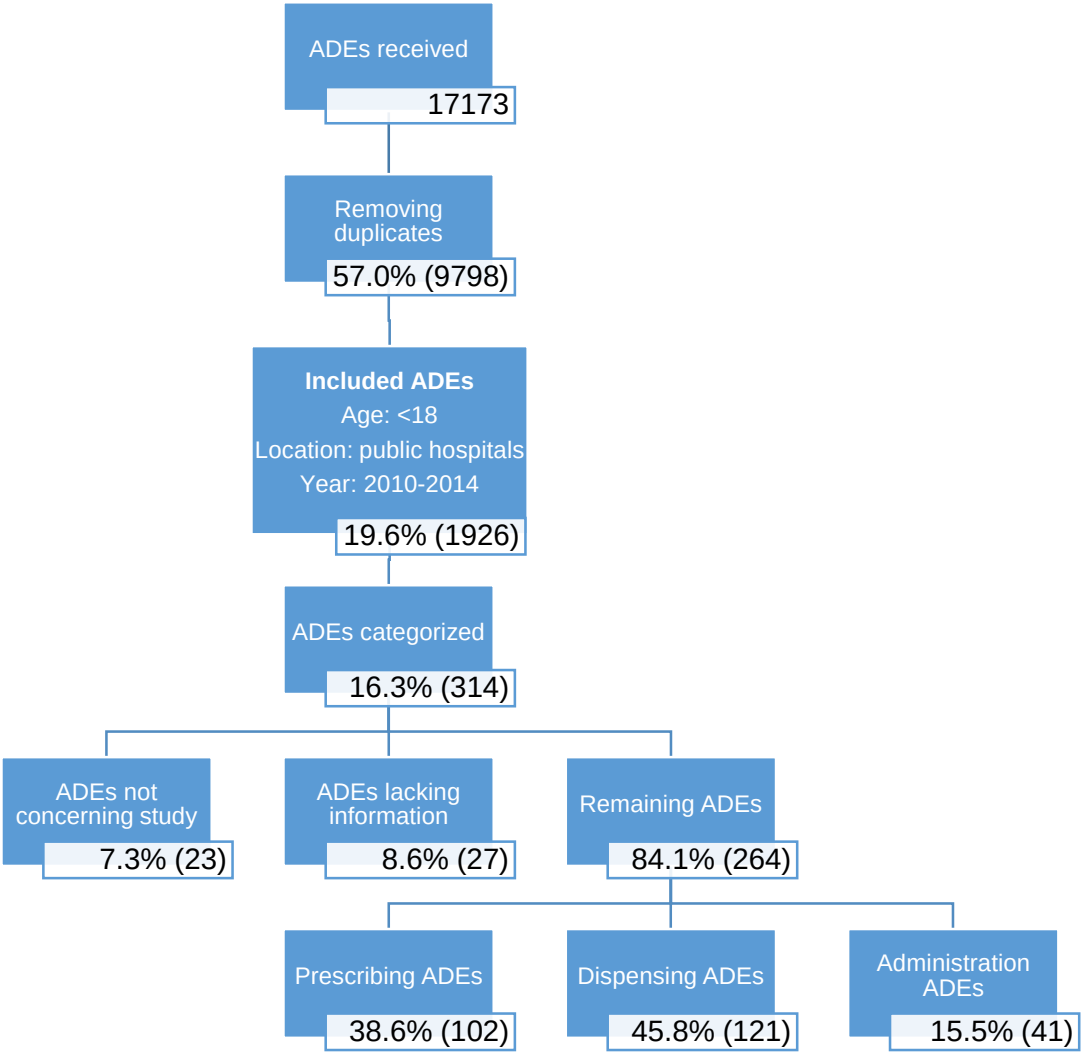

Figure 3. Number of ADEs after each step of cleaning and categorization. ADEs lacking information or not concerning the study excluded since they either did not fulfill the aim of the study or it was not possible to categorize them into what type of incident, medication process stage or type of ADE.

ADEs that did not concern the study and 8.6% (27) were lacking information which made it impossible to categorize into the type of incident, medication process stage and/or type of ADE (See Figure 3). The reasons for missing information were poor quality of the report and errors in the DPSD when generating the Excel document containing the ADEs. The remaining 264 ADEs were categorized by the medication process stage.

4.1 Frequency and Type of ADEs

Of all reviewed ADEs there were 86.4% (228) that reached the patient and 13.6% (36) categorized as a near-miss event. The count and percentage for an ADE either if it reached the patient or not is shown in table 4 for each medication process stage. Of the ADEs that reached the patient, 50.9% (116) were at the time of dispensing and of the ADEs that were near-miss events 77.9% (28) were at the time of prescribing.

Table 4. Type of incidents. Percentage and number of each type of ADE according to medication process stage, chi-squared statistic and p-value

Type of incident	**Prescr. % (n)**	**Disp. % (n)**	**Administr. % (n)**	**Total % (n)**	**Chi-square (df=2)**	**P-value**
Reach Pt.	32.4 (74)	50.9 (116)	16.7 (38)	100.0 (228)	27.20	<0.00001
Near-miss	77.9 (28)	13.9 (5)	8.3 (3)	100.0 (36)		
Number of ADEs	**38.6 (102)**	**45.8 (121)**	**15.5 (41)**	**100.0 (264)**		

The result is significant at $p < 0.05$.

Table 5 lists the total number for type of ADEs for each medication process stage by count and percentage in ascending order, but appendix 5 shows a more detailed categorization for each type of ADE that had a sub-type of ADE (those types of ADEs are marked with * in table 5). Some ADEs were categorized as “other types of ADEs” when the count of type of ADE was only

one. These types of ADEs were wrong patient while prescribing and change in prescription without approval and manipulation error while dispensing. List of ADEs lacking information but were partly categorized are listed in appendix 6.

4.1.1 Prescribing ADEs

The most common types of ADEs at the time of prescribing were wrong dose 64.7% (66), wrong drug 14.7% (15) and wrong time 5.8% (6). For wrong dose 74.2% (49) were overdosages and 18.2% (12) underdosages, but the rest was not reported rather if it was an under or overdosage. The top three explanations for why these wrong dose ADEs occurred were calculation error 15.2% (10), no/wrong medication schedule 7.6% (5) and electronic system error 6.1% (4).

There were 54.6% (36) of ADE reports for wrong dose ADEs at the time of prescribing that did not include any reason for why that certain ADE occurred. Therefore it was not possible to categorize those events according to any particular reason. When removing these ADEs calculation errors would be 33.3% (10), no/wrong medication schedule would be 16.7% (5) and electronic system error would be 13.3% (4)

4.1.2 Dispensing ADEs

The most common ADEs at the time of dispensing were wrong dose 28.9% (35), wrong time 24.0% (29) and wrong drug 15.7% (19). For wrong dose there were 51.4% (18) overdosages and 42.9% (15) underdosages, but the rest was not reported rather it was an under- or overdosage. The top three reasons for why these wrong dose ADEs occurred were because of calculation error 11.4% (4), time pressure and look-a-like drugs 5.7% (2) respectively.

