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Promoting safe use of medicines in hospitalised children

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Promoting Safe Use of Medicines in Hospitalised Children

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Table of Contents

<i>Remerciements</i>	2
<i>Abstract</i>	7
<i>Résumé en français</i>	9
<i>Abbreviations</i>	12
<i>List of publications</i>	13
<i>List of scientific communications</i>	13
<i>List of Tables</i>	14
<i>List of Figures</i>	15
<i>Chapter A: General Introduction</i>	16
1. Fundamental challenges of paediatric drug development.....	16
2. The current situation in paediatric practice.....	22
3. Consequences on child safety.....	30
4. Key strategies to promote drug safety in children.....	43
Bibliography.....	47
<i>Aim of Thesis</i>	55
<i>Chapter B: My articles</i>	56
(Article I) Trigger tools to identify adverse drug events in hospitalised children: A systematic review.....	57
(Article II) Replacing liquid with solid dosage forms in pediatric practice: Feasibility and economic impact from a hospital-based study.....	82
(Article III) Efficacy and safety outcomes of dosage regimens of amikacin in neonates: a systematic review.....	98
<i>Chapter C: General discussion and Conclusion</i>	130
<i>Appendices</i>	141

Appendices of the article (I)	141
Appendices of the article (II).....	149
Appendices related to the article (III)	163
Appendices related to the discussion	170

Abstract

The lack of adequate clinical trials in paediatrics has generated many issues in medicine use for hospitalised children, such as the prescription of off-label or unlicensed drugs, the lack of suitable dosage forms, inadequate safety information, and the lack of evidence-based dosing information. This challenges the prescription and administration of medicines in paediatric settings and impacts drug safety in this population. For these reasons, monitoring drug safety is particularly important in the paediatric population. Despite that, adverse drug reactions (ADRs) in hospitalised children are underestimated and underreported, suggesting the need for improving the existing detection methods.

The aim of this thesis is to promote the safe use of medicines in hospitalised children through three independent objectives. The first objective is to identify all available trigger tools, as a promising detection method of ADR in paediatric inpatients, and describe the performances of paediatric triggers in the purpose of optimising their use in paediatric settings. The second objective is to identify possible practical circumstances allowing dosage form choices to be optimized regarding safety, by replacing liquid formulations with suitable solid dosage forms in hospitalised children, and to assess the economic impact of these potential changes. The third objective is to review the available literature data on the efficacy and safety of amikacin using different dosage regimes in neonates and to attempt to identify the most appropriate dosage regimen for use.

Two systematic reviews and one analysis study of a hospital database were conducted. A total of 179 paediatric triggers detecting adverse drug events (ADEs) were identified in a systematic review study. Triggers' performances were assessed by their positive predictive values (PPVs)

most of the time in the studies. These values varied significantly between studies, suggesting a need for more studies on paediatric triggers. The use of triggers could be optimised by selecting the most pertinent triggers and by creating an electronic real-time detection system. The triggers could be used for three clinical interests (to prevent, detect and report ADRs) when integrated in such a system. In a second study based on an analysis of 3-year data regarding oral drug administrations, 10 drugs, involving 19,671 administrations of liquid formulations, were selected to potentially replace liquid with suitable solid dosage forms in paediatric practice. We proved that there are opportunities to optimise current dosage form choices for hospitalised children by using available dosage forms. In a second systematic review, clinical and pharmacokinetic outcomes regarding efficacy and safety of 37 different dosage regimens of amikacin in neonates were reported. The work to select the most appropriate dosage regimen of amikacin in neonates based on the reported data is continuing.

The results of this thesis can be used by health-care professionals and health policy makers interested in promoting a safer and more appropriate use of medicines in hospitalised children.

Keywords: Paediatric, hospitalised children, pharmacovigilance, adverse drug reaction, trigger tool, detection, drug formulation, dosage form, drug safety, substitution to solid dosage form, amikacin, neonates, drug monitoring, optimal dosage regimen, pharmacokinetics.

Résumé en français

Titre : Sécurisation de l'usage des médicaments chez les enfants hospitalisés

Résumé : Le nombre insuffisant d'essais cliniques en pédiatrie engendre plusieurs problèmes lors de l'utilisation des médicaments chez les enfants hospitalisés, tels que le recours aux prescriptions de médicaments hors Autorisation de Mise sur le Marché (AMM), le manque de formes galéniques adaptées à l'enfant, des informations insuffisantes en matière de sécurité des médicaments et le manque de posologies basées sur de hauts niveaux de preuves. Ceci remet en question la prescription et l'administration de médicaments en pédiatrie et influence la sécurité des médicaments dans cette population particulière. Dans ce contexte, la surveillance de la sécurité des médicaments est particulièrement importante chez les enfants. Malgré cela, les événements indésirables médicamenteux (EIM) chez les enfants hospitalisés sont sous-estimés et sous-déclarés, suggérant un besoin d'améliorer les méthodes de détection actuelles.

L'objectif de cette thèse est de promouvoir la sécurisation de l'usage des médicaments chez les enfants hospitalisés à travers trois sous-objectifs indépendants. Le premier est d'identifier tous les « triggers » disponibles, en tant que méthode prometteuse de détection des EIMs chez les enfants hospitalisés, et de décrire les performances des « triggers » utilisables en pédiatrie dans le but d'optimiser leur utilisation en milieu hospitalier pédiatrique. Le deuxième est d'identifier les circonstances pratiques possibles permettant d'optimiser les choix de formes galéniques, en remplaçant les formulations liquides par des formes solides adaptées, chez les enfants hospitalisés et d'évaluer l'impact économique de ses changements potentiels. Le troisième est d'examiner les données disponibles dans la littérature sur l'efficacité et la sécurité des

posologies d'amikacine chez les nouveau-nés et tenter d'identifier la posologie la plus appropriée à utiliser.

Deux revues systématiques de la littérature et une étude d'analyse d'une base de données hospitalière ont été menées. Un total de 179 « triggers » utilisables en pédiatrie pour détecter des EIM a été identifié par une revue systématique de la littérature. Les performances des « triggers » ont été estimées par leurs valeurs prédictives positives la plupart du temps dans les études. Ces valeurs variaient considérablement d'une étude à l'autre, suggérant la nécessité de mener plus d'études sur les « triggers » en pédiatrie. L'utilisation des « triggers » pourrait être optimisée en sélectionnant les « triggers » les plus pertinents et en créant un système électronique de détection en temps réel. L'utilisation des « triggers » dans un tel système pourraient servir à trois objectifs cliniques (la prévention, la détection et le signalement des EIM). Dans une deuxième étude basée sur une analyse des données d'administrations des médicaments oraux recueillies sur 3 ans, dix médicaments, impliquant 19 671 administrations de formulations liquides, ont été sélectionnés dans le but de pouvoir remplacer ces formes liquides par des formes solides appropriés dans la pratique hospitalière pédiatrique. Dans cette étude, nous avons prouvé qu'il existe des opportunités pour optimiser les choix actuels des formes galéniques chez les enfants hospitalisés, en utilisant des formes galéniques disponibles sur le marché. Dans une deuxième revue systématique de la littérature, les résultats cliniques et pharmacocinétiques concernant l'efficacité et la sécurité de 37 posologies d'amikacine pour les nouveau-nés ont été rapportés. Le travail consistant à sélectionner la posologie d'amikacine la plus appropriée chez les nouveau-nés en se basant sur les données rapportées se poursuit.

Les résultats de cette thèse peuvent être utilisés par les professionnels de santé et les décideurs politiques dans le domaine de la santé intéressés par la sécurisation de l'usage des médicaments chez les enfants hospitalisés.

Mots clés : Pédiatrie, enfants hospitalisés, pharmacovigilance, événements indésirables médicamenteux, détection, formulation du médicament, forme galénique, sécurité du médicament, substitution à la forme solide, amikacine, nouveau-nés, posologie optimale, pharmacocinétique.

Abbreviations

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AE	Adverse Event
C_{peak}	Peak concentration
C_{trough}	Trough concentration
DRP	Drug-Related Problem
ED	Emergency Department
EHR	Electronic Health Record
EIM	Effet Indésirable Médicamenteux
EMA	European Medicines Agency
EMS	Electronic Medication Systems
EREMI	Assessment of the risk of dverse Drug Reactions (Evaluation Du Risque d'Evénements Indésirables Médicamenteux)
FAERS	FDA Adverse Event Reporting System
FN	False Negative
FP	False Positive
GA	Gestational Age
GTT	Global Trigger Tool
HCPs	Health-Care Professionals
HIS	Hospital Information System
IHI	Institute for Healthcare Improvement
IM	Intramuscular
IV	Intravenous
ME	Medication Error
MIC	Minimum Inhibitory Concentration
NAG	N-Acetylglucosaminidase
NICU	Neonatal Intensive Care Unit
NPV	Negative Predictive Value
ORL	Otolaryngology
PCA	Post-Conceptional Age
PICU	Paediatric Intensive Care Unit
PMA	Post-Menstrual Age
PNA	Postnatal Age
PPV	Positive Predictive Value
PRISMA	Preferred Reporting for Systematic Reviews and Meta-Analyses
RCT	Randomised Clinical Trial
SmPC	Summary of Product Characteristics
TN	True Negative
TP	True Positive
UK	United Kingdom
WHO	World Health Organization

List of publications

1. Arab R, Cornu C, Kilo R, Portefaix A, Fretes-Bonett B, Hergibo F, et al. **Trigger tools to identify adverse drug events in hospitalised children: a systematic review.** Therapies [Internet]. 2022 Jan 31; Available from: <https://www.sciencedirect.com/science/article/pii/S0040595722000269>
2. Arab R, Kassai B, Kilo R, Cornu C, Gomes E, Dagonneau T. **Replacing liquid with solid dosage forms in pediatric practice: Feasibility and economic impact from a hospital-based study.** Therapies [Internet]. 2021 décembre ; Available from: <https://www.sciencedirect.com/science/article/pii/S0040595721002651>
3. Kilo R, Laporte S, Arab R, Mainbourg S, Provencher S, Grenet G, et al. **Meta-regression of randomized control trials with antithrombotics: weak correlation between net clinical benefit and all cause-mortality.** Sci Rep. 2021 Jul 19;11(1):14728.

List of scientific communications

<i>Title</i>	<i>Congress</i>	<i>Type of the Year communication</i>
Trigger tools to identify adverse drug events in hospitalised children: a systematic review	Congrès Société Française de Pharmacologie et de Thérapeutique (2021)	Interactive poster 2021
Thirty five percent of oral liquid administrations are substitutable with suitable solid forms among 10 highly substitutable drugs	Congrès Société Française de Pharmacologie et de Thérapeutique (2021)	Interactive poster 2021
Trigger tools to identify adverse drug events in hospitalised children: a systematic review	8th Congress of the European Academy of Paediatric Societies (EAPS 2020)	Oral presentation 2020

List of Tables

Tables of the general introduction

Table 1: Comparison between the four detection methods according to the results of the systematic review conducted by Meyer-Masseti et al.	43
--	----

Tables of the article I

Table 1: Summary of the studies included in the systematic review	72
Table 2: Risk of bias summary of the included studies according to the QUADAS-2* tool	73

Tables of the article II

Table 1: The 10 drugs in liquid dosage forms most frequently administered to children eligible for substitution with authorized suitable alternative solid dosage forms	96
---	----

Tables of the article III

Table 1: Design and target population of each of the identified studies.	112
Table 2: Dosage regimens and main findings of the included studies	117

List of Figures

Figures of the general introduction

- Figure 1: List of the most common challenges that can be encountered during the conduct of a paediatric clinical trial proposed by Chiaruttini et al. 21
- Figure 2: Summary of advantages and disadvantages of existing liquid and solid oral dosage forms for child use (established by Lajoinie et al.) 28
- Figure 3: Venn diagram showing the relationship between adverse events, adverse drug reactions and medication errors 34
- Figure 4: Timeline of pharmacovigilance for a drug from development (pre-market) to post-marketing use 38

Figures of the article I

- Figure 1: Flow diagram for selection of articles 71
- Figure 2: Warning triggers of available PPV, and $PPV > 0$ 74
- Figure 3: Validation triggers of available PPV, and $PPV > 0$ 75
- Figure 4: Reporting Triggers of available PPV, and $PPV > 0$ 76
- Figure 5: Bleeding-related triggers of available PPV, and $PPV > 0$ 77

Figures of the article II

- Figure 1: A. The general stages of data processing. B. Stages of data processing in the substitution assessment and the economic impact assessment for every identified drug. 94
- Figure 2: Flow chart of data analysis. 95

Figures of the article III

- Figure 1: Flow diagram for selection of articles 111
- Figure 2: Proposition of a selection method 123

Chapter A: General Introduction

1. Fundamental challenges of paediatric drug development

1.1. Physiological differences between paediatric and adult populations

There is a large spectrum of physiological differences between the paediatric and adult populations. There are also differences in the paediatric population between paediatric age groups from newborns to adolescents. The paediatric population is therefore divided into five main age categories by the European Medicines Agency; preterm newborns (from day of birth through the expected date of delivery plus 27 days), term newborns /neonates (1 to 27 days of age), infants (28 days to 23 months of age) children (2 to 11 years of age) and adolescents (12 to 16-18 years of age*) (1–3). Contrary to adults, the compositions and the functions of children's bodies and organs are continuously changing during growth. These changes generate drug responses different from those in adults or in children in other age groups. Thus, drugs have different pharmacokinetic and pharmacodynamic properties in children, which could lead to different clinical results. Neonates are the paediatric age group most concerned with these differences (4–6).

1.1.1. Impact of the physiological differences on the pharmacokinetic properties

All pharmacokinetic properties of the drugs (i.e., absorption, distribution, metabolism, and excretion) could be impacted by the physiological particularities of children.

The absorption of orally administered drugs could differ in children because of the changing concentrations of gastric PH through the first 3 years of life (7), the slow gastric emptying within the first 6 months in preterm infants (8,9), the prolonged intestinal transit time in neonates or the reduced one in older infants (10). The bioavailability of intramuscularly

administered drugs could also change in neonates by the decreased blood flow to muscles, which varies quite considerably over the first 2-3 weeks of life, the less muscular mass and the higher proportion of body water. In newborns, this route of administration is therefore unreliable, and the pharmacokinetics are unpredictable (11,12).

The proportions of body fat, plasma proteins, total and extracellular body water change significantly and continuously during the first year of life, which affect the distribution of drugs. The percentage of the total body water reaches 80-90% of body weight in newborns. It decreases to 55-60% by adulthood (13). The extracellular water content is about 45% in neonates compared with 20% in adulthood. Consequently, the volume of distribution in the paediatric population is relatively higher for water-soluble drugs such as gentamicin (10) and lower for fat-soluble drugs such as diazepam (14).

Additionally, the concentration of binding proteins is lower in neonates and infants than adults, as well as their binding capacities. This results in a greater free fraction of the drug in the blood, which increases the drug activity (15,16). Furthermore, neonates often present increased plasma concentrations of bilirubin and free fatty acid, which reduce the drug binding even more (13).

The liver is the most important organ for drug metabolism. In children, liver blood flow and many drug-metabolizing enzymes are reduced. The former reaches adult rates by around one year of age (17). This may result in higher or lower drug plasma levels than those reached in adults and in other paediatric age groups (18). For example, CYP1A2 is an isoenzyme involved in metabolizing many drugs such as caffeine and theophylline. This enzyme is hardly detectable in neonates. It becomes more detectable in infants aged one to three months. Its presence in infants <1 year old is at about 30% of that in adults, at 81% in two year olds and comparable to adult values in children of three years or more (10). The varying levels of CYP1A2 with age

explain the changing values of the half-life of caffeine at different ages (95 hours in neonates, 7 hours in infants, 3 hours in children and 4 in adults) (19).

The decreased renal blood flow in children under two years old and the immaturity of glomerular filtration and renal tubular secretion during the neonatal period restrict the renal excretion of drugs in these age groups. It has been shown that in late infancy and/or childhood, for many drugs such as for cimetidine and levetiracetam, children have a similar or higher rate of clearance from plasma than adults. This often makes administration of a higher dose necessary in this population (20–22).

1.1.2. Impact of the physiological differences on the pharmacodynamic properties

The effect of drugs in paediatric populations including drug action and toxicity could be different from that in adult populations for reasons not related to pharmacokinetic changes. Many changes on drug targets (e.g., receptors, transporters, and channels) occur during the developmental process in children and generate different clinical responses. For example, changes in the receptors of prostanoids, angiotensin II and catecholamines were observed in children (23,24).

Some frequent adverse drug reactions (ADRs) in children were found related to these changes. For example, the respiratory depression and bradycardia related to the administration of opioids are more frequent in newborns despite their insufficient analgesic effect. This is explained by the fact that the opioid receptors in the medulla and pons, where respiratory and cardiovascular centres are located, are developed earlier than those in other parts of the brain (25). Other examples are the acute dystonic reactions or seizures, which are reported more frequently in young children after the administration of the dopamine 2-antagonists metoclopramide or prochlorperazine. This higher level of drug reactions is explained by the developmental changes

that occur in dopamine receptors in this age group (24). Moreover, the therapeutic effect of other drugs could still be achieved in children with decreased concentrations, which is the case of ciclosporin. A greater immunosuppressive response to ciclosporin is reported in infants than in older children and adults (26).

1.2. Challenges in conducting paediatric clinical trials

Randomized clinical trials (RCT) are considered as the gold standard trials for evaluating efficacy and safety of drugs (27). They provide data of the highest degree of evidence, needed in paediatric population. However, conducting such trials has many ethical, scientific and financial issues in the aforementioned population (28,29) (Figure 3). This is reflected by the low number of RCTs conducted in children compared to adults. A study shows that only 12% of clinical trials for the conditions representing high burden paediatric diseases were conducted in paediatric populations (30).

The field of clinical trials in children suffers from a lack of adequate funding. Many pharmaceutical industries do not find enough commercial interest in these trials because of the high costs of studies and the small market size. In addition, paediatric trials are subject to a stringent regulatory scrutiny (31). It was found that the pharmaceutical industry funds only 41% of clinical trials conducted in children, whereas it funds 65% the clinical trials in adults (30). As a consequence, the limited funds of non-profit organizations are frequently used to sponsor paediatric trials (30).

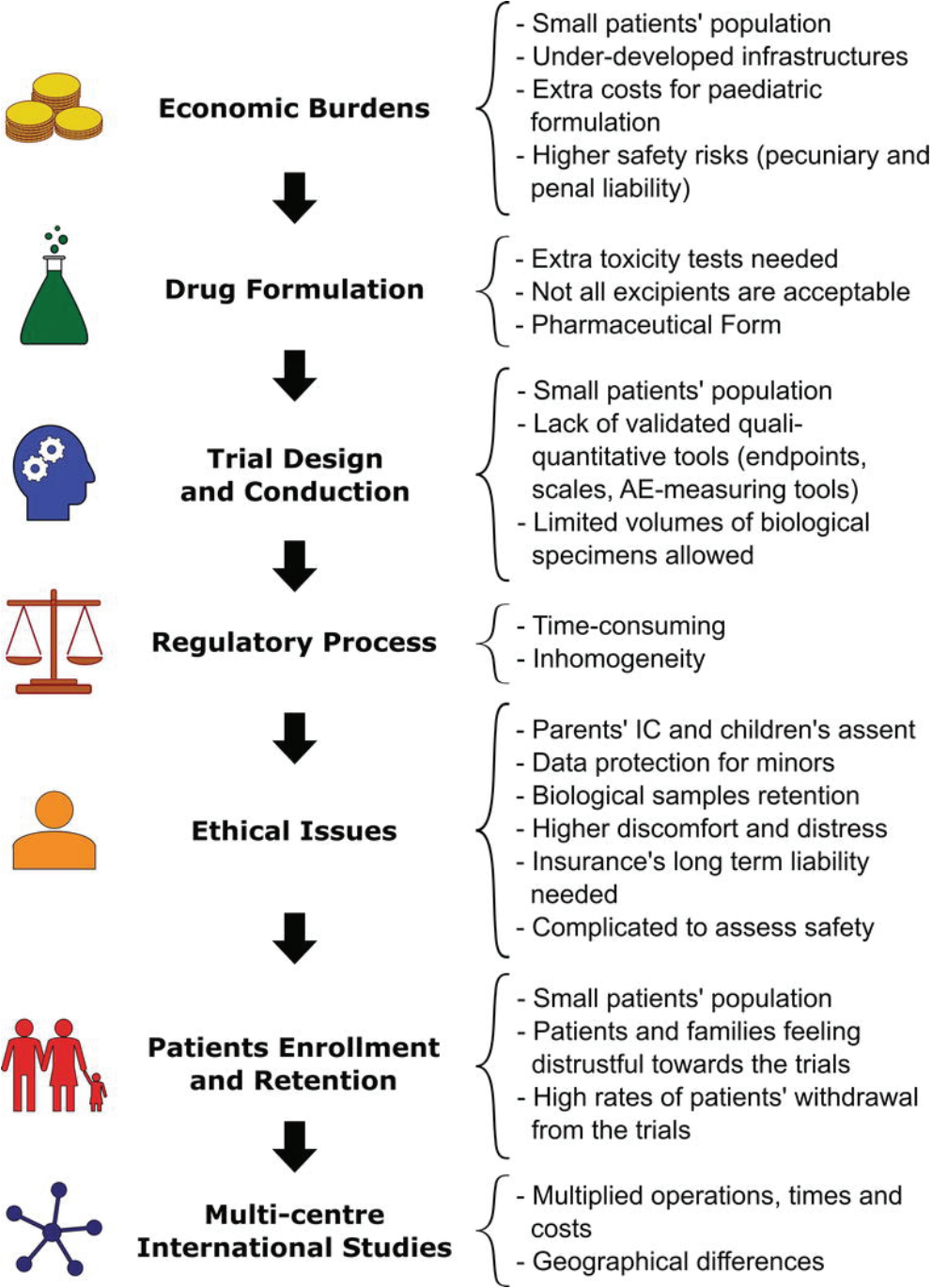
Patient recruitment is the first practical difficulty in conducting a paediatric clinical trial because of the small patient population. Nonetheless, finding the adequate number of paediatric participants is important to provide statistical power for the study. This difficulty becomes major when stratification by age groups is required. This refers to the necessity of allocating a

specific number of patients of each age group. Stratification is used to reduce imbalance between randomized groups when it is known that age factors influence the outcome (32). Recruiting paediatric patients is the hardest in rare diseases when very little number of participants are available (33).

Obtaining proper informed consents from children is an important and critical ethical element. Until now, obtaining a child's consent is not required. Parents or legal guardians are asked to make the decision in their place (32). However, some recommendations encourage involving children as much as possible in the decision-making process, and collecting written assents at school ages (34). Furthermore, paediatric expertise capable of recognizing the individuality and unpredictability of children's responses is needed in these clinical trials. This expertise is also crucial for assessing the research protocols and monitoring safety (35). In the paediatric population, long-term follow-up is needed because of the numerous adverse effects that can manifest later in life (36,37) .

The other main challenges in designing and conducting a paediatric trial are the lack of validated quantitative and quantitative tools for outcome evaluation to use in children and the limited volume of biological specimens allowed (29).

Figure 3: List of the most common challenges that can be encountered during the conduct of a paediatric clinical trial proposed by Chiaruttini et al. (29)



2. The current situation in paediatric practice

The lack of clinical trials in children reflects on the paediatric daily practice. It takes form in the seeking of off-label and unlicensed medicines, the lack of appropriate paediatric drug formulations, the poor prescribing information that leads to the increased risk of medication errors (MEs) and unanticipated ADRs (38).

2.1. Off-label and unlicensed medicine use

“Children are therapeutic orphans”, with these words Dr. Harry Shirkey, in 1963, described the fact that most of essential medicines are not adequately tested and labelled for paediatric use (39).

The role of the licensing process of a drug is to ensure that the drug has been demonstrated to be well tolerated, effective, and of good quality. With unlicensed or off-label medicines, we do not have this assurance as well as the necessary information for its use (38).

The use of a drug is considered "off-label" when it is outside the Summary of Product Characteristic (SmPC) conditions (the package insert recommendations), as its use (40):

1. In contraindication cases,
2. For a different age,
3. Through a different route of administration,
4. In different dose,
5. With a different frequency of administrations.

