Cross-sectional study identifying high-alert substances in medication error reporting among Swedish paediatric inpatients

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Abstract

Aim: The aims were to characterise paediatric medication errors and to identify the prevalence of known high-alert substances in these errors.

Methods: All paediatric drug-related incident reports and complaints nationally reported to the Health and Social Care Inspectorate in Sweden 2011-2017 regarding inpatients were characterised by context and modal details. In addition, drug use at a university hospital was matched to local incident reports. Drug substances were classified using three high-alert lists.

Results: On a national level, there were 160 reports (2.5 per 10 000 patients) in which the three high-alert lists were found in different degrees (17/35/47%). Morphine (n = 12), vancomycin (n = 11) and potassium (n = 7) were most frequently involved. Eighty per cent of the reports concerned patients aged 0-6 years. Intravenous was the most common route of administration (66%). On a university hospital level, the prevalence of all types of drug incidents reports was 1.7% among all inpatients. The prevalence of local incident reports involving high-alert substances was almost double that of non-alert substances.

Conclusion: Existing high-alert drug lists are relevant for paediatric inpatients. A higher awareness and usage of such lists among hospital staff prescribing, dispensing and administering drugs to children may have the potential to reduce medication errors.

KEYWORDS  
child, medication errors, paediatrics, patient safety, risk management

Abbreviations: ATC, anatomic therapeutic chemical classification system; CI, confidence interval; DDA, each day a drug order was administered; ISMP, the Institute for Safe Medication Practices; IVO, The Health and Social Care Inspectorate; ME, medication error; NCC MERP, National Coordinating Council for Medication Error Reporting and Prevention; OR, odds ratio; PICU, paediatric intensive care unit; PPV, positive predictive value; RR, relative risk.

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1 | INTRODUCTION

Medication errors (ME), that is, incorrect drug use reaching the patient, can be reduced with systematic work.1 This work needs to have a multilayer focus. A list of high-alert substances may be useful in teaching and in warning systems and has been suggested by major patient safety institutions.2-4 High-alert lists should be balanced to include substances with a known narrow therapeutic window or risk of life-threatening event if used erroneously and outline drugs frequently causing MEs. Lists with substances used in paediatrics would be of particular benefit due to the pharmacological and developmental challenges related to growth, maturation of organs and hormonal changes.5 In addition, children in hospital have three times higher risk of potential adverse drug events than adults.6 This risk increase is partly explained by the lack of drug treatments adapted to paediatric care resulting in 60% of paediatric inpatients prescribed off-label drugs, that is outside of the product monograph.7

Prescribing drugs to children also comes with miscalculation risks as dosing is generally weight-based, and ten-fold mistakes are relatively common.8 According to Swedish patient safety act, the healthcare provider is obligated to report the exposure or risk for exposure of a serious harm, termed ‘Lex Maria’.9 The history behind the term is an unfortunate mistake, a mix-up between a toxic and a non-toxic substance, committed at the Maria hospital in Stockholm in 1936.10 In Sweden, ‘Lex Maria-events’ must be reported to the Health and Social Care Inspectorate (IVO). In addition to reports from the Health provider, the patient or the parents can also file an independent complaint to IVO.7 The possibility for families to report incidences in hospital settings has shown to have a positive impact on finding additional MEs.11

Several national paediatric high-alert substance lists have been published with the aim to caution prescribers and administrators of an increased risk for harm when used in error.3,12-20 One list published by Maaskant et al21 added an international consensus based on a modified Delphi study process. The published lists have some similarities (eg, morphine, insulin and potassium), but also varies largely in their contents and with recommendations to adapt the lists to the local context.

The primary aim of this study was to characterise MEs by drug-related process in the Swedish paediatric healthcare system and to identify the prevalence of high-alert substances in these MEs comparing three different (short-medium-long) high-alert lists.

The secondary aim was to investigate the use of known high-alert substances in a paediatric university hospital population and its relation to locally reported MEs.

2 | PATIENTS AND METHODS

2.1 | Design

This study used a retrospective, cross-sectional design in one national and one local paediatric inpatient population (Figure 1).

2.2 | Populations

1. National: All national healthcare reports (Lex Maria) and complaints sent to, and classified as ‘medication related’ by, IVO regarding children ‘age 0-17 years’ from January 1, 2011 to December 31, 2017 in Sweden were included. Data were obtained from IVO, and all included reports (n = 204) were investigated based on the root cause analysis and comments from the healthcare provider. The total number of patients was collected from the statistics database for diagnoses in inpatient care provided by the National Board of Health and Welfare.

