Prescribing errors in children

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1. Dedication

I dedicate this thesis to my late grandfather Dr. Alfred Kolorz

and all my ancestors who came before me.

This is for my daughters Alea Josefine and Yuna Rosa who come after me.

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3. Table of Contents

4. Abbreviations

ADE	Adverse drug events
ATC	Anatomic Therapeutic Chemical Classification System
CDS	Clinical decision support
CI	Confidence interval
CPOE	Computerized physician order entry
DRP	Drug related problem
GSASA	Swiss Society of Public Health Administration and Hospital Pharmacists
i.v.	intravenous
NCC MERP	National Coordinating Council for Medication Error Reporting and Prevention
NICU	Neonatal intensive care unit
pADE	Preventable adverse drug event
PCNE	Pharmaceutical Care Network Europe
PHE	Potentially harmful errors (NCC MERP E-I)
PICU	Pediatric intensive care unit
ROA	Route of application
SmPC	Summary of product characteristics
TDM	Therapeutic drug monitoring

5. Summary

Prescribing errors are a well-known safety concern in pediatric patients. The aim of this thesis was to investigate factors related to patients, drugs, and the mode of prescription, that influenced the rate of prescribing errors in a population of 1000 pediatric patients hospitalized on general medical and surgical wards at the University Children's Hospital Zurich. The data were collected during two periods in 2018 and 2019. In total 5022 prescriptions were analyzed.

The prevalence of prescribing errors under different circumstances of prescribing (2299 pre-CPOE prescriptions with semi-structured order forms or handwritten prescriptions versus 2723 post-CPOE prescriptions as electronic prescriptions with limited clinical decision support (CDS)), was investigated in different age groups and different types of drugs. Additionally, the types of errors that occurred and the severity of harm potentially caused by these errors were revealed. Furthermore, associations of errors withs specific drug types or patients were investigated, with a particular emphasis on unlicensed drugs.

In the first study *Prescribing errors in children – what is the influence of a computerized physician order entry (CPOE)?* the influence of the prescribing mode was investigated. The prescriptions of 500 patients before (2018) and after (2019) introduction of a CPOE were analyzed and prescribing errors assessed. It was found that the post-CPOE prescriptions overall contained significantly fewer prescribing errors (25 errors / 100 prescriptions) than pre-CPOE prescriptions (78 errors / 100 prescriptions) ($p < 0.001$). Errors that actually could have led to patient harm with a severity rated as “temporary harm possible” to “death” (further referred to as potentially harmful errors: PHE), were also reduced from 18 errors / 100 prescriptions pre-CPOE to 11 errors / 100 prescriptions post-CPOE ($p < 0.001$). The errors that occurred most frequently in the pre-CPOE period were errors due to missing information. These errors were of minor severity and were strongly decreased post-CPOE, where dosing errors were the most frequent type of error. A statistically significant increase in medication reconciliation errors was observed after CPOE introduction due to remaining hybrid prescriptions in certain cases. Overall, the CPOE had a positive impact on patient safety.

In *Prescribing patterns in pediatric general wards and their association with prescribing errors*, the second study, a sub-analysis of the first study was conducted in which prescribing patterns in the post-CPOE population were revealed. Newborns were excluded from the study due to small sample size, leading to a remaining population of 489 patients with 2693 prescriptions. Drugs for the nervous system, drugs for the alimentary system and anti-infective drugs were the most frequently prescribed drug classes, with paracetamol, metamizole and ibuprofen being the most frequently prescribed active substances. Patient characteristics like age and gender as well as drug use were associated with prescribing errors. Children between 2 and 11 years experienced higher error rates than infants under 2 years of age: 12.2 potentially harmful errors (PHE) / 100 prescriptions, vs. 8.5 PHE / 100 prescriptions ($p = 0.026$). A statistically significant difference was also found for female patients as compared to male patients, with the female patients having higher rates of PHE than the male (25.6 errors or 12.1 PHE / 100 prescriptions vs. 24.7 errors or 9.3 PHE / 100 prescriptions) ($p = 0.035$ for PHE), even though there was no difference in the overall error rates. This finding needs further investigation.

The third study, *Use of unlicensed drugs in a Swiss Pediatric University Hospital and associated prescribing error rates,* another sub-analysis of the first study laid a focus on unlicensed drugs in the population of 1000 patients (pre- and post-CPOE), which accounted for a proportion of 10.8% of all prescriptions. 34% of patients were prescribed at least one unlicensed drug. Oral liquid forms were the most frequently prescribed drug form in unlicensed drugs. In the post-CPOE population unlicensed drugs were more prone to prescribing errors than licensed drugs (32 errors / 100 prescriptions vs. 24 errors / 100 prescriptions, $p = 0.024$). Particularly extemporaneously prepared drugs had high error rates of 36.4 errors / 100 prescriptions. Therefore, licensed drugs are favorable in terms of medication safety.

Overall, this thesis highlights various aspects of prescribing errors in children and illustrates, that pediatric patients are still at a high risk of experiencing a prescribing error. Ongoing efforts are necessary to improve medication safety. These include electronic solutions like CPOE and CDS, multifaceted approaches on healthcare professional and organizational level as well as support from the pharmaceutical industry by licensing more suitable formulations for pediatric patients.

6. Introduction

6.1 Prescribing Patterns in Pediatrics

"Children" or more accurately "pediatric patients" are a heterogeneous population of patients between 0 and 18 years of age. According to the European Medicines Agency, they can be divided into 5 age groups [1]:

- Preterm newborn infants: < 37 weeks of gestational age
- Newborn (term newborn infants): 0 to 27 days
- Infants (infants and toddlers): 28 days to 23 months
- Children: 2 to 11 years
- Adolescents: 12 to 18 years

Pediatric patients differ vastly in size and weight, and their metabolism and physiology changes, as they continuously grow and develop [2]. They may suffer from other diseases than adults and therefore need other drugs, but drug utilization and prescribing patterns in children are not as well studied as they are in adults [3].

In pediatrics, drugs have to be prescribed off-license in many situations, which includes off-label and unlicensed use. The definition of off-label use varies among studies, but Neubert et al [4] defined pediatric off-label use as "*all pediatric uses of a marketed drug not detailed in the summary of product characteristics (SmPC) with particular reference to: therapeutic indication, therapeutic indication for use in subsets, appropriate strength (dosage by age), pharmaceutical form, route of administration*". Off-label prescriptions are frequently necessary in pediatrics, as most medicines are still developed and tested in adults and therefore drug approvals are often limited to adults [5]. A recent study (unpublished) by Tilen et al. [6] found that only 55% of the drugs available on the Swiss market are authorized for the use in children. But off-label use does not necessarily mean off-evidence [7; 8], as there are efforts to provide evidence for the usage of drugs, which are not licensed by the authorities for the use in children [9; 10].

The other part of off-license prescriptions are unlicensed drugs, which are often necessary in pediatrics due to the lack of appropriate dosages and formulations for children on the market [11-14]. Neubert et al [4] define unlicensed use as "*all uses of a drug which has never received a European Marketing Authorization as medicinal for human use in either adults or children*". As our study took place in Switzerland, and Switzerland is not part of the European Union and has its own licensing authority (Swissmedic), the definition was adapted to "*all uses of a drug which has never received marketing authorization by the country's licensing authority as medicinal for human use in either adults or children*".

Unlicensed drugs comprise different types of drugs. Included types vary in the literature. In most studies, drugs that are imported from foreign countries are denoted as unlicensed drugs, as well as drugs, that are specially manufactured by the hospital pharmacy or other manufacturers. In some studies, also any alteration of a drug form, like crushing and dissolving a tablet, are referred to as unlicensed use of drugs [4].

In our studies, imported drugs and specially manufactured drugs (further referred to as “formula drugs”) were included as unlicensed drugs, but manipulated drugs were excluded, as it was not possible to extract these cases from the database.

6.2 Medication Safety in Pediatrics

Patient safety is defined as "*freedom from accidental injury*" caused by healthcare, e.g., harm or death resulting from adverse drug events (ADE), patient misidentification, and healthcare-associated or healthcare-acquired infections [15]. Since the report “To Err is Human” from 2000 [15], medical errors have gained a lot of attention and strategies to prevent patients from harm have evolved. Medication errors are among the most common types of medical errors [15; 16] and are a major issue for drug safety in pediatrics [17], as pediatric patients are known to be at higher risk to experience a medication error than adults [18-20].

A medication error is defined as an *“unintended failure in the drug treatment process, that leads to, or has the potential to lead to, harm to the patient”* [21]. Medication errors include all errors that can occur in the medication process, including prescription, transcription, dispensation, administration, or monitoring [22].

Medication errors can result in ADEs. Patient injuries, that are caused by medication errors are termed preventable adverse drug events (pADE) [15; 23; 24]. ADEs can also occur, when no error is present, for example in cases where a patient experiences an adverse drug reaction [25].

Pediatric patients are not only at higher risk of being affected by a medication error, but also of experiencing an ADE [26]. Off-label and unlicensed drugs are more frequently associated with ADE than licensed drugs because pharmacokinetic data of these drugs are often lacking in the pediatric population and the total systemic exposure is an important determinant of the likelihood of an ADE [27]. Furthermore, ADE are often underreported in pediatrics, due to legal and liability concerns [12].

6.3 Prescribing Errors

One type of medication errors are prescribing errors. Prescribing errors are defined identically for adults and children as *“A clinically meaningful prescribing error occurs when, as a result of a prescribing decision or prescription writing process, there is an unintentional significant (1) reduction in the probability of treatment being timely and effective or (2) increase in the risk of harm when compared with generally accepted practice”* [28; 29].

In adults, approximately 7% of all prescriptions are estimated to contain errors [30], but the rates range widely from 2% to 94% [31]. The rate in children is estimated to be about 17.5% [32], but the ranges also differ widely between studies from 1.0 to 62.7 errors / 100 prescriptions [19]. In general, studies concerning medication errors demonstrate significant heterogeneity, depending on studied wards, the definitions that are applied and the methodology of error assessment and data-collection [19; 33]. Due to this heterogeneity, studies are difficult to compare. On pediatric general wards with electronic prescriptions (CPOE), the rate is estimated to be about 15 to 47 errors / 100 prescriptions, whereas on general wards with paper prescriptions, rates between 4 - 58 errors / 100 prescriptions were found [19].

6.3.1 Risk Factors for Prescribing Errors

Risk factors for prescribing errors are generic factors like prescriber characteristics, organizational problems, working conditions and errors caused by interprofessional communication [34]. These risk factors apply to all prescriptions either in adult or pediatric healthcare.

However, there are several factors, why prescribing errors occur more often in pediatric patients. First of all, drug doses have to be calculated individually, as children are constantly growing, and the size and weight of the patients is highly variable. This leads to the fact that drug dosages have to be frequently adapted and newly calculated. Altogether, this leads to an increased risk of dosing errors [34-36].

The next risk factor is the high extend of off-license prescriptions, including off-label and unlicensed drug prescriptions [13; 34]. Both, off-label and unlicensed are associated with higher rates of prescribing errors [13; 34].

Other pediatrics specific risk factors for prescribing errors are the types of formulations, that are frequently prescribed to children, which are liquid formulations. They often lead to errors due to calculation errors in the conversion of milliliters to milligrams or vice versa [34; 37] or due to errors when prescribing milliliters of a drug of which different strengths are available [38; 39].

The setting also influences the observed rate of prescribing errors. Several studies found that they occur more frequently on pediatric intensive care units (PICUs) [19], on neonatal intensive care units (NICUs) [40] and in emergency departments [19] than on general wards.

6.3.2 Classification of Prescribing Errors and Severity of Harm

Prescribing errors can be divided into different types of errors. There are several classification systems by which drug related problems (DRP) or medication errors can be categorized. In Switzerland many clinical pharmacists and researchers use the Swiss Society of Public Health Administration and Hospital Pharmacists (GSASA) classification tool [41] which allows comparability on a national level. In Europe and worldwide, the classification system of the Pharmaceutical Care Network Europe (PCNE) is well established for the classification of DRP [42; 43]. A DRP is defined as follows: "*a drug-related problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes*" [43]. This classification allows researchers to assess medication errors in a structured way and allows comparability on an international level. The PCNE classification differentiates between problems, causes, planned interventions, intervention acceptance and status of the DRP, whereas "causes" can also be taken as "medication errors" [43]. For the studies in this thesis, the focus was solely on the prescribing step in the medication process. Therefore, the PCNE classification for the categorization of prescribing errors was used, to ensure international comparability. The causes section is divided into 9 primary domains, of which 7 primary domains were relevant to our setting and therefore included in our studies. Of the remaining 22 causes in these primary domains, only 20 causes were used, which best matched the prescribing errors, that were found. All primary domains and causes used in the studies are displayed in table 6-1.

Table 6-1 Types of prescribing errors

Primary domain	Code	Cause
Drug selection	1.1	Inappropriate drug according to guidelines/formulary
	1.2	No indication for drug
	1.3	Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements
	1.4	Inappropriate duplication of therapeutic group or active ingredient
	1.5	No or incomplete drug treatment in spite of existing indication
	1.6	Too many drugs/active ingredients prescribed for indication
Drug form	2.1	Inappropriate drug form/formulation (for this patient)
Dose selection	3.1	Drug dose too low
	3.2	Drug dose of a single active ingredient too high
	3.3	Dosage regimen not frequent enough
	3.4	Dosage regimen too frequent
	3.5	Dose timing instructions wrong, unclear or missing
Treatment duration	4.1	Duration of treatment too short
	4.2	Duration of treatment too long
Dispensing	5.1	Prescribed drug not available
	5.2	Necessary information not provided or incorrect advice provided
Patient transfer related	8	Medication reconciliation problem
Other	9.1	No or inappropriate outcome monitoring (incl. TDM)
	9.2	Other cause; specify
	9.3	No obvious cause

When a prescribing error is detected, not only the type of error is of interest, but also the potential severity of harm of the detected error. The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) developed an algorithm and an index to classify severity of harm of medication errors [44]. This classification system was modified by Forrey et al [45], so that some categories were taken together to achieve higher interrater agreement in severity classification. For all three studies, the adapted version of Forrey et al. was used, which can be seen in table 6-2.

Table 6-2 Severity of error according to NCC MERP Index adapted by Forrey et al [45]

Categories	Description
A: Capacity to cause error	Circumstances or events have the capacity to cause error
B: Does not reach patient	An error could have occurred, but the error would not reach the patient (an "error of omission" does reach the patient)
C: No harm	An error could have reached the patient but would not cause patient harm
D: No harm	The error could have reached the patient and would have required monitoring to confirm that it resulted in no harm to the patient or required intervention to preclude harm
E: Temporary harm	The error may have contributed to or resulted in temporary harm to the patient and required intervention
F: Temporary harm	The error may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization
H: Temporary harm	The error may have required intervention necessary to sustain life
G: Permanent harm	The error may have contributed to or resulted in permanent patient harm
I: Death	The error may have contributed to or resulted in the patient's death

6.3.3 Strategies to Reduce the Prevalence of Prescribing Errors

Several interventions to reduce prescribing errors in children are discussed. Among others are computerized physician order entry (CPOE), clinical decision support (CDS), the clinical pharmacist, preprinted order sheets and check and control checklists [33; 46].