There were 60.0% (14) of ADE reports for wrong dose during dispensing that did not include any reason for why that certain ADE occurred. Therefore it was not possible to categorize those events according to any specific reason. When removing these ADEs calculation errors would be 28.6% (4) and time pressure and look-a-like would both amount to 14.3% (2).

4.1.3 Administration ADEs

The most common ADEs at the time of administration of a drug were wrong time 26.8% (11), wrong technique 26.8% (11) and double dosage 14.6% (6). For wrong time ADEs there were 63.6% (7) of late administration and 36.4% (4) of early administration. There were no outstanding reasons for those ADEs. Of wrong technique ADEs 81.8% (9) were because of wrong rate when administration of the drug in vivo.

Table 5. Type of ADEs. Number of type of ADEs for each medication process stage.

Type of ADE	Prescr. ADEs % (n)	Disp. ADEs % (n)	Administr. ADEs % (n)	Total % (n)
Wrong dose*	64.7 (66)	28.9 (35)	12.2 (5)	40.2 (106)
Wrong time*	5.8 (6)	24.0 (29)	26.8 (11)	17.4 (46)
Wrong drug*	14.7 (15)	15.7 (19)	2.4 (1)	13.3 (35)
Double dosage	2.0 (2)	13.2 (16)	14.6 (6)	9.1 (24)
No drug*	5.9 (6)	11.6 (14)	4.9 (2)	8.3 (22)
Wrong technique*	-	-	26.8 (11)	4.2 (11)
Wrong formulation	1.0 (1)	3.3 (4)	-	1.9 (5)
Wrong route of administr.*	-	-	12.2 (5)	1.9 (5)
Lacking patient info.	4.9 (5)	-	-	1.9 (5)
Expired drug	-	1.7 (2)	-	0.8 (2)
Other types ADEs**	1.0 (1)	1.7 (2)	-	1.1 (3)
Number of ADEs	**100 (102)**	**100 (121)**	**100 (41)**	**100 (264)**

*Sub-types of ADEs are shown in appendix 5.

**Represents three different types of ADEs, but those contained only one category each.

4.1.4 Comparison of Medication Process Stages by Calculating PRR for the Most Common Types of ADEs

PRR was calculated for the three most common types of ADEs at the time of all medication process stages, as shown in table 5. The most common types of ADEs were wrong dose 40.2% (106), wrong time 17.4% (46) and wrong drug 13.3% (35) of all reported ADEs. These common types of ADEs were also the most prominent for the prescribing and dispensing stages, but not for administration. However, wrong time ADE figured clearly in the top three for administration. Table 6 shows the PRR values both clean, as they come in the study and values for PRR as they would be if all ADEs lacking information was included in the calculation.

Wrong dose at the time of prescribing has the highest PRR at 2.62. This means that wrong dose at the time of prescribing is most likely to happen of all the other medication process stages in that study and compared to p-value it is significant ($p < 0.05$). Wrong time of dispensing scored second highest or 2.02 and the third highest was wrong time of administration medication process stage with PRR of 1.71 but that value was not statistically significant.

When comparing clean PRR with ADEs lacking information the most difference was for wrong dose at the time of prescribing where it reduces from 2.65 to 2.44. Wrong time events at the moment of dispensing increases from 2.02 to 2.11. Other changes had difference of 0.07 or less.

Table 6. PRR values for the top three types of ADEs according to all medication process stage.

Type of ADEs	Clean			Including All Missing Information		
	PRR	chi-square	p-value	PRR	chi-square	p-value
Wrong Dose						
Prescr.	2.62	41.71	<0.00001	2.44	37.48	<0.00001
Disp.	0.58	12.16	0.0005	0.60	10.66	0.001
Administr.	0.30	15.79	0.00007	0.27	15.83	0.00007
Wrong Time						
Prescr.	0.24	15.39	0.00009	0.24	14.72	0.0001
Disp.	2.02	6.65	0.01	2.11	7.54	0.006
Administr.	1.71	2.98	0.08	1.78	3.43	0.06
Wrong Drug						
Prescr.	1.19	0.32	0.6	1.22	0.39	0.5
Disp.	1.40	1.16	0.3	1.47	1.50	0.2
Administr.	0.16	4.94	0.03	0.17	4.65	0.03

The result is significant at p<0.05

4.2 Age of Patients at the Time of ADEs

Figure 4 shows which age groups of patients the ADEs affected. There were 40.2% (106) of ADEs that affected 0-1 years old patients.

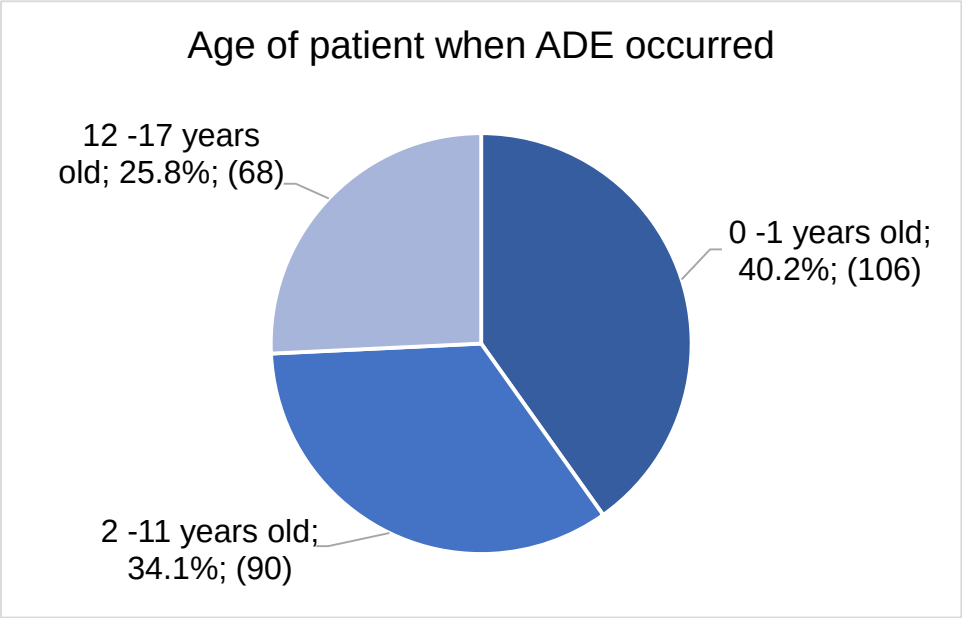

Figure 4. The number and percentage of ADEs according to age group of patients in which the ADEs occurred.

As mentioned earlier, the total number of ADEs received from NAPRC was 1926 which was analyzed partly in this study. Since it was possible to evaluate the age for all the ADEs received from NAPRC, comparisons were made with the analyzed data in this study to see whether the final results would have been altered if all ADEs had been analyzed. The percentage numbers remained similar to the ones analyzed in this study or 36.4% (699) for 0-1 year old patients, 36.4% (699) for 2-11 years old and 27.4% (528) for 12-17 years old.