2. Local: All locally registered incidence reports classified as ‘medication related’ in an incident reporting system at the Department of Pediatrics, Karolinska university hospital during the whole calendar years 2011 and 2017 were included. Data were obtained from the hospital incident reporting system as an extract of all incidents reported or classified as drug-related (n = 1221). The reports were investigated based on a short description of the actual incidence without any root cause analysis.

2.3 | Exclusions

Reports were excluded if substance or drug class was insufficient, occurring in primary health care (outpatients), during delivery, contained duplicates or did not state any possible causality with a drug.

2.4 | Categorisation of medication errors

Medication errors and their consequences for the affected patients were defined according to the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP; Table 1)22. The data were categorised as ME resulting in no harm or minor intervention in patients (NCC MERP categories: A-D), in temporary harm with intervention or prolonged hospital stay (NCC MERP categories: E-F) or long-term harm, major interventions or death (NCC MERP categories: G-I).
2.5 | Categorisation of drugs

Substances and ATC code of drugs in each case were categorised as high-alert as defined by (a) a paediatric short list of five substances by Colquhoun et al\textsuperscript{13} or (b) a paediatric medium list of 14 substances and four drug classes by Maaskant et al\textsuperscript{21} or (c) an acute-care long list of 12 substances and 21 drug classes by the Institute for Safe Medication Practices (ISMP).\textsuperscript{3} If the specific substance was not clarified, it was registered according to drug class as second-level ATC code. In reports where the incident described a mix-up, the route or substance supposed to be used is the one denoted in this study. Both substances involved in mix-ups of wrong drugs or routes are presented in Table S1.

2.6 | Data analysis

All reports were read, and the data were extracted and categorised separately by PN and AK, and discussions were carried out in the case of disagreement. The modal details, process (prescribing, dispensing including reconstitution, administration) and error-type were recorded alongside the contextual details such as substances, ATC code, route, NCC MERP Index,\textsuperscript{22} year of the incident, hospital unit, region (defined as large or medium region with university hospital or other regions), age group and potency of dosing error.\textsuperscript{23}

All substances involved in the incident reports were compiled and compared with the three selected lists of high-alert substances.
2.7 | Data analysis of local drug usage

From the data warehouse of the two local electronic medical record systems used, all administered drugs were extracted with the number of patients receiving drug therapy. Enteral nutrition supplements and blood products were excluded, together with drugs administered in the delivery unit and drugs used in the operating room—all ordered in separate systems. The number of cytotoxic drug doses was calculated as the number of orders sent to the compounding pharmacy.

All drugs were classified by substance, ATC code and high-alert drug status, as defined above. The substances were grouped by patient and day of exposure. The groups were summarised by each Day a Drug order was Administered (DDA). For example, if a patient for 1 day received 20 doses of 10 different substances, it corresponded to 10 DDA. The number of reports generated with or without high-alert substances was compared to the number of DDA.

2.8 | Statistical methods

The prevalence of MEs is reported in actual numbers and percentage of the total number of patients, MEs or DDA. A logistic regression was carried out for crude odds ratio (OR) with 95% confidence interval (CI) regarding the exposure of cases of NCC MERP G-I classification. A multivariate analysis for cases A-D and G-I reported the differences as relative risk (RR) with E-F as a base. Sensitivity, specificity and positive predicted value (PPV) were calculated based on the number of incidents and non-incidents in relation to DDA administered, with the assumption that one incident report was caused by one DDA (Stata 12.0 by StataCorp).

2.9 | Ethics

An ethical approval has been granted for this study by the Regional Ethical Review Board in Stockholm (number 2017/2525-31).

3 | RESULTS

3.1 | Characteristics of national reported errors

Of the 204 eligible national reports, 160 were included and accounted for 80 substances, from 31 different drug classes. Contextual characteristics are presented in Table 2, showing that intravenous administration was the route involved in the highest number of reports (105/160 = 65.6%). The lower number of reports was seen in the early years depending on start-up effects of IVO. Paediatric intensive care units (PICU) and older age groups seem to be reporting more serious events. The analysis of harm by NCC MERP identified 32 (20%) ME with no described harm NCC MERP A-D, 98 (61%) with different degree of described temporary harm NCC MERP E-F and 30 (19%) with more serious harm NCC MERP G-I, classified as 3 (1.9%) MEs resulting in permanent harm NCC MERP G, 21 (13%) that required interventions necessary to sustain life NCC MERP H and six (3.8%) MEs that could have contributed to patient death NCC MERP I. ME due to prescribing (35.6%), administrating (36.3%) or dispensing (27.5%) errors were evenly distributed (Table 3). Type of error varied, but four types occurred more frequently than the others: wrong dose (31.9%, where 2/3 being prescribing), wrong concentration (25.0%, where 3/4 being dispensing), mix-up of wrong drug (11.3%, due to dispensing and administration) and wrong infusion rate (8.1%, only due to administration). Other modal events such as omission, wrong technique and monitoring errors were overrepresented in serious events.