The drug is "unlicensed" when:

1. It has no marketing authorisation in the paediatric population.

2. The dosage form of the medicine is modified before use.
3. It is an extemporaneous preparation.

In absence of labelled medicines, the children's therapeutic needs are covered by medicines labelled for adult-use or for other paediatric population use. For decades, the use of unlicensed or off-label medicines has been common practice in children. This practice has been adopted all around the world whether children were hospitalised or treated at home.

According to a systematic review of studies published between 2007 and 2017, the rate of off-label prescriptions ranged between 3.2% and 95% in paediatric studies (40). The probability of receiving an off-label prescription is reduced with increased age. It is reduced by 3% for every year in age increase, starting at 51.6% probability for less than one-year olds and 29.3% probability for 20-year olds. This probability is even higher when children are hospitalised. In general, inpatient children are 2.9 times more likely to receive an off-label medicine than outpatients (41).

The prescriptions for an unapproved age range or an unapproved indication were generally the main reasons of off-label classification in children, followed by the use of an unapproved dose or and the use of unapproved dosage forms (42).

2.1.1. Prevalence of off-label and unlicensed medicines use in hospitalised children

A systematic review including 34 studies, published in 2015, showed that 0.2 to 47.9% of prescriptions for the hospitalised children were for unlicensed medicines and 12.2 to 70.6% were for off-label drugs. The percentage of children who received at least one off-label and/or unlicensed drug ranged from 42 to 100%. Newborns have the highest chance to receive off-

label and/or unlicensed drugs. The formulation modification was the main purpose of unlicensed prescriptions (3.6–100%) and the dose modification was the main purpose of off-label prescriptions (7.1–73.1%) (43).

A hospital database analysis showed that 78.7% of patients received off-label drugs and 40.5% of medicine cost in the hospital is spent on these medications. The most used off-label drugs in children were central or autonomic nervous system agents, fluids, nutrients, or gastrointestinal tract agents whereas off-label use of antineoplastic drugs was uncommon (44).

2.1.2. Prevalence of off-label and unlicensed medicines use in newborns

Higher rates of off-label and unlicensed drug use in neonates compared to any other population were reported in several studies; A prospective cohort study showed that 96.4% of neonates in neonatal intensive care units (NICUs) were exposed to off-label drugs and 66.8% of them to unlicensed medicines. It indicated that about one-half (49.3%) of medicines were off-label and 24.6% were unlicensed. The main reasons for the off-label and unlicensed classification in neonates were the frequency of administration and the administration of adaptations of pharmaceutical forms (45).

According to a recent national survey comprising 214 perinatal centres in Germany, an approved alternative medication was available for one out of three of the off-label and unlicensed medicines used in neonates. Interestingly, the costs of alternative approved medicines increased in median 405-fold compared with the corresponding off-label/ unlicensed medicines (46).

Studies showed that off-label drug use is associated with an increased frequency of adverse drug events (ADEs). A prospective study involving six paediatric and neonatal centres including 5060 patients showed that a higher risk of an ADE was expected when children

received off-label drug treatment [7.3% vs. 1.2%; $P < 0.01$] (47). This correlation was confirmed by another prospective study (48).

A systematic review found that between 23 and 60% of unlicensed and/or off-label prescriptions were involved in an ADR (49).

2.2. Lack of child-friendly dosage forms

In paediatrics, the choice of a dosage form is an important issue. It impacts the acceptability, compliance, and effectiveness of drug treatment (50).

A main result of the historical underinvestment in paediatric pharmaceutical research by the pharmaceutical industry was the lack of dosage forms designed specifically for children (51). The optimal dosage form for children (child-friendly dosage form) must be safe (e.g., without toxic excipients), well tolerated, easy to use (i.e., palatable and requiring few manipulations), acceptable by children, transportable, easily produced and cost-effective. It must also respect the child's lifestyle, avoid MEs and deliver variable and accurate doses (52–55). Many of the existing dosage forms used in children are originally designed to be used in adults (conventional dosage forms) and none of them meets all these criteria for all pediatric age groups. For example, oral liquid formulations are easy to swallow by children but may contain inappropriate excipients. They are also harder to administer (i.e., require complicated calculations and measurements) (Figure 4).

An Australian study showed that dosage forms of 21.9% to 25% of medicines licensed for paediatric use were not appropriate (56).

The main concerns associated with the use of adult drugs in children are the increased risk of MEs, the excipient safety and the low medicine acceptability by children (57–60).

- Increased risk of dosing errors

Conventional dosage forms often need to be manipulated to meet the smaller required dose in children. Liquid formulations require complex calculations and dilutions to reach the appropriate formulation and dose for children (56,61). Manipulations of some solid dosage forms are also common to obtain an appropriate dose/form for children such as splitting or crushing tablets and opening capsules (62,63).

Such practices are associated with a high risk of dosing errors and could lead to inaccurate doses and unknown drug stability (57). Dosing-related problems were found the most frequent reason of the occurrence of drug-related problems in children (64).

- Safety of excipients

Excipients are commonly utilised to improve the palatability, shelf life, and/or manufacturing processes of medicines. Children's responses to excipients differ from adults' and vary by paediatric age group. Certain excipients are not safe for children because they can slow organ development (e.g., ethanol, propylene glycol, benzyl alcohol and parabens) (58).

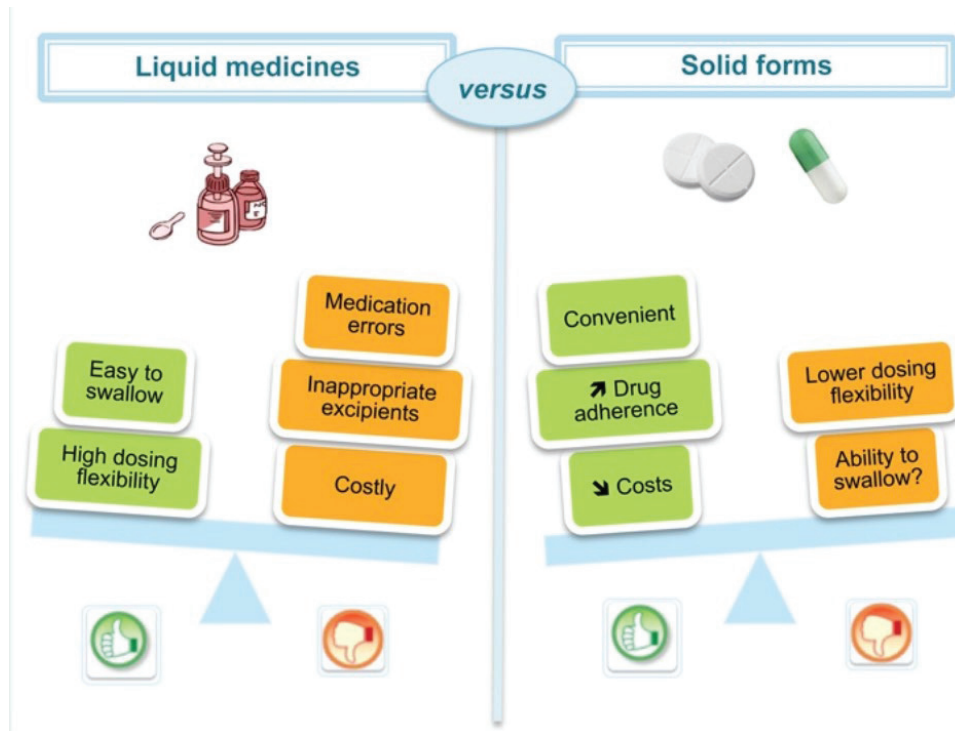
- Low acceptability

The acceptability of a medicine is defined by the European Medicines Agency (EMA) as “the overall ability and willingness of the patient to use and its care giver to administer the medicine as intended” (65). The notion of acceptability is particularly important in designing and prescribing medicines in children. When a medicine is not accepted by a child, it has low chance to be taken correctly, which impacts its safety and efficacy. Acceptability is a multifaceted concept that depends on therapeutic product characteristics such as the route of administration,

appearance, swallowability, palatability and the required dose and frequency as well as patient factors such as age and pathological state (54,65).

The acceptability of existing oral dosage forms varies among children; low acceptability of existing dosage forms is reported for children under 6 years old. The age of the patient, the size of tablets/capsules and the taste of liquids appears to play the main role in determining the dosage form acceptability (59,60). For that, many studies were conducted to define acceptability the existing adult-designed dosage forms by children (59,66,67).

Figure 4: Summary of advantages and disadvantages of existing liquid and solid oral dosage forms for child use (established by Lajoinie et al.(69))



2.3. Inadequate evidence-based dosing information

The use of off-label or unapproved medicines in children is associated with a lack of prescribing information based on a high level of evidence (44). A study shows that the monographs of 72% of the drugs approved between 2007 and 2016 in Canada did not contain any paediatric-specific information and indication (68). A recent survey on paediatric information have found that the SmPCs of 42.4% of the medicines currently available in Germany contained contraindications or warnings for at least one paediatric age group medicinal products (69).

The inadequacy of prescribing information reaches 80% of medicines in neonates according to an Australian study (56).

The lack of high-quality information about medicines in children leads to absence of evidence-based dosing guidelines and to high variabilities in drug use conditions in practice, in addition to discrepancies between existing dosing recommendations (70). For example, large variation in dexamethasone paediatric dosing practices were found between hospitals, according to a recent study (71)

With these discrepancies in dosing recommendations, practitioners are unable to identify the most appropriate using conditions of these medicines and they rely on one available recommendation such as an expert opinion for the age group they are treating, or even on evidence from a different population to guide practice.

A systematic review published in 2022, comprising 18 studies, demonstrated that the inappropriate selection of drug dosage is the main cause of drug-related problems in paediatric patients (64).

This problem is more present in paediatric settings, such as NICUs, where the off-label prescribing practice is more frequent, . A survey comprising 199 NICUs located in 25 European countries reported a great variability in using ciprofloxacin and fluconazole for the treatment of sepsis within and between countries. The detected differences concerned dosage regimens including daily doses, frequency of administrations, unit dose, route of administration and treatment duration. In many NICUs (27%), even a local standard written protocol of a drug use was not established (72). Antibiotics are also largely concerned by this problematic (73,74). A considerable variability of dosage regimens of antibiotics was identified by a French survey conducted in 2015 in 44 French NICUs. The survey identified 444 different dosage regimens for 41 antibiotics. The number of different dosage regimens varied from 1 to 32 per drug. Twelve antibiotics had the highest variability in their used dosage regimens (amikacin, gentamicin, netilmicin, tobramycin, vancomycin administered as continuous infusion,

ceftazidime, cloxacillin, oxacillin, penicillin G, imipenem/cilastatin, clindamycin and metronidazole) (75). Similar results regarding antibiotics were met by many other studies (74,76–78) suggesting the need to optimize the evaluation of drugs in neonates (5).

3. Consequences on child safety

3.1. Drug related problems (DRPs) in children

3.1.1. Definitions of different untoward events

There is a large variety of names in medical publications for the untoward symptoms that follow the use of drugs or the medical interventions. With the same detection methods, some studies could focus on detecting ADEs while others focused on adverse events (AEs) or MEs. In addition, different definitions could be found for each term. Therefore, it would be appropriate to mention the different terms used to describe events associated with drugs and medical care interventions, and provide the different definitions for each one of them. Figure 3 represents the relationship between AE, ADE ADR, and ME.

Drug-related problem

The term of drug-related problem was adopted from van Mil et al. to encompass all medication-related events (i.e., ADEs, ADRs, AEs, processes (causes), and outcomes (effects)), and is not limited to events causing harm (79)

Adverse event

The Institute for Healthcare Improvement (IHI) defines AE as an “unintended physical injury resulting from or contributed to by medical care that requires additional monitoring, treatment or hospitalization, or that results in death” (80). This definition is widely admitted since it implicates events induced by drugs or other medical interventions, and it specifies a minimum

level of harm to be detected. Aronson et al. proposed to define AE as follows “any abnormal sign, symptom, laboratory test, syndromic combination of such abnormalities, untoward or unplanned occurrence (e.g. an accident or unplanned pregnancy), or any unexpected deterioration in a concurrent illness” (81). For Michel et al. it is an “unintended injury caused by medical management rather than by a disease process” (82). In the three definitions, any type of medical care intervention could be the cause of the event. According to Aronson et al., a medical intervention is not even needed as the event should just occur during an illness but not be caused by it.

Adverse drug event

The Institute of Medicine defines ADE as “an injury resulting from medical intervention related to a drug”. This definition encompasses harms that arise from MEs as well as conventional ADRs (81)(83). Nydert et al. adopted this definition considering that it also includes any suspicion of a relation to drug therapy (both preventable and non-preventable). For example, infections, vascular harm or pressure ulcers related to devices used for intravenous delivery or to devices used for enteral feeding (84).

The term ADE is the most confusing term because it is usually used to describe a suspected ADR during which the causality link between the drug and the event is not confirmed or assessed. When this causality is assessed and the event is attributed to the drug, the ADE becomes an ADR and when it is not, it becomes an AE caused by a procedure of care. Using the term ADE always implies that the drug has been directly or indirectly implicated (81) but contrary to an ADR, a confirmed causality link is not required.

The Institute of Medicine also provided another wider definition of ADEs, which integrates the part that the disease of the patient plays in the outcomes: an ADE is “an injury due to medication management rather than the underlying condition of the patient”.

A more complete definition of ADE was presented by the Committee of Experts on Management of Safety and Quality in Health Care as “any injury occurring during the patient’s drug therapy and resulting either from appropriate care, or from unsuitable or suboptimal care”. The committee also explained that an ADE can result in different outcomes, notably in the worsening of an existing pathology, in the lack of any expected health status improvement, in the outbreak of a new pathology or a one could have been prevented, in the change of an organic function, or in a noxious response due to the medicine taken (85)

Adverse drug reaction

The World Health Organization (WHO) defines ADR as “a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function”. Laurence defines it as “a harmful or significantly unpleasant effect caused by a drug at doses intended for therapeutic effect (or prophylaxis or diagnosis), which warrants reduction of dose or withdrawal of the drug and/or foretells hazard from future administration.”(86). By using the words “response” and “caused by”, both definitions require a causal link between the event and the drug to be an ADR. This causality link is what distinguishes an ADR from an ADE. It is usually complicated to confirm or decline this causality link, and when an event is attributed to a medicinal product, the attribution should also be accompanied by a statement of the degree of probability of the attribution. Therefore, all ADRs are ADEs, but not all ADEs are ADRs. This distinction is important in clinical trials, in which not all events are necessarily drug induced. In order to avoid this complexity, the term ADE is more often used.

The seriousness of the harm should always be considered when identifying an ADR. Aronson and Ferner consider that the WHO definition has some defects because it excludes all doses that are not used in the way described by the definition and all adverse reactions that may be

inconvenient but not harmful (81). Laurence also requires a minimum level of harm by excluding minor unwanted reactions.

In case of death, life-threatening event, hospitalisation or prolongation of existing hospitalisation, disability or incapacity or a congenital anomaly or birth defect, the ADR becomes a serious ADR. (86)

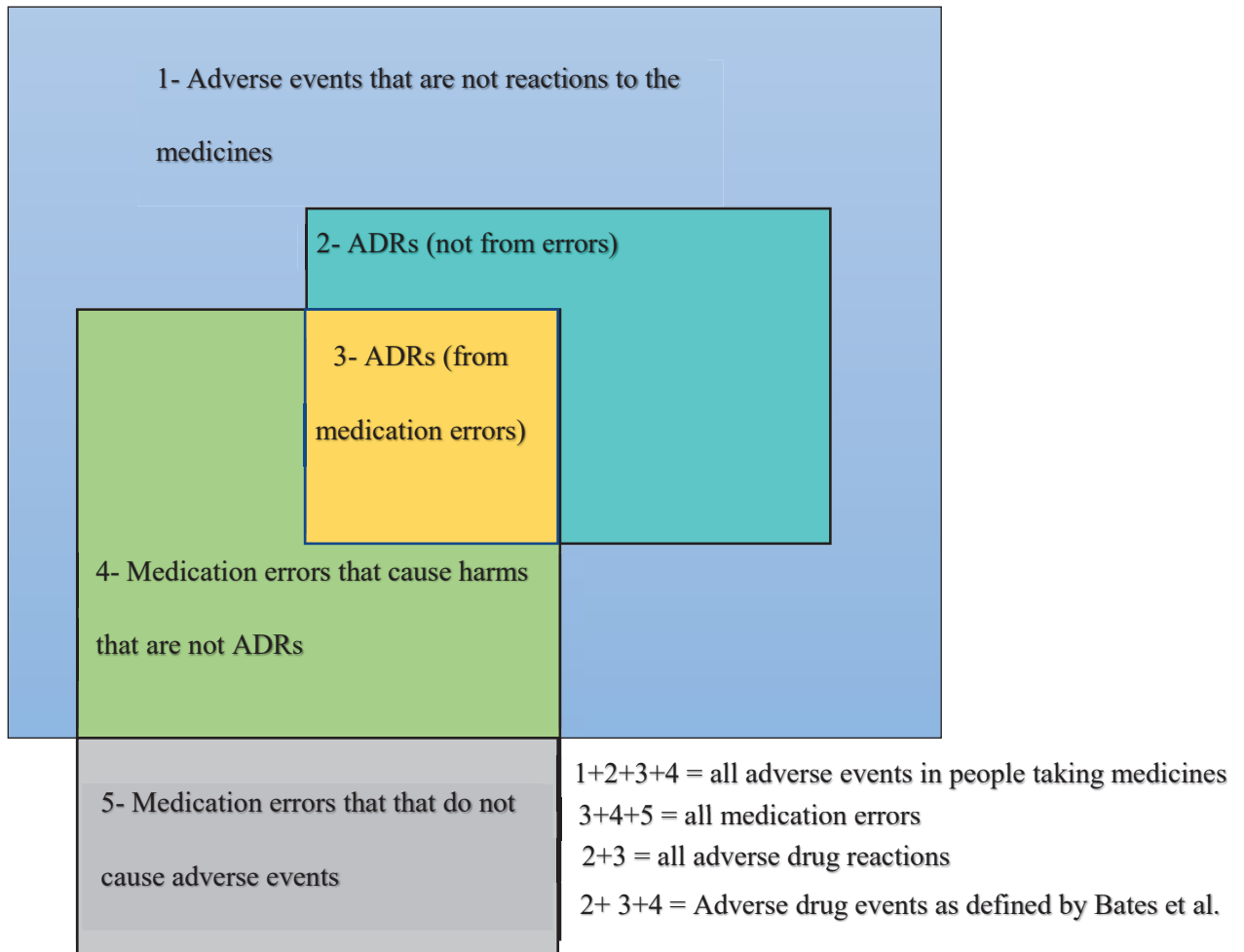
Medication error

The definition of ME, which was proposed by Ferner et al. in 2006, and has been widely accepted is “a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient” (87)

ME includes all types of errors that could occur from the prescription to post administration:

1. Prescribing errors
2. Transcription errors
3. Dispensing errors
4. Administration errors

Figure 3 : Venn diagram showing the relationship between adverse events, adverse drug reactions and medication errors (90)



3.1.2. Prevalence of AEs in hospitalised children

3.1.2.1. Prevalence of ADRs/ADEs

A systematic review published in 2021 including 18 studies indicated that paediatric patients are easily affected by ADRs even though the majority of ADRs were preventable, and their severity is mostly considered minor and moderate (64).

A recent systematic review included 26 studies, based in the UK, reported a median prevalence equal to 25.6% of patients (IQR 21.8–29.9) experiencing ADRs during hospitalisation; 79.2% of the reactions warranted withdrawal of medication (88).

Another systematic review of studies regarding ADRs in children, published in 2001 and including 17 prospective studies, showed that the overall incidence of ADRs in hospitalised children was 9.53% (95% CI, 6.81, 12.26), with severe reactions accounting for 12.29% (95% CI, 8.43, 16.17) of the total number of ADRs (89).

One prospective study, which enrolled 703 patients admitted to 2 general child wards and 1 paediatric intensive care unit at a teaching hospital in Germany, observed that 14.1% of children experienced an ADR during hospitalisation (90).

The main known risk factors of the occurrence of ADRs in children are young age, polypharmacy, prolonged hospitalisation, being critically ill, the use of unlicensed and off-label medications and dosing problems.(47,64)

The ADR-related mortality in children is 0.8% according to a UK study comprising data collected for 37 years (91). However, ADR-related mortality rates differ widely between countries; a systematic review identified rates between 3.4 and 13.0% in North America and between 0.1 and 2.2% in Europe (92).

The high incidence rates of ADRs lead to prolonged hospital stays and additional costs (93). According to a systematic review, ADRs come at a substantial cost to health systems, with an estimated cost of USD 2 401 per hospitalised patient, equating to a 19.86 % increase in overall cost and a 8.25 % increase in hospitalisation time (94).

Beside the higher mortality and morbidity rates as well as the significant financial costs, ADRs have other important consequences, including loss of trust in the health-care system and greater non-adherence to treatment (95).

3.1.2.2. Prevalence of MEs

Because of their unique physiology and developmental needs, children are particularly vulnerable to MEs, which are very common in paediatric inpatient settings. A meta-analysis published in 2019, comprising 56 studies, estimated the rate of MEs of 1 per 7 medication orders in paediatric wards using paper medication charts, with at least 1 error experienced every 2 or 3 paediatric admission. This rate is reduced when using electronic charts. The rate of MEs was found to differ between setting wards; it ranged from 24 to 75% of the admissions in multiple ward studies, from 62 to 75% in general ward studies, from 5.6 to 94.9% in paediatric intensive care units (PICU) studies, from 70 to 91% in NICU studies and from 0.9 to 51% in Emergency Department (ED) studies (96).

According to a systematic review, the most common MEs in the UK hospitals are the drug administration errors, with a median prevalence of 16.3% (IQR 6.4–23), wrong administration techniques represented 53% (IQR 52.7–67.4) of these errors. Prescribing errors came in the second place, with a median prevalence of 6.5% (IQR 4.7–13.3); of which the median rate of dose prescribing errors was 11.1% (IQR 2.9–13) (88). Prescribing errors seemed higher in NICUs, EDs and PICUs than in general wards (96,97).

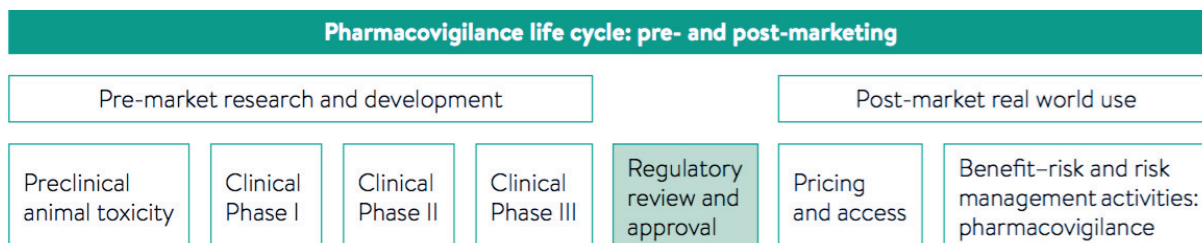
The major factors associated with medication administration errors according to paediatric nurses are being distracted and interrupted as well as being understaffed. Nurses indicated that the main reasons for not reporting MEs were focusing on the patient and the fear of adverse consequences (98). Conversely, the main factors associated with prescribing errors are the moment of consultation (e.g., weekends and early mornings), the severity of the disease, the experience level of the prescriber (99).

3.2. Paediatric pharmacovigilance

The WHO defines pharmacovigilance as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem” (100).

Pharmacovigilance systems should ideally take a life-cycle approach. This approach is carried out throughout the drug development process, from the beginning of research and development to post administration. We distinguish two stages of pharmacovigilance systems (figure 4): pre-marketing surveillance and post-marketing surveillance. Pre-marketing surveillance consists of collecting data concerning ADRs from preclinical screening to Phase I, II and III clinical trials. Post-marketing surveillance includes collecting data on ADRs from drug approval and throughout drug market life

Figure 4: Timeline of pharmacovigilance for a drug from development (pre-market) to post-marketing use (101)



3.2.1. Importance of post-marketing monitoring of medicine safety in children

Post-marketing pharmacovigilance is particularly important in children for both licensed and unlicensed medicines. In both cases, drug safety data are generally limited in children. Concerning licensed medicines, the amount of information collected regarding ADRs during paediatric clinical trials is very limited for many reasons: the sample sizes of patients enrolled in phase I and II trials and in most cases, phase III trials are small. The sample sizes in phase III trials are generally established regarding efficacy endpoints and consider rarely safety endpoints. In addition, many adverse reactions take a long period of time to appear after drug exposure and could not be detected during a clinical trial period. Furthermore, serious adverse events are often rare, thus they are rarely detected through a paediatric clinical trial. It was shown that only very common ($\geq 10\%$) or common (between $\geq 1\%$ and $< 10\%$) ADRs might be detected (102). Therefore, post-marketing monitoring is the most important source of information on ADRs for licensed medicines. In unlicensed and off-label medicines, little or no information is available on clinical safety of drugs in the concerned conditions of use. Additionally, drug safety data collected in the adult population cannot be used for the paediatric population (103). An effective monitoring regarding safety for these drugs is particularly important to rapidly identify any inappropriate and unsafe use.