4.3 Severity of ADEs

ADEs categorized by severity are shown in figure 5. There were 72.2% (192) of the ADEs were reported as no harm to the patient and 1.5% (4) ADEs reported as serious. Out of the serious ADEs there were two events related to the

prescribing and the dispensing medication process stages respectively. The first serious prescribing ADE was a near-miss, wrong dose ADE that occurred for a patient under one year old and occurred because of electronic system error and would have led to a 1000 fold overdosing of a muscle relaxant drug. The second serious prescribing ADE occurred when a patient of eight years old was administered a wrong cytostatic drug for nine days. The consequence for the patient was unnecessary pressure in the bone marrow and occurred because an inexperienced physician prescribed the drug. The first serious dispensing ADE occurred to a three year old patient because of a 10 fold overdosage of an opioid and occurred because of calculation error and led to respiratory stop for the patient. The second serious dispensing ADE occurred for a 12 year old and occurred because a wrong drug was dispensed and administered, the reason was that the drug was wrongly placed in the medication room. The patient became unresponsive and subsequently had cramps.

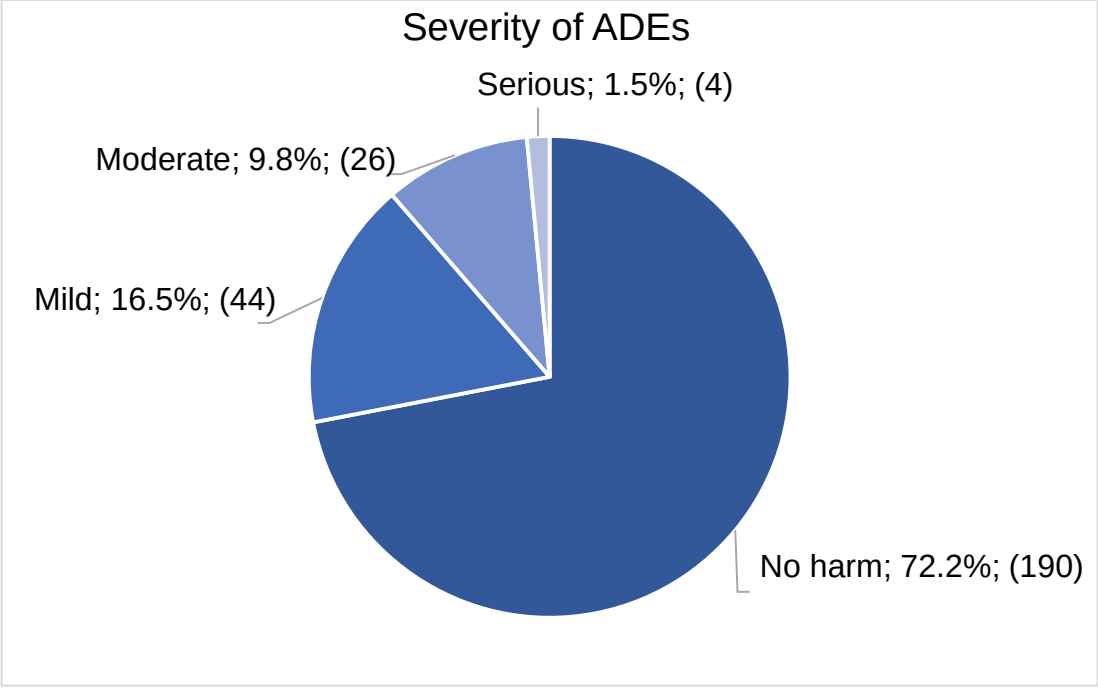

Figure 5. The number and percentage according to severity of the ADEs.

As mentioned earlier total received ADEs from NAPRC was 1926 which was analyzed partly in this study. Since it was possible to evaluate the severity

for all the ADEs received from NAPRC, comparisons were made with the analyzed data in this study to see whether the final results would have been altered if all ADEs had been analyzed. The percentage numbers remained similar to the ones analyzed in this study or No harm was 68.4% (1317) and serious 1.6% (31) out of 1926 ADEs.

4.4 Drugs Involved in ADEs

Not all ADEs in the study had a drug involved or the reports lacked information on the drug. There were 79.5% (210) of ADEs that included specified information about the drug involved. The frequency of each ATC code of a drug prescribed is shown in figure 6 by first letter of ATC code. There were 35.2% (74) ADEs concerned ATC code J and 31.4% (66) that concerned ATC code N. There were 16.2% (12) ADEs of J-ATC-coded drugs concerned gentamicin

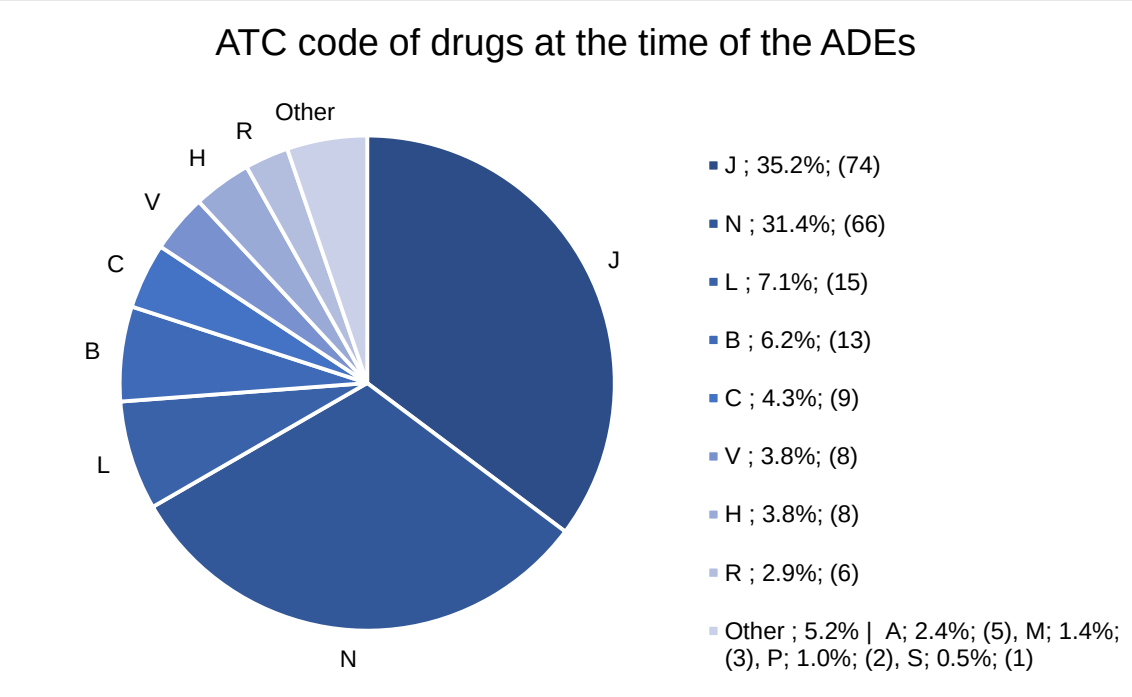

Figure 6. The number and percentage of ADEs by drug group (classified by the first letter of the ATC code for drugs). A - alimentary tract and metabolism; B - blood and blood forming organs; C - cardiovascular system; H - systemic hormonal preparations, excl. sex hormones and insulins; J - antiinfectives for systemic use; L; antineoplastic and immunomodulating agents; M - musculo-skeletal system; N - nervous system; P - antiparasitic products, insecticides and repellents; R - respiratory system; S - sensory organs and V for various.