CPOEs are applications that are used to electronically write down physician's orders [47]. CPOE prescriptions provide structured, legible, and comprehensive information [48]. Data suggest, that CPOE implementation seems to reduce prescribing errors [49-51]. CPOE is usually linked to the health information system of a hospital, where patient's demographic data, laboratory values, notes of physicians and nurses, medical images, etc. are included [52]. At the University Children's Hospital Zurich, the drug master data and the hospital formulary are validated by the hospital pharmacy, so that the data relevant for prescription in the CPOE are reliable and adapted to the needs of the clinicians.

Increasingly, different types of CDS are integrated into the CPOE. CDS provides targeted clinical knowledge, patient information, or other health information and by such enhances medical decision-making [53; 54]. CDS are often used to improve medication safety [54] and also seem to reduce prescribing errors [55]. One example for CDS are dosing guidelines and dose-checks, which are particularly helpful in pediatrics, where dosing errors are frequently encountered. A dosing guideline CDS which is in use in Switzerland and was also used as web interface in our study, but not as CPOE-integrated CDS, is PedEDose.

The functionalities of PedEDose are described by Higi et al [10] and include evidence-based dosing guidelines, comprising the nationally harmonized dosing recommend-dations of SwissPedDose [9; 56], and further clinical information on drugs, a medical-device registered dosage calculator and dose-check, if the CDS is fully integrated into a CPOE (which was not the case in the presented studies).

Other interventions, independent from technology, that have shown to be successful in reducing prescribing errors in children are substitution controls (e.g., voice recognition system for hands-free prescribing), engineering controls (e.g., dedicated prescribing area, no prescriptions outside allowed), or administrative controls like prescribing guidelines [50]. Expert consultations like the participation of pharmacists on ward rounds has also proven to be helpful in reducing prescribing errors [50; 57; 58]. But the most promising way of reducing prescribing errors are bundles of interventions [50].

6.4 References

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7. Aims of the Thesis

The general aim of this thesis was to investigate prescribing errors on pediatric general wards and to describe factors that are associated with the rate, type, and severity of errors.

The first focus of this thesis was to assess prescribing error rates before and after the implementation of a CPOE with limited CDS at the University Children's Hospital Zurich, in order to see how rate and severity of errors were influenced by the prescribing mode.

The second focus of this thesis was to provide information on prescribing patterns on pediatric general wards, describe the most frequently prescribed drugs and explore the characteristics of the drugs. In addition, associations of prescribing errors with certain drugs or patients should be revealed.

The third focus of this thesis was to examine the extend of unlicensed drug prescriptions at the University Children's Hospital Zurich and to provide information on the types of drugs that have to be imported from other countries or manufactured specifically for children. Furthermore, associations of prescribing error rates with the license status of drugs should be provided.

8. Methods, Results and Discussion

The content of this dissertation is the subject of three publications. Thus, the following pages contain these papers, starting with the first study *Prescribing errors in children: what is the impact of a computerized physician order entry?* continuing with the second study *Prescribing patterns in pediatric general wards and their association with prescribing errors: a retrospective observational study* and ending with the third study *Use of unlicensed drugs in a Swiss Pediatric University Hospital and associated prescribing error rates – a retrospective observational study*.

9. First Study: Prescribing Errors in Children: What is the Impact of a Computerized Physician Order Entry?

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RESEARCH

Prescribing errors in children: what is the impact of a computerized physician order entry?

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9.1 Abstract

Purpose: Prescribing errors represent a safety risk for hospitalized patients, especially in pediatrics. Computerized physician order entry (CPOE) might reduce prescribing errors, although its effect has not yet been thoroughly studied on pediatric general wards. This study investigated the impact of a CPOE on prescribing errors in children on general wards at the University Children's Hospital Zurich.

Methods: We performed medication reviews on a total of 1000 patients before and after the implementation of a CPOE. The CPOE included limited clinical decision support (CDS) such as drug-drug interaction check and checks for duplicates. Prescribing errors, their type according to the PCNE classification, their severity (adapted NCC MERP index), as well as the interrater reliability (Cohen's kappa), were analyzed.

Results: Potentially harmful errors were significantly reduced from 18 errors / 100 prescriptions (95% CI: 17–20) to 11 errors / 100 prescriptions (95% CI: 9–12) after CPOE implementation. A large number of errors with low potential for harm (e.g., "missing information") was reduced after the introduction of the CPOE, and consequently, the overall severity of potential harm increased post-CPOE. Despite general error rate reduction, medication reconciliation problems (PCNE error 8), such as drugs prescribed on paper as well as electronically, significantly increased after the introduction of the CPOE. The most common pediatric prescribing errors, the dosing errors (PCNE errors 3), were not altered on a statistically significant level after the introduction of the CPOE. Interrater reliability showed moderate agreement (K = 0.48).

Conclusion: Patient safety increased by reducing the rate of prescribing errors after CPOE implementation. The reason for the observed increase in medication reconciliation problems might be the hybrid system with remaining paper prescriptions for special medication. The lacking effect on dosing errors could be explained by the fact that a web application CDS covering dosing recommendations (PEDeDose) was already in use before the implementation of the CPOE. Further investigations should focus on eliminating hybrid systems, interventions to increase the usability of the CPOE, and full integration of CDS tools such as automated dose checks into the CPOE.

What is Known:

- *Prescribing errors, especially dosing errors, are a common safety threat for pediatric inpatients.*
- *The introduction of a CPOE may reduce prescribing errors, though pediatric general wards are poorly studied.*

What is New:

- *To our knowledge, this is the first study on prescribing errors in pediatric general wards in Switzerland investigating the impact of a CPOE.*
- *We found that the overall error rate was significantly reduced after the implementation of the CPOE. The severity of potential harm was higher in the post-CPOE period, which implies that low-severity errors were substantially reduced after CPOE implementation. Dosing errors were not reduced, but missing information errors and drug selection errors were reduced. On the other hand, medication reconciliation problems increased.*

9.2 Introduction

Medication safety and the reduction of harm due to medication is an ongoing issue in health care. The WHO addresses this problem in the Third Global Patient Safety Challenge 2017, “Medication Without Harm.” [1] Pediatric patients are at particularly high risk of experiencing medication errors, notably prescribing errors [2–5]. A meta-analysis estimated a pooled rate of 17.5% of orders containing a prescribing error [6]. NICUs and PICUs have higher rates of prescribing errors [3]. A previous study by Glanzmann et al. [7] at the PICU in our hospital revealed an error rate of 14%. The situation in pediatric general wards is poorly studied [3].

Computerized physician order entry (CPOE) seems to reduce prescribing errors [8–10], and overall evidence suggests that mortality rates and pADE are reduced by electronic prescribing [10].

On pediatric general wards with CPOE prescribing, errors range from 14.8 to 47.0 errors / 100 prescriptions, whereas paper charts show a range from 4.1 to 58.1 errors / 100 prescriptions [3]. Dosing errors are common due to the great variability of weight and size among children [5, 10, 11]. In total, 2–6% of all orders for pediatric inpatients contain a dosing error [12].

In general, studies about medication errors show a great heterogeneity in definitions and methods [3, 8, 13]. To gain useful insights, clear definitions of the studied errors should be stated, validated error classifications applied, and - in addition to the prevalence of errors - severity of harm should be assessed [4, 9, 14, 15]. Chart review rather than voluntary reporting should be used as data source [3, 13], and interrater reliability should be calculated [13].

The aim of this study was to investigate the impact of the introduction of a CPOE on prescribing errors in children in pediatric general wards. We studied the prevalence, type, and severity of prescribing errors with retrospective chart review and validated our findings by calculating the interrater reliability.

9.3 Materials and Methods

9.3.1 Setting and Patients

This retrospective observational study was conducted at the University Children's Hospital Zurich, which is a tertiary care center and the largest pediatric hospital in Switzerland (220 beds). Eligible for the study were children up to 18 years who were hospitalized in 3 medical or 3 surgical wards. A total of 1000 patients, 500 from each study period, were randomly selected from 1688 (2018) and 1608 (2019) eligible patients, respectively, consisting of 250 medical and 250 surgical cases each. Patients with no prescribed medication (i.e., hospitalized for surveillance reasons) were not eligible. To control for seasonal effects, periods in identical months were included in the sampling frame: October until December 2018 (pre-CPOE) and October until December 2019 (post-CPOE).

9.3.2 CPOE

Until 2019 drugs were prescribed either manually on paper charts or electronically on semi-structured charts. CGM Clinical by CompuGroup Medical Inc. was used as a hospital information system. The pediatrics-specific CPOE tool by CompuGroup Medical Inc. was further developed from the preexisting CPOE tool for adults in cooperation with members of the University Children's Hospital Zurich.

The drug master data were provided by HospINDEX (HCI Solutions Ltd.) and validated by the hospital pharmacy. Drugs from the hospital formulary were marked and provided with appropriate routes of administration so that only these routes of administration could be selected by the prescribing physician in the ordering process. In case of drug shortages, the appropriate substitute was proposed to the prescriber.

The CPOE contained some limited clinical decision support (CDS): an automated drug-drug interaction check and a duplication check based on the data of Pharmavista by HCI Solutions Ltd. [16], which was carried out every time a drug was prescribed.

In March 2019, the CPOE was implemented on all general wards. Implementation was accompanied by user education. Thereafter, most of the medication was prescribed electronically with the CPOE. There were some exceptions that could not be prescribed with the tool for technical reasons, such as patient-controlled analgesia and others, leading to hybrid drug prescription system to a small degree.

9.3.3 Information on Drug Dosing

Prescribers at the University Children's Hospital Zurich had access to several guidelines and databases. They were requested to follow the dosing guidelines provided by the web application CDS by PEDeDose (PEDeus Ltd.), which was described by Higi et al. [17]. These dosing recommendations are based on the national harmonized dosing guidelines by Swisspeddose [18] and contain additional information. Aside from that, internal guidelines from different specialist fields with recommendations for certain disease patterns were available for all prescribers.

9.3.4 Prescriptions and Medication Review

A full medication review was conducted for all included patients, whereby the rater had access to all patient data. An adapted version of the medication appropriateness index [19] was used to guide the rater through the review process (Supplement 1).

All prescriptions within the first 24 h of admission to the ward were included. For patients who were hospitalized for elective surgery, prescriptions were included in the 24 h after surgery and return to the ward from PICU. Excluded medications were parenteral nutrition, lipids, any blood cell transfusions, insulin, solutions for dialysis, solutions for fluid management such as normal saline solution, dextrose 5%, dextrose 5% in normal saline solution, or acetated ringers. Electrolytes were included, even if they were added to parenteral nutrition.

9.3.5 Prescribing Errors

As proposed by Dean et al. [20] the definition of a prescribing error was adopted as follows: “A clinically meaningful prescribing error occurs when, as a result of a prescribing decision or prescription writing process, there is an unintentional significant (1) reduction in the probability of treatment being timely and effective or (2) increase in the risk of harm when compared with generally accepted practice.”

Prescribing errors were classified into different types of errors according to the well-established PCNE Classification V 9.1, German Version [21, 22]. As pictured in table 9-1, a subset of 7 primary domains from the PCNE Classification and 20 causes were used, which best matched the prescribing errors we found in our study. In the PCNE Classification, these causes are classified not only into the area of prescribing, but also into dispensing (PCNE 5), and patient transfer (PCNE 8). Nevertheless, we analyzed only drug prescriptions and no further steps in the medication process. A prescription could have more than one error, but a cause could only be recorded once per prescription. Supplement 2 displays how dosing errors were rated.

To increase the clinical relevance of our findings, we also included the severity of harm due to errors, even though the retrospective rating of the potential harm is likely to be more subjective than the rating of actual harm. [9, 15]. To determine the potential severity of the detected errors, we used the NCC MERP index as adapted by Forrey et al. [15, 23, 24] (see table 9-2).

Table 9-1 Types of prescribing errors according to PCNE Classification V 9.1 [21]

Primary domain	Code	Cause
Drug selection	1.1	Inappropriate drug according to guidelines/formulary
	1.2	No indication for drug
	1.3	Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements
	1.4	Inappropriate duplication of therapeutic group or active ingredient
	1.5	No or incomplete drug treatment in spite of existing indication
	1.6	Too many drugs/active ingredients prescribed for indication
Drug form	2.1	Inappropriate drug form/formulation (for this patient)
Dose selection	3.1	Drug dose too low
	3.2	Drug dose of a single active ingredient too high
	3.3	Dosage regimen not frequent enough
	3.4	Dosage regimen too frequent
	3.5	Dose timing instructions wrong, unclear or missing
Treatment duration	4.1	Duration of treatment too short
	4.2	Duration of treatment too long
Dispensing	5.1	Prescribed drug not available
	5.2	Necessary information not provided or incorrect advice provided
Patient transfer related	8	Medication reconciliation problem
Other	9.1	No or inappropriate outcome monitoring (incl. TDM)
	9.2	Other cause; specify
	9.3	No obvious cause

Table 9-2 Severity of error according to NCC MERP Index adapted by Forrey et al [25]

Categories	Description
A: Capacity to cause error	Circumstances or events have the capacity to cause error
B: Does not reach patient	An error could have occurred, but the error would not reach the patient (an "error of omission" does reach the patient)
C: No harm	An error could have reached the patient but would not cause patient harm
D: No harm	The error could have reached the patient and would have required monitoring to confirm that it resulted in no harm to the patient or required intervention to preclude harm
E: Temporary harm	The error may have contributed to or resulted in temporary harm to the patient and required intervention
F: Temporary harm	The error may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization
H: Temporary harm	The error may have required intervention necessary to sustain life
G: Permanent harm	The error may have contributed to or resulted in permanent patient harm
I: Death	The error may have contributed to or resulted in the patient's death

9.3.6 Interrater Reliability

All patients were reviewed by the first rater (AS), and a random sample of 5% of all patients was additionally reviewed by a second rater (MP). Both raters were pharmacists with several years of experience in pediatric clinical pharmacy.

A procedural manual was created to ensure that both raters approached the review in a similar way and that consistent data could be captured, as suggested by Vassar et al. [25]. Both raters decided on whether or not a prescription contained an error, which PCNE category the error belonged to, and what NCC MERP severity level it might have resulted in.

9.3.7 Database and Statistical Analysis

The study database was built with Microsoft SQL Server 2019 Master Data Services. The personal data from all included patients were automatically exported from the hospital information system into the database.

Statistical analyses were conducted with RStudio 2022.02.1 and IBM® SPSS® Statistics Version 27. The sample size of 1000 patients was estimated according to a previous study by Glanzmann et al. [7], with a reduction of prescribing errors from 14 to 9% based on a power of 0.8 and a one-sided test. Patient demographic data, rates of prescribing error, and severity of harm were compared by *t* -test, chi-square test, or Mann–Whitney test. Interrater reliability was calculated with Cohen's kappa.

9.4 Results

9.4.1 Population

Pre-CPOE and post-CPOE patients did not differ in their demographic characteristics (table 9-3), except for the length of stay. Post-CPOE patients stayed significantly longer on the ward (mean: 2.5 days) than pre-CPOE (mean: 2.1 days, $p = 0.005$, *t*-test).