3.2.2. Challenges of ADR-detection in children

Most of the methods to detect ADRs used in children are originally designed to be used in adults. However, in addition to pharmacokinetic and pharmacodynamic drug particularities, many other particularities inherent to challenge these methods when used in the paediatric population;

- Limited communication skills

Young children are unable to communicate in the same ways that adults can. For example, infants experiencing hallucination may be irritable, but they may not be able to articulate their symptoms appropriately. A Japanese study suggests that the limited linguistic skills of patients under three years old explain the underreporting of ADEs in this age group comparing to those in children aged three years and more (104).

- Child-specific ADRs

Some ADRs are only seen in children, regardless of the effects of growth and development. Other ADRs caused by certain ingredients and excipients may manifest differently in adults and children, e.g., the life-threatening gasping syndrome seen in infants exposed to benzyl alcohol (105).

- Diagnostic challenges

Physical examinations and tests cannot be carried out in the same way that they are in adults (106). Detection methods need to consider the child-specific diagnostic techniques as well as the specific biological values when used for the paediatric population.

Therefore, the validity of detection methods in the paediatric population should be tested. The person or the machine carrying out the detection or the evaluation process should master the Diagnostic particularities in children. (107).

3.2.3. Post-marketing detection methods in hospitalised children

Post-marketing pharmacovigilance can be conducted through passive and active surveillance systems. In passive surveillance, health-care professionals or patients send spontaneous reports to the marketing authorisation holder or regulatory authority in which they describe the ADE after one or more medicinal products are used. Active surveillance involves enhanced or targeted monitoring for certain events or drugs and seeks to ascertain completely the number of ADEs through a pre-planned process. Active surveillance methods include computerised ADE reporting systems, trigger tools and medical note reviews. In general, adopting passive ADE-detection methods is simple and cheap while adopting active methods may be more costly but generates more informative results (101).

Pharmacovigilance consists of two main steps: safety signal identification and risk assessment (108). Safety signal is information on a new or known AE that may be caused by a medicine and requires further investigation. In post-marketing phase, safety signals depend on the number of reports of an ADE and consequently of detected ones.

Many studies were conducted to describe and compare the most commonly used ADE-detection methods in the paediatric population. Four detection methods are commonly used to detect ADEs: incident report review, direct observation, chart review and trigger tools.

- Incident report review

Incident report review is defined as voluntary reporting of incidents by health-care professionals (HCPs), patients, or parents. Reporting can be done on paper, through e-mail, fax, phone, or through an interactive computer system (109). It is the most ancient and the most common detection method used in daily practice. An incident report describes one or more ADEs in a patient who was given or took one or more medical products, and is out of any research perspective or any other structured data collection. This method is based on the reporters' awareness of the presence of a potential drug-related harm and their motivation to report it (110).

Reporting ADEs by HCPs is mandatory only in certain cases. This method is usually the main source of ADE, especially serious ADE, in post-marketing phases (111,112). It has the advantages to provide exhaustive information, including narrative sections of the context and causative factors. This information is necessary to analyse the causes and the contributing factors of ADEs. However, ADEs were found under-detected and under-reported through this method. This leads to limits our knowledge about drug safety in children. In daily practice, the difficulty encountered in detecting ADEs in the hospital environment can still be observed due to factors such as a lack of the ability to suspect it, a false belief that an observed ADE is an 'expected' reaction, which results in only reporting 'unexpected' severe and serious ADEs (112), and a lack of knowledge concerning ADRs (113).

- Direct observation

Direct observation is an active method that refers to a wide range of direct, real-time observation techniques of all aspects of the medication use process (114,115). The main advantage of this method is that a higher number of ADEs can be detected in real time, which allows a better and

faster ADE management. Nevertheless, it consumes a considerable amount of time and human and financial resources.

- Medical chart review

Medical chart review is an active method and includes both concurrent and retrospective reviews of medical records, discharge summaries, pharmacy databases, and laboratory data (116,117). Despite providing high-quality information regarding ADEs, this method has showed serious practical limitations, including the need of trained experts, considerable period of time and significant amount of human and financial resources.(118).

- Trigger tools

A trigger tool is an active method defined as a targeted medical record review, either manually or automatically (80,117). A trigger is a data element (alert) within a health record identifying the presence of an ADE that has occurred or is about to occur (80). The ability of automatization is the major advantage provided by this tool. The main limitation is its long planning process before use, including training, evaluation and automatisation. Many paediatric trigger tools exist, and each one of them represents a unique set of triggers, with many of them are shared by different tools.

A complete comparison between the four methods is provided in (Table 1)

Table 3: Comparison between the four detection methods according to the results of the systematic review conducted by Meyer-Masseti et al. (118)

Methods /advantages	Quantification of ADE	Resource saving	Time saving	Specificity	Sensitivity
Incident report review	✓	✓✓	✓✓	✓✓✓	✓
Direct observation	✓✓✓	✓	✓	✓	-
Medical chart review	✓✓	✓	-	✓✓	-
Trigger tools	✓✓	✓✓	✓✓✓	-	✓✓

The number of ✓ refers to the positive results reported of the method compared to other methods. -: data are not reported.

4. Key strategies to promote drug safety in children

4.1. Generating and collecting more data on paediatric drug safety

Increasing data on paediatric drug safety is essential for the improvement of childcare. Promoting this collection is important in both pre-marketing and post-marketing stages.

4.1.1. Facilitating the conduction of clinical trials in children

In the recent years, legal efforts have been made by regulatory agencies worldwide (119–122), aiming to encourage and facilitate conducting more RCTs in children and to reinforce the requirements to obtain safety information on drugs during these trials. Positive but not enough impacts were reported for these legalisations; The Best Pharmaceuticals for Children Act in 2002 and the Pediatric Research Equity Act in 2003 resulted in an increase in rational prescribing for children, with over 800 labelling changes registered until 2014 (123). However,

the European governmental initiatives, taken until 2007, to promote the conduction of paediatric clinical research had only a limited impact on decreasing the rates of unlicensed and off-label drug use in children (124). Another recent study reviewing all currently available medicines in Germany have concluded that the new EU Paediatric regulation did not succeed in stimulating the conduction of clinical studies for medicines of which the patent had already expired, suggesting that more efforts are still needed (69).

4.1.2. Improving post-marketing paediatric pharmacovigilance methods

Given the significant rates of ADRs reported in hospitalised children, many of which are serious and preventable, better detection methods and interventions are required to improve children's safety (125). Each of the existing detection methods has advantages and limitations.

Until now, there has been no gold standard for detecting ADEs in clinical practice (126). Combining two or more methods appears to be the best pragmatic approach to collect more safety data on drugs and to conclude to a clearer ADR assessment (127). However, the use of each of the existing methods could be improved for paediatric use. The improvement may target signal identification techniques, paediatric-specific detection roles or reporting systems.

Among the available detection methods, we focus in the present document on the trigger tool method and its possible improvement. This method has been recently developed and is a promising practical method used in paediatric inpatients (118).

Trigger tools have shown numerous advantages and are compatible with the growing generation and use of Electronic health records (EHRs). Yet, their use to detect ADEs in paediatric daily practice in many developed countries, including France, is still limited.

The performance of this method varies between the different trigger tools and depends directly on the triggers included in each tool (118). An optimised use of such a method in daily practice

requires selecting triggers effective and pertinent to the targeted population, the settings and the commonly used drugs. Therefore, updated information on available triggers and the description of their performances are needed. It is well known that using irrelevant or ineffective triggers can result in high false positive rates, and consequently over-alerting, a loss of trust in the detection system and increased costs, especially when used in a real-time detection mode.

4.2. Promoting safe practices

4.2.1. Optimizing dosage form choice in children

While waiting for the marketing of novel child-friendly dosage forms, prescribers need to deal with available dosage forms. For many drugs, many liquid and solid dosage forms are often available for oral administration in the paediatric populations. Choosing between them should consider the advantages and the disadvantages of each one of them for the patient age group (65). Prescribers also have to consider the compliance to the child and the family preference, which could differ from the prescriber primary choice, in order to reach the best drug acceptability and adherence (128,129). Studies show that liquid dosage forms were the most frequently oral forms used in practice in all child age groups (130) despite the advantages provided by solid dosage forms for certain paediatric age groups (65). Factors influencing dosage form choice by paediatricians are not well reported. Yet, the properties of dosage forms do not appear to be considered in physicians' prescribing decisions (131)

In order to make the most appropriate dosage form choice for their patients, prescribers need to be informed of the other safe dosage form alternatives available; including information on labelling status, possible dosages, patient acceptability and cost.

4.2.2. Harmonizing dosing recommendations

The different dosage regimens available of a drug in children are based on different levels of evidence and different efficacy and safety results. Recommending one dosage regimen is a complicated process due to the low comparability between studies and the absence of a validated selection strategy considering high variability in terms of population, design, parameters, outcomes, and results. However, providing unique updated dosing guidelines based on the best available evidence for paediatric prescribers for many drugs is a real need that must be addressed. Drug prescriptions in children as in adults should be based on the best available evidence, including data from peer-reviewed scientific studies (132). For that, harmonisation projects need to be initiated with the objective of identifying the most appropriate dosage regimen of drugs and define the type of study(ies) needed to validate it with a higher level of evidence. The harmonization initiatives should target at first the off-label and unlicensed used medicines that are associated with serious potential ADRs, especially those used in neonates. The provided dosage recommendations should be kept up-to-date and consider all new information. All harmonization projects need to collect literature data on the dosage regimens of the drugs in question.

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Aim of Thesis

The overall objective of the thesis is to present data supporting the progression toward safe prescribing and safety monitoring of medicines in hospitalised children.

This thesis has three independent sub-objectives, each of them addresses a specific problem related to the safety of medicine in paediatric inpatients and has been the subject of a scientific article.

The first sub-objective is to review all trigger tools proposed to detect ADRs in paediatric inpatients, describe their performances and propose approaches aiming to optimise their use in daily practice.

The second sub-objective is to identify the best relevant practical circumstances for the substitution from liquid to solid dosage forms in hospitalised children based on hospital database analysis and to assess the expected economic impact of this potential substitution.

The third sub-objective to provide updated literature data on the efficacy and the safety of amikacin using different dosage regimes in neonates, as a drug concerned by the need of a unique recommended dosage regimen for neonates, in the purpose to select the most appropriate dosage regimen for use.

Chapter B: My articles

This chapter includes the three axes of my thesis work. This work meets the three sub-objectives. It is presented in a form of scientific articles. The first two articles are already published. The third is in the process of submission.

Article I meets the first sub-objective. It presents a description of available paediatric triggers and provides suggestions aiming to optimise the performance of this tool in the detection of ADRs in hospitalised children.

Article II meets the second sub-objective. It identifies 10 drugs frequently administered to children in liquid dosage forms and eligible for replacement with suitable authorized solid dosage forms. Applying these replacements could contribute in reducing the rate of MEs in hospitalised children.

Article III meets the third sub-objective. It provides a description of the efficacy and safety of amikacin using the different dosage regimens in neonates. These data are currently used to select the dosage regimen with the best risk-benefit balance in neonates. The adoption of the selected dosage regimen could help reduce the rate of ADRs related to the administration of amikacin in neonates.



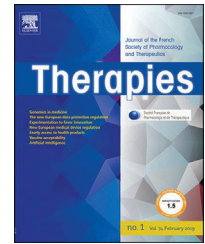
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CLINICAL PHARMACOLOGY

(Article I) Trigger tools to identify adverse drug events in hospitalised children: A systematic review

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KEYWORDS

Adverse drug event;
Trigger tool;
Hospitalized children;
Detection;
Pharmacovigilance;
monitoring

Summary

Aims. — To identify all available trigger tools applicable to the pediatric population in hospital settings to detect adverse drug events (ADEs) and to describe their performances by positive predictive value (PPV).

Methods. — PubMed[®] was searched until December 2021. The reference sections were also consulted for new articles. Studies were selected when they used one or more triggers to identify AEs and used data on pediatric inpatient settings. Studies mentioning triggers related to AEs that were only caused by care procedures were excluded. Only triggers related to ADEs were included. PPVs of triggers were reported. Mean PPVs were calculated for multi-study triggers. The interest of each trigger in a real-time detection system was assessed.

Results. — Thirty studies were included. A total of 271 unique triggers were identified, 179 of which were related to drug-induced harms. Among them, 68 could be used for prevention of ADEs, 80 for verification and 31 for reporting. Nineteen triggers (11%) had a mean PPV between 50% and 100%, including 5 that had a 100% PPV.

Conclusion. — The performances of individual triggers need to be more adequately studied. The detection of ADEs through computerized triggers and/or real-time detection systems remains an emerging field, very much needed in children especially, due to frequent off-label use.

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1. Introduction

Despite their numerous therapeutic benefits, the use of medications may cause adverse drug events (ADEs) and morbidity ^[1]. These aspects have to be considered by clinicians in order to optimize drugs' benefits and minimize or better prevent ADEs.

An ADE is an injury resulting from clinical intervention related to a drug ^[2]. This includes adverse drug reactions (ADRs) and medication errors (MEs). An ADR is defined as any response to a drug that is noxious and unintended which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modifications of physiological function ^[3]. An ME is defined as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer ^[4].

Traditionally, clinical trials and spontaneous reporting systems are the main sources of reported ADEs in post-marketing phases. However, due to a lack of time and motivation, ADEs are underreported by healthcare professionals in their day-to-day practice which results in underestimating the actual rate of ADEs, especially in children ^{[5],[6]}. Three other proactive medication safety assessment techniques have been proposed: direct observation, chart review and trigger tools ^[7-9]. A systematic review of the literature comparing these methods showed that the trigger tool method is the most effective and labor-efficient method to detect ADEs ^[9], even though it is time-consuming, especially the thorough review of the electronic records ^[10]. When computerized, triggers are able to identify 45% of ADEs, chart review 65% and voluntary report 4% while it requires 80% less human-time resources than chart review and twice as many as voluntary report ^[11].

A trigger is defined as a data element within a health record that identifies the presence of an ADE that has occurred or is about to occur ^[12]. A trigger is called positive when it has been

identified in a patient's health records [7]. Typically, these triggers are derived from clinical, medication or laboratory tests [6,14].

A trigger tool is a targeted medical record review that is carried out either manually or automatically [7]. The manual review of triggers is a sampling method based on the evaluation of a limited number of health records. The medical team decides which trigger tool they will use for chart analysis and defines the procedure by which the charts will be analyzed, which ideally are selected randomly. Each selected chart is screened, only through triggers. By contrast, the automated detection is based on the identification of specific triggers in all electronic health records (EHRs) for any given period and is considered as a more time-efficient approach. Once a trigger is detected using any of the methods, a more in-depth review is undertaken to examine the potential for an ADE [5,7-9,14,15]. Trigger performance is usually evaluated using PPV, which is the percentage of patients with a positive trigger who actually have an ADE (true positive [TP]), whereas negative predictive value (NPV) is the percentage of patients with a negative trigger who do not have an ADE (true negative [TN]) [16,17]. The risk analyses through trigger tools can be computerized and systematized through algorithms. These charts have to be further manually analyzed by an experienced professional.

In 1999, the Institute for Healthcare Improvement (IHI) developed the Trigger Tool for Measuring Adverse Drug Events, which was improved in 2009 with a second edition called Global Trigger Tool for Measuring Adverse Events (GTT) [7]. Classen et al. demonstrated that the GTT may identify ten times more serious ADEs than voluntary reports and other tested indicators [18]. The IHI has successfully advocated the use of this approach in adult hospitals [7]. Research on trigger tools applied to children started in Canada in 2005 based on the IHI's methodology [19]. Kirkendall et al. tried to apply the GTT to the pediatric population and found that 25.8% of children had at least one ADE during their hospital stay [20]. To date, this innovative ADE detection tool has been proved to be efficient in the detection of ADEs in adults

but its use is still limited in hospitalized children [17,20–25]. The method could be more effective in detecting ADEs when relevant and adapted triggers for daily practice are selected [23]. To select the most clinically relevant triggers to detect ADEs in children, a review of the literature is necessary to identify the possible triggers and describe their properties.

Objective

The aim of this systematic review is to identify all available trigger tools applicable to the pediatric population in inpatient settings to detect ADEs and to describe their performances by PPV, if available.

2. Methods

Search Strategy and Study Selection

This systematic review was conducted by following the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines. The research was carried out on PubMed on June 16th, 2019 and updated on February 27th, 2020 and on December 07th, 2021 using 3 search strategies to identify relevant studies. Main keywords were combined as follows: trigger tool AND (pediatric OR pediatrics OR paediatric OR paediatrics OR child OR children OR infant OR infants) AND (adverse drug event OR adverse drug events OR adverse drug reaction OR adverse drug reactions OR harm OR harms).

To identify other relevant articles, the reference sections of all included articles were consulted. After screening and removing duplicates, all article titles, abstracts and full texts were independently reviewed for inclusion by two authors of this article. In case of discordance, another author was consulted in order to confirm or reject the inclusion. Articles meeting all of the following criteria were eligible for inclusion: research using one or more triggers to identify AEs and research using data on pediatric inpatient settings. Exclusion criteria were pieces of research using data from only non-hospital or outpatient settings, mentioning triggers related to

AEs caused only by care procedures, research with unavailable or unpublished full texts and research with triggers not provided.

Data Extraction

Extracted data contained information on: first author, country, year of publication, number of triggers used, overall PPV, the PPV of the set of triggers used in the study (%), total positive triggers in the study, total positive AEs in the study, manual or automated triggers, range of individual PPVs [min, max] (an individual PPV is a PPV of one trigger in one study), list of all triggers used, and for each trigger: type, PPV, positive trigger alerts and positive AEs. Data were independently extracted by two authors of this study. When the PPV was not provided, it was calculated by dividing the number of validated AEs by the number of positive triggers.

After extraction, similar or repeated triggers were standardized using one term: types of triggers were also reviewed and standardized using a classification mode based on the potential source of information. Classifications were: medication, laboratory, clinical intervention, clinical sign, administration or combination (when two triggers of two types were combined) (e.g. the trigger “drug level out of range” is classified as a laboratory type trigger because this piece of information would be found in laboratory data). The new terms and classifications of triggers were verified by another author of this article. We also classified triggers if they identify an AE potentially related to a medication (ADE) or only to care procedures. Only triggers that could identify ADEs were considered.

Synthesis of Results

A narrative synthesis of the data was completed by reporting the findings related to the study characteristics, trigger tools and individual triggers (qualitative methods). The PPV was chosen as the main parameter to describe the performances of the individual triggers, because it was the most commonly available in articles reviewed while designing this work. For each trigger,

all available PPVs were reported and the mean PPV was calculated. Due to the heterogeneity of triggers between the different trigger tools and the unavailability of adequate performance data on individual triggers, no further statistical analysis or meta-analysis was performed.

Trigger Assessment

The included triggers were assessed according to their potential clinical use in a real-time detection system by two pediatricians. They were then classified into three categories: Warning triggers, Validation triggers and Reporting triggers. Warning triggers include triggers that are potentially usable for early-detection such as the administration of a high-risk medication, a risk factor or an early abnormal laboratory value. Validation triggers include triggers that are detectable after the occurrence of the ADE but enable the validation of a relationship with a drug. Reporting triggers include late-detection triggers of which the ADE has occurred and has been managed and the suspected medication was identified.

The interest of using warning triggers in a real-time detection system is to warn for a potential ADE in order to prevent it. Using validation triggers allows detecting ADEs and optimizing their management by identifying a potential relationship between the drug and the condition. The interest of using reporting triggers is to report and notify ADEs in a more efficient way than spontaneous reporting. So, all triggers would help improve the quality of care and hospital organization.

Quality Assessment

Two reviewers independently conducted the quality assessment of each of the included studies using the method of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [26]. The time interval between the index test and the reference standard was not considered for the evaluation. The risk of bias was judged “high” when one or more signalling questions were answered negatively.

3. Results

Description of the included studies

We identified 83 articles. After a review of titles and abstracts, we assessed 34 full-text articles of which 24 fulfilled the inclusion and exclusion criteria and were included in the review. A review of the reference sections of the included articles identified six additional articles. In total, 30 articles were included [14,17,20–25,27–48] (Figure 1 - Table 1). The studies were published between 2006 and 2020.

The most commonly used method to detect triggers was chart review with 20 studies using it while 10 used automated trigger tools.

In 23 studies, triggers were applied on a general pediatric population, 2 on acutely ill inpatients, 2 in pediatric intensive care units (PICUs), 1 in a neonatal intensive care unit (NICU), 1 in a pediatric otolaryngology service (ORL) and 1 in a psychiatric ward.

The number of triggers used in the studies varied between 3 and 88. Twenty-four studies provided information about the overall PPV of trigger tools. Overall PPVs varied from 2% to 49%. Twenty-one included studies provided information regarding individual PPVs. Studies were undertaken in 10 countries. Twenty studies were located in North America, four in Europe, two in South America, three in Asia and one in Africa. Fifteen studies focused on AEs in general, thirteen on ADEs, one on MEs and one on any type of harm (Table 1).

Description of the included triggers

Nine hundred and sixty-six non-unique triggers were extracted. After the standardization process, 271 unique triggers were identified and 179 were included. The most common type of included triggers was laboratory abnormalities (51 triggers), 45 were related to medications, 42 to clinical signs, 18 to clinical interventions, 14 were combinations of triggers of 2 different types, and 9 were administrative data.

Two triggers were tested in more than 20 studies, 17 triggers were tested in 10 to 20 studies and 160 in fewer than 10 studies, of which 93 triggers were tested in one single study. Elevated anti-epileptic drug level, naloxone administration, early readmission and romazicon administration were the most frequently triggers studied (in 27, 23, 19 and 19 studies, respectively).

For 61 triggers (34%), no PPV was available in the included studies. The mean PPV for 26 triggers (14%) was 0. The mean PPV for 73 triggers (41%) was between 0 and 50. Only 19 triggers (11%) had a mean PPV of 50% or more, 5 of which had a PPV of 100% (i.e., anesthesia-related harm, medication reaction, hallucinations/delirium/ICU syndrome, phentolamine administration and urinary retention).

Sixty-eight triggers were classified as warning triggers. Eighty triggers were classified as verification triggers and 31 triggers were classified as reporting triggers. Figures 2,3 and 4 respectively show the warning triggers, the verification triggers and the reporting triggers for which a PPV is available and > 0 (a complete list of the triggers is presented in appendix A).

Forty-six of the included triggers were created to detect an undefined ADE (e.g. anesthesia-related harm and medication reaction), while 133 triggers were designed to detect one or more defined ADEs (e.g. the 10 triggers related to bleeding that are presented in Figure 5: 8 of them are classed for warning and 2 are classed for verification).

Quality assessment

Table 2 presents the methodological quality assessment (risk of bias) of the included studies. Two types of risk of bias were commonly found across the included studies. The first one concerned the reference standard (in 28 studies). The reference standard was usually a physician review, which was only performed when the index test (trigger test) was positive by reviewers aware of this positivity. The second risk of bias concerned patients' flow and timing (in 27 studies). Records with a negative trigger test did not receive a reference standard and were not

considered for the performance analysis of triggers. The quality results regarding patient selection and index test as well as the applicability results were generally satisfactory (three or fewer high risks for each).

4. Discussion

About 38% of the identified triggers (i.e., warning triggers) could be used in the prevention of ADEs, although the studies do not particularly specify this utilisation. Some of the included triggers, which were well-studied and had a high mean PPV, were undefined (e.g., occurrence of a complication and abrupt medication stop).