(J01GB03), 16.2% (12) ADEs concerned cefuroxime (J01DC02) and 12.2% (9) concerned ampicillin (J01CA01). Of all N-ATC-coded drugs there was 33.3% analgesics (N02), 27.3% of sedatives (N05) and 27.3% of psychoanaleptics (N06). Five ADEs included opioids (N02A)**.** There were 24.2% (16) ADEs of N-ATC-coded drugs concerned paracetamol (N02BE01) and 10.6% (7) concerned methylphenidate (N06BA04).

5 DISCUSSION

5.1 Discussion of Results

Most reported ADEs reached the patient evaluated as no harm including the type of ADE as wrong dose and occurred at the time of dispensing when antibiotic, analgesic or sedative was prescribed. Patients were mostly at age group 0-1 years old.

5.1.1 Discussion of Frequency and Type of ADEs

Reported ADEs occurring for pediatric inpatients from 2010-2014 were in total 1926. Compared to data from the Statistic Bank of Denmark the average number of pediatric hospitalizations from 2010-2013 (information for the year of 2014 was not available) each year was 224409 (Danmarks Statistiks, n.d.). Assuming that the number of pediatric hospitalizations in 2014 was the same as the average for the years 2010-2013, then from 2010-2014 in total there were 1122045 hospitalizations of pediatric patients over 5 years. This means that 0.2% of actions with the opportunity for an ADE to occur within hospitals in Denmark resulted in an ADE that was reported. Studies were mentioned in a systematic review that stated the proportion of medication errors of potential errors. Studies using spontaneous reporting as a method of detecting medication errors found 0.15-17.2% medication errors and other studies that used chart review found 5.7-24% medication errors. This indicates a low reporting rate of adverse events related to drugs in Denmark in comparison of other studies (Ghaleb et al., 2006).

A Pearson's chi-squared test showed that the distribution of ADEs either reaching the patient or not was not equally distributed among the medication process stages. The majority of the ADEs reached the patient and these were six times more frequent than near-miss events. This is not in accordance with a review by Walsh et al. where near-miss events were 1.5-4.0 times higher than ADEs reaching the patient (Walsh et al., 2005). The results of this study are closer to the results of a prospective observation study where near-miss events

was 5.0% of all ADEs compared to 13.6% near-miss events in this study (Alexander et al., 2009).

ADEs at the time of dispensing consisted of almost half of all reported ADEs followed by approximately one third prescribing ADEs while administration of drug included fewest reports. This is unlike the Walsh et al study review where most studies found most ADEs in the administration stage of the medication process. The results of that review depend on the methods used which were mostly incident reports which could have caused the variation (Walsh et al., 2005). In this study the ADEs were not evaluated as an administration ADE unless it obviously occurred after drug dispensing. Most often it was not clear in which stage of the medication process the ADEs occurred, but if a drug was administered to a patient and the patient was not supposed to receive that certain drug in comparison to the prescription, the ADE was evaluated as occurring during dispensing since the drug should neither have been dispensed nor administered. The aim was to evaluate the ADEs based on their origin and not from where they were observed. Compared to the studies in the review by Walsh et al. this study was a retrospective study reviewing ADEs in a national database of obligatory reports.

The potential cultural differences between the hospitals' wards included in the other studies could possibly have an effect on the differences observed.
It is also possible that most ADEs occur at the time of dispensing for pediatric inpatients in relation to their complex physiology. The factors mentioned above can potentially influence the results found in the different studies.

The most reported types of ADEs for prescribing and dispensing were wrong dose, wrong time and wrong drug. In the administration stage the most common reported types of ADEs were wrong technique, wrong time and double administration of a drug. When comparing the calculated PRR values it was found that the wrong dose at the time of prescribing was the most common type of ADE to occur in comparison to all other medication process stages. The second most common type of ADE in comparison of all other medication process stages was wrong time at the time of dispensing. Those results were statistically significant. A systematic review of 32 studies showed that the wrong

dose was the most commonly reported ADE in 10 studies and wrong drug in eight studies. The wrong route of administration was the third most common reported ADE in the review, but that was the fifth most common ADE in this study (Ghaleb et al., 2006). To see if the results would have been different if those ADEs lacking part of the information had been included, a PRR was calculated for those ADEs as well. The largest difference observed was 0.18 lower when those ADEs lacking part of information were included for the wrong dose at the time of prescribing. This did not change the final results, since the wrong dose at the time of prescribing would also have been the most frequent type of ADE compared to all other medication process stages when ADEs lacking part of information were included. From this it can be assumed that missing information did not significantly change the final results of this study. It was not possible to find another study that calculated PRR for each type of ADE since that statistical test has not been used for this purpose before.

5.1.2 Age of Patients

ADEs occurring in the age group 0-1 years old was 40.2% of all reported ADEs which is in accordance with two other studies with 47.0-50.0% reports for the same age group. One of the studies conducted an analysis of records submitted into MEDMARX voluntary, internet-accessible, error-reporting database and the other study was a prospective direct-observation of drug administration errors (Alexander et al., 2009; Prot et al., 2005). A comparison to all other ADEs received from NAPRC was performed to see if it would have made any difference to the final results if all those ADEs would have been analyzed. Those results gave a similar frequency of 36.3% for 0-1 year old patients. There are more risk factors for an ADE to occur for this age group such as rapid growth, off-label medication use, variable and changing pharmacokinetic parameters and medical instability which could explain why an ADE occurs more often for that group (Alexander et al., 2009). There is probably more focus on this age group because health care professionals are more aware of the risks and therefore report more ADEs occurring for that age group than older patients.

On average patients 0-1 years old were 37.1% of all pediatric inpatients from 2010-2014 (by assuming that the average of 2010-2013 was the same for 2014) (Danmarks Statistiks, n.d.b). This is close to the percentage of ADEs for 0-1 year old patients in this study, 40.2% which could explain why the largest number of ADEs was for that age group.

5.1.3 Severity of ADEs

For 72.2% of the reported ADEs the severity was no harm and 1.5% ADEs were deemed serious. A comparison to all other ADEs was performed to see if it would have made any difference to the final results if all ADEs received would have been analyzed. Those results gave similar frequency or 68.4% as no harm and 1.6% of serious. Only three studies investigated the severity of ADEs being spontaneously reported compared to a systematic review. Medication errors were generally of moderate severity and no permanent harm was caused. Severity evaluated as mortal was 0.2-5.6% in two different studies reviewed (Ghaleb et al., 2006). This is also in accordance with a review that showed 96.0% errors classified as minor at time of reporting (Ross et al., 2000). However, those studies defined their severity levels differently from this study.