Table 9-3 Demographic comparison before and after CPOE

Categories	pre-CPOE N = 500	post-CPOE N = 500	*p* Value
Sex			0.750
Female	219 (43.8%)	214 (42.8%)	
Male	281 (56.2%)	286 (57.2%)	
Age (in categories)			0.444
Preterm	3 (0.6%)	0 (0%)	
Neonates	19 (3.8%)	11 (2.2%)	
Infants	161 (32.2%)	167 (33.4%)	
Children	225 (45.0%)	222 (44.4%)	
Adolescents	92 (18.4%)	100 (20.0%)	
Age (mean)	years	years	0.549
	5.86 ± 5.39	6.06 ± 5.39	
Weight	kg	kg	0.774
	23.33 ± 19.50	23.68 ± 19.02	
Height	cm	cm	0.879
	112.05 ± 37.56	112.59 ± 38.33	
Body Surface	[m2]	[m2]	0.835
	0.861 ± 0.497	0.871 ± 0.480	
Diagnosis (mean)	quantity	quantity	0.285
	3.12 ± 2.89	3.33 ± 3.19	
Length of stay	days	days	0.005*
mean	2.08 ± 2.23	2.52 ± 2.71	
median	1	2	

* Indicates significant value

9.4.2 Drug Prescriptions

A total of 5022 drug prescriptions for 1000 patients were analyzed: 2299 drug prescriptions pre-CPOE and 2723 post-CPOE. Patients were prescribed more drugs post-CPOE than pre-CPOE (mean = 5.5 drugs vs. mean = 4.6 drugs, $p < 0.001$).

Handwritten prescriptions were significantly reduced by the CPOE (38.9% vs. 0.5%, $p < 0.001$).

9.4.3 Number of Errors Overall

A total of 2485 errors for all prescriptions was found, of which 1802 errors occurred pre-CPOE and 683 errors post-CPOE. Consequently, 78.4 errors per 100 prescriptions (95% CI: 76.2–80.6) were found before the introduction of the CPOE vs. 25.1 errors per 100 prescriptions (95% CI: 23.0–27.1) after introduction of the CPOE ($p < 0.001$, *t*-test). This means that 69.2% (95% CI: 67.4–71.0) of all prescriptions pre-CPOE contained at least one error vs. only 22.8% (95% CI: 21.2–24.5) of all prescriptions post-CPOE, which implies a significant reduction of errors ($p < 0.001$). In 100 admissions, 360 errors could be found pre-CPOE vs. 137 in post-CPOE ($p < 0.001$).

Table 9-4 Types of errors overall

Categories	pre-CPOE N = 1802	post-CPOE N = 683	*p*-Value
PCNE primary domains			
1 drug selection	102 (5.7%)	109 (16.0%)	0.450
2 drug form	10 (0.6%)	17 (2.5%)	0.361
3 dose selection	203 (11.3%)	203 (29.7%)	0.088
4 treatment duration	8 (0.4%)	5 (0.7%)	0.266
5 dispensing	1452 (80.6%)	305 (44.7%)	<0.001*
8 patient transfer related	4 (0.2%)	17 (2.5%)	0.010*
9 other	23 (1.3%)	27 (4.0%)	0.975

* Indicates significant value

The most frequent type of error (80.6% of all errors pre-CPOE and 44.7% of all errors post-CPOE) was in PCNE primary domain 5 (dispensing) (table 9-4). More precisely, 79.5% of all errors pre-CPOE and 44.1% of all errors post-CPOE were type 5.2 errors: “Necessary information not provided or incorrect advice provided.” Examples of this type of error pre-CPOE are: “Missing or incorrect information about the route of administration,” “active ingredient missing,” (only product name prescribed) or “drug form missing.” Post-CPOE, the most frequent error 5.2 was due to the additional selection of a mode of administration, like buccal or lingual, where it was not appropriate. Most of these errors 5.2 were of minor severity (NCC MERP severity grades A–D). Some of the 5.2 errors, though were rated as “temporary harm possible,” such as analgesic prescriptions in reserve with a frequency but no maximum number of doses prescribed.

9.4.4 Severity of Harm Due to Errors

The overall severity of harm increased significantly after the introduction of the CPOE. Mean rank pre-CPOE was 1175 vs. 1423 post-CPOE (p = 0.000, Mann–Whitney test).

Table 9-5 Severity of harm according to adapted NCC MERP index

Severity NCCMERP	pre-CPOE N = 1802	post-CPOE N =683	*p*-Value
capacity to cause error (A)	91 (5.0%)	18 (2.6%)	<0.001*
does not reach patient (B)	291 (16.1%)	81 (11.9%)	<0.001*
no harm (C + D)	996 (55.3%)	297 (43.5%)	<0.001*
temporary harm (E + F + H)	422 (23.4%)	284 (41.6%)	<0.001*
permanent harm (G)	2 (0.1%)	3 (0.4%)	0.826
death (I)	0	0	

* Indicates significant value

Overall, the majority of the documented errors were of minor severity (NCC MERP A–D): 76.4% pre-CPOE and 58% post-CPOE (table 9-5). These errors with minor severity are unlikely to result in any harm for the patient (see the “Prescribing errors” section [20]). Therefore, we decided to focus on errors with severity E–I that might have resulted in potential harm.

9.4.5 Numbers of Errors Causing Potential Harm (NCC MERP E-I)

After exclusion of errors with severity A–D, we counted a remaining total of 711 errors with potential severity of harm, E–I, which were 424 errors pre-CPOE and 287 errors post-CPOE. The overall error rate of 18.4 errors / 100 prescriptions (95% CI: 16.8–19.9) before CPOE was reduced to 10.5 errors / 100 prescriptions (95% CI: 9.1–12.0) after introduction of the CPOE, which was a significant reduction of the error rate (p < 0.001). Therefore, 16.8% of all prescriptions before CPOE contained at least one error (95% CI: 15.5–18.2), whereas the error rate after CPOE was only 9.8% (95% CI: 8.6–11.1) (p < 0.001). The rate of errors per 100 admissions was significantly reduced from 84 errors / 100 admissions pre-CPOE to 57 errors / 100 admissions post-CPOE (p = 0.001).

Table 9-6 Types of prescribing errors according to PCNE classification with NCC MERP E-I

PCNE primary domains and causes	pre-CPOE [errors / 100 prescriptions]	post-CPOE [errors / 100 prescriptions]	*p*-Value
1 drug selection	3.00	2.01	0.031*
1.1 Inappropriate drug	0.48	0.29	0.298
1.2 No indication for drug	0.13	0.15	0.877
1.3 Inappropriate combination of drugs	0.30	0.33	0.870
1.4 Inappropriate duplication	1.48	0.44	<0.001*
1.5 No or incomplete drug treatment	0.61	0.73	0.589
1.6 Too many different drugs	0	0.07	0.157
2 drug form (2.1 inappropriate drug form / formulation)	0.13	0.18	0.638
3 dose selection	5.57	5.17	0.555
3.1 Drug dose too low	1.74	2.35	0.126
3.2 Drug dose too high	2.52	1.98	0.201
3.3 Dosage regimen not frequent enough	0.61	0.29	0.102
3.4 Dosage regimen too frequent	0.61	0.26	0.063
3.5 Dose timing instructions wrong, unclear or missing	0.09	0.29	0.086
4 treatment duration	0.35	0.19	0.226
4.1 Duration of treatment too short	0.05	0.04	0.905
4.2 Duration of treatment too long	0.30	0.15	0.248
5 dispensing	8.70	1.91	<0.001*
5.1 Prescribed drug not available	0	0	
5.2 “Missing information”	8.70	1.91	<0.001*
8 patient transfer related (8.1 Medication reconciliation problem)	0.17	0.62	0.010*
9 other	0.43	0.44	0.975
9.1 No / inappropriate monitoring	0.26	0.37	0.506
9.2 Other cause	0.17	0.07	0.321
Total	18.35	10.52	<0.001*

* Indicates significant value

9.4.1 Type of Errors Causing Potential Harm (NCC MERP E-I)

As table 9-6 shows, the most frequent primary domain of errors causing potential harm pre-CPOE was domain 5 (dispensing), while post-CPOE the most frequent was domain 3 (dosing errors). Type 5 errors decreased significantly from 8.7 errors / 100 prescriptions to 1.9 errors / 100 prescriptions ($p < 0.001$), and type 1 errors (drug selection) decreased from 3.0 to 2.0 errors / 100 prescriptions ($p = 0.031$).

The third domain that showed a significant change from pre- to post-CPOE was PCNE 8 "patient transfer related." These errors increased significantly from 0.2 errors / 100 prescriptions to 0.6 errors / 100 prescriptions ($p = 0.010$). Type 8 errors were coded when two valid prescriptions for the same patient and time were found in different media, e.g., one CPOE prescription and one prescription on a paper chart. The doubled prescriptions contained, in some cases, the same information but sometimes slightly different dosages or instructions.

There were no statistically significant differences from pre- to post-CPOE in the other primary domains. In particular, dosing errors (type 3) showed no significant change (pre-CPOE: 5.6 errors / 100 prescriptions, post-CPOE: 5.2 errors / 100 prescriptions, $p = 0.555$). The PCNE causes are also displayed in table 9-6.

9.4.2 Handwritten vs. Electronically Written Prescriptions Causing Potential Harm

Pre-CPOE, we compared the error rates in handwritten and electronically written prescriptions. Handwritten prescriptions showed a significantly higher rate of errors (22.6 errors / 100 prescriptions) than electronically written prescriptions (15.7 errors / 100 prescriptions) ($p < 0.001$). A total of 20.9% of handwritten prescriptions contained at least one error, while only 14.2% of electronically written orders contained an error.

9.4.3 Interrater Reliability

Cohen's Kappa for the agreement on whether or not an error occurred in a prescription was 0.476. This implies a moderate interrater agreement [26]. The agreement on primary domains and causes showed perfect agreement with $k = 1.000$, but for severity of harm, a kappa of only 0.158 (slight agreement) was calculated.

9.5 Discussion

After the implementation of the CPOE, patients were prescribed more drugs than before (5.5 vs. 4.6). The fact that many adjustments to a CPOE prescription, such as an adaption of the dose, resulted in a new prescription line may have influenced this finding.

The overall error rate decreased significantly after implementation of the CPOE. This finding complies with the results of a recent systematic review in pediatrics by Koeck et al. [9], indicating that CPOE reduces prescribing errors.

The rate of potentially harmful errors (NCC MERP E-I) of 18.4% (95% CI 16.8–19.9) before introduction of the CPOE was higher than the error rate of 14%. Glanzmann et al. [7] found 9 years ago in our PICU, where a semi-structured order sheet was in use. Usually, error rates in PICUs are higher than those in general wards. One explanation for the higher error rate in our study might be that the PICU had a clinical pharmacist on rounds once or twice per week for years, while the general wards were not visited by a clinical pharmacist, except for one medical ward with irregular visits once per week at maximum. Besides that, the study of Glanzmann et al. was prospective, where uncertainties about the prescription could be clarified by direct discussion with the prescriber, whereas we conducted a retrospective study.

The CPOE especially improves the quality of prescriptions, which can be seen in the largest reduction of potentially harmful errors (NCC MERP E-I) in PCNE errors 5.2 (“lacking or wrong information”) from 8.7 to 1.9 errors / 100 prescriptions ($p < 0.001$). This is consistent with the findings of Jungreithmayr et al. [27], who showed that a CPOE increased the quality of the prescription documentation.

Drug selection errors (PCNE 1) and especially cause 1.4 “inappropriate duplication of therapeutic group or active ingredient” were significantly reduced post-CPOE. This could be contributed to the duplication-check CDS.

Interestingly, cause 1.3 concerning drug-drug interactions did not decrease, even though one CDS tool (Pharmavista) offered an automatic drug-drug interaction check. This could be attributed to either alert fatigue [29] or poor usability of the integrated tool [30].

Nevertheless, a new hybrid-systems-related error did occur, as medication reconciliation problems (PCNE 8) increased significantly with remaining paper prescriptions for special medication. This type of error might be prevented through the integration of all prescriptions into the CPOE and the complete elimination of prescriptions on paper.

The CPOE had no effect on dosing errors. This finding might be explained by the fact that the web application CDS covering dosing recommendations (PEDeDose) was already in use before implementation of the CPOE, and there was no automated dose check to validate the prescriptions. The lacking effect of CPOE on dosing errors was also seen by Roumeliotis et al. [28]. Dosing errors could be prevented more effectively by a fully integrated CDS that offers dosing support and automated dose check [31].

The fact that handwritten prescriptions contained more errors than electronic prescriptions is a plausible finding, as CPOE leads to standardized, legible, and complete prescriptions [32].

The errors that occurred post-CPOE were more severe than pre-CPOE. This implies that a large number of minor severity errors like “missing information” (PNCE 5.2) and others no longer occurred after the introduction of the CPOE. It also indicates that the introduction of the CPOE was not able to reduce the severity of harm but only the rate of errors.

9.6 Limitations

Due to the retrospective nature of our study, we had to interpret previously recorded data on patients’ history and their prescriptions. This could have led to the conclusion that an error had occurred, although there was a plausible reason for the deviation from the norm, which was however not recorded in the patient’s charts. For this reason, the retrospective nature of our study imposes a limitation not only on the rate of errors but especially on the interpretation of the severity of harm.

Furthermore, not optimal interrater reliability imposes another limitation to our study. Even though a procedure manual existed, there was only limited training and coordination between the two raters. One rater might have tried to capture errors comprehensively, whereas the other had a more pragmatic way of assessment of the prescriptions. Rater 1 reviewed all 1000 patients and therefore had more routine in the procedure, while rater 2 only reviewed 50 patients.

9.7 Conclusion

In conclusion, our findings imply a positive impact of the CPOE on patient safety by reducing the prevalence of prescribing errors. Especially the high number of errors with low harming potential (NCC MERP A–D) was reduced, but also potentially harmful errors were significantly reduced.

Hybrid systems of CPOE and paper charts carry a risk for errors and should therefore be eliminated. Future research might focus on interventions to increase the usability of the CPOE and on the full integration of CDS tools, for example, dosing support and notably automated dose check into the CPOE.

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9.9 Supplement 1 – Adapted Medication Appropriateness Index (MAI)

1. Is there an indication for the drug?
2. Is the medication effective for the condition?
3. Is the dosage correct?
4. Has therapeutic drug monitoring been prescribed (if necessary)?
5. Has the dosage been adjusted for kidney/hepatic function?
6. Are there clinically significant drug-drug interactions?
7. Are there clinically significant drug-disease/condition interactions?
8. Are the directions correct and practical?
9. Is the drug form suitable for the patient and the indication?
10. Is there unnecessary duplication with other drug(s)?
11. Is the duration of therapy acceptable?
12. Is a drug missing for an indication or as a preventive drug?

9.10 Supplement 2 – Rating of Dosing Errors

All drug dosages were validated by using the following databases or literature:

- PEDeDose (www.pededose.ch)
- SwissPedDose (www.swisspeddose.ch)
- Drug label (www.swissmedicinfo.ch)
- Hospital internal guidelines
- Uptodate (www.uptodate.com)
- Lexicomp (www.lexicomp.com)
- Other

A drug dosage was categorized as an error, if the prescribed dosage deviated from the literature by more than a certain percentage (see table 9-7) and there was no reason evident for the deviation like altered organ function, obesity, drug-drug-interactions, or other clinical reasons.

Some deviations (column “could be an error”) were only rated as errors, if there were other risk factors that the prescribed dosage could lead to patient harm (for example reduced kidney function). If there were no risk factors evident, these dosages were not categorized as errors.

Table 9-7 Dosage ranges adopted from PEDeus AG [1]

Active ingredient	Limit	No error	Could be an error	Error
Broad therapeutic index	Below	90 - 111%	80 - 90%	< 80%
	Above		111 - 125%	> 125% or above maximum dosage
Narrow therapeutic index	Below	95 - 105%	90 - 95 %	< 90%
	Above		105 - 111%	> 111% or above maximum dosage

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10. Second Study: Prescribing Patterns in Pediatric General Wards and Their Association with Prescribing Errors: a Retrospective Observational Study

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ORIGINAL RESEARCH ARTICLE

Prescribing Patterns in Pediatric General Wards and Their Association with Prescribing Errors: A Retrospective Observational Study

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10.1 Abstract

Purpose: There are only limited data on drug utilization patterns in pediatric inpatients, especially on general wards. The aim of the study was to describe prescribing patterns and their associations with prescribing errors in a university children's hospital in the German-speaking part of Switzerland.