The use of trigger tools in pediatrics is limited. Laboratory data provide the richest information source of triggers. The majority of identified triggers were employed in more than one study.

The performance indicated by the PPVs of the majority of included trigger was quite poor (PPV < 50). Generally, reporting triggers tend to perform better than verification triggers and verification triggers better than warning triggers. However, there are no specifically defined thresholds for the interpretation of a PPV. The seriousness and the severity of the related ADE have to be considered when selecting clinically relevant triggers. To be selected, a trigger for serious ADEs (e.g., death) may have a low PPV, whereas, for ADEs with a non-significant level of harm, the probability of affirming the presence of the ADE must be high. In order to refine triggers in some of the included studies, various limits were defined: Landrigan et al. chose triggers with a PPV $\geq 10\%$ with a frequency ≥ 10 occurrences^[41] while Matlow, A. G. et al. eliminated triggers with a low PPV and a ratio of false-positive to true positive predictors > 0.7^[22].

Bleeding, hypoglycemia, allergic reactions and drug intoxications were the most frequent ADEs identified when using triggers.

All mean PPVs of 100% reported in this study were related to 1 single study [31,34]. Selection of the best performing triggers needs to integrate the number of studies where the trigger was used and their sample sizes.

PPVs depend on the trigger, the type of population, and how the study was designed and conducted. The use of triggers in specific pediatric population looks promising; the overall PPVs of 4 specific-population studies (PICU, NICU, ORL, acutely ill patients) [24,29,45,47] were higher than the overall PPVs of 18 general population studies. Furthermore, Stockwell et al. showed that a notable increase of PPV is observed when triggers are well combined. The hypoglycemia trigger defined as “all serum glucose values less than 50 mg/dL” has a PPV between 0% and 38% [20,22,25,27,28] while the combined trigger “serum glucose values less than 50 mg/dL and insulin administration” has a PPV of 61% and 100% [29,30]. The adoption of a lower threshold of glucose level of 40mg/dL for the definition of hypoglycemia did not significantly improve the PPVs, which were of 28% and 56% [14,27].

The combination of certain triggers enables to consider time and clinical context. For instance, the administration of an antihistamine as prophylaxis treatment to the hypersensitivity effect of certain drugs would not be associated with any ADE whereas the administration of an antihistamine in the existence of a drug-induced allergic reaction generates a valid ADE.

Lemon et al. assessed a trigger for anticoagulation-related ADEs through a combination of an International Normalized Ratio (INR) >4, an activated partial thromboplastin time (aPTT)>100 seconds, Anti-Factor Xa Activity (anti-Xa)>1.5 IU/mL or administration of protamine. It has led to the restructuring and standardization of anticoagulation therapy protocols as well as the modification of thresholds [14].

Some trigger PPVs differed largely across studies. The PPVs of 8 triggers ranged from 0 to 100%. This could be explained by the type of hospital units involved, whether a manual or automated tool was used, the duration of the study and the type of patients. For example,

naloxone administration had a PPV ranging from 0% to 78% [14,20–22,27,29,31–34] and flumazenil administration a PPV ranging from 0% to 100% [14,17,20,29,31–33]. It seems that in these situations PPVs were higher when using an automated trigger tool. These findings suggest that the triggers need to be tested more in pediatrics in order to get better estimations of their performances in this context.

A complete examination of patient records is an essential step to validate the existence of an ADE when a positive trigger is identified. It also allows us to determine the nature of the ADE (ADR or ME), the severity, the drug causality and the preventability using specific evaluation methods. For example, reviewing data on drug administrations, calculations, prescriptions and patient characteristics is necessary to determine whether the bleeding event associated with a vitamin K administration trigger resulted from a dose calculation error, an administration error, a preparation error, a prescription error, a drug interaction or happened during a standard anticoagulant dosing adjustment. Since medication errors are common in pediatric patients [49,50], triggers could be used in order to detect harmful medication errors and take corrective actions. However, the examination of ADEs through trigger tools has a tendency to concentrate on patient harm rather than errors [33].

In this paper, in addition to identifying triggers, they were also classified considering the clinical relevance for their use in daily practice. However, selecting clinically relevant triggers for internal use and defining each trigger is recommended before implementing the method in daily practice detection. After selecting triggers, an internal feasibility evaluation considering detectability of selected triggers from the internal electronic data records, expected number of positive triggers, estimated time needed per trigger, available human resources and the possibility of an automated transmission could be necessary. Proper training of in-depth reviewing of patient's records would be probably needed.

Our study has several limitations. The interpretation of the mean PPVs of triggers could be biased since it does not consider the sample sizes of the studies. However, the recommended meta-analysis methods for such diagnostic test should combine either specificity and sensitivity parameters or PPV and NPV. The information provided on individual triggers by the included studies does not allow performing any of these methods. Indeed, the sensitivity and specificity provided in some studies concerned only the entire trigger tool used.

Another potential limitation is that we grouped biological triggers that were employed with various definitions across the studies as part of the standardization of term process. This point may have influenced the mean PPV since a trigger with narrower limits is expected to have a higher PPV. For example, the category “high serum partial thromboplastin time (PTT) trigger” gathered 13 PTT >100 seconds, 1 PTT >140 seconds and 1 PTT with no threshold mentioned. However, the integration of the PTT >140 seconds trigger did not appear to highly influence the total PPV in this example (from 24% to 28%).

The included studies were mainly performed in the United States of America where the population and settings differ from other countries, which limits the applicability of these studies’ findings in other countries. We suggest considering the clinical relevance of triggers in the first place in any selection of triggers to be tested or applied in a hospital.

The search for studies was carried out on one single database (Medline), which could restrict the number of publications. However, Halladay et al. suggested that it may have little impact [51].

The physician’s judgment is considered as a reference standard for the determination of the causative relation of an adverse event [52]. The quality of determination varied between studies. For example: Mouton et al. used a multidisciplinary experienced team [36], Stockwell et al. used a multi-phase assessment by physician-reviewers [27] while Kilbridge et al. used a single-stage assessment performed by pharmacists only [29].

The detection process of triggers with a high PPV has the potential of being fully automated in practice ^[52]. The automation of trigger tools could enable a continuous and more exhaustive detection of ADEs and offers additional advantages like saving time, allowing real-time intervention when facing ADE, better understanding ADEs and improving their outcome ^{[8,15],[9,14]}. In three of the included studies, a near real-time detection system was established based on automated triggers and daily review of positive triggers by a specialist ^[14,32,44].

Further research would focus on diagnostic and prognostic models for semi-automatic or automatic detection and prevention of clinically significant ADEs. Diagnostic models using combinations of triggers and considering the clinical context of hospitalized children may increase the performance of ADE detection, help identify new risk factors of ADE, and contribute to early detection and prevention of severe ADE. The prognostic models would be useful for the proactive prevention of ADE.

Our aim for further research is to develop a model combining a selection of triggers relevant to clinical practice to detect related ADEs, and to implement a tool in the hospital information system to screen electronic patient data on a continuous basis. In summary, ADEs would be reported in a time-efficient manner, reducing the burden of filling in voluntary reports. Corrective actions will be implemented to improve the model, in case of false positive results. Care delivery could be performed earlier and ADE impact may be mitigated. Underreporting may also be investigated leading to a better estimate of ADE incidence and to the implementation of preventative actions to reduce their rate. The clinical utility of such models should then be assessed in clinical trials.

Conclusion

We found articles identifying many triggers, with very varying performances across studies; further studies are needed in children to assess precisely triggers' performances. As diagnostic

test performances are measured primarily using their sensitivity, specificity, PPV and NPV; similarly, the use of these parameters should be generalized to evaluate triggers' performances in future studies. The detection of ADEs through computerized triggers and/or real-time detection systems remains an emerging field, very much needed in children especially, due to frequent off-label use. This study proposes the use of three types of triggers for ADE early-detection and prevention, validation and reporting. We suggest that significant PPV thresholds based on the severity of the ADEs could be defined.

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Disclosure of interests:

The authors declare that they have no competing interest

Figure 1: Flow diagram for selection of articles

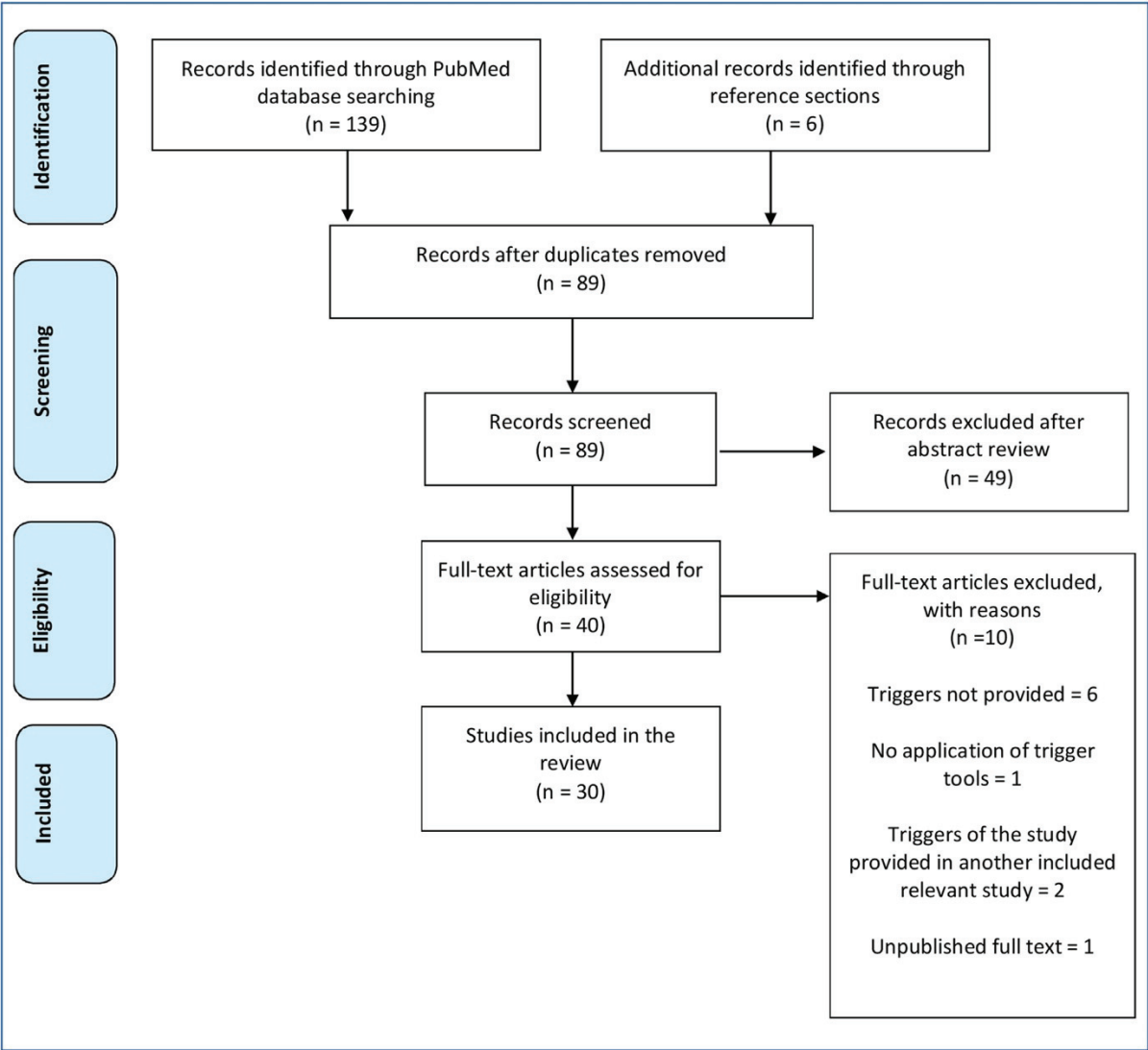


Table 1: Summary of the studies included in the systematic review

First Author Last Name	No. of Triggers	Overall PPV (AE+/Triggers +)	(%)	Individual PPV (%) [Min-Max]	Country
Automated trigger tool					
Stockwell et al. [31]	22 ^a	34.4 (3,264/9,492) ^b		[0—100] ^c	USA
Fortenberry et al. [38]	12	27.5 (1,055/3,836)		[0—100]	USA
Ivashchenko et al. [37]	18	19.5 (51/261)		[0—100]	Russia
Ferranti et al. [32]	57 ^d	5.1 (78/1,537) ^e		no data	USA
Patregnani et al. [42]	4	2 (33/1,664)		[0—23]	USA
Kilbridge et al. [29]	32	49 (60/1,226)		[0—100]	USA
Long et al. [30]	11	6.2 (14/225)		[0—61]	USA
Call et al. [23]	6	16.1 (114/706)		[0—60]	USA
Lemon et al. [14]	18	26.6 (2,441/9,143)		[2.3—92.5]	USA
Kirkendall et al. [44]	3	No data		No data	USA
Manual trigger tool					
Solevag et al. [43]	39 ^f	19.8 (48/242) ^g		[0—100]	Norway
Landrigan et al. [41]	54 ^h	No data		No data	USA
Stockwell et al. [27]	51 ⁱ	22 (240/1,093)		[0-92.3]	USA
Kirkendall et al. [20]	52	21.8 (88/404)		[0—100]	USA
Larsen et al. [46]	29	No data		No data	USA
Ji et al. [25]	31	13.3 (304/2,291)		[0—100]	China
Maaskant et al. [39]	17 ^j	2.8 (19/688)		[0—84]	The Netherlands
Mouton et al. [36]	72	No data		No data	South Africa
Lander et al. [45]	42	39 (92/236)		No data	USA
Stroupe et al. [40]	54	44.4 (20/45) ^e		No data	USA
Davenport et al. [28]	52	18 (52/289)		[0—100]	Argentina
Unbeck et al. [34]	88 ^k	22.9 (824/3,598)		[0—100]	Sweden
Matlow et al. [22]	47 ^l	No data ^m		[0—83]	Canada
Sharek et al. [47]	17	38 (841/2,218)		[8—100]	USA
Nydert et al. [35]	88	No data		No data	Sweden
Agarwal et al. [24]	22	44 (1,250/2,816)		[20—100]	USA
Takata et al. [21]	11	4.7 (79/1,669)		No data	USA
Chapman et al. [33]	40	13.9 (1,001/7,199)		[0—80]	UK
Takata et al. [17]	15	3.7 (89/2,388)		[0—20]	USA
Liu et al. [48]	33	24.9 (98/394)		[0—100]	China
PPV: positive predictive value.					
^a 15 and 7 triggers in both hospitals.					
^b PPV = 23.5 and PPV = 86.2 in both hospitals.					
^c [0—96.4] and [0—100] in both hospitals.					
^d 23 triggers identified.					
^e Overall PPV is calculated.					
^f Only 20 of 39 triggers were identified in the study.					
^g PPV (admissions) = 23.2% and PPV (outpatient care) = 10.8%.					
^h the 54 triggers were refined to 27 used in the study, the entire list of triggers was considered for this review.					
ⁱ 36 triggers were identified.					
^j only 2 triggers were identified.					
^k 29 triggers selected in the final trigger tool.					
^l 35 triggers selected in the final trigger tool.					
^m Sensitivity = 0.88 (% of trigger-positive charts that physicians judged to have an ADE) and specificity = 0.44 (% trigger-negative charts that had no ADE according to physicians' review). AE: adverse event. ADE: adverse drug event.					

Table 4: Risk of bias summary of the included studies according to the QUADAS-2* tool

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Stockwell et al. [31]	😊	😊	😞	😞	😊	😊	😊
Fortenberry et al. [38]	😞	😊	😞	😞	😞	😊	😊
Ivashchenko et al. [37]	😊	😊	😞	😞	😊	😊	😊
Ferranti et al. [32]	😊	😊	😞	😞	😊	😊	😊
Patregnani et al. [42]	😊	😊	😞	😞	😊	😊	😊
Kilbridge et al. [29]	😊	😊	😞	😞	😊	😊	😊
Long et al. [30]	😊	😊	😞	😞	😊	😊	😊
Call et al. [23]	😊	😊	😞	😞	😊	😊	😊
Lemon et al. [14]	😊	😊	😞	😞	😊	😊	😊
Kirkendall et al. [44]	😊	😊	😞	?	😊	😊	😊
Solevag et al. [43]	😞	😊	😞	😞	😞	😞	😊
Landrigan et al. [41]	😊	😊	😞	😞	😊	😊	😊
Stockwell et al. [27]	😊	😊	😞	😞	😊	😊	😊
Kirkendall et al. [20]	😊	😊	😞	😞	😊	😊	😊
Larsen et al. [46]	😊	😊	😞	😞	😊	😊	😊
Ji et al. [25]	😊	😊	😞	😞	😊	😊	😊
Maaskant et al. [39]	😊	😊	😞	😞	😊	😊	😊
Mouton et al. [36]	😊	😊	😞	😞	😊	😊	😊
Lander et al. [45]	😊	😊	😊	😊	😊	😊	😊
Stroupe et al. [40]	😞	😊	😞	😞	😊	😊	😊
Davenport et al. [28]	😊	😊	😞	😞	😊	😊	😊
Unbeck et al. [34]	😊	😊	😞	😞	😊	😊	😊
Matlow et al. [22]	😊	😊	😊	😊	😊	😊	😊
Sharek et al. [47]	😊	😊	😞	😞	😊	😊	😊
Nydert et al. [35]	😊	😊	😞	😞	😊	😊	😊
Agarwal et al. [24]	😊	😊	😞	😞	😊	😊	😊
Takata et al. [21]	😊	😊	😞	😞	😊	😊	😊
Chapman et al. [33]	😊	😊	😞	😞	😊	😊	😊
Takata et al. [17]	😊	😊	😞	😞	😊	😊	😊
Liu et al. [48]	😊	😊	😞	😞	😊	😊	😊

😊 Low Risk 😞 High Risk ? Unclear Risk *Quality Assessment of Diagnostic Accuracy

Studies

Figure 2: Warning triggers of available PPV, and PPV > 0



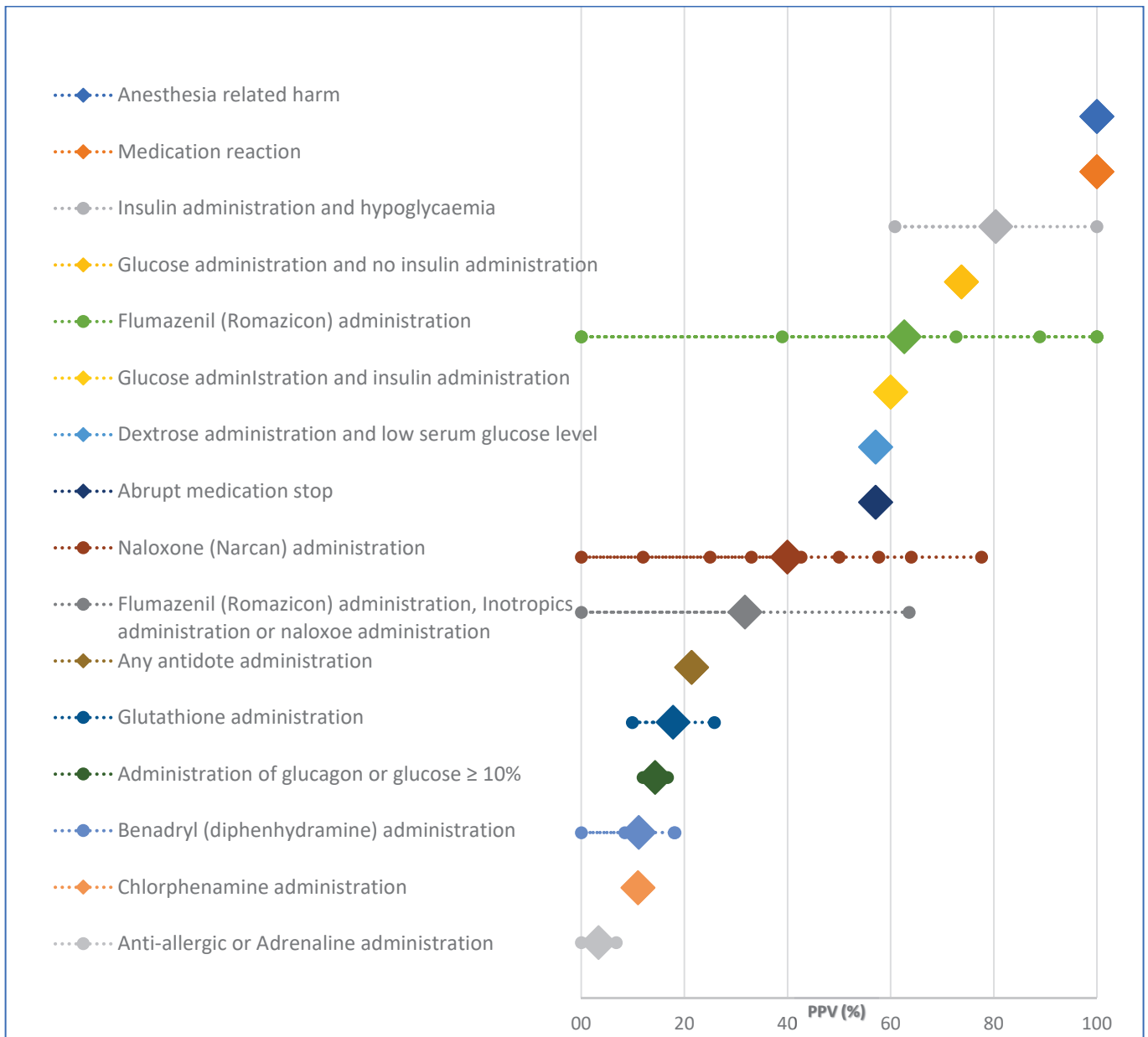
PPV: Positive predictive value. PTT: partial thromboplastin time. INR: international normalized ratio. This figure presents 36 identified triggers classified as Warning triggers in our review, of which 1 PPV at least was available (complete list of the identified triggers is presented in appendix A). Each discontinued line links the different identified PPVs of one trigger: ♦ is the mean PPV (%) of the trigger calculated by the author and • is an extracted PPV (%) of the trigger per study

Figure 3: Validation triggers of available PPV, and PPV > 0



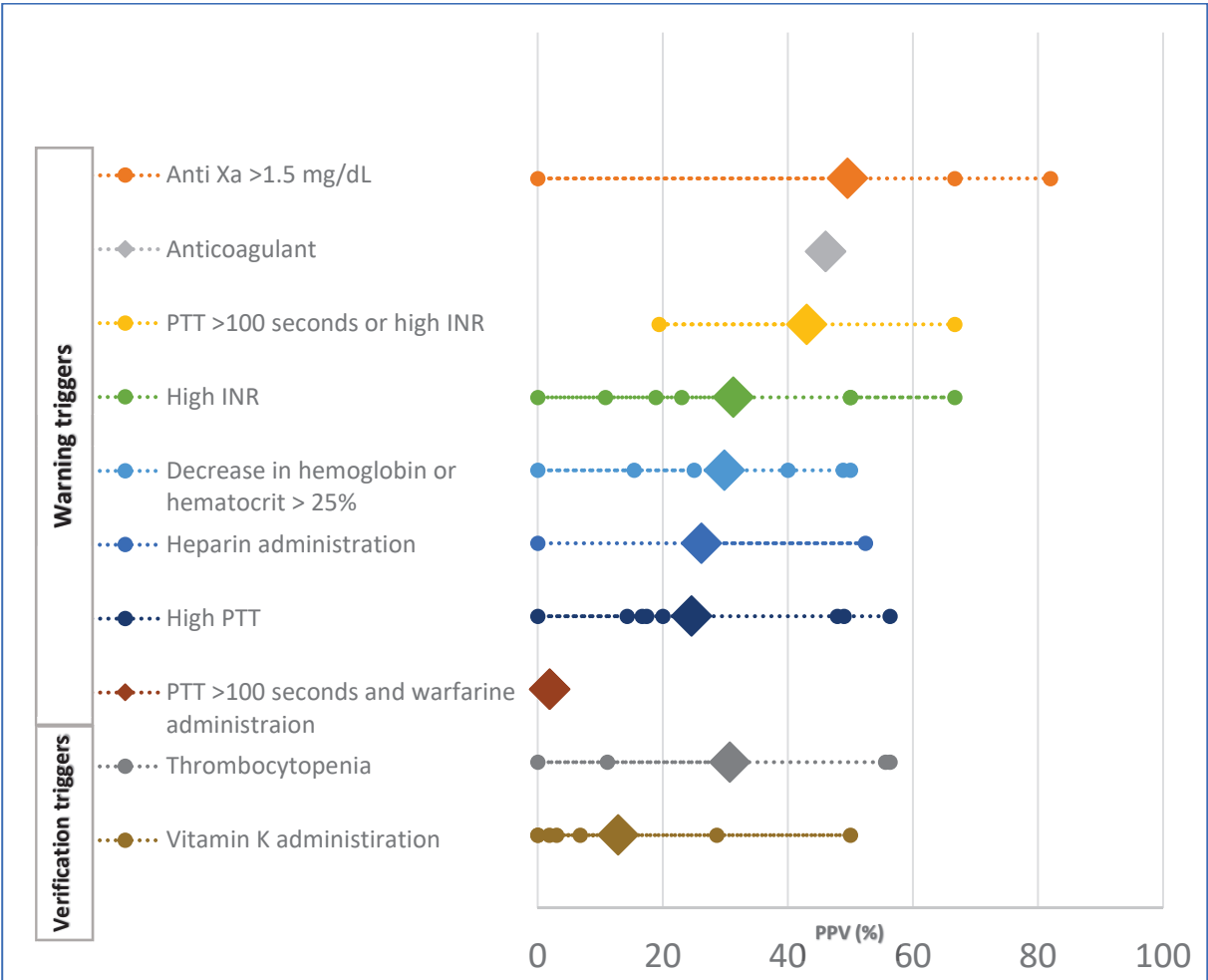
PPV: positive predictive value. ICU: intensive care unit . This figure presents 40 identified triggers classified as Verification triggers in our review, of which one PPV at least was available (complete list of the identified triggers is presented in appendix A). Each discontinued line links the different identified PPVs of one trigger: ♦ is the mean PPV (%) of the trigger calculated by the author and • is an extracted PPV (%) of the trigger per study

Figure 4: Reporting Triggers of available PPV, and PPV > 0



PPV: positive predictive value. This figure presents 16 identified triggers classified as Reporting triggers in our review, of which 1 PPV at least was available (complete list of the identified triggers is presented in appendix A). Each discontinued line links the different identified PPVs of one trigger: ♦ is the mean PPV (%) of the trigger calculated by the author and • is an extracted PPV (%) of the trigger per study.