5.1.4 Drugs Involved in ADEs

The most commonly reported drug classes were antibiotics, drugs for the nervous system including analgesics, sedatives and psychoanaleptics. That is in accordance with a systematic review, which could be because these classes of drugs are the most widely prescribed (Ghaleb et al., 2006). Sold drugs in Danish private pharmacies from 2010-2013 for 0-19 year olds per 1000 inhabitants showed that on average the top five most sold drugs were antiinfectives for systemic use (J; 224 per 1000 inhabitants), Dermatologicals (D; 134 per 1000 inhabitants), drugs for sensory organs (S; 127 per 1000 inhabitants), drugs for respiratory system (R; 110 per 1000 inhabitants) and drugs for genito-urinary system and sex hormones (G; 61 per 1000 inhabitants). Drugs for the nervous system were the seventh most commonly sold drugs (N; 32 per 1000 inhabitants) while immunomodulating agents were the least sold drugs in 14th place (L; 1 per 1000 inhabitants) (Statens Serum Institut, 2013).

This is not in accordance with the drugs most frequently involved in the reported ADEs. It was not possible to get the same drug utilization data for pediatric inpatients and therefore this information does not indicate the use of drugs in public hospitals in Denmark.

Number of hospitalizations for 0-19 years old from 2010-2014 was earlier stated as 1122045. Aside from 25.9% of the hospitalizations for births and 17.3% for undefined symptoms, the top four reasons for hospitalizations were 11.6% for respiratory diseases, 8.1% because of trauma, poisoning and other grievous bodily injuries, 4.7% for digestive diseases and 4.7% for infections or infestations.

This means that large numbers of inpatients were hospitalized because of infections and infestations that lead to a high number of prescriptions for antiinfectives and therefore large amount of ADEs for that certain drug group. The same approach was used for diseases in the nervous system and mental disorders which gave 4.0% and 0.9% respectively of all hospitalizations for 0-19 year old (Danmarks Statistiks, n.d.). However, respiratory drugs should give the largest number of ADEs, but there were only 2.9% (6) of ADEs for that group of drugs.

There are few possible reasons for the overrepresentation of ADEs related to antiinfectives, drugs for the nervous system and immunomodulating agents in comparison to the top sold drugs in Denmark or the top causes for hospitalizations. It could be because of difficult calculations for antibiotics for that age group, many drugs for the nervous system have a narrow therapeutic index and immunomodulating agents can often be toxic (Coupey, 1997; Becker, 2007; Kummar et al., 2006; American Society of Health-System Pharmacists, 2012). Although there are number of respiratory diseases that cause the use of antiinfective drugs which can indicate their high use compared to respiratory drugs.

5.2 Strengths and Limitations of the Methodology

The majority of studies on ADEs have been conducted in adult patients and therefore there is a need for more studies in children. This is the first study that researches ADEs within pediatric inpatients in Denmark and it was important to analyze the available data.

The researcher had the opportunity to practice categorizing skills before arriving at the NAPRC and received feedback from a supervisor knowledgeable about the data. This helped to make the categorization more valid. However, since the reported ADEs were written in Danish, which is not the native language of the researcher, there could have been some misunderstanding which potentially could also lead to wrong ADE categorization. Further, the quality of the reports was poor due to multiple reasons. First, because of errors during transfer of information from the DPSD and generating the Excel document containing the ADEs which was performed by a consultant at NAPRC, some information accidently got excluded so part of sentences in the reports disappeared. Secondly, a high number of typographical errors by the reporter made it possible to search for those words in a dictionary. Thirdly, a numbers of ADEs did not include much information which could have led to the wrong analysis of data because of information that was not obligatory to report. An example is that it was not always reported which drug was involved so the results are not conclusive.

To assess the prevalence of ADEs various reporting procedures have been used, but normally more ADEs are observed than reported (Classen et al., 2011). In this study only events that contained information about the patients' age were included in the search, but it was not required for reporters to report age of patient. It is therefore likely that the total number of ADEs received from NAPRC did not state all reported ADEs from public hospitals in Denmark. Other limitations for the total number of ADEs are that not all ADEs are reported when a reporting system is voluntary. That kind of a system is simple, but still it leads to under-reporting and leads to a "bandwagon" effect (Edwards and Aronson, 2000). This meaning that people mimic each other's behavior (Long et al., 2007). In this case if some nurses normally report ADEs then others would

more likely do so too. Conversely, if physicians in a certain hospital do not normally so, it is also more likely that other colleagues would not. In a survey of hospital personnel, 89.0% of nurses had completed some incident reports in the past 12 months, while only 54.0% of physicians had. Physicians and nurses were more likely to report certain types of errors than others. Serious errors were more likely to be reported than those that were less serious and events that reached the patient were more likely to be reported than those that did not. Overdosing errors such as 10-fold morphine dose were most likely reported while overdosing reports of amoxicillin was most likely not reported. Of those ADEs that were evaluated trivial most likely late administration of seizure medication was reported. The most likely reason for not reporting was uncertainty about whether it was an ADE or not and secondly they were concerned about implicating others. Other reasons included uncertainty about whose responsibility it was for reporting a certain ADE, concerns about being blamed or judged, or the belief that it was not important to report errors that did not lead to harm or did not reach the patient (Taylor et al., 2004). In Denmark health care workers are required to report an observed ADE within seven days and this is therefore not a completely voluntary reporting system. However, 30.0% of interviewed health care workers were aware of ADEs that were not reported (Sundhedsstyrelsen, 2006). It is also difficult to punish the health care workers for not reporting since there is no control on whether if it is reported or not and therefore it can be difficult to require the staff to report an ADE.

Since the severity was not categorized by this researcher, but by the person who reported the ADE, it is difficult to know the real severity of the ADEs since they were evaluated by many and different health care workers. For example an ADE was evaluated as no harm when a newborn child of a HIV-infected mother received antiretroviral drug too late. That event could have infected the child. Most mother-to-child transmissions of HIV occurs around the time of labor and is therefore recommended that all children born to HIV positive mothers receive a six-week course of antiretroviral drug, but the administering of this drug is required to start within six to 12 hours after the baby is born. (U.S. Public Health Service's, 2015).

A slight modification of the categorization was necessary after analyzing the ADEs to avoid overlap of types of ADEs. Therefore the researcher went to NAPRC again to go through the categorization. The researcher did not have time to go through all the ADEs again, but had in advance decided which ADEs should be rechecked out from sequential number of an ADE. There are still possibilities for overlaps of types of ADEs and therefore categorization was potentially affected by subjectivity. It is difficult to avoid subjectivity when categorizing reports based on free text and this can affect the reliability of the results (Bowling, 2009). To test the reliability a test-retest method could have been used (Hendrickson et al., 1993). By estimating test-retest reliability it would be depending on that there were five ADEs evaluated differently for medication process stage and unknown number of types of ADEs were changed within the medication process stages. The test-retest reliability would also depend on the condition that 16 days passed before reviewing some of the ADEs again from leaving NAPRC until coming back to NAPRC again. The categorization was also changed in a way that some categories were combined in one and an extra category was made to explain why an ADE occurred (Trochim, 2006; Korb, n.d.). The researcher believed it would ease and improve the quality of the categorization.

Only 16.3% of all the ADEs received were analyzed and aside from randomization there is still a possibility for coincident systemic order in the ADEs in relation to the medication process stages. However, a comparison of frequency of the ADEs analyzed and the ADEs that were not analyzed showed very little difference.