3.2 | Prevalence of high-alert substances in national reports

The 160 national ME reports occurred in 629 063 inpatients corresponding to a prevalence of 0.025% (2.5 reports per 10 000 inpatient). Morphine (n = 12) and vancomycin (n = 11) were represented in the highest number of MEs followed by potassium (n = 7), midazolam (n = 5), heparin (n = 5) and dalteparin (n = 5) presented in Table 4. The 16 most frequent substances caused half of all incidents reported. Each of the remaining substances occurred once or twice in the incident reports (Table S2).

Antibacterial drugs for systemic use are one of the most used drug classes in paediatric inpatient care and occurred in the highest number of MEs reports (n = 25) followed by opioids (n = 24), fluids and electrolytes (n = 19) and antithrombotic agents (n = 12). These four classes represented half of all reports.

The three different high-alert lists identified 27 (16.9%, short), 56 (35%, medium) and 76 (47.5%, long) of drugs involved in the incident reports. The process of administration did not favour a longer list compared to dispensing and prescribing which have the largest flora of substances involved in the incident reports (46, 57.5%), as shown in Table 5. For the medium list, 57 (35.6%) of the incident reports were related to the use of 13 of the 14 high-alert substances and 3 of the 4 drug classes. If we were to add six substances (midazolam, clonidine, intravenous iron, sodium chloride, promethazine and rifampicin), two drug classes (anaesthetic drugs and anti-epileptics) and two drugs with a specified process (omission of salbutamol or vaccines) a medium + local list would contain all serious cases (NCC MERP G-I) in Sweden 2011-2017.

3.3 | Multivariate analysis of high-alert substances in national reports

A logistic regression with a multivariate analysis (Table S3, with RR and 95% CI) indicated that patients above 6 years of age (7.0, 2.2-23), other modal details (9.2, 1.7-51) and the medium high-alert lists (4.1, 1.5-11) were more frequently associated with serious adverse drug
The same pattern was valid for the other two high-alert lists. Reports on errors that did not reach the patient or reached the patient without causing harm were more commonly filed as a complaint (10, 2.7-40) compared to those causing temporary harm (NCC MERP E-F).

### 3.4 Prevalence of high-alert substances in local reports

The 885 local incidence reports were generated by 50,823 inpatients. The local reports included 14 (1.6%) Lex Maria reports giving a 2.8 Lex Maria reports per 10,000 inpatients. As expected, the local incident reports constituted of less serious MEs (90% categorised as NCC MERP A-D as compared to 20% in ME reported to the National Inspectorate). All 885 incidents generated 1.7 reports per 100 patients or 1.7 reports per 1000 DDA. The prevalence of reports among high-alert drugs (also described as the positive predictive value) was almost doubled that of non-alert drug reports (Table 6). But the number of DDA needed to be administered to generate a report was twice as many between the short and medium list and almost tripled between the short and long high-alert list. Adding drugs to the high-alert list with regard to the local context (medium + local) increased the sensitivity but decreased the specificity.