Figure 5: Bleeding-related triggers of available PPV, and PPV > 0



PPV: Positive predictive value. PTT: partial thromboplastin time. INR: international normalized ratio.

This figure presents 10 identified triggers used to detect drug-induced bleeding, of which one PPV at least was available (complete list of the identified triggers is presented in appendix A). Eight bleeding related triggers were classified as Warning triggers in this review while two were classified as Verification triggers. Each discontinued line links the different identified PPVs of one trigger: ♦ is the mean PPV (%) of the trigger calculated by the author and • is an extracted PPV (%) of the trigger per study.

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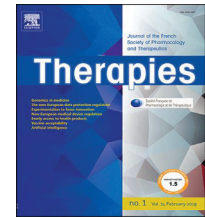
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CLINICAL PHARMACOLOGY

(Article II) Replacing liquid with solid dosage forms in pediatric practice: Feasibility and economic impact from a hospital-based study

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KEYWORDS

Drug formulation;
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Substitution to
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Summary

Aim of the study. — To identify the 10 drugs most frequently administered to children in liquid dosage forms which are eligible for replacement with suitable authorized solid dosage forms and to assess the expected economic impact of this substitution.

Methods. — The health record data from 312,152 oral drug administrations were analyzed. Ten drugs were selected according to their frequency of administration in liquid dosage forms, the availability of solid form alternatives, and the suitability of these alternatives for the children receiving the corresponding liquid forms. Potential hospital cost savings of the suggested substitutions were calculated.

Results. — The 10 drugs identified as most frequently administered and for which suitable solid forms were available were: paracetamol, cyamemazine, valproic acid, clonazepam, furosemide, prazepam, hydroxyzine, alfacalcidol, amitriptyline, and levetiracetam. Thirty-four point six of the administrations of these drugs in liquid dosage forms could be delivered using suitable solid dosage forms without additional cost.

Conclusion. — Opportunities exist for substituting liquid dosage forms with market-available solid dosage forms suitable in size and dosage for the pediatric population.

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1. Introduction

The need for age-appropriate dosage forms in pediatric patients has been a major concern for the pediatric community since the Paediatric Regulation (EC) No. 1901/2006 ^[1] was adopted. The development of age-appropriate formulations has constituted a challenge for pharmaceutical scientists ^[2,3], since such forms must be easily produced, cost-effective, and commercially viable ^[1].

The ideal dosage form for pediatric use should permit accurate dose administration, minimize dosing frequency, limit impact on lifestyle, reduce the risk of medication errors, and contain only safe excipients ^[1,2,4]. Dosage forms available in pediatric doses are scant, and many formulations are therefore used off-label in children ^[5].

Due to their dosing flexibility and high swallowability, liquid dosage forms (i.e. solutions, syrups, suspensions, and emulsions) are usually recommended for young children unable to swallow ^[6]. However, liquid dosage forms exhibit some major disadvantages in comparison to solid dosage forms, such as poor stability, taste masking difficulties, low transportability, and excipients inappropriate for children ^[1,2,7,8]. Dosing errors are more likely when using liquid dosage forms (i.e., inhomogeneous distribution in suspensions, errors in counting drops, incorrect calculation or measurement of liquid volume) ^[9].

Oral solid dosage forms are considered more suitable for children's everyday life (i.e., easy to transport and store), do not usually require using a dosing tool, and allow low dosing frequency, which can enhance drug compliance ^[9,10].

Liquid dosage forms remain the most frequently administered oral forms in children, even for ages 6 years and older ^[11]. The inadaptability of solid dosage forms for pediatric use ^[3,12] and the inability of some children to swallow a tablet or a capsule are presented by healthcare professionals as the main limitations to the use of solid dosage forms in children under 6

years^[5,13], and even under 7.3 years according to nurses ^[10]. Many studies, however, have reported good acceptability of mini-tablets for these age ranges ^[14]. Single-unit dosage forms for reconstitution (i.e., dispersible tablets, powders, granules, pellets, or sprinkles) are effective delivery strategies, as they maximize the advantages of the conventional solid dosage forms while providing better swallowability and greater dosing flexibility ^[1,9].

A recent study, using prescription data over a one-week period in a hospital in England, showed that two-thirds of the liquid dosage forms administered in children over 2 years old could have been substituted with suitable solid dosage forms^[15].

In a previous study, we reported a low use of solid dosage forms in our hospital and a need for more research on the acceptability of oral solid dosage forms in children ^[11].

The first objective of this study was to identify the 10 drugs most frequently administered to children in liquid dosage forms eligible for replacement with suitable authorized solid dosage forms (i.e., easy to swallow and available in the proper dosage). The second objective was to assess the expected economic impact of this potential substitution.

2. Materials and methods

2.1. Data sources

This study was conducted on data collected over a 3-year period (February 6, 2013 – February 5, 2016) within the pediatric unit of the teaching hospitals in Lyon, France (*Hôpital Femme Mère Enfant*, HFME). Information on oral drugs administered to hospitalized children was provided by the EREMI study database. EREMI is a prospective cohort of children staying at the hospital for more than 3 days, which assesses the relationship between adverse drug reactions and unlicensed or off-label drug use in hospitalized children. The EREMI database automatically and prospectively collects data on drugs administered to children between the ages of 0 and 15 years and receiving at least one drug during their hospital stay. For all children

included, our Hospital Information System (HIS) provides data on every drug and on the children's characteristics (i.e., age, weight, height) at every administration. Labile blood products, investigational drugs, and electrolyte solutions are not included in the EREMI study. All study data are coded using untraceable anonymized numbers to respect the confidentiality of children's information. Approval for this observational study was obtained from the National Data Protection Agency (*Commission Nationale de l'Informatique et des Libertés*, CNIL, Ref. MMS/MTE/AR1411279) and the Advisory Committee for Data Processing in Health Research (*Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé*, CCTIRS, Ref. 13.546).

All information about available dosage forms and their prices was retrieved from the institution's drug formulary.

Solid form sizes were retrieved from the information file for drug identification maintained by the Poison Control Center (*Centre Antipoison et de Toxicovigilance*) in Nancy, France.

The EREMI database contains information on drugs, administration circumstances, and patients. The drug information extracted was (i) trade name, (ii) International Nonproprietary Name (INN), (iii) drug Anatomical Therapeutic Chemical Class (ATC), (iv) drug dosage form, (v) total number of administrations, and (vi) code of Common Unit of Dispensation (CUD).

The information on administration extracted concerned (i) quantity administered, (ii) measurement unit, (iii) time of administration, and (iv) route of administration. The patient information collected was sex, age, height, and weight at each administration.

2.2 Data analysis

The data recorded over 3 years were analyzed in terms of route of administration, dosage form (i.e., solid, liquid, dispersible solid form, and others), number of active ingredients, and type of preparation (i.e., industrial manufacture and extemporaneous preparation). Liquid dosage forms

included solutions, syrups, suspensions, and emulsions. The general stages of data processing are presented in figure 1A.

2.3 Drug selection

The criteria for identifying oral liquid dosage drugs which could be potentially substituted with solid forms were: containing a single active ingredient, industrially manufactured, available in at least one solid dosage form in the hospital pharmacy.

Data concerning children who could not even receive the minimal dosage of a given solid form (i.e. younger than the authorized age, lighter than the authorized weight, unable to swallow the smallest tablet) were discarded from the drug selection analysis. We then selected the 10 most frequently administered drugs which were eligible for a thorough substitution assessment.

The Summary of Product Characteristics (SmPC) was used to identify authorized age groups and the Clinical Investigation of Medicinal Products in the Pediatric Population guidance was used to identify the age range for each category (newborns, infants, etc.) [16]. The Committee for Medicinal Products for Human Use (CHMP) guideline was used to identify at what age children could swallow the minimum dose tablets [9]. Of note, when the minimum dose was achieved by tablet division, half of the diameter was considered.

2.4 Substitution assessment

In order to determine the age/weight categories of eligible patients for each drug and administration substitution, the dosage acceptability and then the size suitability of the available solid dosage forms for the patients receiving the liquid dosage forms were assessed (figure 1B).

The substitution analysis aimed to determine, for each of the 10 drugs identified as most frequently administered to children and eligible for substitution with authorized suitable alternative solid forms, the number of administrations for which a suitable solid form was possible referred to herein as substitution frequency.

2.4.1 Dosage acceptability

First, all daily doses achievable using the available solid dosage form(s) were identified. During this step, the recommended dosing frequency was followed, the division of breakable tablets (when accepted in the SmPC) was allowed, but the combination of two different solid dosage forms was not. The weight and age ranges of patients who could receive these daily doses were then determined according to the recommended posology provided by the SmPC.

Secondly, the number of administrations using liquid dosage forms performed in these weight/age ranges was determined.

When more than one daily dose was possible for a patient, the minimum dose was considered for the substitution analysis. It was decided that all solid dosage forms should be taken without further manipulation (e.g., no tablet crushing or capsule opening). Missing data concerning body weight were replaced using the Last Observation Carried Forward technique during the same hospital stay for a given patient. When age or weight could not be replaced, administrations were not assessed.

2.4.2 Size suitability

For every substitution that was possible in terms of dosage, the size suitability of the alternative solid form or, in other words, the children's ability to swallow it, was assessed. The age of the children at the time of administration was confronted with the size of the suggested solid dosage form. The standards from the Pharmaceutical Development of Medicines for Paediatric Use ^[9] guidelines were then used to determine if the solid dosage form was suitable (i.e., 3–5 mm diameter tablets are acceptable above 2 years, 5–10 mm diameter tablets are acceptable above 6 years, 10–15 mm diameter tablets are acceptable above 12 years, and tablets larger than 15 mm diameter are not acceptable for the entire pediatric population under 18 years of age).

2.5 Economic impact

For each drug, the cost of every suggested daily dose using the solid dosage form was compared with the cost of the same daily dose using the liquid dosage form. The cost difference of the substitution was then calculated. Potential cost savings for the hospital were also calculated, assuming that this substitution was performed at every opportunity of substitution identified. This calculation was done by multiplying the cost difference of every daily dose by the number of real treatment days of the concerned patients. The sum of these values represents the potential cost difference for the hospital over the 3-year analysis period.

It was assumed that no medication waste occurred (all tablet sections were administered when a tablet division was needed and that the total amount of liquid in the bottles was administered in liquid dosage forms).

3. Results

Data on 488,762 administrations were recorded between February 6, 2013 and February 5, 2016. As shown in figure 2, a total of 121,274 oral administrations using liquid dosage forms (female: 58,737 and male: 62,538) from 129 different industrially manufactured drugs were identified over 3 years. They were given to 3,402 inpatients during 4,769 hospital stays. The mean age of children at admission was 3.9 years (SD 4.6 years). The mean duration of stay was 132 days (appendix A).

3.1 Drugs selected for substitution

Among the 129 drugs, 90 drugs were available in solid dosage forms, corresponding to 98,741 administrations in liquid dosage forms given to 3,127 inpatients. Of the 90 drugs, the 10 drugs identified as most frequently administered to children and eligible for substitution with authorized suitable alternative solid form were, in decreasing order of substitution frequency: paracetamol, cyamemazine, valproic acid, clonazepam, furosemide, prazepam, hydroxyzine,

alfacalcidol, amitriptyline, and levetiracetam. Table 1 shows the categories of patients eligible for the substitution, the alternative solid form, and the number of liquid form administrations for each drug that could be performed using suitable solid dosage forms. The 10 most frequently administered drugs represent 58% (56,924/98,741) of the total drug administrations in liquid dosage forms available in solid dosage forms. Among these, 34.6% (19,671/56,924) could be delivered using suitable solid dosage forms (the summary of the substitution assessment of the 10 drugs is presented in appendix B). There were 6 alternative solid dosage forms suitable for children aged at least 6 years old, 1 for children aged 10 to 12 years, and only 2 for younger children aged 28 days or more.

(Table 1)

3.2 Economic impact

Overall, 74.5 % (14,657/19,671) of the substitutions could be achieved with a less expensive suitable solid form. For 7 of the 10 drugs (i.e., cyamemazine, clonazepam, furosemide, prazepam, hydroxyzine, amitriptyline, and levetiracetam), all the substitutions were associated with potential savings for the hospital. Regarding paracetamol, the suggested substitutions were associated with a positive economic impact for 72% (5,066/7,045) of the administrations.

The computed potential cost savings for the hospital over 3 years was €145.6 for paracetamol, €10,537.80 for cyamemazine, €2.20 for clonazepam, €247.54 for furosemide, €18.59 for prazepam, €31.69 for hydroxyzine, €19.88 for amitriptyline, and €18.56 for levetiracetam.

For valproic acid and alfacalcidol, all suggested substitutions were associated with a negative economic impact. The potential loss for the hospital over 3 years would be €173.19 for valproic acid and €79.89 for alfacalcidol.

The cost differences of daily doses and the potential cost savings for the hospital for each of the 10 drugs are detailed in appendix C.

4. Discussion

This study found that about one third of the administrations of 10 drugs, frequently administered using liquid dosage forms in a pediatric population, could be substituted with at least one active, safe, and easy-to-swallow suitable solid dosage form. Notably, almost all liquid dosage forms of prazepam and cyamemazine used could be replaced with solid dosage forms (>97%).

The suggested substitutions were not found to be associated with substantial economic savings for the hospital. A large difference in costs between liquid and solid forms was observed only for cyamemazine but not for the other drugs (mean cost difference per daily dose: €6.90 for cyamemazine versus €0.2 for all the other drugs). These findings differ from those of a study in a British pediatric hospital ^[15] which found significant savings from drug substitution. The disparities in drug prices between various European countries and the difference in sets of studied drugs between both studies may explain this inconsistency. However, the calculation made herein did not account for the potential cost savings in terms of transportation and storage of solid dosage forms which present with decreased weights and volumes.

Unexpectedly, some highly used drugs in pediatric settings that are generally available in solid dosage forms, such as antibiotics, were not identified as appropriate for direct substitution with solid dosage forms in the present study. For example, during the 3-year period, 4,295 administrations of amoxicillin in liquid dosage forms were performed, 1,624 for rifampicin, and 1,049 for ciprofloxacin. The lack of possible substitution observed for these drugs can be explained by the fact that: the alternative solid form for amoxicillin was authorized only for children weighing 40 kg or more and no administration of amoxicillin was recorded for this category of patients; the available capsule of rifampicin was authorized only for children aged 6 years and older and only 38 administrations of rifampicin were recorded for this category of patients; ciprofloxacin was only available in large tablets (18 mm diameter for a 500 g tablet) and was not considered acceptable for the pediatric population ^[9]. This underlines that

alternative solid forms available for very young children are still scarce, confirming the need to develop formulations specific to this group ^[17].

In the present study, tablet division was considered acceptable as long as it remained in accordance with the instructions of the SmPC. Division increases the dosing flexibility of tablets. Additionally, scored tablets could provide ease in swallowing and may reduce costs. However, they could cause inaccurate dosing depending on the manufacturing quality ^[18].

The main limitation of this study is that all drug prescriptions were considered as compliant with the SmPC, as no information about the indication was available in the database, despite the frequency of off-label drug prescriptions in pediatrics. The use of a theoretical daily dose instead of the observed administered dosages of oral liquid dosage forms potentially overlooked administrations of hard-to-substitute low dosages to very young children and may have provided overestimated substitution rates. Inversely, liquid dosage forms can demonstrate different pharmacokinetic properties compared to solid dosage forms and necessitate more frequent administrations of lower dosages, which could yield artificially lower substitution rate findings. Interestingly, the substitution findings herein were lower than the 41% reported in a study based on the observed dosages in a pediatric hospital ^[15]. Although the criteria used were comparable to those of the present study, the sample was smaller with only 440 administrations analyzed. The use of real health data in the present study had the benefit of providing meaningful substitution assessments in an inpatient setting. It should be noted that other solid dosage forms not available in the hospital's pharmacy could be available on the market, meaning additional substitutions could be possible for outpatients or inpatients in other hospitals.

A major strength of this study lies in the fact that all suggested substitutions were completely in accordance with the drug marketing authorizations. Converting current inpatients from liquid to solid dosage forms according to the suggestions described herein is encouraged in our

hospital as well as in other hospitals. Pediatricians should be informed and sensitized to the benefits of using solid forms when possible ^[19]. However, improvement is needed regarding the availability of mini-tablets and other flexible solid oral dosage forms of the most commonly prescribed drugs in pediatrics. Producing more tablets and capsules available in different dosages is also encouraged. This study could guide all parties involved in the development and manufacture of medicinal products to improve the availability of suitable pediatric forms by defining the real and important needs in pediatric practice. In future research, we intend to develop an algorithm which could help practitioners choose a suitable alternative solid form when possible.

Conclusion

Despite the current limited use of oral solid dosage forms in pediatric practice in the HFME in Lyon, substitution from liquid to solid forms appears feasible. The 10 drugs identified as most appropriate for substitution were: paracetamol, cyamemazine, valproic acid, clonazepam, furosemide, prazepam, hydroxyzine, alfacalcidol, amitriptyline, and levetiracetam. Solid dosage forms for these drugs could have been used in about 35% of the total administrations that occurred using liquid dosage forms. Suitable alternative solid forms are generally available for children aged 6 years and older, while more flexible oral dosage forms are still needed for younger children. We intend to develop an intelligent algorithm that could suggest the prescription of a suitable alternative solid form to practitioners, when appropriate.

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Disclosure of interests:

The authors declare that they have no competing interest

Figure 1. A. The general stages of data processing in the substitution assessment and the economic impact assessment for every identified drug. B. Stages of data processing in the substitution assessment and the economic impact assessment for every identified drug.

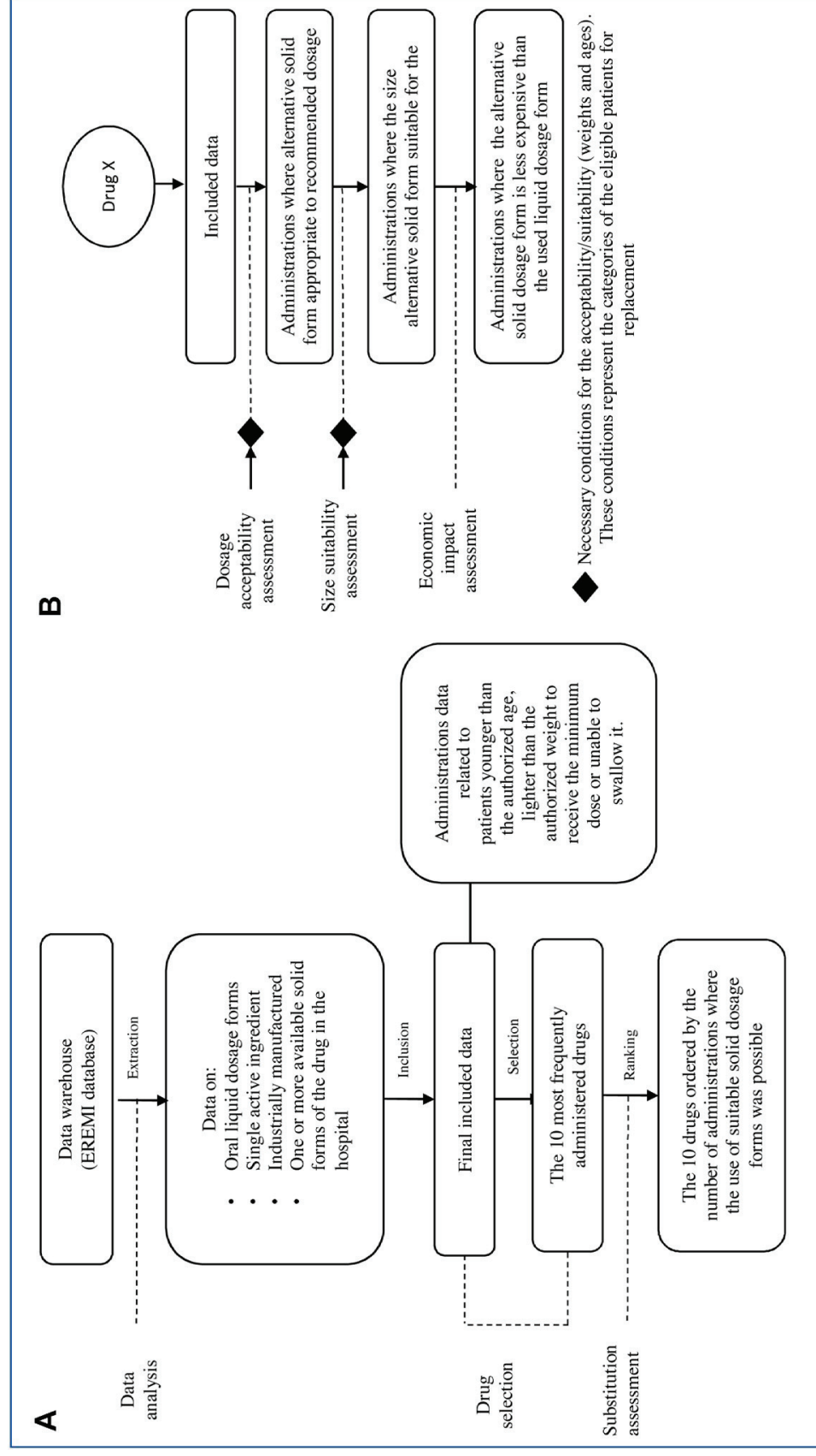


Figure 2: Flow chart of data analysis.