5.3 The Role of Clinical Pharmacists in the Medication Process

In order to improve the quality of the pediatrics medication process a few suggestions are provided on how pharmacists can be part of clinical care for preventing ADEs. Some important system changes have been reported or proposed in order to improve pediatric medication prescribing, transcribing, dispensing and administration including for example, increasing participation of clinical pharmacists on inpatient units as member of the patient care team

(Neuspiel and Taylor, 2013; Committee on Drugs, & Committee on Hospital Care, 2003; Leape et al., 1995).

Further to these improvements, a checklist was made by the Patient Safety Committee in Argentina focusing on health care professionals' education. The checklist included three specific strategies to reduce medication errors where one of the strategies focused on grand rounds and demanded an active interaction with pharmacists during rounds (Otero et al., 2008). A systematic review of studies was performed of 18 studies. Since pharmacological factors in children increases the risk of errors there is unique opportunities for pharmacists to improve the quality of care for pediatric patients. It showed that a pharmacist review of medication charts is very important in identifying medication errors and is likely to be the most effective method of improving drug therapy in children. It further showed that 93.0% of interventions had a positive impact on patient care and 8.5% of interventions were classified as life-saving (Sanghera et al., 2006). For preventing serious ADEs a clinical pharmacist could develop a specific list of pediatric drugs of high-risk and provide education to patients and caregivers about their medications (Committee on Drugs, & Committee on Hospital Care, 2003). Another approach would be to move dispensing of drugs away from nurses (Flynn et al., 1999). This would improve the quality of dispensing and release nurses of a large part of drug related responsibility which is not their professional focus. Nurses' workload could be reduced, removing stress and long shift hours that are said to increase errors made by health care workers (Sundhedsstyrelsen, 2009).

Other examples would be advising physicians about complicated patient groups and their relation to drug treatments, substitution of a drug, contraindications, interactions and solving problems of polypharmacy (Lægemiddelstyrelsen, 2005). Changing physicians' decisions regarding the choice of drugs for children requires changes in beliefs that may be most successfully altered by an academically based pharmacist (Leape et al., 1995). Follow-up monitoring of a medication treatment could also be a task for a pharmacist instead of a physician and especially for the patients with

polypharmacy. Finally pharmacists could be an important teacher for patients about their use of drugs (Lægemiddelstyrelsen, 2005).

5.4 Future Studies

It is a problem that different studies use various methods with different definitions for both ADEs and type of ADEs and are therefore not easy to compare. A multicenter study using standard methods and definitions could provide a better picture of ADEs worldwide which requires an internationally accepted definition. The quality of this research could be improved by setting criteria and standards. The size of the problem and causes of ADEs in pediatrics is still not well established (Ghaleb et al., 2006). Future research should therefore concentrate on interventions to reduce medication errors in children (Ghaleb et al., 2010). Since pharmacists are professionally focussed on drugs it would be an advantage if pharmacists lead such a study.

6 CONCLUSION

This study reviewed ADEs within public hospitals in Denmark for pediatric inpatients which were reported into the DPSD. The results of the study show that most ADEs occur at the dispensing stage in the medication process. Within the stage of prescribing the majority of ADEs concerned wrong dose ADEs. Half of all the ADEs occurred concerning 0-1 year old patients but were mostly evaluated as no harm. Fortunately, no ADE resulted in death of the patient, but four were evaluated as serious. The most common type of drugs involved in ADEs were antiinfectives and drugs for the nervous system.

For better categorization it is necessary to use widely accepted definitions of error categories and similar methods to facilitate comparison between studies. It is important to further analyze ADEs for pediatrics in Denmark. What is needed is a study where a larger sample of the reported ADEs are analyzed. It would also be interesting to study the impact on ADE occurrence if pharmacists and pharmacy technicians would take responsibility of the dispensing process.

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APPENDIX

APPENDIX 1

Fictive example of categorization. Note that they are translated from Danish to English and are altered in such a way as they won´t be recognized.

Date of ADE	Number of ADE	Severity	Location	Hospital of ADE	Ward of ADE	Description of ADE	Consequence
19.04.2014	xxx	Ingen skade	Offentlige sygehuse	Region Syddanmark Psykiatrien Kolding B & U PSY U2 afsnit (Kolding)	PSY U2 afsnit (Kolding)	Kl.10 dosis ikke givet. Opdaget af aftenvagten da dagvagten er taget hjem	Medicinen er ordineret til patientens da denne har en infektion.Kan naturligvis have fatale konsekvenser hvis ikke patienten får den ordinerede medicin tilrettelagt efter patientens diagnoseMedicinen blev givet senere på dagen end ordineret efter fejlen

Suggestion of intervention	Description of follow-up	Comments to the NAPRC	Categorization by NAPRC. DPSD main category	Categorization by NAPRC. DPSD process	Categorization by NAPRC. DPSD problem
Bedre nomering i afdelingen når der er komplekse børn i afdelingen der tager meget tidDer var 2 sygeplejersker til at passe en del syge børn med mange komplekse og alvorlige problemstillinger.Fejlen er i dagvagten givetvis sket pga travlhed	Sagen tages op med afsnitsledelsen.		Medicinering herunder væsker	Administration (Udlevering, indgift og indtagelse)	Medicin ikke givet

Categorization by WHO. WHO Main category	Categorization by WHO. WHO process	Categorization by WHO. WHO problem	Date of case closure	Age	Sex	Involved locations	Involved institution types	Role of event
Medicinering	Administration	Forkert dosis / tidspunkt / frekvens / ikke givet	26.05.2014	10	mand	Region Syddanmark Odense Universitets Hospital Børneafd. Hm	Offentlige sygehuse	Andet

Name of ADE	ATC code	Active substance	Producer	Concentration
Gentamicin	J01GB03	gentamicin	B.Braun	40 mg/ml

The Categorization:

Type of incident: Reach patient (1) Near miss (2)	Medication process stage	Type of ADE	Sub-type of ADE	Explanation	Active Substance 1	Brand Name 1	ATC code 1	Active Substance 2	Brand Name 2	ATC code 2
1	Dispensing	Wrong time	late		gentamicin	Gentamicin	J01GB03			

Age	Date of ADE	Date of Case Closure	Sex	Lacking informations (1) Full category (0)
10	19.04.2014	26.05.2014	male	0

APPENDIX 2

The Coding Table. Potential ADEs at the time of medication process stages and definitions of the sub-types of ADEs. This is a categorization both of those which were prepared before categorization based on studies and with add-ons while analyzing and categorizing at the NAPRC. They are not based on studies to better fit each category (those categories are marked with *).

Medication process stage	Type of ADE	Sub-type of ADE	Definition of sub-type of ADE
Prescribing ADEs	**Double dosage**		
	No drug		
	Wrong patient		
	Contraindication		
	Lacking patient information		
	Wrong dose	Overdosage	When drug is being dosed prescribed in higher dose than supposed compared to weight or other factors of patient. Could happen because of e.g. calculation error, electronic system error.