Method: This was a subanalysis of a retrospective single-center observational study. Patient characteristics and drug use of 489 patients with 2693 drug prescriptions were associated with prescribing errors. Drugs were categorized by the Anatomic Therapeutic Chemical Classification System (ATC), patients were categorized by age group according to European Medicines Agency guidelines, and prescribing errors were analyzed by type [Pharmaceutical Care Network Europe (PCNE) classification] and severity of error [adapted National Coordinating Council for Medication Error Reporting (NCC MERP) index].

Results: The most frequently prescribed ATC classes were nervous system (N) (42.6%), alimentary system (A) (15.6%), and anti-infective drugs (J) (10.7%). Eighty-two percent of patients were prescribed an analgesic. Most drugs were prescribed for oral (47%) or intravenous (32%) administration, but the rectal route was also frequent (10%). The most frequently prescribed drugs were paracetamol, metamizole, and ibuprofen. The high number of metamizole prescriptions (37% of patients were prescribed metamizole) is typical for German-speaking countries. Older pediatric patients were prescribed more drugs than younger patients. A statistically significant difference was found in the rate of potentially harmful errors across age groups and for gender; children between 2 and 11 years had a higher rate of potentially harmful errors than infants under 2 years ($p = 0.029$) and female patients had a higher rate of potentially harmful errors than male patients ($p = 0.023$). Recurring errors were encountered with certain drugs (nalbuphine, cefazolin).

Conclusion: Our study provides insight into prescribing patterns on pediatric general wards in a university children's hospital in Switzerland and highlights some areas for future research. Especially, the higher risk for prescribing errors among female pediatric patients needs further investigation.

10.2 Key Points

- This article gives an insight into prescribing patterns on pediatric general wards in a university children's hospital in Switzerland and the properties of the prescribed drugs as well as the association of the prescriptions with patient age and gender.
- The top 20 most prescribed drugs are identified in different age groups.
- Prescribing errors associated with certain drugs or patients are described, to focus on in future research.

10.3 Introduction

“Medication without harm” is still in the Global Safety Action Plan 2021–2030 of the World Health Organization [1]. It is known that children bear a higher risk for medication errors and especially prescribing errors [2–4]. The basis for any initiative to improve medication safety in a population is knowing their drug utilization. In pediatric inpatients, there is only limited data available on drug utilization [5]. Most pediatric studies focus on newborn patients [6–9], on pediatric outpatients [10], or on certain medications such as antimicrobial drugs [11], analgesics [12, 13], or antiepileptics [14].

On pediatric general wards, Rashed et al. [15] investigated drug utilization in five countries in different areas of the world and found that older patients (aged between 11 and 18 years) were prescribed more drugs than younger patients. The most frequently prescribed therapeutic groups in countries comparable to Switzerland such as Germany, the UK, or Australia were systemic anti-infectives, drugs for the nervous system and alimentary tract, and metabolism drugs, with the most frequent active ingredients being paracetamol, ibuprofen, and salbutamol.

In Austria, a neighboring country of Switzerland, Rauch et al. [16] investigated prescribing patterns in pediatric hospital care, where drug dispensing data from the hospital pharmacies was obtained. They found amoxicillin/betalactamase inhibitor, ibuprofen, and paracetamol to be the most frequently prescribed compounds.

In the French-speaking part of Switzerland, a study by Di Paolo et al. [17] on pediatric outpatients of the University Hospital Lausanne in 2005 and 2010 showed the most frequently prescribed 15 drugs accounted for 80% of all prescriptions, with ibuprofen and paracetamol being the most frequently prescribed. Recently, Tilen et al. [18] compiled a list of the 40 most frequently used drugs in pediatrics in Switzerland, based on drug consumption data from the hospital pharmacies for the compilation of nationwide harmonized drug dosage recommendations. They did not rank the drugs according to the frequency of usage.

10.4 Aim

To date, there are no data available on drug prescribing patterns on pediatric general wards in Switzerland, and only scarce data from Europe in general. Therefore, we aimed to provide insight on what drugs are prescribed in daily practice on pediatric general wards at the University Children's Hospital Zurich and explore the characteristics of the drugs.

As prescribing errors are a major safety problem in pediatric patients, we also aimed to explore the types of errors that occur in association with the prescribed drugs and the characteristics of the patients to potentially find recurring errors that could be avoided in the future.

10.5 Materials and Methods

We conducted a subanalysis of a database compiled for a retrospective single-center observational study, which was published in March 2023 [19].

10.5.1 Patient Data

The database and the methods used to obtain these data are described in detail in a previous publication [19] of the same authors. The most important key points of our subset of data are as follows: we assessed the drug prescriptions of 500 patients (age 0–18 years) hospitalized at the University Children's Hospital Zurich on six pediatric general wards (surgical and medical wards) between October and December 2019. The University Children's Hospital Zurich is a tertiary care center. Drugs were prescribed by using a computerized physician order entry (CPOE) with limited clinical decision support including drug–drug interactions and check for duplicates. All prescriptions issued within the first 24 h of admission were recorded except for the following: parenteral nutrition, lipids, any blood cell transfusions, insulin, solutions for dialysis, solutions for fluid management such as normal saline solution, dextrose 5% in normal saline solution, dextrose 5%, or acetated Ringers. Only patients with at least one drug prescription were eligible for the study.

Patients were categorized into four age groups according to the European Medicines Agency guidelines [20]. As there were no preterm patients in our population, a preterm category was not included.

- Newborn (term newborn infants): 0-27 days
- Infants (infants and toddlers): 28 days to 23 months
- Children: 2-11 years
- Adolescents: 12-18 years

10.5.2 ATC Classification

The anatomical therapeutic chemical (ATC) classification system classifies the active ingredients of drugs in different levels [21]. Of all drugs prescribed, the name of the active ingredient, the trade name, and the related ATC code was recorded. ATC level 1 (anatomical/pharmacological group), ATC level 2 (pharmacological/therapeutic group), and ATC level 5 (chemical substance) were evaluated as outcomes.

10.5.3 Prescribing Errors

All prescriptions were checked by a pharmacist on prescribing errors and classified according to the Pharmaceutical Care Network Europe (PCNE) classification v9.1, German Version [22, 23] into different types of errors. Dosing errors were assessed according to a manual presented in Supplement 1. The severity of harm was rated according to the National Coordinating Council for Medication Error Reporting (NCC MERP) index in the adapted version by Forrey et al. [24–26], with categories A = capacity to cause error, B = does not reach patient, C + D = no harm, E + F + H = temporary harm, G = permanent harm, and I = death. Error rates were calculated as overall error rates (NCC MERP severity A–I) and as potentially harmful error (PHE) rates for NCC MERP severity E–I.

Five percent of prescriptions were validated by a second pharmacist, and interrater reliability was calculated (see previous publication [19]).

10.5.4 Database and Statistical Analysis

The study database was built with Microsoft SQL Server 2019 Master Data Services. Evaluation and visualization of the anonymized data was carried out with Microsoft Power BI Desktop, and statistical analyses were conducted with RStudio 2022.02.1 and IBM® SPSS® Statistics Version 27.

We intended to perform logistic regression to find factors that influence whether a prescription contains an error or not. We tested the following predictors: route of administration (ROA), ward, and age of patients. We found only models that, although significant, showed an effect < 0.1 (R^2). Therefore, we decided to only analyze the data descriptively and to not use logistic regression. The number of prescriptions or number of errors were compared by *t*-test or one-sided ANOVA.

10.6 Results

Five hundred patients were randomly selected from 1608 eligible patients (see Fig. 1). Of these patients, 11 were neonates, 167 were infants, 222 were children, and 100 were adolescents. The number of newborns was very low as most patients at this age stay on the neonatal intensive care unit rather than on pediatric general wards. For this reason, we did not consider the sample to be representative and excluded newborns from the study.

Of the remaining 489 patients (Fig. 10-1), 210 were female and 279 male. The mean age was 6.2 ± 5.4 years, mean weight was 24.1 ± 19 kg, and mean height was 113.2 ± 38 cm. The patients stayed for a mean of 2.5 days and had on average 3.4 diagnoses.

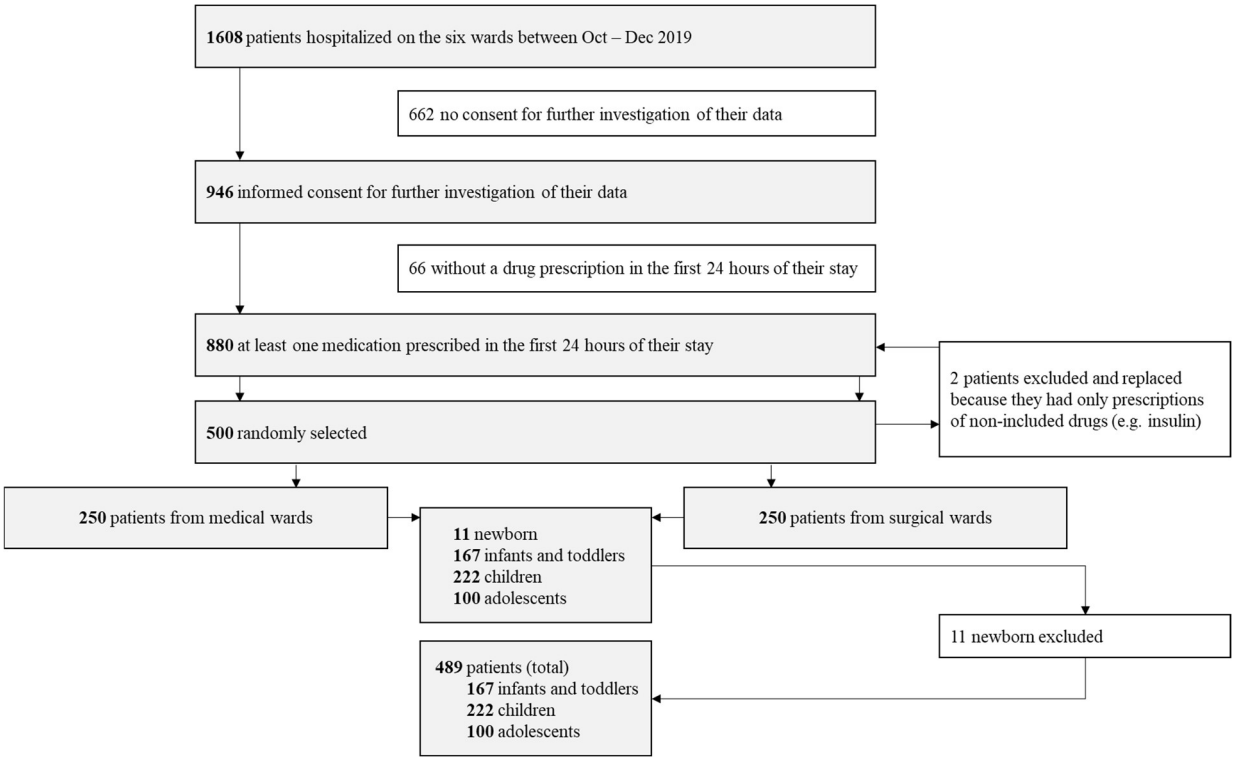

Figure 10-1 Patients included in the study

10.6.1 Drugs Prescribed by Anatomical Class and Therapeutic Group (ATC Levels 1 and 2)

A total of 2693 prescriptions were analyzed. Table 10-1 shows that drugs for the nervous system (N) were prescribed most often, followed by drugs for the alimentary system (A), anti-infectives (J), and drugs for the musculoskeletal system (M). More than three-quarters (77.8%) of all prescriptions contained one active ingredient of these four main ATC classes. 423 patients received at least one drug for the nervous system (N), resulting in a proportion of 86.5% of patients.

Table 10-1 displays that analgesics (N02) and antiinflammatory and antirheumatic products (M01), which include nonsteroidal antiinflammatory drugs (NSAIDs), accounted for 41.4% of all prescriptions.

Analgesics such as metamizole, nalbuphine, and paracetamol (N02) were prescribed to 400 patients (81.8%). Antiinflammatory and antirheumatic products such as ibuprofen and diclofenac (M01) were prescribed to 187 patients (38.2%). Antibacterials for systemic use such as amoxicillin/clavulanic acid, cefazoline, and amoxicillin (J01) were prescribed to 184 patients (37.6%), and the antiemetics and antinauseants ondansetron and granisetron (A04) were prescribed to 161 patients (32.9%).

Table 10-1 Most frequent ATC levels 1 and 2 per age group and in total: number of prescriptions and rate in brackets. Not all ATC codes of level 1 and 2 are displayed.

Anatomical level/therapeutic level (ATC Code)	Total prescr. (n=2693)	Infants (n=781)	Children (n=1323)	Adolescents (n=589)
(N) Nervous system	1147 (42.6%)	267 (34.2%)	614 (46.4%)	266 (45.2%)
(N02) Analgesics	880 (32.7%)	230 (29.4%)	464 (35.1%)	186 (31.6%)
(N05) Psycholeptics	147 (5.5%)	31 (4.0%)	73 (5.5%)	43 (7.3%)
(N03) Antiepileptics	88 (3.3%)	2 (0.3%)	58 (4.4%)	28 (4.8%)
(A) Alimentary tract	421 (15.6%)	142 (18.2%)	189 (14.3%)	90 (15.3%)
(A04) Antiemetics and antinauseants	172 (6.4%)	17 (2.2%)	103 (7.8%)	52 (8.8%)
(A11) Vitamins	116 (4.3%)	99 (12.7%)	15 (1.1%)	2 (0.3%)
(A06) Drugs for constipation	47 (1.7%)	6 (0.8%)	29 (2.2%)	12 (2.0%)
(A02) Drugs for acid related disorders	34 (1.3%)	10 (1.3%)	14 (1.1%)	10 (1.7%)
(J) Antiinfectives for systemic use	288 (10.7%)	94 (12.0%)	140 (10.6%)	54 (9.2%)
(J01) Antibacterials for systemic use	266 (9.9%)	89 (11.4%)	129 (9.8%)	48 (8.1%)
(M) Musculo-skeletal system	238 (8.8%)	64 (8.2%)	124 (9.4%)	50 (8.5%)
(M01) Antiinflammatory and antirheumatic products	234 (8.7%)	64 (8.2%)	122 (9.2%)	48 (8.1%)
(R) Respiratory system	218 (8.1%)	91 (11.7%)	99 (7.5%)	28 (4.8%)
(R03) Drugs for obstructive airway Diseases	110 (4.1%)	48 (6.1%)	53 (4.0%)	9 (1.5%)
(R01) Nasal preparations	51 (1.9%)	31 (4.0%)	16 (1.2%)	4 (0.7%)
(R06) Antihistamines for systemic use	49 (1.8%)	11 (1.4%)	24 (1.8%)	14 (2.4%)
(C) Cardiovascular system	141 (5.2%)	61 (7.8%)	41 (3.1%)	39 (6.6%)
(C03) Diuretics	50 (1.9%)	37 (4.7%)	5 (0.4%)	8 (1.4%)
(B) Blood and blood forming organs	101 (3.8%)	29 (3.7%)	48 (3.6%)	24 (4.1%)
(B01) Antithrombotic agents	42 (1.6%)	8 (1.0%)	19 (1.4%)	15 (2.5%)
(H) Systemic hormonal preparations, excl. sex hormones and insulins	71 (2.6%)	17 (2.2%)	40 (3.0%)	14 (2.4%)
(H02) Corticosteroids for systemic use	64 (2.4%)	17 (2.2%)	34 (2.6%)	13 (2.2%)
(L) Antineoplastic and immunomodulating agents	28 (1.0%)	0	15 (1.1%)	13 (2.2%)
Other ATC codes	40 (1.5%)	16 (2.0%)	13 (1.0%)	11 (1.8%)

10.6.2 Drug Prescriptions in Different Age Groups

Older patients were prescribed significantly more drugs than younger patients: adolescents were prescribed a mean of 5.9 drugs (95% CI 5.1–6.7), children 6.0 drugs (95% CI 5.4–6.5), and infants 4.7 drugs (95% CI 4.2–5.1). One-sided ANOVA showed statistically significant differences in the mean number of drugs prescribed between infants and children ($p = 0.006$). The top ten of all prescribed drugs differed among the age groups (Table 10-2).