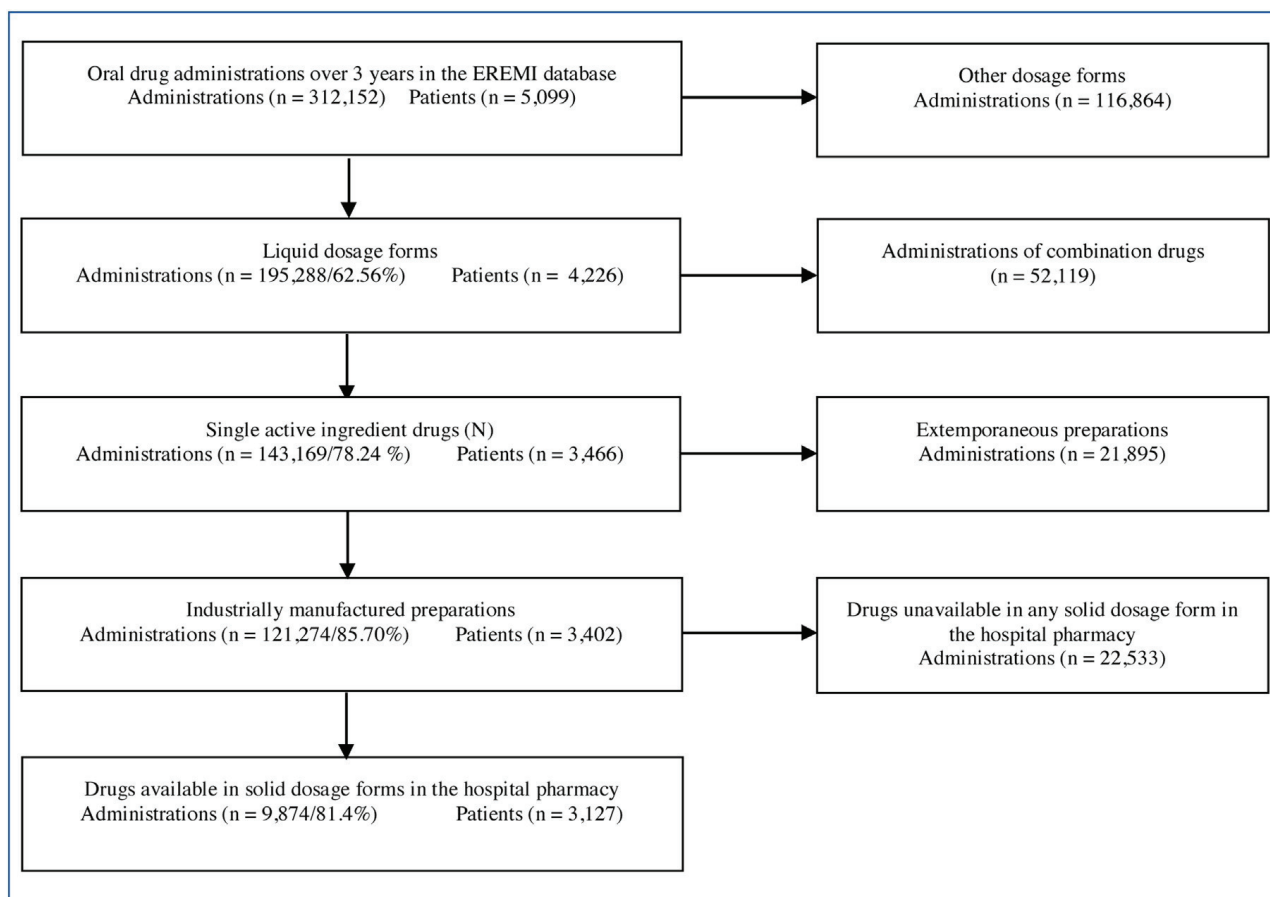


Table 1: The 10 drugs in liquid dosage forms most frequently administered to children eligible for substitution with authorized suitable alternative solid dosage forms.

Drug (NNT)	Eligible patients for the substitution		Alternative solid dosage form	Number of drug administration using liquid dosage forms ^a	Administrations in liquid dosage forms which could be performed using suitable solid dosage forms	
	Appropriate age range for substitution	Appropriate weight range for substitution (kg)			(n)	(% of total drug administration using liquid dosage forms)
Paracetamol	>=28 days	>=6	Powder for reconstitution and effervescent tablet.	12,452	7045	56.6
Cyamemazine	>=6 years	>=6.25	Tablet	3784	3672	97
Valproic acid	>=28 days	(>=3.33 and <=5) or >=6.67	Granule in sachets	2792	2460	88.1
Clonazepam	>=6 years	>=10	Tablet	4318	1798	41.6
Furosemide	>=6 years	>=10	Tablet	21,106	1303	6.2
Prazepam	>=6 years	—	Tablet	1276	1276	100
Hydroxyzine	>=6 years >=12.5 kg and <25 kg >=12 years and >25 kg		Tablet	3003	1019	34
Alfacalcidol	>=6 years	>20	Tablet	3742	575	15.4
Amitriptyline	>=10 years	—	Tablet	1367	437	32
Levetiracetam	>=12 years	>=25 and <50	Tablet	3084	86	2.8
Total				56,924	19,671	35

A number of administrations that could not be performed with an available solid dosage form was discarded from the drug selection analysis and the remaining was determined after a detailed substitution assessment.

^a The total drug administrations using liquid dosage forms = administrations that could be performed using suitable solid dosage forms + administrations that could not be performed with an available solid dosage form because of inappropriate age or weight.

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(Article III) Efficacy and safety outcomes of dosage regimens of amikacin in neonates: a systematic review

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KEYWORDS

Drug safety, Amikacin,
Neonates, Optimal
dosage regimen,
Pharmacokinetic

Summary

Aim of the study. —To identify amikacin dosage regimens evaluated in neonates and to describe their efficacy and safety results.

Methods. — a systematic review carried out following PRISMA guidelines. A bibliographic search was conducted until March 2021 on PubMed and until April 2021 on Cochrane. All studies evaluating efficacy and safety of amikacin in neonates were considered for inclusion.

Results. — This review included 59 studies involving 7,681 neonates. Among these studies, 12 were randomized controlled trials. One included data on clinical efficacy, eight on nephrotoxicity and six on ototoxicity. Thirty-seven studies provided data on amikacin serum concentrations and nineteen provided data on achievement of target serum concentrations. Serum concentration targets were variable between studies; 15 different target ranges of peak concentrations and 13 of trough concentrations were identified. From these publications, 37 different amikacin dosage regimens were proposed, most frequently based on post-natal age and/or on body weight. Rates of reported renal function impairment varied between 0 and 70%. Rates of reported ototoxicity varied between 0 and 20%. Mean peak concentrations ranged between 9.5 and 46.7 mg/L. Mean trough concentrations ranged between 1.2 and 14.4 mg/L. Rates of target achievement ranged between 14% and 100%.

Conclusion. — Numerous dosage regimens of amikacin were proposed for use in neonates. The next stage of our work will be to select the most appropriate dosage regimen based on the reported data in this systematic review.

Introduction:

Unlicensed or off-label drug prescriptions concern almost every infant in neonatology and can be more frequently observed as the gestational age (GA) decreases ^{1,2}. This is due to the lack of clinical studies in neonatology, which are difficult to conduct in new-borns for a variety of reasons, including ethics, parental permission, recruitment and lack of industrial investment ³.

Identifying the optimal dosage regimen of a drug for a new-born is complicated in the absence of clinical evidence-based data. This should not result from a simple adjustment of adult dosing according to the new-born weight or body surface area ^{4,5}.

At birth, some body organs are not yet mature, especially in preterm infants. High interindividual variability in drug pharmacokinetics is observed, due to ongoing changes in neonates' organ functions⁶.

The lack of evidence-based data on drug dosage regimens in neonates results in significant discrepancies between existing guidelines and recommendations. These discrepancies have been observed in practice at both national ⁷ and international levels ⁸. Leroux et al. observed 1 to 32 different dosage regimens per antibiotic in a survey conducted in 44-French neonatal intensive care units. For every drug used in new-borns, the optimal dosage regimen is ideally established by means of pharmacokinetic studies (PK) in neonates and validated in clinical safety and efficacy studies. A pragmatic approach to obtain acceptable data was proposed by the US Food and Drug Administration (FDA) in 1994 ^{9,10}. This approach was based on the extrapolation of efficacy findings from adults to the paediatric population in order to maximise the use of adult data.

Amikacin is an aminoglycoside bactericidal antibiotic. It was identified as the most commonly off-label antibiotic used in the neonatal intensive care units of our hospital ² and as 1 of the 20 drugs most frequently related to neonatal serious Adverse Drug Reactions (ADRs) reported

over 26 years in the French Pharmacovigilance Database ¹¹. Ototoxicity and nephrotoxicity are the two major adverse events associated with amikacin therapy. These events are more likely to occur in premature new-borns.^{12,13}

Despite the frequent use of amikacin in neonatology to treat suspected neonatal sepsis and its serious side effects, numerous different dosage regimens are used for neonates in practice. Since amikacin has a narrow therapeutic window ¹⁴, inaccurate dosage regimens can cause a lack of efficacy or conversely, reach toxic ranges ¹⁵. Both efficacy and safety of amikacin depend directly on its plasma concentrations ¹⁶⁻¹⁹. These concentrations depend on physiological factors in neonates, mainly on body water volume and renal function since amikacin diffuses in the extracellular space and is eliminated by glomerular filtration^{14,8}. These factors are continuously changing in new-borns according to age and weight. The percentage of extracellular water to total body weight in neonates is high at birth, it then decreases then with age, influencing the amikacin volume of distribution ²⁰⁻²². The renal function development occurs in the gestational period and continues after birth. It is observed day-to-day in neonates and impacts amikacin clearance ^{23,24}. Therefore, there is a need to consider these maturational changes when establishing a dosage regimen of amikacin.

The aim of this study was to identify all dosage regimens of amikacin that have been proposed for administration in neonates in the literature and to report the relationship between the different dosage regimens and their clinical or pharmacokinetic outcomes.

Methods:

Study identification

This systematic review was conducted following the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines. PubMed was searched until March 2021 and Cochrane was searched until April 2021. The search formulas used to define studies on PubMed were: *(aminoglycos*[title/abstract] OR amika*[Title/Abstract] OR*

("Amikacin"[Mesh] AND "Drug Administration Schedule"[Mesh]) OR "Amikacin/administration and dosage"[Mesh] OR "Amikacin/pharmacokinetics"[Mesh]) AND ("Neonatology"[Mesh] OR "Infant, Newborn"[Mesh] OR newborn[Title/Abstract] OR neonat*[Title/Abstract]).* The formula was simplified for Cochrane as follow: *Amikacin AND (infant OR neonate OR newborn).*

Study selection

Inclusion criteria were defined according to the Population, Intervention, Comparison, Outcome and Study (PICOS) design process, as follows:

Participants: neonatal infants (from birth to 28 days of age), term or preterm.

Interventions: studies focusing on amikacin alone or associated with other drugs.

Comparison: with or without comparator.

Outcomes: mean serum concentrations, or mean extravascular concentrations, or target achievement, or other outcomes on safety and efficacy of amikacin defined by the study.

Study design: interventional studies, observational studies, prospective, retrospective, or cross-sectional.

Case reports, review articles, comments or letters to editors were excluded. Meta-analyses were consulted to identify relevant included studies. We excluded bacteriological and epidemiological studies, fundamental studies, biochemical studies, infectious disease or clinical pathophysiological studies, studies focused on medication errors, quality, good clinical practices or cost-effectiveness analyses, articles that did not provide any data on dosage regimens of amikacin, non-human studies, articles written in languages other than English or French, and registered trials with no published articles.

After screening and removing duplicates, all article titles and abstracts, and full texts were independently reviewed for inclusion by two authors of this article. In case of discordance, one other author was consulted to confirm or reject the inclusion.

Data extraction and synthesis

Data were extracted independently by two authors. The following information was collected for each eligible article: first author's name, year of publication, route of administration, number of patients, main characteristics of studied population (weight, age), study design, therapeutic target if defined in the study, amikacin dosage regimen and variables considered for efficacy and toxicity results: mean peak concentrations, mean trough concentrations, rate of patients in and out of therapeutic range and other relevant findings.

Results

Bibliographic search:

A total of 1658 records were identified, of which 1551 were obtained from PubMed and 107 from Cochrane databases. After eliminating duplicates as well as checking titles and abstracts, 180 records were kept for a full text review. A total of 59 articles fulfilled the inclusion criteria and were included in our review (Figure 1).

Characteristic and findings of the included studies

Objectives, designs and population

A total of 7,681 neonates received amikacin in the 59 included studies. Eighteen studies included only preterm infants, 7 included term infants and 34 included both term and preterm infants. There were 28 studies that evaluated efficacy and/or toxicity of a given dosage regimen, 22 that focused on investigating the covariables affecting amikacin serum concentrations, 10 that evaluated amikacin toxicity, 6 that investigated amikacin concentrations in extravascular compartments and 1 that evaluated treatment duration. Twenty-five studies were prospective studies^{23,25-48}, 25 were retrospective studies^{13,15,49-72}, 4 used a mixed methodology⁷³⁻⁷⁶, 1 was a cross-sectional study⁷⁷ and 4 had unclear designs^{69,78-80}. Among the prospective studies, 12 were randomised controlled trials (RCTs)^{28-31,33-39,81}. Among the RCTs, 6 studies compared once-daily doses with multiple-daily doses, 4 compared amikacin with another antibiotic agent,

1 compared 2 durations of treatment and 1 compared the intravenous (IV) administration route with the intramuscular (IM) administration route.

Amikacin was administered intravenously in 44 studies, intramuscularly in 6 studies, intracerebroventricularly in 1 study and using different parenteral routes in 6 studies and there was no information provided regarding the route of administration in 2 studies. In 41 studies used IV route, the duration of administration was provided, 20 studies used IV infusion (>30min) and 31 studies used IV bolus (<30min), 4 of them used rapid IV bolus (< 5min) (Table 1).

Target serum concentrations

As shown in Table 2, 25 studies predefined target serum concentrations of amikacin, 23 predefined both target peak concentrations and target trough concentrations, and 2 predefined only target peak concentrations. We identified 15 target ranges for peak concentration and 13 for trough concentration. Target peak concentrations ranged from 15 to 40 mg/L, measured typically 30 min after the end of administration. Target trough concentrations ranged from 0 to 10 mg/L measured typically 30 min before the next administration.

Dosage regimen used

As shown in Table 2, 37 different dosage regimens (including 2 dosing charts) were identified from the included studies. The dosing schedule used in most cases was 7.5 mg/kg/12h (15 studies), while most of the remaining dosage regimens were mentioned in single studies. Twelve dosage regimens involved 1 covariable, 14 involved two covariables or more and 11 did not involve any covariables. The covariables identified were patient age (GA, postnatal age [PNA], post-conceptual age [PCA] and post-menstrual age [PMA]) patient weight and creatinine clearance levels. Patient weight and PNA were the most frequent covariables considered since PNA was involved in 17 dosage regimens and patient weight in 16 dosage

regimens (alone or with other factors). Patient weight and PNA were involved together in 9 dosage regimens.

Outcomes

Twelve studies, including four RCTs^{31,35,37,81}, provided results on clinical outcomes regarding safety and efficacy, one study evaluated clinical efficacy³⁵, eight reported data on renal toxicity of amikacin (measured by biological parameters)^{13,28,29,31,36,37,42,68,80}, six reported data on ototoxicity^{13,31,40,47,68,81} and three provided information on overall mortality^{25,78,80}.

Most of the included studies analysed serum concentrations: 31 studies, involving 23 different dosage regimens measured both peak and trough concentrations of patients, 3 studies involving 4 dosage regimens measured peak concentrations alone and 3 studies involving 2 dosage regimens measured trough concentrations alone. Mean peak concentrations ranged between 9.5 and 46.7 mg/L. Mean trough concentrations ranged between 1.2 and 14.4 mg/L.

Concerning achievement of target serum concentrations, 15 studies, involving 19 different dosage regimens, revealed rates of patients who achieved target serum concentrations, 4 studies, involving 3 different dosage regimens, showed rate of patients who did not achieve target serum concentrations. Rates of neonates who reached the target serum concentrations, defined by the authors, ranged between 14% and 100%.

Other pharmaceutical outcomes were also provided by the studies: 12 studies provided results on covariables influencing amikacin pharmacokinetics, 3 studies measured amikacin concentrations in the cerebrospinal fluid and 1 in the epithelial lining fluid (Table 2).

Discussion

This systematic review confirms that limited high-quality evidence data are available regarding the efficacy and safety of amikacin dosage regimens in neonates. This explains the absence of a unique recommended dosage regimen for neonates. Only one study dealt with the clinical efficacy of amikacin to evaluate the treatment duration of a given dosage regimen. The study

carried out by Pasha et al. used the treatment failure, defined as the reappearance of symptoms confirmed by laboratory findings as a primary outcome. It concluded that there is no evidence to support a duration of a five-day treatment instead of three³⁵. However, since this RCT allowed excluded patients with treatment failure at the 3th day of treatment before randomization and associated amikacin with other antibiotics, it does not provide information on the efficacy of the specific dosage regimen that was used.

Rates of ototoxicity varied between 0 and 20% for 7 different dosage regimens^{27,31,40,47,68,81}. Both highest and smallest rates were reported for the same dosage regimen (15 mg/kg/24h) indicating the need for studies including larger sample sizes. Because of the small sample sizes of the studies investigating ototoxicity, it is neither possible to conclude on any relation between a dosage and ototoxicity, nor to establish a frequency level of this adverse drug reaction. The low number of studies investigating this side effect could be attributed to the fact that ototoxicity takes long time to be diagnosed, is difficult to demonstrate in neonates and is reversible in around one out of two cases^{79,82}. Demonstrating ototoxicity prospectively requires patients to be followed-up for several years and a high number of participants⁸³. The unique RCT investigating ototoxicity followed-up patients only until the 10th day of treatment⁸¹. However, available data seem to point that hearing alterations could be induced by a long duration of treatment and serum trough concentrations ≥ 10 mg/mL^{13 77}. These high levels of trough concentrations are more likely to be reached with short dosage intervals³⁷.

Rates of renal function impairment caused by amikacin varied between 0 and 70%^{13,31,37,80}. The dosage regimen of 7.5 mg/kg/12h was the most frequently associated with reported cases of renal toxicity.^{29,31,36,68,80} The RCTs conducted by Kotze, Abdel Hady and Vasquez-Mendoza compared one-daily doses to twice-daily doses, and failed to demonstrate a significant difference in renal toxicity between both treatment groups because of their small sample sizes^{28,31,37}. The frequency of the nephrotoxicity cases was associated with high levels of serum

trough concentrations (>8 mg/L) in two RCTs^{29,37}. Different markers were employed to detect renal toxicity of amikacin across studies, such as levels of serum creatinine and N-acetylglucosaminidase (NAG). The sensitivities of these markers were different: NAG was a sensitive marker of tubular injury, but it was not sufficient alone to predict clinical impact³¹. On the contrary, the use of serum creatinine could underestimate the nephrotoxicity of amikacin in neonates because the increase in creatinine clearance by maturation could affect the results⁸⁴. Multiple cofactors could interfere with the evaluation of amikacin tolerance. Assessing nephrotoxicity could be biased by hypoxia, septic status and the specificity of markers. Assessing ototoxicity could be difficult to highlight because of the rarity of cases, sensitivity of the tests, and time to onset. Assessing both ototoxicity and nephrotoxicity caused by the different dosage regimens of amikacin could also be biased since amikacin was also associated with other antibiotics, suggesting that trough concentrations of amikacin should always be considered.

Regarding the pharmacokinetic results, 6 dosage regimens employed in 6 studies succeeded to reach target serum concentrations established by the authors in 70% of patients for both C_{peak} and C_{trough}^{31,45,50,73–75} while 16 dosage regimens used in 13 studies^{26,28,30,31,45,46,48,50,51,57,73–76} succeeded to reach target serum concentrations in 50% of patients. The majority of these 16 dosage regimens considered one or more covariables (8 dosage regimens considered 2 covariables, 6 others considered 1 covariable). This is supported by the fact that preterm infants were expected to reach toxic concentrations more frequently compared to term infants when using the same dosage⁵³. Two other dosage regimens were used in three studies^{38,80,85} and achieved mean serum concentrations in the therapeutic targets defined by the authors.

Serum concentration targets were widely different across studies. The target peak concentrations of amikacin progressed over time: it was defined between 15–30 mg/L in the 80s^{70,76,80}, then between 20–30 mg/L for several years^{25,38,45,74} and between 24–35 mg/L in

more recent studies^{15,49,51,85}. Labaune et al. proposed an adaptation of the target C_{max} with GA⁷⁵. The adoptions of these targets were not justified in the studies. It is agreed that peak concentrations of amikacin should ideally reach eight to ten times the minimum inhibitory concentration (MIC). The MIC depends on the pathogen and local bacterial resistance⁸⁶. Safe trough concentrations less than 5 or 10 mg/L were the most frequently used for years. Target trough concentrations between 3-8 mg/L were clearly defined for the first time by Cookson et al. in 1980. Deramoudt-Dutrus et al. defined a stricter target from 2 to 5 mg/L in 1989 as an optimal target with a target less than 10 mg/L being considered to be safe³⁰. Later, another author considered a target between 4 and 10 mg/L in 1991⁴⁵. Target trough concentrations were also adapted with GA in 2001⁷⁵. Vucicevic et al. defined different targets according to the number of administrations per day⁸¹. Two strict targets less than 3 mg/L were proposed in 3 recent studies^{15,46,49}.

Many covariates were found to correlate with the serum concentrations of amikacin in neonates. These covariates reflect the changes in amikacin distribution and elimination during maturation and explain interindividual variability. The anthropometric covariates identified were weight^{15,27,56,63,64,69,87}, GA^{27,39,63,66,69,72}, PNA^{15,66,70}, PMA and PCA^{45,54,57,65,73,76}. Although PMA and PCA indirectly reflect both PNA and GA, their use could be less accurate in reflecting maturation changes before and after birth compared to the use of GA and PNA separately. Other medical conditions were also found to influence pharmacokinetic values of amikacin in neonates such as hypoxemia^{27,69}, respiratory distress syndrome⁶⁷, clinical state of the patient⁸⁸, renal function^{51,54} and the coadministration of ibuprofen, indomethacin or acetylsalicylic acid^{44,58,60,62,89}. These medical conditions associated with amikacin prescriptions were considered for adjusting the dosage regimen in very few studies. De Cock et al. mentioned that the time interval between doses should be extended from 6 to 10 hours in case of asphyxia or co-

administration of ibuprofen^{15,46}. Illamola et al. proposed an adapted dosage regimen for neonates with renal failure⁵¹.

Our systematic review showed the wide range of dosage regimens of amikacin in neonates. The results could be used to select the dosage regimen of interest for clinical evaluation.

This review has several limitations. The majority of studies had a small number of participants as only 12 of the 59 studies included more than 200 patients. The small sample sizes are an obstacle to detect the impact of amikacin on organ functions. Many studies therefore did not detect toxicity. Others did but could not conclude on the onset frequency of the adverse effects for the same reason. There were only 12 RCTs included in this review, 7 of which were published before 2000, and their randomization method was not clearly reported. A total of 28 included studies were published before 2000, which means that they may not reflect the current practice. Reported duration of administration, sampling time and assay methods of serum concentrations differed between studies.

In a further step, we intend to select the most appropriate dosage regimen for term and preterm infants through a critical reading of the available data and propose to use it in our neonatal services. This selection is challenging due to the variability of their level of evidence, target ranges and types of outcomes. We did not identify a selection method that considers all these variabilities. Furthermore, no acceptable thresholds were identified for both clinical and pharmacokinetic outcomes. The definition of these thresholds by experts appears to be essential for the selection. The Delphi technique could be used for this step. Once done, we will select the most appropriate dosage regimen based on three main items: the level of evidence of the study, the consideration of specific covariables for dosing in neonates (i.e., age, weight) and the results of efficacy and safety of the drug. This proposition could be done as follows: first, by classifying the included studies according to their level of evidence as presented in Figure 2, then, by critically examining the data from the studies with the highest level of evidence to

determine if it is possible to recommend a dosage regimen. This examination could be performed by a panel of two persons or with the help of the three following questions: does the dosage regimen consider specific covariable(s) for dosing in neonates? Are the results on the efficacy and safety of the drug satisfying? Is the number of patients sufficient? Each examination of a set of studies should finish either by recommending a dosage regimen or considering that it is not possible to recommend a dosage regimen from the available data. As a second option, some dosage regimens could be eliminated and other considered for further examination: the studies classified in the next lower level of quality of evidence could be included in this case. This strategy allows us to select dosage regimens with different level of evidence from published data. An assessment of the quality of the included studies will be carried out to facilitate this selection. Given the different types of included studies, the use of different assessment tools will be necessary.