		Underdosage	When drug is being prescribed in lower dose than supposed compared to weight or other factors of patient. Could happen because of e.g. calculation error, electronic system error.
	Wrong formulation		
	Wrong drug	Discontinued drug administered*	When a drug was supposed to be discontinued it is not the "right" drug anymore and the sub-type of ADE in that is therefore a discontinued drug is administered.
		Interaction	Represents drug-disease; drug-drug or drug-food/nutrient. When a drug leads to patients´ interaction it would be an ADE if there were disregard of former information of patient or because of missing therapeutic monitoring and therefore a wrong drug.
	Wrong time	Early	Prescription that includes wrong instructions of usage that leads to early administering

		Late	Prescription that is either prescribed too late or includes wrong instructions of usage that leads to late administering
	Other		
Dispensing ADEs	**Double dosage**		
	Expired drug		
	Manipulation	Crystallization	When irresponsible mixing of a drug with wrong liquid it could lead to crystallization
	No drug		
	Wrong dose	Overdosage	
		Underdosage	
	Wrong drug	Discontinued Drug administered*	When drug is discontinued but still dispensed it could be because of omission of reading schedule and leads to administering.
	Wrong formulation		
	Wrong patient		
	Wrong storage		
	Wrong time	Early	Early dispensing compared to prescription because of e.g. Omission of reading schedule

		Late	Late dispensing compared to prescription because of e.g. Omission of reading schedule
	Change prescription without approval		
	Other		
Administering ADEs	**Double dosage**		
	No drug		
	Wrong dose	Overdosage	
		Underdosage	
	Wrong drug		
	Wrong formulation		
	Wrong patient		
	Wrong route of administration	Left confused with right	When administering drug into wrong side of the body, for example confusing left leg with right leg
		Wrong injection	Injecting drug for example i.v. Instead of i.m.
	Wrong technique	No drug*	When e.g. nothing would come out of a medication pump or forgotten to turn on
		Wrong volume	
		Wrong rate	
	Wrong time	Early	
		Late	

	Other		

* Sub-categories of errors without references but were used during categorization

APPENDIX 3

The Standard Operating Procedure

The process at NAPRC

When arriving at NAPRC start by opening an Excel document from Pia Knudsen and Morten Sonne from a USB stick that is kept, and will always be kept, at the NAPRC. This Excel document contains all the ADEs that have been finalized from public hospitals in Denmark relating to children 18 years old and younger during the period of 1.1.2010-31.12.2014. Next remove all ADEs that are not concerning the research. Keep the ADEs with age of patient under 18 years old, location of public hospitals and the events concerning medication reported as classified by WHO. The document will be changed and saved as follows:

1. The first document is the document from NAPRC and should be saved without any changes at all (Title: Børn). That document includes different sheets categorized by years.

2. The second document should gather all the documents from each year in one sheet (Title: All ADEs)

3. One document beyond number 2 is the same but duplicates should be removed. ADEs not concerning the study as well as those that are not ADEs containing age of patient under 18, location of public hospitals, and ADEs other than concerning medication as reported by WHO should also be removed. (Title: All ADEs – removed ADEs not concerning study and duplications)

4. One document is the same as number 3 but randomized. (Title: All ADEs – randomized)

    - To randomize a table in an excel document, first make a new column, write “=rand()“ in all rows that should take

place in randomization, copy those numbers and paste by values (so that these numbers will not appear as formula anymore) in a new column. Next sort that column with pasted randomized numbers from largest to smallest. Be aware that randomization is correctly done by numbering the rows before randomization in one column to observe that after randomization those numbers will appear in different order.

5. One document is the same as number 4 but it is the working copy (do not change the randomization). Categorization of adverse events will be accomplished as much as possible. (Title: All ADEs – Document of work)

    - At the end of existing row of definitions for each ADE these columns will be added as the head of a column:

Type of incident; Adverse event (1) Near miss (2)	**Medication process stage**	**Type of ADE**	**Sub-type of ADE**	**Explanation**
Severity	**Active substance 1**	**Brand Name 1**	**ATC code 1**	**Active substance 2**
Brand Name 2	**ATC code 2**	**Age**	**Date of ADE**	**Date of case closure**
ADE not Categorized (1)				

    - Next: While categorizing each column should be completed (as much as possible) for each ADE. Always use the exact

same words as in the Coding Table (note that excel remembers what has been written before each column) so the pivot table 'understands'. One should not worry about spelling mistakes because it will be discovered quickly when starting to work with the pivot table

- In some of the columns it is possible to do a copy-paste operation from former existing columns. If it is needed then it is possible to translate all phrases of the column at once from Danish to English with a special technique described below. A copy-paste operation can be made from these columns: **Severity, Brand Name 1, Active Substance 1, ATC-code 1, Age, Date of Case** and **Date of Case Closure**. Note that sometimes these columns have not been filled so in those cases it is required to find information differently or mark the column as missing "head name of column".

    - Technique to change all columns at once in Excel:

        - Choose the whole column at once by clicking the letter of that column after a 'down-arrow' appears, Ctrl+F, Choose 'replace' and write the Danish word in the column 'find what' and the English word in the column 'replace with', Choose 'Replace all'. There will appear a note about how many changes were made. Choose 'ok'. Repeat this until all phrases have been translated.

- Sometimes there is missing information or ADEs not concerning the research and in that case type **1** in the column **"ADE not Categorized"**.

- That category will not be analyzed further.

- Sometimes there are ADEs that lacks a piece of information. In those cases type missing “head name of column” where it belongs. If the piece is one of the most important categories (type of incident, medication process stage or type of ADE) then type 1 in the column **“ADE not Categorized”**, but not if the lacking information refers to least important categories (sub-type of ADE or explanation).

- When there is an ADE that actually concerns two different ADE, remember to make a duplicate from them.

- For each column, these phrases should be used:

Type of incident: Adverse event vs. Near-miss-event

- Under the column of “type of incident**;** Adverse event (1) Near miss (2)” type;
    - If adverse event press 1
    - If near miss event press 2

Medication process stage

- Prescribing
- Dispensing
- Administering

Type of ADE

- Use the Coding Table to find each type of ADE
    - E.g. Wrong drug, wrong dose

Sub-type of ADE

- Use the Coding Table to find each sub-type of ADE
    - E.g. overdosage, underdosage

Explanation

- Remember to write short explanation of why an ADE occurred if reported, to keep a better overview after going out of NAPRC without the main data.

Severity

- Copy-paste and the Danish words are translated to these English words.
    - Ingen skade → No harm
    - Mild
    - Moderat →Moderate
    - Alvorlig →Serious
    - Dødelig →deathly
- Note that these events will stand just as they were reported in to the database. Even though they sometimes do not fit with how the researcher evaluates the severity of the event.

Active Substance 1

- An active substance number 1 is the one prescribed and should have been dispensed and administered.

- Note that the column of active substance 1 is sometimes active substance 2 and in those cases be aware and switch columns when necessary.

- For this column you can make a copy-paste operation but be aware that sometimes it is not listed and then is must be done it manually.