### TABLE 2 Context details of national reported ME

| Characteristics | Total (%) | NCCMERP G-I (%) | Crude OR (95% CI) | P |
|-----------------|-----------|-----------------|-------------------|---|
| **Type**        |           |                 |                   |   |
| Complaints     | 16 (10)   | 2 (6.7)         | 1                 |   |
| Lex Maria      | 144 (90)  | 28 (93)         | 1.7 (0.4-7.8)     | .5|
| **Year**       |           |                 |                   |   |
| 2011           | 10 (6.3)  | 1 (3.3)         | 1                 |   |
| 2012           | 15 (9.4)  | 2 (6.7)         | 1.4 (0.1-18)      | .8|
| 2013           | 28 (17)   | 6 (20)          | 2.5 (0.3-23)      | .4|
| 2014           | 23 (14)   | 7 (23)          | 3.9 (0.4-37)      | .2|
| 2015           | 24 (15)   | 2 (6.7)         | 0.8 (0.1-10)      | .9|
| 2016           | 28 (17)   | 4 (13)          | 1.5 (0.1-15)      | .7|
| 2017           | 32 (20)   | 8 (27)          | 3 (0.3-27)        | .3|
| **Age**        |           |                 |                   |   |
| 0-6            | 127 (79)  | 18 (60)         | 1                 |   |
| 7-12           | 14 (8.7)  | 5 (17)          | 3.5 (1.2-10)      | .02|
| 13-17          | 19 (12)   | 7 (23)          | 3.4 (1.0-11)      | .05|
| **Unit**       |           |                 |                   |   |
| Paediatric     | 102 (64)  | 17 (57)         | 1                 |   |
| Neonatal       | 27 (17)   | 5 (17)          | 1.1 (0.4-3.4)     | .8|
| Adult          | 19 (12)   | 4 (13)          | 1.2 (0.4-4.5)     | .6|
| PICU           | 6 (3.8)   | 4 (13)          | 10 (1.7-59)       | .01|
| Ambulance      | 3 (1.9)   | –               | –                 | –  |
| Pharmacy       | 3 (1.9)   | –               | –                 | –  |
| **Transfer**   |           |                 |                   |   |
| No             | 117 (73)  | 20 (67)         | 1                 |   |
| Yes            | 43 (27)   | 10 (33)         | 1.5 (0.6-3.5)     | .4|
| **Region**     |           |                 |                   |   |
| Large (n = 3)  | 108 (67)  | 19 (63)         | 1                 |   |
| Medium (n = 4) | 23 (14)   | 5 (17)          | 1.3 (0.4-4)       | .6|
| Other (n = 9)  | 29 (18)   | 6 (20)          | 1.2 (0.4-3.4)     | .7|
| No cases (n = 5)|          | –               | –                 | –  |
| **Route**      |           |                 |                   |   |
| Intravenous    | 105 (66)  | 21 (70)         | 1                 |   |
| Peroral        | 34 (21)   | 4 (13)          | 0.5 (0.2-1.7)     | .3|
| Other          | 21 (13)   | 5 (17)          | 1.3 (0.4-3.8)     | .7|
| **Potency**    |           |                 |                   |   |
| –              | 55 (34)   | 14 (47)         | 1                 |   |
| <10            | 47 (29)   | 6 (20)          | 0.2 (0.07-0.7)    | .01|
| ≥10            | 58 (36)   | 10 (33)         | 0.5 (0.2-1.2)     | .1|
| **All**        | 160 (100) | 30 (100)        |                   |   |

Note: Presented with crude odds ratio (OR, 95% CI) and P-value in each group for the risk of severe ME (NCC MERP G-I) compared to non-severe ME (NCC MERP B-F).

aError during or because of, the transfer between hospital units.

The same pattern was valid for the other two high-alert lists. Reports on errors that did not reach the patient or reached the patient without causing harm were more commonly filed as a complaint (10, 2.7-40) compared to those causing temporary harm (NCC MERP E-F).
In Figure 2, the frequency of local incident reports and DDA is shown for different drug classes. The highest number of national and local incident reports was in the high-use categories of fluid therapy, including electrolytes (B05), antibacterial drugs for systemic use (J01) and analgesics, including opioids (N02). Drug classes for diabetes, including insulin (A10) and immunosuppressive drugs (L04), had low usage but produced a higher number of incidents reports. Some drugs as ibuprofen and drugs in category of anti-inflammatory drugs (M01) were not involved in MEs despite high usage (not shown).

### TABLE 3 Modal details of national reported ME

|                      | Prescribe (%) | Dispense (%) | Administrate (%) | Total (%) | NCCMERP G-I (%) | Crude OR (95% CI) | P     |
|----------------------|---------------|--------------|------------------|-----------|-----------------|--------------------|-------|
| **Modal—Dosing**     |               |              |                  |           |                 |                    |       |
| Wrong dose           | 34 (60)       | 3 (6.7)      | 14 (24)          | 51 (32)   | 4 (13)          |                    |       |
| Wrong concentration  | 8 (14)        | 30 (67)      | 2 (3.4)          | 40 (25)   | 7 (23)          |                    |       |
| Wrong rate           | –             | –            | 13 (22)          | 13 (8.1)  | 3 (10)          |                    |       |
| Wrong duration       | 2 (3.5)       | 1 (2.2)      | 1 (1.7)          | 4 (2.5)   | –               |                    |       |
| **Modal—Identity**   | –             | 10 (22)      | 21 (36)          | 31 (19)   | 6 (20)          | 1.6 (0.6-4.6)      | .4    |
| Wrong drug           | –             | 9 (20)       | 9 (16)           | 18 (11)   | 4 (13)          |                    |       |
| Wrong route          | –             | –            | 9 (16)           | 9 (5.6)   | 2 (6.7)         |                    |       |
| Wrong patient        | –             | –            | 3 (5.2)          | 3 (1.9)   | –               |                    |       |
| Wrong dosage form    | –             | 1 (2.2)      | –                | 1 (0.6)   | –               |                    |       |
| **Modal—Other**      | 13 (23)       | 1 (2.2)      | 7 (12)           | 21 (13)   | 10 (33)         | 6.1 (2.1-17)       | .001  |
|                      | 5 (8.8)       | –            | 3 (5.2)          | 8 (5.0)   | 3 (10)          |                    |       |
|                      | 6 (11)        | –            | –                | 6 (3.8)   | 3 (10)          |                    |       |
|                      | –             | –            | 3 (5.2)          | 3 (1.9)   | 3 (10)          |                    |       |
|                      | 2 (3.5)       | –            | –                | 2 (1.3)   | 1 (3.3)         |                    |       |
|                      | –             | 1 (2.2)      | 1 (1.7)          | 2 (1.3)   | –               |                    |       |
| **All**              | 57 (100)      | 45 (100)     | 58 (100)         | 160 (100) | 30 (100)        |                    |       |