Conclusion

Numerous dosage regimens of amikacin for neonates were identified. The designs, dose regimens, therapeutic targets, and types of outcomes were highly variable between studies. Most of the studies evaluated amikacin in both term and preterm neonates. Clinical efficacy and safety of amikacin in neonates are not well studied. Our knowledge regarding the majority of dosage regimens is based on their pharmacokinetics results. High variability in target serum concentration ranges of amikacin was detected. In the next step, we intend to select the most appropriate dosage regimen among available ones based on a pre-established selection method considering the level of evidence of the study, the consideration of covariables in the dosage regimen, and the efficacy and safety results. Defining acceptable safety results of different types of outcomes by experts is recommended. Future studies would be needed to investigate the

clinical safety or/and safety of one or more selected dosage regimens. A large number of participants would be required for these studies.

Figure 1: Flow diagram for selection of articles

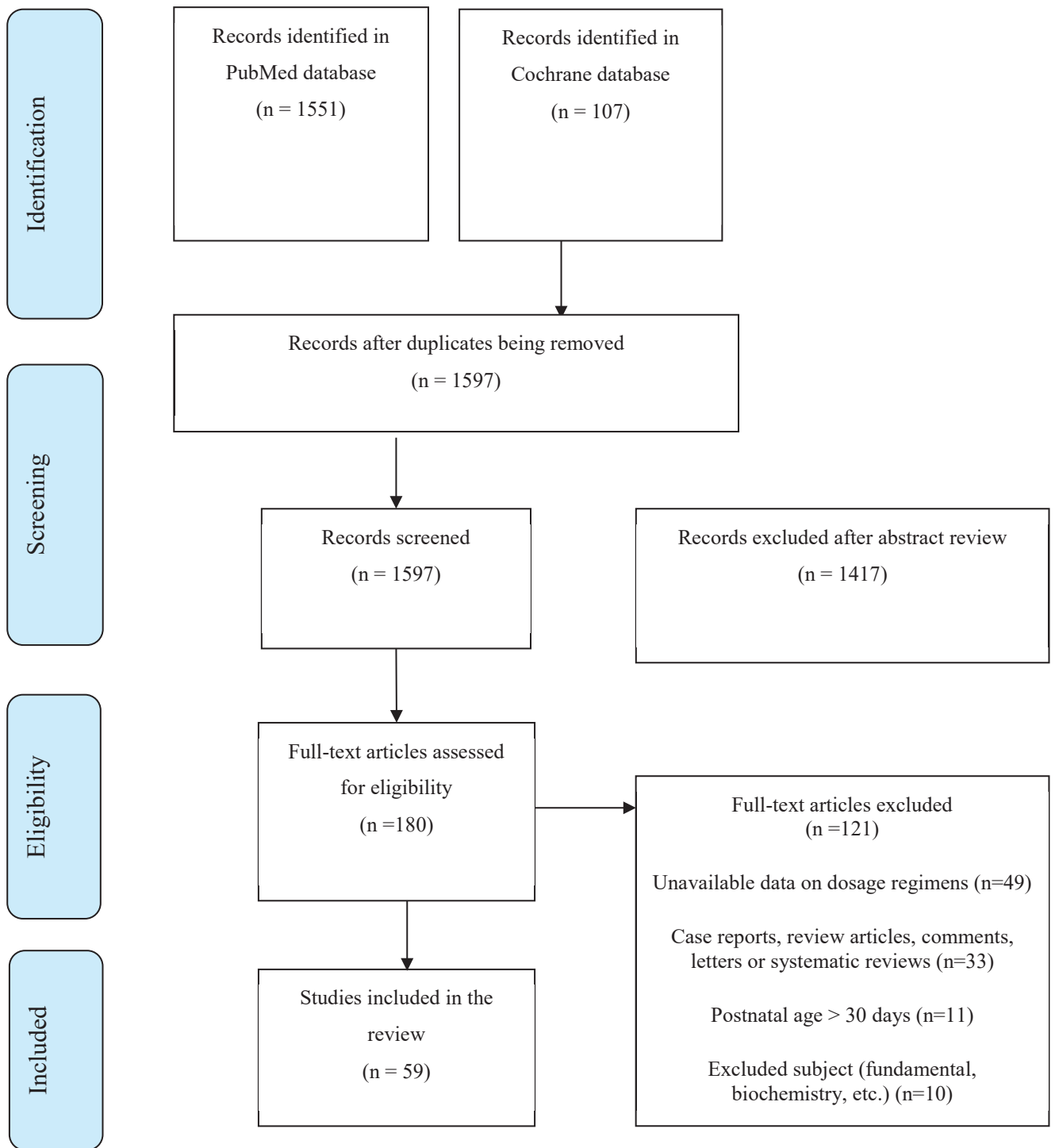


Table 1: Design and target population of each of the identified studies.

Design	Articles	Year	Main objective	Route and Duration of Administration	Nb. of Subjects and Characteristics	Observed Age: GA (w) PNA (d) PMA (w) Mean \pm SD (min-max)	Birth weight (kg) Mean \pm SD (min-max)	
Prospective	(OD x MDD)	Bordbar et al. ³⁸	2018	TE	IV (30-60 min)	40 preterm infants (group1 multiple dose: 20, group 2 single dose:20)	Group1: GA: 33.1 \pm 2.1 Group2:GA: 32.1 \pm 2.1 Group1: 2.203 \pm 0.538 Group2: 1.974 \pm 0.577	
		Pasha et al. ³⁵	2014	TDE	IV (N.D)	60 near term infants (group1 3day: 30 group2 5day: 30)	Group1: GA:37 \pm 1.66 PNA: 8.3 \pm 10.9 Group2: GA:37.2 \pm 2.09 PNA: 17.5 \pm 19.5	
	(OD x TD)	Vucicevic et al. ⁴⁸	2014	DRE	IV (60min)	31 term infants (group1 OD: 15 group2 TD: 16)	N.D	Group 1: 3.44 \pm 0.66 Group2: 3.37 \pm 0.52
		Abdel Hady et al. ²⁸	2011	DRE	IV (60min)	30 term infants ^b (group1 OD: 15, group2 TD: 15)	Group 1: GA: 37.8 \pm 1.6(35-40) Group2: GA: 38.1 \pm 1.4(36-41)	Group 1: 2.9 \pm 0.4(2.4-3.5) Group2: 3.1 \pm 0.5(2.3-4.2)
	RCT	Vasquez-Mendoza et al. ³⁷	2007	DRE, TE	IV (30min)	120 term infants (group1OD: 60 group2TD: 60)	Group1: PNA: 2.3 \pm 4.8 GA: 38.8 \pm 1.1 Group2: PNA: 1.4 \pm 2.5 GA: 38.7 \pm 1.1	Group1: 3.144 \pm 0.4 Group2: 3.099 \pm 0.5
		Kotze et al. ³¹	1999	DRE, CE	IV (30sec)	40 term infants (group1 OD: 20, group2 TD: 20)	Group 1: PNA: 0.67(0-4.3) GA: 39.9(37-41) Group1: PNA: 0.64(0-2.8) GA: 39.9(37-41)	Group 1: 3.086 (2.710-3.640) Group1: 3.194 (2.5-3.910)
	(IM x IV)	Langhendries et al. ³²	1993	DRE	IV (30min)	22 preterm infants (group1 OD:10, group2 TD: 13)	Group1: PNA: 1.4 \pm 1.2 GA: 37.6 \pm 2.32 Group2: PNA: 1.54 \pm 1.2 GA: 39.1 \pm 1.8	Group1: 2.91 \pm 0.795 Group2: 3.413 \pm 0.612
		Deramoudt-Dutrus et al. ³⁰	1989	DRE	IM, IV (30min)	26 preterm and term infants (group IV: 26 group IM: 18)	Group IV: PNA: 3.6 GA: 31.4 Group IM: PNA: 6.5 GA: 31.5	GroupIV:1.648 GroupIM:1.969
	(drug x drug)	Adelman et al. ²⁹	1987	TE	IV (30min)	Preterm infants (Amikacin:56 mezlocillin: 56)	GA: 30.8 \pm 1.8	1.509 \pm 0.240
		McCracken et al. ³⁴	1984	EXV	IM, IV (N.D)	Amikacin ^a : 11 preterm and 13 term infants Moxalactam ^a : 12 preterm and 10 term infants	PNA:19 \pm 18	N.D
Rajchgot et al. ³⁶		1984	TE	N.D	Preterm infants (amikacin: 47 gentamicin: 60 chloramphenicol: 26)	PNA: 10.6 \pm 1.3 GA: 30.7 \pm 0.5	1.457 \pm 0.74	
	Marks et al. ³³	1978	DRE, EXV	IV (60 min)	Term and preterm infants (amikacin: 20 gentamicin:20 tobramycin:20)	PNA: 2.1 (0 - 5)	11 < 2.5 9 \geq 2.5	

Table 1: Design and target population of each of the identified studies (continued)

Design	Articles	Year	Main objective	Route and Duration of Administration	Nb. of Subjects and Characteristics			Target Population	
								GA (w) PNA (d) PMA (w) (min-max)	Observed Age: (min-max)
Controlled (drg x drg) N-R	Finizzo-Hieber et al. ⁴⁰	1985	TE	IM, IV (N.D)	Term and preterm infants: 50 with amikacin 49 netilmicin 51 non-treated		GA: 35.5 (28-41)		N.D
	Alinejad et al. ⁴²	2018	TE	IV (30 min)	80 term infants (amikacin:40, gentamicin:40)		GA: 35.4 \pm 5.39 PNA: 3.22 \pm 2.50.		2.470 \pm 0.78
	Amponsah et al. ²⁵	2017	DRE, CE	IV (2-3 min)	247 (term: 116 preterm: 131)		GA: 35(25-44) PNA: 1.23(0.16-21.75)		2.3 (0.9 - 5.2)
	Smits et al. ⁴⁶	2015	DRE	IV (20 min)	579 term and preterm infants		GA: 34(24-41) PNA: 2(1-30) PMA: 34(24-45)		CW: 2.1 (0.42-5.04)
	Tayman et al. ²³	2011	EXV	IV (20 min)	17 term and preterm infants		PNA: 3.5(2-37) PMA: 31.9(25.1-41)		1.715 (0.55-3.54)
	Ruggieri-Marone et al. ⁴⁷	2007	TE	IV (N.D)	67 infants (control term :33, term +amikacin: 19 preterm+amikacin:15)		N.D		N.D
	Berger et al. ²⁶	2004	DRE	IV (30 min)	25 preterm low weight infants		PNA: 18(6-97) GA: 25(23-30)		0.739 (0.5-1.345)
	Langhendes et al. ⁴⁴	1998	DRE	IV (30 min)	177 term and preterm infants		GA: 33.6 \pm 4.1		N.D
	Langhendes et al. ³⁹	1993	DRE	IV (30 min)	114 near-term (3 age groups: group1 GA< 31:14 group2 GA 31-34: 24 group3 GA 34 - 37: 38 group4 37 - 41: 38)		Group1: GA: 27.7 \pm 1.12 Group2: GA: 32.0 \pm 0.69 Group3: GA: 35.5 \pm 0.32 Group4: GA: 38.7 \pm 1.32		Group1: 1.052 \pm 0.287 Group2: 1.733 \pm 0.22 Group3: 2.311 \pm 0.42 Group4: 3.157 \pm 0.585
	Petersen et al. ⁴⁵	1991	DRE	IV (30 min)	38 term and preterm infants		PNA: 4.1 \pm 6.8(1.0-21.0) GA: 33.1 \pm 4.4(25.0-40.0)		2.1 \pm 1 (0.6-5.4)
Prospective	Wright et al. ⁴¹	1981	EXV	ICV	8 ^a Term and preterm infants with meningitis		PNA: 30.6(7-70)		N.D
	Want et al. ⁴³	1979	DRE	IM	22 preterm infants		GA: 30(26-34)		1.32 (0.76-2.43)
	Sardeman et al. ²⁷	1976	DRE	IM	5 term and preterm infants		PNA : 3.8 (1-7)		3.058 (1.500-4.080)

Table 1: Design and target population of each of the identified studies (continued)

Design	Articles	Year	Main objective	Route and Duration of Administration	Nb. of Subjects and Characteristics	Target Population
						Observed Age: GA (w) PNA (d) PMA (w) Mean \pm SD (min-max)
						Birth weight (kg) Mean \pm SD (min-max)
Cross-sectional	Poblano et al ⁷⁷	2003	CE	N.D	35 term and preterm infants (mostly preterm)	GA: 31.49 \pm 2.98 PMA: 40.31 \pm 6.72 1.409 \pm 0.509
	An et al ⁷⁴	2014	DRE	IV (30 min)	181 : 127 preterm infant, 54 term infants (group1 analysis : 107 group2 validation: 74)	Group 1: GA: 32.9 \pm 5(24.1-41.4) PNA: 24.8 \pm 21.9(2-112) PMA: 36.3 \pm 4.9 (25.1-46.7) Group 2: GA: 33.3 \pm 5.3(24.7-41.0) PNA: 23.9 \pm 22.5(3-108) PMA: 36.7 \pm 5.2(26.3-49.9) PNA < 2 GA: (24-41)
Retrospective PK modeling and prospective validation	Labauane et al ⁷⁵	2001	DRE CE	IV (1 min)	term and preterm infants (modeling:63 validation:57) validation GA < 30 weeks, n = 8; 30 < GA < 34weeks,n=18; term infant=31)	(0.5-4.6)
	Kenyon al ⁷³	1990	DRE	IV (45 min)	88 preterm, low weight infants (group1-modeling:59 group2-validation: 29)	Group1: PMA: 30.57 \pm 3.46 Group2: PMA: 31.45 \pm 5.32
	Roze et al ⁷⁶	1989	DRE	IV (N.D)	127 term and preterm infants (group1-modeling: 64. Group2-validation: 63)	Group1: PNA: 13.3 \pm 17.92 GA: 34.7 \pm 4 PMA: 36.7 \pm 4.1 Group2: PNA: 9.8 \pm 16.1 GA: 34.6 \pm 4.3 PMA: 36.12 \pm 4.5
	Illamola et al ⁹⁰	2016	CE DRE	IV (30-60min)	202 term and preterm infants (modeling: 149 external test: 53)	GA: 31.8(24.3-41) PNA:28(1-86) PMA: 35.4(24.3-41)
Retrospective PK modeling and external validation	De Cock et al ¹⁵	2012	CE	IV (20-30min)	874 term and preterm infants (modeling database1: 162 external database2: 712)	Database1: PNA: 2(1-3) GA: 28(24-30) Database2: PNA: 2(1-30) GA: 33(24-43)
	Cristea et al. ⁴⁹	2017	DRE	IV (20-60min)	930 near term neonates with Perinatal Asphyxia Treated with Hypothermia	GA: 32(24-41) PNA: 2(1-30).
	Hughes. et al. ⁵⁰	2017	DRE	IV (N.D)	278 term and preterm infants (group1dose1: 144 group2 dose2: 134)	Group1: GA: 34.3(30-37.9) PNA:1(0-2) PMA: 35(30-38) Group 2: GA: 36.9 (30.1-38.9) PNA: 1(0-2) PMA: 37.0(33-39)
	Allegaert et al ⁵⁷ (Br J Clin Pharmacol)	2006	CE	IV (20min)	205 preterm infants (group1-dose1:129 group2-dose 2: 76)	Group1,2: GA: 28 (24-30)
						Group1: 1.047 \pm 0.346 Group2: 1.11 \pm 0.341

Table 1: Design and target population of each of the identified studies (continued)

Design	Articles	Year	Main objective	Route and Duration of Administration	Nb. of Subjects and Characteristics	Target Population	Birth weight (kg) Mean \pm SD (min-max)
Retrospective	Allegaert et al. ⁵⁹ (Pediatr Crit Care)	2006	CE	IV (15min)	240 preterm infants (Group1+dopamine: 115, without dopamine: 125)	Observed Age: GA (w) PNA (d) PMA (w) Mean \pm SD (min-max)	Group1: 0.89 \pm 0.331 (0.45-1.98) Group2: 1.165 \pm 0.308 (0.475-1.88)
	Allegaert et al. ⁶⁰ (Pediatr Nephrol)	2005	CE	IV (15min)	142 preterm infants (group1+ibuprofen: 50, group2 control: 59 group3+acetylsalicylic acid: 33)	Group1: GA: 27 \pm 1.8(24-30) Group2: GA: 29 \pm 1.2(24-30) Group1,2,3: 28 (24-30)	Group1: 1.02 (0.48-1.91) Group2: 0.98 (0.45-1.98) Group3: 0.94 (0.475-1.55)
	Allegaert et al. ⁶¹	2005	CE	IV (15min)	204 preterm infants (group1+ ibuprofen: 93, group2 +placebo: 111)	Group1: 29 \pm 2.6(24-34) Group2: 29 \pm 2.5(24-34)	Group1: 1.237 \pm 0.505 Group2: 1.2 \pm 0.504
	Allegaert et al. ⁶² (Biol Neonate)	2004	CE	IV (15min)	73 preterm infants (group1+ ibuprofen: 34, group2 +placebo: 39)	Group1: 27.4 \pm 1.7 Group2: 27.8 \pm 2	Group1: 9.82 \pm 0.38 Group2: 1.064 \pm 0.39
	Palix et al. ⁶⁶	1986	DRE	IV (30 min)	23 preterm infants (2 groups/2 doses)	GA: 32.48 \pm 2.66 (27-37)	1.682 \pm 0.395 (1.08-1.5)
	Philips et al. ⁷¹	1982	DRE	IV (N.D)	18 term and preterm infants (group1 \leq 1g: 5, group2 $>$ 1g: 13)	Group1: GA: (24-30) Group2: GA: (27-40)	Group1 \leq 1 Group2 $>$ 1
	Endo et al. ¹³	2019	TE	IV (30-60 min)	20 preterm infants	GA: 30 \pm 5.1	1.28 \pm 0.81
	Allegaert et al. ⁵⁴ (Covariates)	2008	CE	IV (20min)	715 term and preterm infants	PMA: (24-43)	(0.385-4.780)
	Allegaert K et al. ⁵⁵	2008	EXV	IV (20min)	43 term and preterm infants	PNA: 3 (1-29) GA: 35(25-41) PMA: 36(26-41)	2.43 (0.865-3.86)
	Allegaert et al. ⁵⁶	2007	CE	IV (20min)	513 preterm infants (amikacin: 282)	GA: 28(24-30) PMA: 27.8 \pm 1.8(24-30)	0.970 (0.45-1.980)
Allegaert et al. ⁵⁸ (Methods Find Exp Clin Pharmacol)	2006	CE	IV (15min)	205 preterm infants	PMA: 27.8 \pm 1.8(24-30)	1.07 \pm 0.340 (0.45-1.98)	
Descriptive	Bleyzac et al. ⁶³	2001	CE	IV (N.D)	131 term and preterm infants	PNA < 2 GA: (24-41)	N.D
	Botha et al. ⁶⁴	1999	CE	IV (2min)	53 term and preterm infants	PNA: 3.1 \pm 3.1 GA: 35.1 \pm 3.6	2.1 \pm 0.8
	Padovani et al. ⁶⁵	1993	CE	IM	32 (preterm: 19 term: 13)	Preterm: GA: 32.0 \pm 3.6 Term: GA: \geq 37	Preterm: 1.74 \pm 0.81 Term: 3.190 \pm 0.82
	Rusconi et al. ⁶⁷	1983	CE	IM	39 term and preterm infants	GA 34.7 \pm 3.4	2.158 \pm 0.95 (0.93-4.55)
	Parini et al. ⁶⁸	1982	TE	IM	35 term and preterm infants	GA: 34.9 \pm 3.5(28-42)	2.18 \pm 0.89
	Assael et al. ⁷²	1982	CE	IV (N.D)	29 term and preterm infants	GA: 34.5 \pm 3.3(28.5-42)	1.98 \pm 0.92
	Prober et al. ⁷⁰	1981	DRE	IV (60min)	40 premature infants	GA: 29.5 \pm 3.4 PNA: 26 \pm 26(3-124)	1.21 \pm 0.69
	Sherwin et al. ⁸⁵	2009	DRE, CE	IV (30min)	80 term and preterm infants of PNA >3d	PNA: 9(3-64) GA: 28(24-41) PMA: 29.43(24.7-44)	0.970 (0.44-4.4)
	Siddiqi et al. ⁵³	2009	TE	IV (30min)	104 (group1 preterm: 52, group2 term: 52)	Group2: PNA: 1.4 \pm 0.8(1-3) GA: 32.2 \pm 2.1(29-36)	Group1: 1.9 \pm 0.48 Group2: 2.7 \pm 0.4
	PK modeling					Group2: PNA: 2.1 \pm 1.1(1-5) GA: 38.7 \pm 1.1(37-40)	

Table 1: Design and target population of each of the identified studies (continued)

Design ⁵	Articles	Year	Main objective	Route and Duration of Administration	Nb. of Subjects and Characteristics	Target Population	GA (w) PNA (d) PMA (w) Mean \pm SD (min-max)	Observed Age: (min-max)	Birth weight (kg) Mean \pm SD (min-max)
	Cookson et al. ⁸⁰	1980	DRE	IM	35 preterm low weight newborns (3groups)		GA: 28.5(24-37)		1.393 (0.77-2.9)
	Myers et al. ⁶⁹	1977	DRE, CE	IM, IV (30min)	36 preterm low weight infants (Normoxemic:11 Hypoxemic:25) (IV:15, IM:16)		PNA: 2.2 GA: 36 (30-42)		2.499 (0.780-4.495)
Unclear	Howard et al. ⁷⁸	1976	DRE, EXV	IV (20min) IM, ICV	Term and preterm infants (pharmaceutical evaluation: 11 clinical evaluation: 45)		N.D		N.D
	Howard et al. ⁷⁹	1975	CE	IV (20min), IM	32 Term and preterm infants		N.D		N.D

Main objective abbreviations: TE: toxicity evaluation ; DRE: dosage regimen evaluation ; CE: Covariate exploration ; TDE: treatment duration evaluation ; EXV: extravascular compartment study

Design abbreviations: RCT: randomized controlled trial; N-R: not randomized; N-C: not controlled

Route of administration abbreviations: IV: intravenous; IM: intramuscular; ICV: Intracerebroventricular

Target population abbreviations: N.D: No data; OD: once-daily; TD: twice-daily; PCA: post conceptual age; PNA : postnatal age; PMA: Post-menstrual age; GA :gestational age; CW: current weight

^a Including infants with PNA > 30d

^b Age (GA) \geq 36, weight \geq 2500 g

When two drug groups are studied, only the ages and weights of amikacin group patients were retrieved.

Table 2: Dosage regimens and main findings of the included studies

First author	Year	Target Serum Concentrations (mg/L) C _{peak}	Variables Involved	Dosage Regimen Used		Main Finding		Other findings	
				Dosage Regimen	Dosage Regimen	Levels in Therapeutic Range	Infra /Supratherapeutic		
Bordbar et al. ³⁵	2018	20–30	Age (PNA) and weight	Group1: 1) 7.5 mg/kg/12h 2) 10 mg/kg/12h 3) 7.5 mg/kg/8h 4) 10mg/kg/8h Group2:	Group1: 16.92±8.08 Group 2: 24.38±10.08 (P <0.05)	Group1: 7.04±5.03 Group 2: 4.31±2.96 (P <0.05)	N.D	N.D	N.D
Pasha et al. ³⁵	2014	Non	Weight	1) 7.5mg/kg/12h 2) 10mg/kg/12h	N.D	N.D	N.D	N.D	Clinical treatment failure Group1:1 Group2: 0
Vucicevic et al. ⁴⁸	2014	TD: 30 (unclear)	Age (PNA) 1) ≤ 7 d 2) > 7 d	Group1: 1) 15 mg/kg/24h 2) 20 mg/kg/24h Group2: 1) 7.5 mg/kg/12h 2) 10 mg/kg/12h	Group 1: 36.39 ± 9.75 Group2: 21.79 ± 6.22	Group 1: 3.99 ± 1.97 Group 2: 5.67 ± 2.20	Group 1: 100% < 10 93% < 5 Cpeak: 86% < 30 Group2: 100% < 10 31.25% < 5 Cpeak:87.5% > 30	Group1: Cthrough:7% Group2: Cthrough: 69% < 5 . Cpeak:12.5%	No cases of ototoxicity in both groups (until the 0 th day of treatment)
Abdel Hady et al. ²⁸	2011	Non	Non	Group1:15 mg/kg/24h Group2:7.5mg/kg/12h	Group1: 27.7±6.6 (13.6-43.3)	Group1: 2.3±1.47 (0.5-6.6)	Group1: Cthrough:100% Group2: Cthrough: 87%	Group1: Cthrough: 0 % Cpeak:100 % Group2: Cthrough: 100 % Cpeak:40 %	No significant difference between groups in nephrotoxicity
Vasquez-Mendoza et al. ³⁷	2007	Non	Non	Group1 OD: 20mg/kg/24h Group 2 TD: 10mg/kg/12h	Group 1: 24.2±12.5 Group 2: 22.6±8.2 P>0.05	Group 2: 4.6±2.5 (2.8-11.3) Group 1: 4.2±3.4 Group 2: 8.2±3.6 P<0.05	Group1: Cthrough: 100 % Cpeak:100 % Group2: Cthrough: 100 % Cpeak:40 %	Group1: Cthrough: 0 % Cpeak:0 % Group2: Cthrough: 0% Cpeak: 60%	Renal toxicity: group : 20% Group1: 70% (14/20) Group2: 31.6%. P<0.05
Ketze et al. ³¹	1999	> 20	Non	Group1: 15mg/kg/24h Group2: 7.5mg/kg/12h	Group1: 30.57±2.81 (25.81-35.12) Group2: 18.49±4.02 (13.08-26.82)	Group1: 1.74±0.84 (0.14-3.95) Group2: 3.57±2.40 (0.13-9.37)	Group1: Cthrough: 100 % Cpeak:100 % Group2: Cthrough: 100 % Cpeak:40 %	Group1: Cthrough: 0 % Cpeak:0 % Group2: Cthrough: 0% Cpeak: 60%	Renal function impairment Group1: 70% (14/20) Group2: 55% (11/20) (P<0.05) Otoxicity: 0% in both groups.