Table 10-2 Top ten in three age groups (number of prescriptions and rate of patients with a prescription of this drug in brackets)

Rank	Infants	Children	Adolescents
1	Paracetamol: 153 (78.4%)	Paracetamol: 235 (79.7%)	Paracetamol: 90 (71.0%)
2	Cholecalciferol: 96 (57.5%)	Metamizole: 126 (43.2%)	Metamizole: 59 (48.0%)
3	Ibuprofen: 63 (31.7%)	Ibuprofen: 114 (38.7%)	Ondansetron: 52 (50.0%)
4	Metamizole: 46 (23.4%)	Ondansetron: 101 (42.3%)	Ibuprofen: 43 (38.0%)
5	Salbutamol: 42 (12.0%)	Nalbuphine: 83 (35.1%)	Nalbuphine: 30 (29.0%)
6	Amoxicillin: 25 (11.4%)	Salbutamol: 45 (11.7%)	Midazolam: 26 (19.0%)
7	Nalbuphine: 22 (12.6%)	Amoxicillin/ Clavulanic acid: 38 (13.5%)	Epinephrine: 12 (8.0%)
8	Oxymetazoline: 20 (11.4%)	Midazolam: 36 (15.8%)	Macrogol: 11 (10.0%)
9	Furosemide: 15 (6.0%)	Cefazolin: 27 (11.7%)	Prednisolone: 11 (9.0%)
10	Spironolactone: 13 (7.8%)	Epinephrine: 25 (6.8%)	Cefazolin: 11 (9.0%)
number of patients	167	222	100

10.6.3 Drug Prescriptions for Female and Male Patients

Female patients were prescribed a mean of 5.4 drugs (95% CI 4.9–5.9), whereas male patients were prescribed 5.6 drugs (95% CI 5.1–6.0). This difference was not statistically significant ($p = 0.680$, *t*-test).

10.6.4 Routes of Administration (ROA)

Almost half of all prescriptions were prescribed for oral use (47%). The second most prescribed ROA was intravenous (32%), followed by rectal application (10%), inhalation (5%), nasal application (2%), topical application (1%), subcutaneous (1%), intramuscular (1%), and other routes (1%).

10.6.5 Therapeutic Drug Monitoring (TDM)

Therapeutic drug monitoring was prescribed for ten different active ingredients. The most frequent were tacrolimus (11 prescriptions with TDM) and gentamicin (9 prescriptions with TDM). Furthermore, TDM was ordered for the following active ingredients: mycophenolic acid (7), phenobarbital (4), lamotrigine (3), valproic acid (2), brivaracetam (2), sirolimus (1), ciclosporin (1), levetiracetam (1).

10.6.6 The 20 Most Frequently Prescribed Drugs

As presented in Table 10-3, by far the most frequently prescribed active ingredient was paracetamol in 379 (77.5%) patients: 153 (31.3%) received it as regular medication, 198 (40.5%) prescribed "as needed," and 28 (5.7%) had both regular and "as needed" paracetamol prescriptions.

Table 10-3 The 20 most frequently prescribed drugs (total number of patients = 489)

Rank	Active ingredient (number of prescriptions)	Number of patients with prescription (percentage of patients with prescription)
1	Paracetamol (478)	379 (77.5%)
2	Metamizole sodium (231)	183 (37.4%)
3	Ibuprofen (220)	177 (36.2%)
4	Ondansetron (170)	160 (32.7%)
5	Nalbuphine (135)	128 (26.2%)
6	Cholecalciferol (vitamin D_2) (110)	110 (22.5%)
7	Salbutamol (93)	52 (10.6%)
8	Midazolam (69)	61 (12.5%)
9	Amoxicillin-Clavulanic acid (59)	49 (10.0%)
10	Cefazolin (47)	43 (8.8%)
11	Epinephrine (43)	27 (5.5%)
12	Oxymetazoline (38)	37 (7.6%)
13	Amoxicillin (37)	30 (6.1%)
14	Prednisolone (34)	29 (5.9%)
15	Macrogol (33)	32 (6.5%)
16	Diazepam (31)	28 (5.7%)
17	Clemastine (30)	26 (5.3%)
18	Metronidazole (25)	20 (4.1%)
19	Cefuroxime (24)	20 (4.1%)
20	Enoxaparin (22)	20 (4.1%)

10.6.7 Prescribing Errors and Characteristics of the Drugs and Patients

Most prescribing errors were of minor severity, NCC MERP grade A–D. In Table 10-4, the overall error rates and the rates of potentially harmful errors (PHE) are displayed for the ten most frequently prescribed active ingredients, for the four most common routes of administration, for female and male patients, and for the four age groups. The error rate of PHE did not differ significantly between routes of administration. The error rate of PHE between age groups differed statistically significantly ($p = 0.024$), with children experiencing more PHE than infants ($p = 0.029$). Female and male patients showed a significant difference in PHE overall ($p = 0.035$), and in the age group of children between 2 and 11 years ($p = 0.026$).

Table 10-4 Prescribing errors in the most frequently prescribed active ingredients

Active ingredient	Number of prescriptions	Number of errors overall	Number of PHE (NCC MERP E - I)	Rate of errors overall [x / 100 prescriptions]	Rate of PHE [x / 100 prescriptions]	*p*-Value (PHE)
Paracetamol	478	70	24	14.6	5.0	
Metamizole	231	31	9	13.4	3.9	
Ibuprofen	220	55	14	25.0	6.4	
Ondansetron	170	19	9	11.2	5.3	
Nalbuphine	135	26	23	19.3	17.0	
Cholecalciferol	110	23	3	20.9	2.7	
Salbutamol	93	41	6	44.1	6.5	
Midazolam	69	10	2	14.5	2.9	
Amoxicillin-clavulanic acid	59	11	4	18.6	6.8	
Cefazolin	47	22	5	46.8	10.6	
ROA						**0.858**
oral	1254	363	119	29.0	9.5	
intravenous	860	160	90	18.6	10.5	
rectal	280	42	26	15.0	9.3	
inhalation	135	58	15	43.0	11.1	
Gender						**0.035***
female	1139	292	138	25.6	12.1	
male	1554	384	145	24.7	9.3	
Age groups						**0.024***
Infants	781	187	66	23.9	8.5	0.247
female	301	63	21	20.9	7.0	
male	480	124	45	25.8	9.4	
Children	1323	360	162	27.2	12.2	0.026*
female	601	164	88	27.3	14.6	
male	722	196	74	27.1	10.2	
Adolescents	589	129	55	21.9	9.3	0.100
female	237	65	29	27.4	12.2	
male	352	64	26	18.2	7.4	
Errors overall	2693	676	283	25.1	10.5	

* Indicates significant value

We investigated the PCNE type of errors that occurred in the top ten active ingredients and found the following peculiarities:

- 13 of the 24 PHE that occurred in paracetamol prescriptions were dosing errors (PCNE 3).
- There were no underdosing errors (PCNE 3.1) observed with ibuprofen.
- The high rate of PHE in nalbuphine prescriptions was a recurring error: the maximum number of repetitions allowed in case of acute pain was lacking.
- Cefazolin was prescribed most of the times for perioperative antibiotic prophylaxis. A frequent error we detected was that the prescription was not stopped after surgery. These errors were rated as PCNE 1.2 “no indication for drug” and to be of minor harm.
- 83% of the errors that occurred in salbutamol prescriptions were due to lacking information (PCNE 5.2), but of minor severity.
- Underdosing errors (PCNE 3.1) were observed most frequently with paracetamol (pain treatment) and midazolam (seizures emergency treatment).
- Overdosing errors (PCNE 3.2) were observed most frequently with paracetamol (pain/fever treatment).
- An inappropriate duplication of therapy (PCNE 1.4) occurred most often with drugs for the nervous system (N) and in particular with analgesics (N02).

10.7 Discussion

10.7.1 Drugs Prescribed by Anatomical Class and Therapeutic Group (ATC Levels 1 and 2)

The exposure prevalence of patients receiving a drug for the nervous system (N) is very high, at 86.5%. It must be considered that we only included patients who were actually prescribed at least one drug. Patients without any drug prescription were excluded. This influences the rate of patients that received a certain drug in relation to the total number of patients.

The three predominant ATC classes N, alimentary system (A), and anti-infectives for systemic use (J) were the same as found by Rashed et al. [15], but our findings differ regarding the classes respiratory system (R) and musculoskeletal system (M). In our study, class M was prescribed more frequently and class R less frequently. Rauch et al. [16] also found these three classes (N, A, and J) to be predominant in the hospital care setting, but found anti-infectives (J) to be the class with the highest frequency of prescription, whereas we found drugs for the nervous system to be the most frequently used.

The percentage of patients prescribed an analgesic (81.8% of patients) was higher in our study than found by Botzenhardt et al. [13]. They found that 56.8% of all patients received analgesics, including those without any drug prescription. If we correct our rate of 81.8% by calculating the rate including patients without any drug prescription, the rate is 76.1%, which is still considerably higher than Botzenhardt's rate. At the University Children's Hospital Zurich, an elaborate pain concept exists, which is based on international guidelines [27, 28], and regular pain assessment is an important tool [29]. Considering the prevalence of pain in hospitalized pediatric patients of 59–94% [30], the high prescription rate of analgesics appears to be reasonable. In addition, N02 analgesics such as paracetamol and metamizole were not only prescribed as analgesics, but also as antipyretics or spasmolytics (metamizole), which might have contributed to the high prescription rate.

10.7.2 Drug Prescriptions in Different Age Groups

Not surprisingly, cholecalciferol was the second most prescribed drug for infants and toddlers, as it is recommended for every infant up to the age of 1 year to take daily 400–500 E of cholecalciferol [31].

Children and adolescents have a similar pattern of drug prescriptions with the same five most frequently prescribed drugs, with the only difference in ibuprofen and ondansetron ranking.

The fact that older patients were prescribed more drugs than younger patients was also seen by Rashed et al. [15].

10.7.3 Drug Prescriptions for Female and Male Patients

We did not find a difference in the number of prescribed drugs for female and male patients. This contradicts the finding of Sturkenboom et al. [32], who described a difference in the number of prescribed drugs with an age-related gender reversal: older girls (over 10 years of age) were prescribed more drugs than boys of the same age, whereas in younger patients it was opposite.

Earp et al. [33] reported that boys are being rated to experience more pain than girls in pediatric pain assessment, suggesting that a gender bias exists in pediatrics. We compared the mean number of prescribed analgesics (paracetamol, metamizole, ibuprofen, and nalbuphine) for female and male patients, and found no difference: females were prescribed 2.6 analgesics/patient and males 2.5 analgesics/patient ($p = 0.592$). Therefore, we could not confirm the results of Earp et al. [33].

10.7.4 Routes of Administration (ROA)

The pattern of ROAs prescribed was similar to the pattern reported by Rashed et al. [15], with oral being the most frequent route, followed by intravenous administration. Only the rate of rectal route was remarkably higher with 10% versus 2.5% of prescriptions, which shows the high acceptability of the rectal route in the German-speaking part of Switzerland [34].

10.7.5 Therapeutic Drug Monitoring (TDM)

TDM practice in pediatrics has not yet been well described [35]. Not surprisingly, the main therapeutic areas covered by TDM in our hospital were antibiotics, immunosuppressants, and antiepileptic drugs. Our findings offer an insight into TDM practice in a tertiary care hospital in Switzerland.

10.7.6 The 20 Most Frequently Prescribed Drugs

Paracetamol was by far the most frequently prescribed drug. This result is not surprising, as paracetamol is the analgesic and antipyretic drug of choice for children [36]. The high rate of metamizole prescriptions is a peculiarity in countries such as Switzerland, Germany, or Austria. A recent study of Zahn et al. [37] found 31.7% of pediatric inpatients (university hospital) were prescribed metamizole, which is comparable to our findings of 37.4%. In the study of Zahn, metamizole was predominantly (about 90%) administered intravenously (i.v.), whereas in our hospital, the rate of oral administration was 55% and that of i.v. administration was 43%.

Roughly half of our top 20 list was included in the top 40 list of most frequently used drugs in pediatric hospitals in Switzerland as described by Tilen et al. [18], except for the following: cholecalciferol, nalbuphine, salbutamol, cefazolin, oxymetazoline, diazepam, enoxaparin, clonazepam, acetylsalicylic acid, levetiracetam, clemastine. The gap between our findings might be due to the fact that our study focused on pediatric patients on general wards, whereas the data of Tilen et al. covered all drugs used at the hospitals (including emergency department, pediatric/neonatal intensive care unit, oncology, psychiatry, ambulatory patients, etc.).

Our top three active ingredients were also found as top three drugs in Germany in the study by Rashed et al. [15], but in a different order. Di Paolo et al. [17] also found, for the French-speaking part of Switzerland, paracetamol and ibuprofen to be the most frequently prescribed active ingredients. Ranking third, they listed normal saline (NS) as nose drops which does not appear in our top 20 list as we did not document use of NS.

In salbutamol prescriptions, it is noteworthy that the number of prescriptions was remarkably higher than the number of patients prescribed salbutamol. Salbutamol dosages are adjusted to the symptoms in the course of the treatment, and this adjustment generates a new prescription in the CPOE each time.

10.7.7 Prescribing Errors and Characteristics of the Drugs and Patients

The finding that no underdosing errors occurred in ibuprofen prescriptions contradicts the finding of Milani et al. [38], who found underdosing errors to be frequent in acute pain management with paracetamol and ibuprofen. An explanation for this might be the clear dosing recommendations used in our hospital by Swisspeddose [18] and PEDeDose [39].

The typical nalbuphine error that occurred frequently (lacking number of maximum repetitions on demand) could be prevented by further development of the CPOE with integrated “must” field for the number of repetitions. The very low rate of PHE for cholecalciferol is not surprising, as it is a low-risk drug.

We found that dosing errors were frequent in paracetamol and midazolam. As paracetamol was by far the most frequently prescribed drug, it is not surprising that it is also at the top of the table in terms of dosing errors. Midazolam, which is used in emergency treatment of seizures, is often underdosed. This suggests that the on-demand prescription for emergency seizure treatment contains a high rate of prescribing errors. Causes for this finding might be lack of adaption of the dosages on current patients’ weight, or that too little attention was paid to the reserve medication because it was not needed in the current scenario.

ROA

We found no difference in the error rates between the different ROAs and could not find literature supporting the idea that prescribing errors occur more often in certain ROAs. There are only studies about errors involving the ROA itself [40]. Therefore, we assume that the chosen ROA does not influence prescribing error rate.