*Note: Presented with crude odds ratio (OR, 95% CI) and P-value in each group for the risk of severe ME (NCCMERP G-I) compared to ME (NCCMERP B-F).*

### TABLE 4 Top 10 substances of national reported ME

| Substance       | Total | Process | NCCMERP |
|-----------------|-------|---------|---------|
|                 |       | Prescribe | Dispense | Administrate | A-D | E-F | G-I |
| morphine<sup>SML</sup> | 12 (7.5) | 3 (5.3) | 1 (2.2) | 8 (14) | 2 (6.2) | 6 (6.1) | 4 (10) |
| vancomycin      | 11 (6.9) | 4 (7.0) | 3 (6.7) | 4 (6.9) | 2 (6.2) | 9 (9.2) | – |
| potassium<sup>SML</sup> | 7 (4.4) | 2 (3.5) | 3 (6.7) | 2 (3.4) | 1 (3.1) | 2 (2.0) | 4 (10) |
| midazolam<sup>L</sup> | 5 (3.1) | 2 (3.5) | 2 (4.4) | 1 (1.7) | – | 4 (4.1) | 1 (3.3) |
| heparin<sup>SL</sup> | 5 (3.1) | – | 2 (4.4) | 3 (5.2) | 1 (3.1) | 3 (3.1) | 1 (3.3) |
| dalteparin<sup>L</sup> | 5 (3.1) | 1 (1.8) | 4 (8.9) | – | – | 5 (5.1) | – |
| furosemide      | 4 (2.5) | 2 (3.5) | 1 (2.2) | 1 (1.7) | – | 4 (4.1) | – |
| clonidine       | 4 (2.5) | 1 (1.8) | 2 (4.4) | 1 (1.7) | – | 3 (3.1) | 1 (3.3) |
| insulin<sup>SML</sup> | 4 (2.5) | – | 2 (4.4) | 2 (3.4) | 1 (3.1) | 3 (3.1) | – |
| fluid therapy   | 4 (2.5) | – | – | 4 (6.9) | 3 (9.4) | 1 (1.0) | – |
| High-alert<sup>S</sup> | 27 (17) | 6 (11) | 7 (16) | 14 (24) | 4 (12) | 14 (14) | 9 (30) |
| High-alert<sup>M</sup> | 56 (35) | 15 (26) | 16 (36) | 25 (43) | 11 (34) | 29 (30) | 16 (53) |
| High-alert<sup>L</sup> | 76 (47) | 23 (40) | 29 (64) | 24 (41) | 12 (37) | 43 (44) | 21 (70) |
| All             | 160 (100) | 57 (100) | 45 (100) | 58 (100) | 32 (100) | 98 (100) | 30 (100) |

*Note: Stated as bold if the substances are classified as high-alert with elevated letter for the short<sup>S</sup>, medium<sup>M</sup> or long<sup>L</sup> list. Data are shown by process and degree of harm, with the number of reports (per cent of total).
This study has five main findings with clinical patient safety implications. (a) Substances from the three high-alert lists were identified in different degrees (17/35/47%) of national reports. (b) All high-alert lists did identify a higher proportion of reports with severe outcome. (c) The processes identified in national reports were dependent on specific ME types, for example prescribing did mainly relate to dosing errors. (d) The number of local reports was related to the number of DDA, grouped by second-level ATC code. (e) Finally, the prevalence of local reports with high-alert substances was found to be two-fold compared to reports with non-alert substances, independent on the length of the high-alert list.