- When there is an ADE concerning e.g. anti-biotic or hydrating fluid that has not mentioned the name of the drug or active substance, write “anti-biotic” or “hydrating fluid” in that column, so at least you can know the frequency of anti-biotic in general

Brand Name 1

- A brand name number 1 is the one that should have been administered.
- For this column you can make a copy-paste operation but be aware that sometimes it is not listed and then it must be done manually.
- Note that the column of brand name 1 is sometimes brand name 2 or and in those cases be aware and switch columns when necessary.

Active Substance 2

- An active substance number 2 is the one that was administered.
- Also, if there is an event concerning two drugs, always write both, not only when there is confusion between two drugs, because the categories will tell what kind of an event it is.
- Each square is made when a new medicine is handled e.g. paracetamol or ibuprofene (note that the reporters write drug names differently so be aware of change that consequently)
- When there is an ADE concerning e.g. anti-biotic or hydrating fluid that has not mentioned the name of the drug or active substance, write “anti-biotic” or “hydrating fluid” in that column, so at least you can know the frequency of anti-biotic in general.

Brand Name 2

- A brand name number 2 is the one that was administered.

- Each square is made when a new medicine is handled e.g. Paratabs or Ipren

ATC-code 1

- ATC-code number1 is the one prescribed
- For this column you can make a copy-paste operation but be aware that sometimes it is not listed and it must be done manually.
- Sometimes the codes do not appear, then use pro.medicin.dk to search for ATC-code.

ATC-code 2

- ATC code number 2 is the one that was administered.
- Each square is made when a new medicine is handled e.g. N02BE01.

Age

- For this column you can make a copy-paste operation.
- If it is reported in months, please change into years (if under 1 year then 0).

Date of Case Closure

- For this column you can make a copy-paste operation.
- Change the date so only the month and year is seen by doing these formulas in two different columns.
    - For month: “=MONTH(Table1[@[Date of ADE]])”
    - For year: “=YEAR(Table1[@[Date of ADE]])”

6. One document should include adverse events for a supervisor when feeling uncertain about something. (Title: 5 - ADEs for supervisor).

7. Last, there has to be a document of adverse events that is allowed to be taken out of the NAPRC. That could be a document with a table that is further made into a pivot table when working with the ADEs. (Title: 6 - ADEs to Take Home)

    - This is a document that will be a copy-paste of all the extra columns made in document number 5 (Document of work)

Other documents

- A word document should be made to write down a new kind or unexpected event that has not been put into the coding table or any other changes made during the categorization. Mark these documents with the number of the event.

- A word document should be made to write down questions and ideas of interventions. Mark it with the number of the event.

- A word document should be made to write down why an adverse event happened if necessary. Mark it with the number of the event.

Other notifications

- Always save document number 4 in a new document for each day by typing the date in front (start with the year, month and then day so they save in the right order). That is to ensure that if you change something from day by day and maybe doubt about it on the third day you can go back and see what you did there. This protects freezing the document from unexpected computer error.

- In the document number 7 (All ADEs – ADEs to take home) it is also possible to count frequency by using pivot tables related to the purpose of that thesis.

- *Brugerhåndbog* is a book of categorization that should help with uncovering the responsibilities inherent in the health care system.

APPENDIX 4

This is a copy of approval for accessing the *Danish Patient Sikkerheds Database*

Kontrakt mellem Patientombuddet og den analyseansvarlige.

Kontrakt om indhentning og analyse af data fra Dansk Patientsikkerhedsdatabase

Denne kontrakt omfatter levering af data fra Dansk Patientsikkerhedsdatabase (DPSD) til eksterne analyseansvarlige. Kontrakten erstatter en evt. tidligere indgået kontrakter.

Undertegnede rekvirent:	
Navn	Heidrós Tinna Hannesdóttir Pharmaceut Speciale Studerende
Adresse	SDU, Institut for Sundhedstjenesteforskning
Post nummer/by	
Telefon	
Ansvarlige kontaktperson	Anna Birna Almarsdóttir, SDU Pétur S. Gunnarsson, University of Iceland
Sæt kryds ☐ Offentlig myndighed ☐ Koncessioneret selskab ☒ Privat eller offentlig virksomhed SDU	

Oplysningerne fra ejendomsdataregistrene ønskes anvendt til følgende formål, som bedes beskrevet fyldestgørende:	
Oplysningerne ønskes anvendt til markedsføringsformål	☐ Ja ☒ Nej
Hvilke oplysninger ønskes i listerapporten:	Handelsesdato, Alder, Lokation, Handelssted, Afdeling, Handelsesbeskrivelse, Konsekvens. Forslag til forebyggelse, beskrivelse af sagsopfølgning, Bemærkninger til RKB, Hovedgruppe, proces, problem, Sagsafslutningsdato Alder, Køn, Handelses kode, ATC, Indhold, Fabrikant, Styrke
Den ønskede leverancetype	☒ Engangsudlevering ☐ Flergangsudlevering
Format	☐ Word ☒ Excel ☐ PDS ☐ Andet
Formålet med datatrækket eller analysen:	At opnå viden om UTHer ved medicinering af børn på offentlige hospitaler, som skal bruges i et ph.d. projekt til at forsøge at forbedre patientsikkerheden ved medicinering af børn

Evt. særlige aftaler vedr. dataudtrækket og analysen.	

Dato og analyseansvarliges underskrift:

27.3.2015 Hildigis Tinna Hannesdóttir

Dato Underskrift

Patientombuddet tiltræder herved, at udlevering af data kan finde sted:

27/3-2015

Dato Underskrift

APPENDIX 8

Each medication process stage categorized into type of ADE and sub-type of ADE

Type of ADE →**Sub-type of ADE**	**Prescribing ADEs % (n)**	**Dispensing ADEs % (n)**	**Administering ADEs % (n)**
Manipulation error			
Crystallization	-	1.5 (1)	-
Wrong dose			
Overdosage	66.2 (49)	27.7 (18)	6.3 (2)
Underdosage	16.2 (12)	23.1 (15)	9.4 (3)
Wrong drug			
Discontinued drug administered	6.8 (5)	3.1 (2)	-
Interaction	2.7 (2)	-	-
Wrong route of administration			
Right confused with left	-	-	6.3 (2)
Wrong injection	-	-	9.4 (3)

Wrong technique			
No drug	-	-	3.1 (1)
Wrong rate	-	-	28.1 (9)
Wrong volume	-	-	3.1 (1)
Wrong time			
Early	4.0 (3)	13.9 (9)	12.5 (4)
Late	2.7 (2)	29.2 (19)	21.9 (7)
Wrong discontinuation	1.4 (1)	-	-
Total	100.0 (74)	100.0 (64)	100.0 (32)

APPENDIX 6

ADEs that lacked information

Type of incident	Medication process stage	Type of ADE	Number of incidents
Adverse Drug Event	**Missing Type of Process Stage**	Disregard for Contraindications	1
Adverse Drug Event	**Missing Type of Process Stage**	Double Dose	1
Adverse Drug Event	**Missing Type of Process Stage**	No Drug	1
Near-miss Event	**Prescribing**	Missing type of Problem	1
Missing incident categorization	**Prescribing**	Missing type of Problem	1
Missing incident categorization	**Dispensing**	Wrong Dose	1
Total			**9**