Age groups

Children had a statistically significantly higher rate of PHE than infants. As the risk for an error increases with the number of prescribed drugs and as children were prescribed significantly more drugs than infants, this is a plausible finding. Condren et al. [41] found children between 0 and 4 years to be at highest risk for experiencing a prescribing error. As they used other age groups, our results are not comparable. In the study of Glanzmann et al. [42] on a pediatric intensive care unit in our hospital, infants (28 days to 1 year) and adolescents had higher error rates than toddlers and children.

Maaskant et al. [43] found newborn and infants to be at the highest risk of all age groups, which contradicts our finding. As pediatric patients are a heterogeneous population, it would be useful if future research would focus on differences in prescribing errors in different age groups.

Gender

Our result shows a relevant gender gap, with a greater risk for female pediatric patients and especially female children, for experiencing a PHE error than male patients. The overall error rate did not differ significantly, but only the rate of potentially harmful errors. This is a surprising finding with possible explanations being gender bias of the prescribers, a bias in the rating of error severity, or that this is a false-positive finding. We could not find a difference in the profile of drug prescriptions between female and male patients that would explain the higher PHE rate in females.

In adults, gender bias in medicine is known to impact treatment of patients [44], but little is known about gender bias in prescribing errors in pediatrics. To our knowledge there is no large study that investigated the difference in error rates between female and male pediatric patients. As there are no other studies that investigated differences in error rates between female and male pediatric patients, further research is needed to estimate whether there is a difference in potentially harmful prescribing errors, and if so, what the contributing factors are.

10.7.8 Limitations

The limitations of this study are its retrospective nature and the fact that we investigated the prescribing patterns of a random sample in a single center, which may weaken the generalizability of our results. Therefore, our study may not be comparable with other drug utilization studies, as we conducted a secondary analysis of data that were captured for another study [19]. Nevertheless, we analyzed a large number of patients and validated our findings through review by a second rater (previous publication [19]). The rater had access to all patient data for evaluation of the prescribing errors.

10.7.9 Interpretation

Prescribing patterns on pediatric general wards in Switzerland are similar to those in other countries, though there are features specific to the German-speaking area: high rates of metamizole prescriptions and higher rates of rectal administration than in other countries. Prescribing errors occurring frequently in certain active ingredients such as nalbuphine and cefazoline demand a closer look at an institution level. We seem to be the first to describe a difference in the error rate between male and female pediatric patients.

10.7.10 Further Research

In the future, the possible gender bias in pediatric patients should be considered and future studies should investigate whether there really is a difference in prescribing error rates between female and male pediatric patients, and what the reasons for this difference might be.

10.8 Conclusions

In this study we describe the drug prescribing patterns on pediatric general wards in a university children's hospital in the German-speaking part of Switzerland. The most frequently prescribed drugs were paracetamol, metamizole, and ibuprofen. The high rate of metamizole prescriptions is typical for German-speaking countries. The rate of patients prescribed an analgesic (81.8%) is higher than in other studies, and may be interpreted as a good coverage of pain in pediatric patients. The most frequently used route of administration was oral followed by intravenous, with a considerably high rate of rectal administration. Cefazolin and nalbuphine had the highest rates of prescribing errors, which must be addressed in future quality assurance measures. A significant difference in the prescribing error rate occurred between the age groups of children and infants and between female and male patients, which requires further investigation.

10.9 Supplement 1 – Rating of dosing errors

All drug dosages were validated by using the following databases or literature:

- PEDeDose (www.pededose.ch)
- SwissPedDose (www.swisspeddose.ch)
- Drug label (www.swissmedicinfo.ch)
- Hospital internal guidelines
- Uptodate (www.uptodate.com)
- Lexicomp (www.lexicomp.com)
- Other

A drug dosage was categorized as an error, if the prescribed dosage deviated from the literature by more than a certain percentage (see table 10-5) and there was no reason evident for the deviation like altered organ function, obesity, drug-drug-interactions, or other clinical reasons.

Some deviations (column “could be an error”) were only rated as errors, if there were other risk factors that the prescribed dosage could lead to patient harm (for example reduced kidney function). If there were no risk factors evident, these dosages were not categorized as errors.

Table 10-5 Dosage ranges adopted from PEDeus AG [1]

Active ingredient	Limit	No error	Could be an error	Error
Broad therapeutic index	Below	90 - 111%	80 - 90%	< 80%
	Above		111 - 125%	> 125% or above maximum dosage
Narrow therapeutic index	Below	95 - 105%	90 - 95 %	< 90%
	Above		105 - 111%	> 111% or above maximum dosage

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11. Third Study: Use of Unlicensed Drugs in a Swiss Pediatric University Hospital and Associated Prescribing Error Rates – a Retrospective Observational Study

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11.1 Summary

Aims of the study: Unlicensed drugs are frequently used in pediatric care. It is unclear to what extent they are prescribed in hospital care in Switzerland. As prescribing errors seem to occur more frequently in unlicensed drugs, we aimed to assess the prevalence of unlicensed drug prescriptions in two study periods (2018 and 2019) at the University Children's Hospital Zurich, to compare these periods and to investigate whether unlicensed drugs were more prone to prescribing errors than licensed drugs.

Methods: We conducted a sub-analysis of a retrospective single-center observational study and analyzed 5022 prescriptions for a total of 1000 patients from 2018 and 2019 on pediatric general wards. The rate of unlicensed drugs, consisting of imported or formula drugs, was investigated. The prescriptions from 2019 were furthermore analyzed on prescribing errors to see whether errors occurred more often in unlicensed or licensed drug use.

Results: 10.8% of all prescriptions were unlicensed drugs, with about half of them being imported and formula drugs each. 34% of patients were prescribed at least one unlicensed drug. Younger pediatric patients were prescribed more unlicensed drugs than older pediatric patients (newborn: 15.8% of prescriptions, infants: 13.4%, children: 10.6%, adolescents: 7.1%). Ibuprofen suppositories, midazolam oral solution, and gentamicin i.v. solution were the most frequently prescribed imported drugs. Macrogol powder, lisinopril oral suspension, and potassium chloride i.v. solution were the most frequently prescribed formula drugs. The most common drug forms in unlicensed drug use were oral liquid forms and iv solutions. Unlicensed drugs had a significantly higher rate of prescribing errors than licensed drugs (31.6 errors / 100 prescriptions (95% CI: 26.1 – 37.0) versus 24.3 errors / 100 prescriptions (95% CI: 22.3 – 26.2), p = 0.024). Especially formula drugs carried a higher risk (36.4 errors / 100 prescriptions, p = 0.012).

Conclusions: Unlicensed drugs are frequently prescribed in a pediatric hospital setting in Switzerland. About every tenth drug prescription is an unlicensed drug. As unlicensed drugs show a significantly higher rate of prescribing errors, licensed drugs are favorable in terms of medication safety and should be prescribed whenever possible. If no licensed drug is available, imported drugs should be favored over formula drugs, due to lower prescribing error rates. To increase medication safety in pediatrics in Switzerland, efforts are necessary to increase the number of suitable licensed drug formulations for pediatric patients, including developing new innovative drug formulations for children.

11.2 Introduction

Unlicensed drugs are medicines which have no marketing authorization in the country in which they are utilized [1-3]. In Switzerland this applies to drugs without market authorization by Swissmedic. These may be either medicines which are imported from foreign countries, further referred to as “imported drugs”, or medicines which are prepared by a hospital pharmacy or by another licensed manufacturer, further referred to as “formula drugs”. In Switzerland, drugs can be imported by health care professionals, if there is a valid market authorization in a country with a comparable regulatory system, and if no alternative drug authorized for the same indication is available in Switzerland [1]. Formula drugs do not have to be authorized by the licensing agency but have to be manufactured by authorized manufacturers [1].

Worldwide, the proportion of unlicensed prescriptions in pediatrics differ vastly across regions and ranges between 0.1 – 74.4% [4, 5]. Recent studies from Europe showed rates between 3.2 and 30% [6-8]. To our knowledge, there is only one study from Switzerland from 2006, in which Di Paolo et al. [9] described the extent of pediatric off-label and unlicensed use in a university hospital in the French speaking part of Switzerland. They found that 24% of all prescriptions were unlicensed drugs.

The most important reasons for the use of unlicensed drugs in pediatrics are lack of a suitable galenic formulation, dosage, or a specific substance on the national market for pediatric patients [4, 5, 10]. Another increasingly important reason for drugs to be imported or manufactured are drug shortages [11, 12].

Unlicensed drugs carry a higher risk of being prescribed erroneously [4, 13-15] as they have neither proper labelling (undesirable effects, cautions, and contraindications) nor dosing instructions. This applies especially to formula drugs, whereas imported drugs do have a summary of product characteristics (SmPC), but often in a foreign language [9]. Unlicensed use is furthermore associated with a higher rate of adverse events [16] and underreporting of adverse events [4]. Extemporaneously prepared formula drugs additionally carry the risk of compounding errors, of non-validated stability, and of possible reactions to ingredients and excipients [4].

In studies on unlicensed drugs, “off-label” use is also often included [5, 8]. Off-label use describes the use of a licensed drug outside of the SmPC in terms of age, indication, route of administration, or other deviations from registered use. [3]. Off-label use is also frequent in the pediatric population [4].

In Europe the proportion of off-label use of drugs is estimated to be between 13% and 69% of all drug use in the hospital setting [17].

As Bonati et al. [18] argued, clinical evidence is the most important reason for the use of medicine, but not necessarily the official license. In past years, efforts are underway to provide evidence for drug use in case there is no license.

The evidence for commonly used drugs in pediatrics in Switzerland has been collected in the databases SwissPedDose [19] and PedEDose [20]. Hence, many drugs at the University Children's Hospital Zurich may indeed be prescribed off-label, but their use is still evidence based. Therefore, we decided to focus on unlicensed medicines, as these are drugs which are completely lacking on the Swiss market for the pediatric population. Furthermore, it is unclear to what extent imported and formula drugs are currently being prescribed in hospital care in Switzerland.

The study of di Paolo et al. [9] was conducted several years ago. Since then, no additional data from the German speaking part of Switzerland available. The prevalence of unlicensed drug prescriptions differs from country to country. The costs of unlicensed drugs are often not covered by insurance, or only after bureaucratic approval, which is relevant for patients who leave the hospital with prescriptions for unlicensed drugs. Furthermore, as unlicensed drugs are associated with a higher risk for patients [4, 13-16], we aimed to qualify unlicensed drug use in the University Children's Hospital Zurich and to explore if unlicensed drugs are more prone to prescribing errors than licensed drugs. This will help understanding the current situation on pediatric general wards in Switzerland.

11.3 Materials and Methods

We conducted a sub-analysis of a retrospective observational single-center study, which previously investigated the influence of a computerized physician order entry (CPOE) on prescribing errors in pediatrics [21].

The database for this study comprised 1000 patients, which were randomly selected among all patients who stayed at six general wards at the University Children's Hospital Zurich during the study periods. Each 500 patients were selected from all patients hospitalized in two timeframes (1688 patients in Oct – Dec 2018 and 1608 patients in Oct – Dec 2019), which allowed a comparison of the two periods on the development of the rate of unlicensed, imported and formula drugs over time. Only patients with at least one prescribed medication were eligible. All medications prescribed within the first 24 hours after admission were included except for the following: parenteral nutrition, lipids, any blood cell transfusions, insulin, solutions for dialysis, solutions for fluid management such as NS, NS-D5W, D5W, or acetated Ringers.

All drugs were assigned if they were licensed or unlicensed. The unlicensed drugs were further divided into imported drugs or formula drugs. The galenic drug formulations were categorized into 5 main classes, which comprised several similar drug forms: rectal forms (suppositories and other rectal forms), oral liquid forms (suspensions, solutions, syrups, etc.), oral solid forms (tablets, capsules, soft capsules, etc.), i.v. solutions (i.v. concentrated solutions, powder for the preparation of an iv solution, i.v. infusion solutions, etc.), or other (nasal sprays, topical ointments, solutions for intravesical instillation, etc.).

Patients were divided into 4 age groups according to the EMA classification [22]: newborn (term newborn infants: 0 – 27 days), infants (infants and toddlers: 28 days to 23 months), children (2 to 11 years), or adolescents (12 to 18 years).

Medication review was performed on all patients to assess prescribing errors. Errors were categorized according to the PCNE classification [23], and their severity according to the NCC MERP index as adapted by Forrey et al [24]. To validate prescribing error assessment and severity classification, interrater reliability was calculated in the following way: all patients underwent medication review by the first rater a clinical pharmacist, and a random sample of 5% of all included patients underwent additional second review by the second rater another clinical pharmacist. Consequently, interrater reliability could be assessed.

As described in our previous article, the overall error rate was lower in 2019 after the implementation of the CPOE than in 2018 [21]. As error rates differed significantly between the two years, we decided to analyze only error rates related to prescriptions in 2019 to exclude the influence of the CPOE.

The study database was built with Microsoft SQL Server 2019 Master Data Services. Data were collected by the first rater. Evaluation and visualization of the anonymized data was carried out with Microsoft Power BI Desktop, and statistical analyses were conducted with RStudio 2022.02.1 and IBM® SPSS® Statistics Version 27. Rates of unlicensed / imported / formula drugs versus licensed drugs, as well as rates of prescribing errors, were compared by t-test or chi-square-test where appropriate. A significance level of 0.05 was defined.

11.4 Results

11.4.1 Unlicensed Drug Use in 2018 and 2019

The total 1000 patients from both periods were prescribed 5022 medicines, of which 544 (10.8%) were prescriptions of unlicensed drugs. 5.1% were imported drugs and 5.7% were formula drugs. 340 Patients (34%) received at least one unlicensed drug. 244 (95%) of the imported drugs came from Germany, the remaining 14 (5%) from countries such as the USA, GB, Italy, Sweden, or the Netherlands.

In 2018, 243 (10.6%) of the total 2299 drug prescriptions were unlicensed drugs, and in 2019, 301 (11.1%) of the total 2723 prescriptions (table 11-1). This increase was not statistically significant. The proportion of formula drugs did not differ either between the two years, but the rate of imported drugs increased statistically significantly from 4.3% to 5.8% (p = 0.019). On a patient-level, 151 (30.2%) patients were prescribed at least one unlicensed drug in 2018, and 189 (37.5%) patients in 2019. The proportion of patients who were prescribed an imported drug also increased statistically significantly from 17.8% (2018) to 26.8% (2019).

Table 11-1 Rate of unlicensed, formula and import drugs in 2018 and 2019.

Category	Prescriptions 2018 (n = 2299)	Prescriptions 2019 (n = 2723)	p-Value	Patients 2018 (n = 500)	Patients 2019 (n = 500)	*p*-Value
Unlicensed	243 (10.6%)	301 (11.1%)	0.582	151 (30.2%)	189 (37.5%)	0.011*
Formula	143 (6.2%)	143 (5.3%)	0.143	84 (16.8%)	91 (18.2%)	0.560
Import	100 (4.3%)	158 (5.8%)	0.019*	89 (17.8%)	134 (26.8%)	0.001*

*indicates significant value

11.4.2 Unlicensed Use in Different Age Groups

As table 11-2 shows, newborns had the highest proportion of unlicensed drugs, and adolescents the lowest. Unlicensed drug use in adolescents increased statistically significantly from 2018 to 2019, whereas there was no difference in the other age groups over time.