The study did also show that incidents among older age groups and other types of modal events are more commonly reported as serious events. It could be an effect of lower-harm cases being more routinely discovered and reported for younger patients. Or, signaling that older age groups and other types of modal events needs more serious events to be noticed. The prevalence of ME reported to IVO among paediatric inpatients in Sweden was found to be 2.5 per 10 000 patients. A Danish study found 487 harmful ME during a 5-year period. This corresponds to a four times higher rate in Denmark rather to the results in our study, but the three predominant drug classes were the same.

In the United States, 163 neonatal units reported 6749 ME during 7 years of which 244 had the category NCC MERP E-I with a significant overrepresentation of substances from the same long high-alert list used in our study. The medium high-alert list was validated with data from the Dutch incident registration based on 1043 paediatric reports from 43 hospitals for two and a half years. They found only four out of 14 of their high-alert substances that resulted in serious temporary harm or worse, while additional nine were confirmed with potential harmful incidents. In comparison, our study found 10 of the high-alert substances among the ME with harm NCC MERP G-I.

The high-alert substances can vary depending on the patient group, treatment traditions, pharmacy workflow, country and hospital usage and prerequisites. It is therefore of value to investigate both nationally and regionally which drugs that poses as high-alert substances and are involved in most errors. A French study found similar drugs as the medium high-alert list and recommended that the list should be updated on a regular basis, not too long, and include jokers applicable for the local unit. When we included a local list to the medium high-alert list, the possibility to catch more events increased with a decreased specificity. In practice, to be able to implement alerts for longer lists, the usage of clinical decision support systems would be helpful, for example dose range checking systems.

### Table 5

| High-alert list | Reported substances, n (%) |
|-----------------|-----------------------------|
| Short           | 5 (6.2) 3 (6.5) 4 (14) 4 (11) |
| Medium          | 22 (27) 11 (24) 10 (34) 13 (36) |
| Long            | 28 (35) 18 (39) 16 (55) 12 (33) |
| No list         | 48 (60) 27 (59) 13 (45) 20 (56) |
| All             | 80 (100) 46 (100) 29 (100) 36 (100) |

Note: Number (N) of published high-alert substances plus drug classes (Classes) of the three different lists (short-medium-long). Number (n) and percentages of reported substances (including substances within the drug classes) to the Health and Social Care Inspectorate.

### Table 6

| High-alert list | N (%) | DDA (%) | PPV | Sensitivity/Specificity | OR (CI 95%) |
|-----------------|-------|---------|-----|-------------------------|-------------|
| Short           | 88 (10) | 33 420 (6.3) | 0.26% | 10%/94% | 1.6 (1.3-2.0) |
| Medium          | 249 (28) | 68 247 (13) | 0.36% | 28%/87% | 2.7 (2.3-3.1) |
| Long            | 294 (33) | 95 049 (18) | 0.31% | 33%/82% | 2.3 (2.0-2.6) |
| Medium + Local  | 344 (39) | 119 086 (22) | 0.29% | 39%/78% | 2.2 (1.9-2.5) |
| All             | 885 (100) | 530 184 (100) | 0.17% | | |

Note: Positive predictive value (PPV) with odds ratio (OR), specificity and sensitivity of high-alert lists involved in incident reports (N) with relation to drug use (DDA) at a Children’s Hospital with combined data for 2011 and 2017. The Medium + Local list describes the suggested local additions of Sweden to the medium list.

4 | DISCUSSION

This study has five main findings with clinical patient safety implications. (a) Substances from the three high-alert lists were identified in different degrees (17/35/47%) of national reports. (b) All high-alert lists did identify a higher proportion of reports with severe outcome. (c) The processes identified in national reports were dependent on specific ME types, for example prescribing did mainly relate to dosing errors. (d) The number of local reports was related to the number of DDA, grouped by second-level ATC code. (e) Finally, the prevalence of local reports with high-alert substances was found to be two-fold compared to reports with non-alert substances, independent on the length of the high-alert list.

The study did also show that incidents among older age groups and other types of modal events are more commonly reported as serious events. It could be an effect of lower-harm cases being more routinely discovered and reported for younger patients. Or, signaling that older age groups and other types of modal events needs more serious events to be noticed. The prevalence of ME reported to IVO among paediatric inpatients in Sweden was found to be 2.5 per 10 000 patients. A Danish study found 487 harmful ME during a 5-year period. This corresponds to a four times higher rate in Denmark rather to the results in our study, but the three predominant drug classes were the same.

In the United States, 163 neonatal units reported 6749 ME during 7 years of which 244 had the category NCC MERP E-I with a significant overrepresentation of substances from the same long high-alert list used in our study. The medium high-alert list was validated with data from the Dutch incident registration based on 1043 paediatric reports from 43 hospitals for two and a half years. They found only four out of 14 of their high-alert substances that resulted in serious temporary harm or worse, while additional nine were confirmed with potential harmful incidents. In comparison, our study found 10 of the high-alert substances among the ME with harm NCC MERP G-I.

The high-alert substances can vary depending on the patient group, treatment traditions, pharmacy workflow, country and hospital usage and prerequisites. It is therefore of value to investigate both nationally and regionally which drugs that poses as high-alert substances and are involved in most errors. A French study found similar drugs as the medium high-alert list and recommended that the list should be updated on a regular basis, not too long, and include jokers applicable for the local unit. When we included a local list to the medium high-alert list, the possibility to catch more events increased with a decreased specificity. In practice, to be able to implement alerts for longer lists, the usage of clinical decision support systems would be helpful, for example dose range checking systems.
In prescribing, we have found a large flora of incident-reported substances that should be implemented in the existing Swedish pediatric dosage-range check system. Since those systems are automated, the list do not need restrictions in length, considering that the boundaries of such systems are set wisely to limit the risk of warning fatigue.

Regarding dispensing, the European Directorate for the Quality of Medicines and Healthcare have developed a risk assessment method for the reconstitution process which encapsulates more than the pharmacological aspects, such as risk of microbial contamination, incorrect composition and work environment hazards.

Here, a designated personal is central to evaluate the risk introduced by a high-alert drug at the ward. For the risk evaluation of reconstitution, a list based on the known cases of mix-up between drug names and strengths is of importance. It is also evident that the existing longer high-alert lists are more specified in discovering those types of MEs. A hospital-specific high-alert list should be accompanied by risk evaluations before introducing those drugs to the medication room at the ward.

The process for administration does not seem to benefit from a longer list. Here, the Canadian short high-alert list is interesting which chose only the top five substances that cause harm to children, being morphine, potassium chloride, insulin, fentanyl and omission of salbutamol. We also found omissions of salbutamol alongside vaccines among drugs on the list with serious outcome. Omission has been described as potential life-threatening if not administrated. This implicates that high-alert lists for administration should be based on further detailed processes. But starting off with a short list would potentiate the communication within the large community of nurses and preferably all staff working with medicines. There is also a need to be trained in the use of high-alert substances. Lo et al suggested, based on questionnaires, training during in-school nursing education as well as of hospital-based continuing education.

4.1 | Strengths and limitations

All reports were retrieved with appurtenant root cause analyses and were read thoroughly. Anyhow, the collected reports are only...
the tip of the iceberg of incidents that occur. The description of the outcome in the incident reports can vary, especially in the local reports which increase the risk of misclassification of NCC MERP. The characteristic of harm by NCC MERP is also a simplification of the national incident reports, and this study lacks details on adverse drug events, focusing primarily on the details of substance and ME. The number of MEs caused by each drug can partly be explained by the extent of which it is used. In this study, the extent was measured in DDA which could underestimate the volume for substances with a high number of daily doses. Another source of error is the fact that incidents possibly may have been categorised into other types of incidents than drug-related by IVO. The study only collected reported harm from IVO and local incidents from one university hospital. For example, we have not included MEs originating from pharmacies reported to the Medical Product Agency, patient and parental complaints reported to a county-based board for patients. Neither adverse drug reactions are included, which have shown to give a different spectra of substances in high-alert lists.30

Future studies should proceed on identifying which drugs that poses as the biggest threats when it comes to ME and to analyse what measures could be done to prevent the errors from happening again. Implementation of high-alert lists would preferably be dependent on process. To reduce the risks when prescribing drugs, a long list of all known dosing errors should be included in the national automated dose range check. To minimise reconstitution errors, a list of all known mix-up events may guide local risk assessments performed by a designated person. The published short list would be a good start, especially in the administration process, creating better awareness of high-alert drugs among all healthcare staff working with paediatric drug therapy. Sweden should also consider using systems to better collect, coordinate and present available incident reports for a continuous update on high-alert drugs and processes.

5 CONCLUSION

In conclusion, this report shows that the previously published high-alert drug lists are relevant for paediatric inpatients and should be adapted by process. While the prevalence of national incident reports is probably an underestimation, the prevalence of high-alert substances within those reports is almost double that of other substances. A higher awareness with the help of specific high-alert lists among hospital staff prescribing, dispensing and administering drugs to children may have the potential to enhance reporting and eventually reduce medication errors.

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CONFLICT OF INTEREST

No conflict of interest.