Table 11-2 Unlicensed prescriptions in the four age groups

Age groups	Prescriptions 2018	Prescriptions 2019	Prescriptions Total	*p*-Value
Newborn	11 (16.9%)	4 (13.3%)	15 (15.8%)	0.660
Infants	82 (12.0%)	114 (14.6%)	196 (13.4%)	0.139
Children	129 (11.3%)	133 (10.1%)	262 (10.6%)	0.324
Adolescents	21 (5.2%)	50 (8.5%)	71 (7.1%)	0.037*

* indicates significant value

11.4.3 Top 10 Imported Drugs

Table 11-3 shows the 10 most frequently imported drugs. All drugs in the top 10 list were imported from Germany.

11.4.4 Top 10 Formula Drugs

All formula drugs were produced by authorized manufacturers (other hospital pharmacies, community pharmacies or drug manufacturers), but not by the hospital pharmacy of the University Children's Hospital, due to lack of suitable premises. The 10 most frequently prescribed formula drugs are displayed in table 11-4.

Table 11-3 Top 10 imported drugs

Imported drug product name	Substance	Prescriptions (% of unlicensed prescr.)	Patients	2018 prescr.	2019 prescr.	Reason for import
Nurofen Junior suppositories 60 mg	ibuprofen	59 (10.8%)	54	19	40	No suppository in pediatric dosage on the CH-market
Midazolam ratiopharm oral solution 2 mg/ml	midazolam	36 (6.6%)	36	1	35	Formulation not on the CH-market
Gentamicin-Ratiopharm SF 40 mg/ml iv solution	gentamicin	35 (6.4%)	35	20	15	Formulation not on the CH-market
Nurofen Junior suppositories 125 mg	ibuprofen	28 (5.1%)	27	10	18	No suppository in pediatric dosage on the CH-market
Prednisolut 50 mg powder w solv for iv use	prednisolone	21 (3.9%)	21	3	18	Formulation not on the CH-market
Lasix liquidum oral solution 10 mg/ml	furosemide	12 (2.2%)	11	6	6	Formulation not on the CH-market
Prednisolut Trockensub 25 mg powder w solv for iv use	prednisolone	11 (2.0%)	11	4	7	Formulation not on the CH-market
Gentamicin-Ratiopharm SF 80 mg/2ml iv solution	gentamicin	8 (1.5%)	7	7	1	Formulation not on the CH-market
Petnidan oral suspension 50 mg/ml	ethosuximide	6 (1.1%)	6	3	3	Formulation not on the CH-market
Novalgin suppositories 300 mg	metamizole	6 (1.1%)	4	2	4	No suppository in pediatric dosage on the CH-market

Table 11-4 Top 10 formula drugs

Formula drug product name	Substance	Prescriptions (% of unlicensed prescr.)	Patients	2018 prescr.	2019 prescr.	Reason for formula manufacture
Macrogol 4000 Plv	macrogol	69 (12.7%)	56	36	33	Clinical reasons
Lisinopril Susp 1 mg/ml	lisinopril	21 (3.9%)	21	10	11	Formulation not on the CH-market
Kaliumchlorid Inf Lös 15%	potassium chloride	21 (3.9%)	19	13	8	Safety concerns
Adrenalin Inj Lös 10 mg/10ml	epinephrine	19 (3.5%)	19	2	17	Size of the ampule
Spironolacton Susp 5 mg/ml Ora-Blend SF	spironolactone	19 (3.5%)	19	7	12	Formulation not on the CH-market
NaCl 25% Inf Konz 5 g/20ml	sodium chloride	14 (2.6%)	13	8	6	Vial instead of glass ampule and size
Hydrochlorothiazid Susp 5 mg/ml OraBlend SF	hydrochlorothiazide	11 (2.0%)	11	2	9	Formulation not on the CH-market
Spironolacton Kaps 6 mg	spironolactone	6 (1.1%)	6	6	0	Dosage not on the CH-market
Tacrolimus Susp 0.5 mg/ml Ora-Blend SF	tacrolimus	6 (1.1%)	5	3	3	Dosage not on the CH-market and safety concerns
Captopril Lös 1 mg/ml	captopril	5 (0.9%)	5	4	1	Substance not on the CH-market
Hydrochlorothiazid Kaps 6 mg	hydrochlorothiazide	5 (0.9%)	5	5	0	Dosage not on the CH-market

11.4.5 Drug Formulations

The most frequently prescribed drug forms of unlicensed drugs were oral liquid forms, followed by i.v. solutions, rectal forms and oral solid forms (Figure 11-1).

The rate of rectal forms increased significantly in 2019 (p = 0.028), whereas the rate of oral solid drug forms decreased significantly (p = 0.017). The other drug forms had no significant difference in their rate.

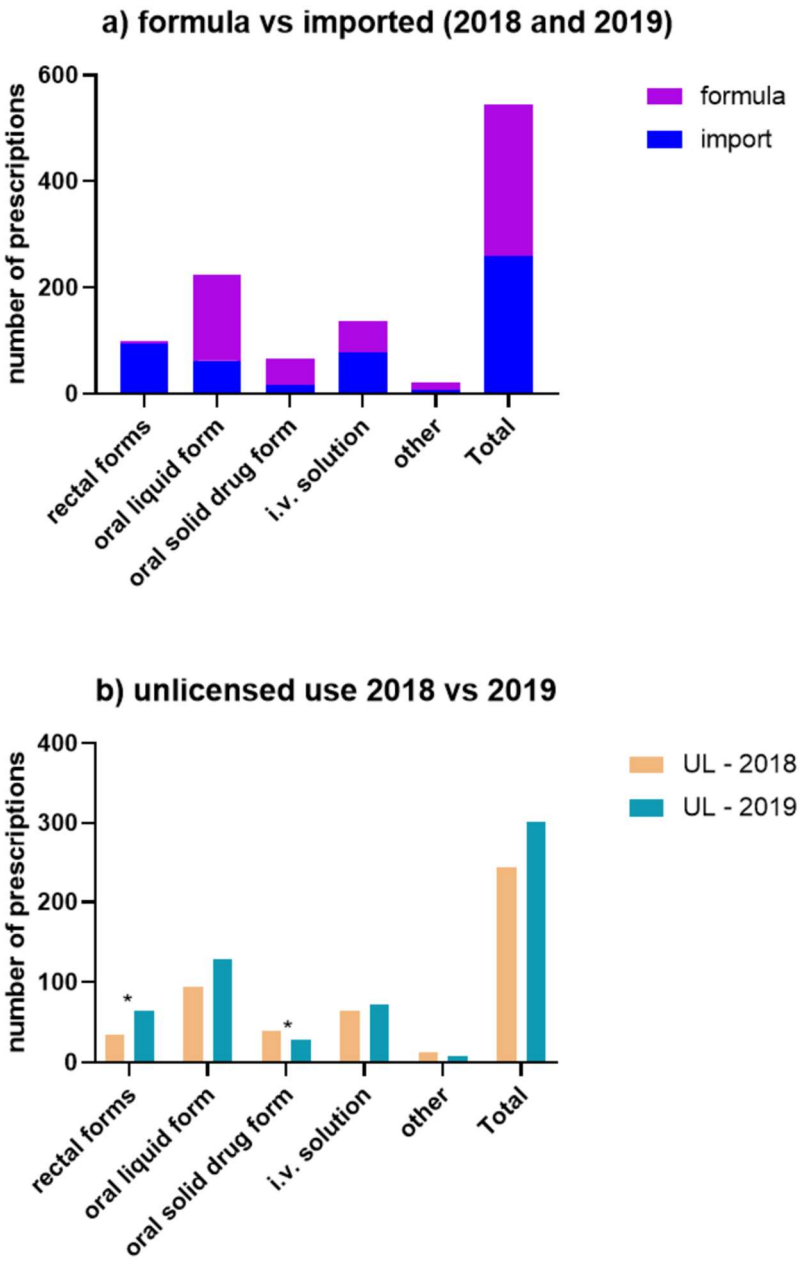

Figure 11-1 drug forms

11.4.6 Prescribing Errors in the 2019 Data

Use of unlicensed drugs was associated with statistically significantly more prescribing errors than use of licensed drugs: 31.6 errors / 100 prescriptions (95% CI: 26.1 – 37.0) versus 24.3 errors / 100 prescriptions (95% CI: 22.3 – 26.2), $p = 0.024$. Particularly formula drugs were prone to errors with 36.4 errors / 100 prescriptions (95% CI: 28.4 – 44.2) in formula drugs, vs. 24.5 errors / 100 prescriptions (95% CI: 22.6 – 26.3) in non-formula drugs (licensed in Switzerland or another country), $p = 0.012$. Imported drugs were not associated with increased error rate: 27.2 errors /100 prescriptions (95% CI: 19.6 – 34.8) in imported drugs vs 25.0 errors / 100 prescriptions (95% CI: 23.1 – 26.8) in not imported drugs (licensed in Switzerland or formula drug), $p = 0.570$. Most of the errors were of minor severity. To estimate, whether errors were clinically relevant, we took a closer look at those errors which could potentially lead to harm (NCC MERP severity E-I). Here we found a rate of 14.6 errors / 100 prescriptions (95% CI: 10.9 – 18.3) in unlicensed drugs versus 10.0 errors / 100 prescriptions (95% CI: 8.7 – 11.3) in licensed drugs ($p = 0.060$). This difference just missed the significance level. Use of formula drugs led to a rate of 11.9 potentially harmful errors / 100 prescriptions (95% CI: 6.5 – 17.3) versus non-formula: 10.5 / 100 prescriptions (95% CI: 9.2 – 11.7) ($p = 0.616$). Use of imported drugs was associated with a rate of 17.1 potentially harmful errors / 100 prescriptions (95% CI: 11.9 – 22.2) vs. not-imported drugs with 10.1 potentially harmful errors / 100 prescriptions (95% CI: 8.9 – 11.4) ($p = 0.045$).

In total 95 errors were detected in the 301 prescriptions of unlicensed drugs in 2019. 52 errors occurred in the 143 formula drug prescriptions. The most frequently observed error overall was PCNE type 5.2 error “necessary information not provided”. This type of error comprised in the majority of cases minor formal errors, such as missing drug form, missing route of administration or missing concentration of the solution but could also include errors of potentially harmful severity (NCC MERP E-I) such as missing number of maximum doses that may be administered in case of on demand analgesics. This error type 5.2 occurred in 32 cases (62%) in formula drugs, whereas the rate in licensed drugs was 46% of all errors and in imported drugs 28%. Dosing errors (PCNE 3.1 – 3.5) were found in 29 unlicensed prescriptions. Most frequently affected by dosing errors were prednisolone i.v. solution, epinephrine i.v. solution, ethosuximide oral solution, furosemide oral solution, ibuprofen suppositories, metamizole suppositories and midazolam nasal spray.

11.5 Discussion

11.5.1 Rate of Unlicensed Use in 2018 and 2019

The overall proportion of unlicensed drugs of 10.8% was lower than the 24% reported by Di Paolo et al [9]. It must be considered that Di Paolo investigated unlicensed drugs on different kinds of wards, including pediatric intensive care units and neonatal wards, where use of unlicensed drugs is known to be higher [5]. The proportion of such use on medicine wards in Di Paolo's study was 16%, which is closer to our rate. In relation to the results reported by Gore et al [4] and Shuib et al. [5] in their review articles (0.1% – 74.4%), our rate is in the lower range. Kaisto et al. [25] recently reported 8% unlicensed drug prescriptions in Finland, also describing a reduction of unlicensed use from 2011 to 2021. Therefore, the reduction of the proportion of unlicensed use compared to the finding of 2006 by Di Paolo seems to be a plausible finding.

Even though the prescription rate of unlicensed drugs did not differ significantly between 2018 and 2019, the proportion of patients prescribed an unlicensed drug increased significantly. This finding may be explained by the increase in drug shortages that took place in recent years [11, 12]. A look at the drug stock at the hospital pharmacy of the University Children's Hospital Zurich shows that in 2019, 15.7% of the drugs were unlicensed drugs (8.0% imported drugs, 7.7% formula drugs). In 2022, 16.8% of the drugs in stock were unlicensed, with 9.2% being imported drugs and 7.6% being formula drugs. Therefore, unlicensed drugs remain an important pillar in the treatment of pediatric patients.

The significant increase in prescriptions of imported drugs and in patients receiving an unlicensed drug in 2019 can be explained by the fact that –if there is no licensed option in Switzerland available - the hospital pharmacy tries to favor drugs that are at least licensed in other countries over formula drugs in most cases. Therefore, there may have been adaptions of the hospital formulary, leading to an increased proportion of imported drugs and to a reduction of formula drugs. Imported drugs are licensed drugs in other countries which underwent an authorization process, whereas formula drugs are not subject to regulatory review.

Most of the imported drugs were purchased in Germany. This brought the advantage that the SmPC was also in German language.

11.5.2 Unlicensed Use in Different Age Groups

The distribution of unlicensed use on the four age groups showed that the use of unlicensed drugs was higher the younger the patients were. This complies with the findings of others [9, 25] and could be another factor explaining the lower use of unlicensed use in our study compared to Di Paolo [9]: the patients in our population were older with a median age of 4.3 years (range 0 – 18.8 years), whereas the patients in the Di Paolo study had a median age of 1.6 years. This finding is also explicable by the fact that younger pediatric patients are not able to swallow tablets and therefore need other galenic formulations.

11.5.3 Top 10 Imported Drugs

All drugs in the list of top 10 imported drugs were imported because there is no identical galenic form on the Swiss market, or because the available galenic form is not on the market in an appropriate dosage for pediatric use (e.g. ibuprofen and metamizole), but there are appropriate forms licensed in other countries. Three substances are listed twice in the top 10 list (different dosages): ibuprofen suppositories, gentamicin iv solution and prednisolone iv solution. Ibuprofen suppositories would not only be helpful for pediatric patients in hospital care, but also for ambulatory patients in either primary or pharmacy care.

An explanation that these drugs are licensed in other countries, but not in Switzerland, could be the fact that the Swiss market is small compared to other markets; therefore, pharmaceutical companies are not interested in licensing a drug in all available formulations in Switzerland.

11.5.4 Top 10 Formula Drugs

Formula drugs are manufactured for several reasons. Lack of appropriate dosage and galenic formulation (especially oral liquid formulations) on the Swiss market were the main reasons for which a drug was manufactured as a formula drug (table 11-4). Other reasons for the production of formula drugs were safety concerns, especially with potassium chloride ampules. The concentrated drug is rated to be of high risk [26]; therefore, it is favorable if the manufactured drug label has features which make it well distinguishable from other drugs. The potassium chloride formula drug comes with an orange label, whereas the licensed products do not have special labels to mark the high alert drug.

Other reasons to use formula drugs instead of licensed drugs were lack of appropriate ampule sizes (adrenaline, sodium chloride 25%), clinical reasons (macrogol), or that the substance was not at all available in Switzerland as licensed drug (captopril). Overall, the variety of reasons why a drug was produced as formula drug was higher than what the reasons were to import a drug. The advantage of formula drugs is that they can be manufactured exactly the way users need them, i.e., in any given ampule size required in clinical practice and in many dosages and concentrations, given that there are data on product stability. Formula drugs may even be necessary in case licensed products do not fulfill the requirements of a hospital in regard to safety, like the example of potassium chloride ampule in our study.

11.5.5 Drug Forms

The comparison of the two years (figure 1 b) displays that the number of oral solid drugs decreased, whereas the number of oral liquid formulations increased over time. This can be explained by the fact that - wherever possible - the hospital pharmacy tries to find an oral liquid formulation instead of capsules, as this is easier to adapt the dosage to the weight of a patient. Only where no established liquid formulation is available, capsules are produced. Unfortunately, liquid oral forms do not seem to be profitable for companies and therefore are often not on the market.