REFERENCES

1. Leape LL. Preventing adverse drug events. Am J Health System Pharm. 1995;52(4):379-382.
2. The Joint Commission. Medication Management Maintenance Standard MM.01.01.03. 2013.
3. ISMP (Institute of Safe Medication Practices). High risk drug for acute care settings. 2018. https://www.ismp.org/recommendations/high-alert-medications-acute-list
4. IHI (Institute of Healthcare Improvement). High-alert medication safety.
5. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kaufmann RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. N Engl J Med. 2003;349(12):1157-1167.
6. Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. J Am Med Assoc. 2001;285(16):2114-2120.
7. Kimland E, Nydert P, Odlind V, Böttiger Y, Lindemalm S. Paediatric drug use with focus on off-label prescriptions at Swedish hospitals – a nationwide study. Acta Paediatr. 2012;101:772-778.
8. Doherty C, Mc DC. Tenfold medication errors: 5 years’ experience at a university-affiliated pediatric hospital. Pediatrics. 2012;129(5):916-924.
9. Sveriges Riksdag. Patientsäkerhetslag [In Swedish] 2010:659. 2010.
10. Wennergren G. Four lethal injections resulted in Lex Maria. Lakartidningen. 2005;102(4):242-243.
11. Khan A, Coffey M, Litterer KP, et al. Families as partners in hospital error and adverse event surveillance. JAMA Pediatr. 2017;171(4):372-381.
12. Bataille J, Prot-Labarthe S, Bourdon O, Joret P, Brion F, Hartmann JF. High-alert medications in a French paediatric university hospital. J Eval Clin Pract. 2015;21(2):262-270.
13. Colquhoun M, Orrbine E, Sheppard I, et al. National collaborative: top five drugs reported as causing harm through medication error in pediatrics. Dynamics. 2009;20(4):20-22.
14. Dos Santos L, Heineck I. Drug utilization study in pediatric prescriptions of a university hospital in southern Brazil: off-label, unlicensed and high-alert medications. Farm Hosp. 2012;36(4):180-186.
15. Franke HA, Woods DM, Holl JL. High-alert medications in the pediatric intensive care unit. Pediatr Crit Care Med. 2009;10(1):85-90.
16. Irwin D, Vaillancourt R, Dalgleish D, et al. Standard concentrations of high-alert drug infusions across pediatric acute care. Paediatr Child Health. 2008;13(5):371-376.
17. Labib JR, Labib-Youssef MR, Fatah S. High alert medications administration errors in neonatal intensive care unit: a pediatric tertiary hospital experience. Turk J Pediatr. 2018;60(3):277-285.
18. Melo VV, Costa MS, Soares AQ. Quality of prescription of high-alert medication and patient safety in pediatric emergency. Farm Hosp. 2014;38(1):9-17.
19. Sinha Y, Cranswick NE. Prescribing safely for children. J Paediatr Child Health. 2007;43(3):112-116.
20. Stavroudis TA, Shore AD, Morlock L, Hicks RW, Bundy D, Miller MR. NICU medication errors: identifying a risk profile for medication errors in the neonatal intensive care unit. J Perinatol. 2010;30(7):459-468.
21. Maaskant JM, Eskes A, van Rijn-Bikker P, Bosman D, van Aalderen W, Vermeulen H. High-alert medications for pediatric patients: an international modified Delphi study. Expert Opin Drug Saf. 2013;12(6):805-814.

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22. NCCMERP. National coordinating council for medication error. Reporting and prevention index for categorizing medication errors.
23. Aronson JK. Medication errors: definitions and classification. Br J Clin Pharmacol. 2009;67(6):599-604.
24. Rishoej RM, Almarsdottir AB, Christesen HT, Hallas J, Kjeldsen LJ. Medication errors in pediatric inpatients: a study based on a national mandatory reporting system. Eur J Pediatr. 2017;176(12):1697-1705.
25. Stultz JS, Nahata MC. Complexities of clinical decision support illustrated by pediatric dosing alerts. Ann Pharmacother. 2015;49(11):1261-1264.
26. Committee of Ministers Council of Europe. Resolution CM/Res(2016) 2 on good reconstitution practices in health care establishments for medicinal products for parenteral use. 2016.
27. Grissinger M. Your high-alert medication list is relatively useless without associated risk-reduction strategies. P T. 2016;41(10):598-600.
28. Grissinger MC. Omission of high-alert medications: a hidden danger. Am J Nurs. 2017;117(7):66-70.
29. Lo TF, Yu S, Chen IJ, Wang KW, Tang FL. Faculties’ and nurses’ perspectives regarding knowledge of high-alert medications. Nurse Educ Today. 2013;33(3):214-221.
30. Schepel L, Lehtonen L, Airaksinen M, Lapatto-Reiniluoto O. How to identify organizational high-alert medications. J Patient Saf. 2018.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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