A disadvantage of the oral liquid formulations can be their taste; pediatric patients often do not accept or like the taste of the liquid drug, even when masked with sirup or other flavored liquids. The capsule content, on the opposite, can be dissolved in liquids with a flavor of the patient's choice. Rectal drug forms also increased significantly, though we could not find a direct reason for this finding and interpret it rather as random finding.

11.5.6 Prescribing Errors in 2019

Our finding that prescriptions of unlicensed drugs were more prone to errors is in line with previous findings [4, 13-15]. It is also noticeable that formula drugs were at especially high risk of being prescribed inappropriately. They showed a strikingly high rate of PNCE errors 5.2 ("necessary information not provided"). This is a plausible finding, as formula drugs do not have a SmPC or a leaflet, in which prescribers could find additional information on the drug, dosage, administration, potential adverse drug reactions, etc.

Therefore, it is no surprise that prescriptions of these drugs were not comprehensive enough, but often lacked information. This finding implies that imported drugs are in many cases the better option for patient safety than formula drugs.

Dosing errors occurred often in reserve drugs for anaphylactic reactions (prednisolone i.v. and epinephrine i.v.), which can be explained by the fact that routine anaphylaxis treatment is used in these cases, where fixed dosages are more likely to result in doses outside of the range recommended by the literature. Fixed dosages were also the reason why dosing errors occurred frequently in suppositories (ibuprofen, metamizole).

The other types of prescribing errors did not display any special pattern of errors that could be attributed to the licensing status of the drugs.

11.6 Strengths and Limitations

Strengths of this study are the considerable size of the study sample, and that the findings were validated through review by two independent raters. All patient data were accessible for the rater to evaluate prescribing errors, leading to a comprehensive medication review.

A limitation of our study is that our findings may not be generalizable to the wider population in Switzerland or worldwide, as we investigated only general pediatric wards, whereas neonatal / pediatric intensive care patients and oncologic patients are known to have especially high rates of unlicensed prescriptions. We also did not include primary care or multiple centers. Furthermore, the retrospective nature of our study imposes a limitation on error rating. In studies where the authors did include drugs that have to be manipulated as unlicensed drugs, the proportion of unlicensed drugs was accordingly higher than in our study. We decided not to include such cases, and it was not possible to extract them from the database. Therefore, our results may not be directly comparable to these studies.

11.7 Conclusion

To our knowledge, this study is the first that describes the prevalence of unlicensed drug use on pediatric general wards in the German-speaking part of Switzerland. Unlicensed drugs are frequently prescribed in pediatric hospital care. About every tenth drug prescription on general wards in the University Children’s Hospital Zurich is an unlicensed drug. Imported and formula drugs each account for about half of the unlicensed prescriptions.

Oral liquid solutions were the most frequently prescribed drug form in unlicensed drugs. Prescribing errors occurred significantly more often in unlicensed drugs than in licensed drugs, and formula drugs had the highest rate of prescribing errors compared to imported licensed drugs. In the light of an increasing number of drug shortages, leading to the fact that more and more licensed drugs have to be replaced by unlicensed drugs for short- or long-term treatment, our findings shed light on the risk that unlicensed drugs carry.

In the future, efforts by politics and by pharmaceutical companies should be made to ensure that more drugs suitable for children are licensed in Switzerland.

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12. Conclusion

This thesis provides an insight on prescribing errors in pediatric patients, that were hospitalized on general wards at the University Children's Hospital Zurich in 2018 and 2019. The focus was on factors related to patients, medications and the mode of prescription that influence the rate of prescribing errors in children.

In the retrospective observational study **"Prescribing errors in children: What is the impact of a computerized physician order entry?"** [1] information on prescribing error rates on pediatric general wards in a University Children's Hospital in Switzerland are provided. It was found that prescribing errors were statistically significant reduced after introduction of the CPOE ($p < 0.001$). Not only overall error rates but also PHE rates were reduced ($p < 0.001$). In particular the many formal errors that occurred in semi-structured order prescriptions and handwritten prescriptions were strongly reduced through the CPOE and quality of prescriptions was improved. The rates that were found in the post-CPOE period (25 errors / 100 prescriptions) align with the findings of Gates et al, who reported a range of 15 to 47 errors / 100 prescriptions in their systematic review and meta-analysis [2]. Overall, the CPOE had a positive impact on patient safety.

However, a problem was found that was newly introduced with the CPOE: Since not all prescriptions could be issued electronically, paper form prescriptions were sometimes necessary. This led to hybrid prescriptions and subsequently to an increase in PCNE type 8 errors (medication reconciliation problem). CPOE introduced errors are disclosed by several papers [3-6] and also the hybrid error that was found is well-known [7]. Hybrid prescription techniques impose a risk on patient safety and should be eliminated. At the University Children's Hospital Zurich, this type of error presumably will vanish over time [3], as paper prescriptions are planned to be eliminated and all prescriptions will be made with the CPOE.

For this thesis, one intervention to reduce prescribing errors was studied, which was the introduction of a CPOE with limited CDS. Generally, CDS are promising tools to reduce prescribing errors and improve medication safety [8]. The basis for many CDS are the clinical data provided by the CPOE. Therefore, the CPOE introduction was the first step to provide the basis for any further technological solutions. To bring the most benefit, any CDS tool should be well designed and fully integrated into the CPOE [9; 10]. Furthermore, usability of all electronic tools like CPOE and CDS should always be reevaluated and improved over time, as it is known that any health information technology also brings unintended consequences which can lead to errors and patient harm [6].

Especially dose-check functionalities seem to reduce the most frequent prescribing errors in children, which are dosing errors [11]. With a dose-check, the dosage of a drug prescribed by a physician with the CPOE, can be validated by comparing it to an evidence-based dosing database. If the prescribed dosage deviates from the recommended range by a certain amount, an alert is displayed to warn the prescriber, that there might be an unintended divergence to the recommended dosage [12]. In the presented setting, the dose-check functionality, offered by PedEDose, is planned to be integrated into the CPOE in the future, but unfortunately was not yet implemented at the point of data collection.

One problem that arises with tools that generate an alert, is alert fatigue. Alert fatigue can lead to missed alerts [13-15]. The drug-drug interaction check and the duplication check in this study also generated alerts for the prescriber. In the future, after introduction of the dose-check, it would be useful to assess prescribing errors again, to check the effect of the dose-check on dosing errors, with a special focus on alert fatigue through dosing alerts, drug-drug interaction alerts and duplication alerts.

Highly topical, also artificial intelligence may provide tools in the future, by which medication safety can be improved [16; 17]. For example, some methods have already been published, like a machine learning model, that distinguishes false alarms from clinically relevant alarms and therefore reducing alert fatigue, or through models like deep learning that can predict adverse drug reactions [17].

In any case, prescribing error rates should be monitored over time by any hospital, to evaluate which interventions are of benefit in the specific environment and which are not.

In the second study **"Prescribing patterns in pediatric general wards and their association with prescribing errors: a retrospective observational study"** [18] a sub-analysis of the first study was conducted and prescribing patterns and the properties of drugs that were prescribed on general medical and surgical wards were investigated. Furthermore, it was analyzed if certain medications were more prone to prescribing errors than others.

The investigations revealed prescription patterns similar to those observed in other countries [19], with the most frequently prescribed substances being paracetamol, metamizole and ibuprofen. The high rate of metamizole prescriptions is frequently found in German speaking countries, whereas metamizole is not licensed in many other countries due to safety concerns [20]. In the future, it would be interesting to investigate, if prescribers are aware of the risks of metamizole prescriptions and to compare the safety profile of these three most frequently prescribed drugs.

Getting deeper into data, patients' characteristics were evaluated, and it was found that the rate of PHE differed statistically significant across age groups, with children between 2 and 11 years experiencing higher rates of PHE than infants ($p = 0.029$). Furthermore, a statistically significant difference for gender was found: Female pediatric patients had a greater risk of experiencing a PHE than male patients ($p = 0.035$). This was a surprising finding which certainly requires further research. Gender bias in children is not yet well studied. A study of Rashed et al. [21] showed no difference in the rate of experienced ADRs between female and male patients, whereas in adults more studies are known, that implicate a greater risk for improper therapy for female patients than for male patients [22-25]. The reasons for the present result in the pediatric population can only be speculated about, as children of different gender do not differ in their physiology regarding pharmacotherapy – as known until today – until they reach puberty [26]. Therefore, social factors must play a role, if the findings of this study are confirmed by other researchers.

Looking at drug properties, the route of administration by which a drug should be administered, had no impact on the rate of prescribing errors ($p = 0.858$), nor did we find any other striking pattern of drug properties, that was associated with higher rates of prescribing errors, except for unlicensed drugs.

In the third study **"Use of unlicensed drugs in a Swiss Pediatric University Hospital and associated prescribing error rates – a retrospective observational study"** [27] the focus was on unlicensed drugs, and it was found, that unlicensed drugs were prescribed in 10.8% of all prescriptions. About half of them were imported drugs and the other half formula drugs. Although the rate of unlicensed drug prescriptions in our study, is lower than earlier rates found by Di Paolo et al [28], unlicensed drugs are still an important part of drug therapy for pediatric patients. Drugs needed in therapy on general wards in pediatric hospitals in suitable formulations for young children are still a sparsity on the market. In the future, the use of unlicensed drugs should be further reduced by increasing the number of licensed drugs for the pediatric population. If unlicensed drugs are inevitable, imported drugs should be favored over formula drugs, as they have a better safety profile regarding the quality of the drugs.

For several years, regulations on European and national level have been introduced which should increase the rate of licensed drugs for pediatric patients [29-32]. These regulations enforce pharmaceutical companies to investigate quality, safety, and efficacy of drugs by submitting a pediatric investigational plan. The regulations did succeed in increasing the information of pediatric relevance in the SmPCs, but child-appropriate formulations are still lacking in many cases [33; 34]. This leads to the fact that unlicensed drugs still have to be either imported or manufactured in child-appropriate drug forms.

Prescribing errors occurred significantly more often in unlicensed drugs than in drugs that were licensed (31.6 errors / 100 prescriptions versus 24.3 errors / 100 prescriptions, $p = 0.024$). Formula drugs, manufactured by hospital pharmacies or other licensed manufacturers, were especially prone to prescribing errors with a rate of 36.4 errors / 100 prescriptions).

Prescribing errors generally result from an interplay of multiple factors. In this thesis some of these factors were investigated: Regarding the properties of the drugs, unlicensed drugs were identified to be at especially high risk. Concerning patient's properties, female patients, and children between 2 and 11 years were found to be at higher risk than others and as to prescribing mode, CPOE-prescriptions were found to be safer than non-CPOE prescriptions. Nevertheless, there are even more contributing factors, which we could not investigate. These are related to healthcare professionals (skills, accuracy, following the guidelines, responsibility, and attitude), teams (division of work and flow of information) and organizations (resources, work environment, training) [35; 36].

Overall, pediatric patients are still at higher risk of experiencing a prescribing error than adults. Further initiatives are needed to reduce this medication safety problem in this vulnerable population, including the use of CDS tools and the exploration of artificial intelligence. Additionally, a multifaceted approach involving healthcare professionals, teams, and organizations is essential for mitigating prescribing errors. Also, the pharmaceutical industry is required to provide more drugs that are appropriate for pediatric patients either with established drug forms or by developing new innovative galenic drug forms that are suitable for children. This way, all players can contribute to an increase in medication safety in children.

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13. Index of figures and tables

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14. Publications

- Use of unlicensed drugs in a Swiss Pediatric University Hospital and associated prescribing error rates; Aylin N. Satir; Miriam Pfiffner; Christoph R. Meier; Angela Caduff Good; accepted by Swiss Medical Weekly on 27.10.2023, Journal article.

- Prescribing patterns on pediatric general wards and their association with prescribing errors – a retrospective observational study; Aylin N. Satir; Miriam Pfiffner; Christoph R. Meier; Angela Caduff Good; Drugs – Real World Outcomes, published 13.10.2023, https://doi.org/10.1007/s40801-023-00392-0, Journal article.

- Prescribing errors in children: what is the impact of a computerized physician order entry?; Aylin N. Satir; Miriam Pfiffner; Christoph R. Meier; Angela Caduff Good; European Journal of Pediatrics, published 18.03.2023, DOI: 10.1007/s00431-023-04894-5 , Journal article.

- Kinder-Palliativmedizin Essentials, Das Wichtigste für die Palliative Care bei Kindern, Jugendlichen und ihren Familien; Jürg Streuli, Eva Bergsträsser, Maria Flury, Aylin Satir, published 05.11.2018, Hogrefe Verlag, ISBN: 978-3-456-85883-8, Book.

- Digoxin toxicity in a neonate caused by the interaction with carvedilol; Alexia Moser-Bracher; Christian Balmer; Anna Cavigelli; Aylin Satir; Angela Caduff Good; Dietrich Klauwer; Klinische Pädiatrie, published 03.2017, DOI: 10.1055/s-0043-100220 , Journal article.

- How to keep drug data up-to-date; Aylin Satir, Katja Bouwman, Priska Vonbach; Le Pharmacien Hospitalier et Clinicien, published 21.03.2017, https://doi.org/10.1016/j.phclin.2017.01.031 , Poster abstract.

15. Poster Presentations

- Prescribing errors in children: what is the impact of a computerized physician order entry?; Aylin N. Satir; Miriam Pfiffner; Christoph R. Meier; Angela Caduff Good, Congress: European Association of Hospital Pharmacists, 2023, Lisbon, Portugal

- How to keep drug data up-to-date, Aylin Satir, Katja Bouwman, Priska Vonbach, Congress: Journées Franco-Suisses de Pharmacie Hospitalière, 2016, Bern, Switzerland

16. Oral Presentations

- GSASA Kongress (Swiss Association of Public Health Administration and Hospital Pharmacists), 11 – 12 November 2021, Lugano: Presentation “GSASA Forschungsprojekt 2014, Verordnungsfehler in der Pädiatrie – Welchen Impact hat ein CDSS?” (Virtual presentation)

- Teachingwoche, Morgenteaching, University Children's Hospital Zurich, 04 November 2018, Presentation “Arzneimittel in der Muttermilch”

- Klinisch-pharmazeutisches Fallkolloquium, University of Basel, 12 January 2017, Presentation Themenworkshop Pädiatrie, “Fallpräsentation”

- GSASA Workshop klinische Pharmazie, 30 November 2016, Bern: Workshop “Unerwünschte Wirkungen – ungenügende Daten, kindergerechte Therapie?”

- Teachingwoche, Mittagsteaching, University Children's Hospital Zurich, 16 June 2015, Presentation “Medikationsfehler – Update 2015

17. Congress Participations

- 27th Congress of the EAHP (European Association of hospital pharmacists), 22 – 24 March 2023, Lisbon, Portugal
- GSASA Kongress (Swiss Association of Public Health Administration and Hospital Pharmacists), 9 - 10 November 2022, Lucerne, Switzerland
- GSASA Kongress (Swiss Association of Public Health Administration and Hospital Pharmacists), 15 – 16 November 2018, Fribourg, Switzerland
- Journées Franco-Suisses de Pharmacie Hospitalière, 1 – 2 December 2016, Bern, Switzerland
- 20th Congress of the EAHP (European Association of hospital pharmacists), 25 – 27 March 2015, Hamburg, Germany