First author	Year	Target Serum Concentrations (mg/L)			Dosage Regimen Used		Main Finding				Other findings
		Peak	C _{trough}	C _{trough}	Variables Involved	Dosage Regimen	mean C _{trough}	Levels in Therapeutic Range	Infra /Supratherapeutic		
Langhendries et al. ³²	1993	Non	Non	Non	Non	Group 1: 15 mg/kg/24h Group 2: 7.5 mg/kg/12h	Group 1: 23.06±3.3 Group 2: 7.5±1.19	N.D	N.D	N.D	
Deramond-Dutrus et al. ³⁰	1989	Optimal: 15–25 Safe: < 35	Optimal: 2–5 Safe: < 10	Non	Non	7.5 mg/kg/12h then adjusted	Group 2: 3.55±1.36 Group IV: 28.4 day3, 26.6 day8 Group IM: 21.3 day3, 25.8 day8	N.D	N.D	Group IV: C _{trough} : 50% (13/26) C _{peak} : 34.6% (9/26) Group IM: C _{trough} : 22.2% (4/18) C _{peak} : 33.3% (6/18)	N.D
Adelman et al. ²⁹	1987	Non	Non	Non	Non	7.5 mg/kg/12h or 7.5 mg/kg/8h	26.3±9.4	N.D	N.D	12% raise in creatinine clearance. 40% decline in creatinine clearance and NAG increased.	
McCracken et al. ³⁴	1984	Non	Non	Age (PNA) and weight 1) < 6d + < 2000g 2) < 6d + > 2000g 3) 7-30d + < 2000g 4) 7-30d + > 2000g 5) > 30d	Non	1) 7.5 mg/kg/12h 2) 10 mg/kg/12h 3) 10 mg/kg/12h 4) 10 mg/kg/8h 5) 10 mg/kg/8h	N.D	N.D	N.D	C _(5h) = 3.9 (0.8-11.2) Mortality: 5 cases (15.2%)	
Rajehgot et al. ³⁶	1984	Non	Non	Non	Non	Mean dose: 7.2±0.5 mg/kg/12h for 13 ±3 doses	N.D	N.D	N.D	9.6 ±4 (2.5-18.1) second day of life	C _{trough} increases significantly with respiratory detresse and PNA < 72 h
Marks et al. ³³	1978	Non	Non	Age (PNA) 1) < 7 2) ≥ 7	Non	1) 7.5 mg/kg/12h 2) 5 mg/kg/8h	Dose 1: 7.0 (< 1.25 - 12.0) Day 7: 14.0 (2.3 - 27.0)	N.D	N.D	Day 3: 6.6 (< 1.25 - 16.0)	ECC < 1.25 mg/l
Finitizo-Hieber et al. ⁴⁰	1985	Non	Non	Age (PNA) 1) < 7 2) > 7	Non	1) 7.5 mg/kg/12h 2) 7.5 mg/kg/8h	21.3 (4.6-110)	N.D	N.D	N.D	Possible ototoxicity cases in 2 patients with amikacin (4%)
Alinejad et al. ⁴²	2018	Non	Non	Age (PNA) and weight 1) ≤ 7d+1200–2000g 2) ≤ 7d+>2000g 3) > 7d+1200–2000g 4) > 7d+>2000g	Non	1) 7.5 mg/kg/12 to 18 h 2) 10 mg/kg/12 h 3) 7.5 mg/kg/8 to 12 4) 10 mg/kg/8h	N.D	N.D	N.D	N.D	No difference between amikacin and gentamicin in nephrotoxicity.

First author	Year	Target Serum Concentrations (mg/L)			Dosage Regimen Used		Main Finding				Other findings
		Peak	C trough	Cpeak	Variables Involved	Dosage Regimen	mean C _{trough} (min-max) (mg/l)	Levels in Therapeutic Range	Infra /Supratherapeutic		
Amponsah, et al. ²⁵	2017	20-30	<5	<5	Age (GA) 1) >37 2) <37	Loading dose: 15 mg/kg. Maintenance dose 7.5 mg/kg/12h	1) 6.2±3.4 2) 9.2±5.7 (P=0.02)	1) Crough: 20% and Cpeak: 33% 2) Crough: 14% and Cpeak: 36%	1) Crough: 80% and Cpeak: 67% 2) Crough: 86% and Cpeak: 64%	Overall mortality: 8.1%	
Smits et al. ⁴⁶	2015	>24	<3	<3	Weight and age (PNA)	Appendix A, table A3 (optimized from De Cock 2012)	N.D	Crough: 60.2% and Cpeak: 90.5%	Crough: 39.8% and Cpeak: 9.5%		
Tayman et al. ²³	2011	Non	Non	Non	Age (GA)	Dosage regimen of Langhendries JP et al 1998 ⁴⁴	39.1(24.1-73.2)	N.D	N.D	amikacin concentration in epithelial lining fluid : 6.5 (1.5-23)mg/l	
Ruggieri-Marone et al. ⁴⁷	2007	Non	Non	Non	Age (PNA, GA and PCA)	Neofax® Appendix A, table A4	N.D	N.D	N.D	Amikacin did not alter the amplitude of the otoacoustic emissions in all groups	
Berger et al. ²⁶	2004	>20.3	<3.94	<3.94	Age (PNA) and weight 1) < 7+ < 1500 2) ≥ 7+ < 1500	1) 10 mg/kg then 7.5 mg/kg/24h 2) 17 mg/kg then 15 mg/kg/24h	21.5 (10.7-91.6) 3.7 (0.8-13.3)	**Crough: 85% Cpeak: 88%	N.D	N.D	
Langhendries et al. ⁴⁴	1998	Non	Non	Non	Age (GA)	Appendix A table A11	≈ 26.4-28.8	N.D	N.D	Recovery rate 99.4%	
Langhendries et al. ³⁹	1993	Non	Non	Non	Non	15 mg/kg/24h	Group1: ≈ 19.8 Group2: ≈ 22.2 Group3: ≈ 24.5	N.D	N.D	N.D	
Petersen et al. ⁴⁵	1991	20-30	4-10	4-10	Weight and age (PNA)	Appendix A, table A12	Group4: ≈ 26.5	Crough: 71.1 % 76.3 %	Crough: 28.9% 23.7%	C _(cst) = 81.5 (12-184)	
Wright et al. ⁴¹	1981	Non	Non	Non	Non	5 mg/24h ICV Then adjusted to maintain through level 5 to 10 MIC	N.D	N.D	N.D		
Want et al. ⁴³	1979	Non	Non	Non	Non	7.5 mg/kg/12h	18.2±4.6 (13-32) 21.7 (15.0-29.0)	N.D	N.D	N.D	
Sardemann et al. ²⁷	1976	Non	Non	Non	Age (PNA)	Appendix A, table A14	7.1 (2-13.5)	N.D	N.D	N.D	
Pobiano et al. ⁷⁷	2003	15-30	1-8	1-8	Non	7.5-10 mg/kg/24h	13.22±10.91	N.D	N.D	N.D	
An et al. ⁴	2014	20-30	<5	<5	Group1: age (PNA, GA and PCA) Group 2: age (PNA and PCA)	Group1: Neofax® Appendix A, table A4 Group2: developed from group1 results (Appendix A, table A5)	Group1: 26.9±7.8 Group2: 25.8±4.9	Group1: Crough: 85.1% Group2: Crough: 87.5%	Group1: Crough: 14.9% Group2: Crough: 12.5%	Group1: Crough: 50.7% Group2: Crough: 88.7%	

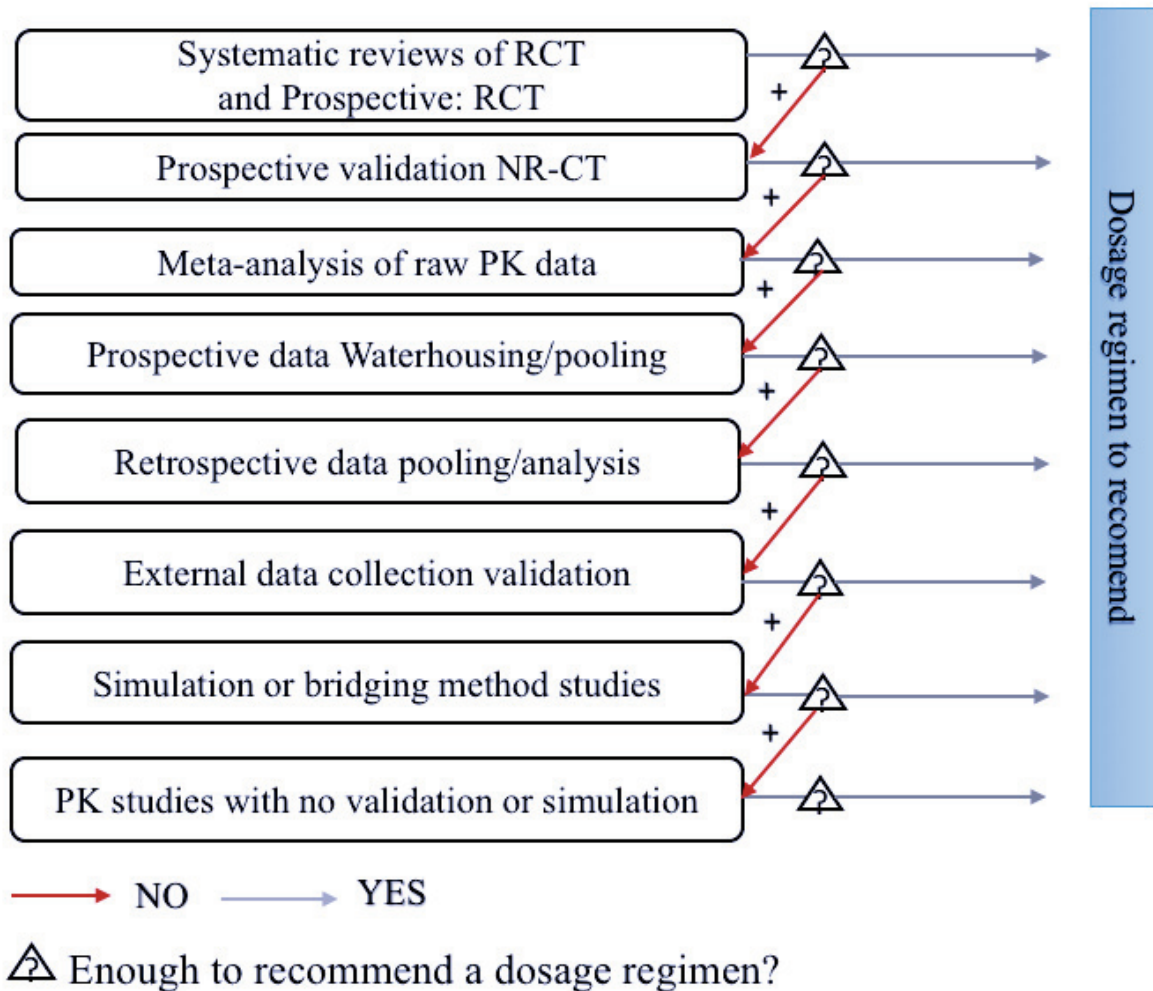
First author	Year	Target Serum Concentrations (mg/L) C _{peak}	Variables Involved	Dosage Regimen Used		Main Finding			Other findings
				Dosage Regimen	Dosage Regimen	Levels in Therapeutic Range	Infra /Supratherapeutic	Other findings	
					mean C _{peak} (min-max) (mg/l)	mean C _{trough} (min-max) (mg/l)			
Labanne et al. ⁷⁵	2001	1)GA<30: 20–32 2)GA30–34: 24–38 3)GA>34: 28–42	Birth weight and age (GA)	Appendix A table A10	N.D	N.D	Overall: C _{trough} : 100% C _{peak} : first doses:62-80% second dose:80-100% GA<30:62% GA30–34: 80% GA>34 : 63%	N.D	N.D
Kenyon al. ⁷³	1990	20–30 <10	Age: Group1 (PNA): 1) ≤ 7 2) > 7 Group2 (PCA): 1) < 30 2) > 30	Group1: 1) 7.5 mg/kg/12h 2) 7.5 mg/kg/8h Group2: 1) 9 mg/kg/18h 2) 9 mg/kg/12h	Group1: 21.88±4.88 Group2: 23.9±4.25	Group1: 9.10±3.77 Group2: 8.26±2.99	Group1: C _{trough} :67% C _{peak} : 68% Group2: C _{trough} :72% C _{peak} : 79%	Group1: C _{trough} :33% C _{peak} : 30% Group2: C _{trough} : 28% C _{peak} :21%	N.D
Roze et al. ⁷⁶	1989	15–35 3–8	Group1: Non Group2: Age (PCA)	Group1: 7.5 mg/kg/12h Group2: Appendix A, table A13	Group1: 18.5±4.6 Group2: 21.6±5.9	Group1: 5.2±3.7 Group2: 5.7±3.1		Group1: C _{trough} : 48.7% C _{peak} : 27% Group2: C _{trough} : 23.7% C _{peak} : 16%	
Illamola et al. ⁹⁰	2016	25–35 1–5	Model 1: Weight and Cler. Model 2: weight and age (PNA)	Appendix A, table A2	N.D	N.D	Model 1: C _{trough} : (50 to 75)%, C _{peak} : (36 to 64)% Model 2: C _{trough} : (56 to 80)%, C _{peak} : (36 to 69)%	N.D	Birthweight and postnatal predict amikacin clearance
De Cock et al. ¹⁵	2012	24–35 1.5–3	Age (PNA), weight	Appendix A, table A6	N.D	N.D		N.D	
Cristea et al. ⁴⁹	2017	24–35 <3	Weight 1) 1.200–2.000 g 2) 2.000–2.800 g 3) >2.800 g	1) 15 mg/kg, 48 h 2) 15 mg/kg, 48 h 3) 15 mg/kg, 42 h	N.D	N.D	1) C _{trough} : 54% and C _{peak} : 43 % 2) C _{trough} : 52% and C _{peak} : 45% 3) C _{trough} : 49% and C _{peak} : 43%	1) C _{trough} : 46% and C _{peak} : 57% 2) C _{trough} : 48% and C _{peak} : 55% 3) C _{trough} : 51% and C _{peak} : 57%	N.D
Hughes, et al. ⁵⁰	2017	20–35 <8	Age (PNA and PMA)	Group 1: Neoflox® Appendix A, table A4 Group 2: Appendix A, table A1	Group 1: 37.7±7.3 Group 2: 28.5±5.8 (p < 0.01)	Group 1: 2.3±1.6 Group 2: 2.0±1.7 (p > 0.01)	Group 1: C _{trough} : 99% and C _{peak} : 34% Group 2: C _{trough} : 98% and C _{peak} : 84%	Group 1: C _{trough} : 1% and C _{peak} : 65% Group 2: C _{trough} : 2% and C _{peak} : 16%	
Allegaert et al. ⁵⁷ (Br J Clin Pharmacol)	2006	>20 <5	Age (GA) in both groups Group 1 1) < 30 2) 30–35	Group 1: 1) 20 mg/kg/36h 2) 20 mg/kg/24h Group 2: dosage regimen proposed by Laignehendries JP et al. 1998	Group1: 45.7±17.8 (10.4-100) Group2: 38.13±12.4 (14.2-71.2)	Group1: 8.2±4.4 (1.1-21.8) Group2: 4.8±2.4 (0.8-15)	Group 1: C _{trough} : 27.9% C _{peak} : 94.5% Group2: C _{trough} : 61.8% C _{peak} : 94.2%	Group 1: C _{trough} : 72.1% C _{peak} : 6.5% Group2: C _{trough} : 38.2% C _{peak} : 5.7%	N.D

First author	Year	Target Serum Concentrations (mg/L)			Dosage Regimen Used		Main Finding			Other findings
		Cpeak	Ctrough	Variables Involved	Dosage Regimen	mean C _{peak} (min-max) (mg/l)	mean C _{trough} (min-max) (mg/l)	Levels in Therapeutic Range	Infra /Supratherapeutic	
Allegaert et al. ⁵⁹ (Pediatri Crit Care)	2006	Non	Non	Age (GA)	The same 2 dosage regimens of Allegaert et al 2006. ⁵⁷	Group 1: 42.5±16.9 (14.8-100) Group 2: 39.6±14.3 (10.4-89)	Group 1: 6.6±4.3 (0.8-21.8) Group 2: 4.4±3.3 (0.8-16.9)	N.D	N.D	N.D
Allegaert et al. ⁶⁰ (Pediatri Nephrol)	2005	Non	Non	Age (GA)	1) 20 mg/kg/36h 2) 20 mg/kg/24h	N.D	N.D	N.D	N.D	ibuprofen and acetylsalicylic acid reduce the clearance of amikacin
Allegaert et al. ⁶¹	2005	Non	Non	Age (GA)	1) 20 mg/kg/36h 2) 20 mg/kg/24h	N.D	N.D	N.D	N.D	significant decrease in amikacin clearance was documented in preterm infants up to 34 weeks GA when ibuprofen was administered during the 1st day of life.
Allegaert et al. ⁶² (Biol Neonate)	2004	>20	<4	Age (GA)	1) 20 mg/kg/36h 2) 20 mg/kg/24h	Group 1: 46.7(24.5-89) Group 2: 40.9 (10.4-88.1)	Group 1: 9.9 (3.5-19) Group 2: 6.2 (1.0-19)	Ctrough: 19% <4 mg/l 34% <10 mg/l Cpeak: 92% (70/76)	Ctrough: 81% (68/84) >4 mg/l Cpeak: >10 mg/l Cpeak: 8%	amikacin was significantly lower in infants who received ibuprofen-lysine
Palix et al. ⁶⁶	1986	Non	Non	Weight and Age (PNA) Group 1: period 1: 1) < 15d < 32w 2) < 15d ≥ 32w 3) ≥ 15 < 32w Group 2: period 2: ≥ 32	Group 1: 7.5 mg/kg then 3.75 mg/kg/12h Group 2: 7.5 mg/kg then 5 mg/kg/12h	1) 11.53±0.61 2) 9.52±0.92 3) 12.26±2.29 4) 15.08±2.62	1) 4.12±0.3 2) 2.94±0.59 3) 2.83±0.36 4) 4.28±0.78	N.D	N.D	p < 0.01
Philips et al. ⁷¹	1982	<40	Non	Non	Initial loading dose 10 mg/kg then 7.5 mg/kg/12h	Group 1: 16.6±11.9 Group 2: 6.4±4.3	Group 1: 60% (3/5) >40 Group 2: 30% (4/13) >40	N.D	N.D	N.D
Endo et al. ¹³	2019	Non	Non	Non	15 mg/kg/24h	29.1 (19.4-42.5)	7.86 (1.8-28.4)	N.D	N.D	100% success in renal function safety 80% in regarding ototoxicity. Ctrough ≥ 10 mg/mL significantly affects ototoxicity in neonates.
Allegaert et al. ⁵⁴ Covariates	2008	Non	Non	Age (GA)	Dosage regimen of Langhendries JP et al 1998 ⁴⁴	N.D	N.D	N.D	N.D	92% of clearance variability was predictable in the first month of life
Allegaert K et al. ⁵⁵	2008	Non	Non	Age (GA)	Dosage regimen of Langhendries JP et al 1998 ⁴⁴	Cpeak _{0h} = 35.7±5.9	Ctrough _{0h} = 3.8±2.5	N.D	N.D	C _{cr50} = 1.08 (0.34-2.65)
Allegaert et al. ⁵⁶	2007	Non	Non	Age (GA)	The same 2 dosage regimens of Allegaert et al 2006. ⁵⁷	N.D	N.D	N.D	N.D	Renal drug clearance is significantly lower in preterm neonates born small GA

First author	Year	Target Serum Concentrations (mg/L) C _{peak}	Variables Involved	Dosage Regimen	Main Finding			Other findings
					mean C _{peak} (min-max) (mg/l)	mean C _{trough} (min-max) (mg/l)	Levels in Therapeutic Range	
Allegaert et al. ⁵⁸ (Methods Find Exp Clin Pharmacol)	2006	Non	Age (GA)	The same 2 dosage regimens of Allegaert et al 2006. ⁵⁷	N.D	N.D	N.D	Significant and clinically relevant reduction in drug clearance is observed when ibuprofen is coadministered GA and weight are the most important covariables
Bleyzac et al. ⁶³	2001	Non	Non	Not reported	N.D	N.D	N.D	Intra-individual variability was 29%. Birth weight is an important covariable
Botha et al. ⁶⁴	1999	Non	Non	17.5 mg/kg then 15 mg/kg/24h Or: 10 mg/kg then 7.5 mg/kg/12h	N.D	N.D	N.D	Intra-individual variability coefficient 28.9%
Padovani et al. ⁶⁵	1993	Non	Non	Initial dose: 5 mg/kg Individualized dosage 6 to 18.3 mg/kg/24h	N.D	N.D	N.D	
Ruscioni et al. ⁶⁷	1983	Non	Non	Mean dose: 7.2±0.5 mg/kg/12h for 13 ±3 doses	N.D	9.6 ±4 (2.5-18.1) second day of life	N.D	Crough increases significantly with respiratory detresse and PNA < 72 h
Purini et al. ⁶⁸	1982	<30	Non	Mean dose: 7.4±0.5mg/kg/12h	N.D	N.D	N.D	2.8% (1/35) mild hearing loss and NAG increases significantly with amikacin
Assael et al. ⁷²	1982	Non	Non	7.5 mg/kg/12h	N.D	≈ (1.5-11)	N.D	N.D
Prober et al. ⁷⁰	1981	15-30	Non	7.5 mg/kg/12h	(10.5-35.0)	(0.5-13)	N.D	N.D
Sherwin et al. ⁶⁵	2009	24-35***	Studied: Age (PNA and GA) Proposed: Age (PMA)	Studied and finally proposed DR in Appendix A (tables A7, A8)	27.7 (17.1-36.8)	N.D	N.D	N.D
Siddiqi et al. ⁵³	2009	Non	Weight for the proposed DR	Studied DR: 15 mg/kg/24h Proposed DR (Appendix A, table A9)	N.D	Group 1 preterm: 14.4*±9.28 (1.5-42.6) Group 2 term: 9.97*±5.67 (2.81-31.0)	N.D	N.D
Cookson et al. ⁸⁰	1980	15-30	3-8	Group 1: 7.5mg/kg/12h Group 2: loading dose 10mg/kg then 7.5mg/kg/12h Group 3, 4: 10 mg/kg/12h	Group 1: 9.45±3.6 Group 2: (7.8-12) Group 3: 21.5±4.5	Group 1: 1.23±1.69 Group 2: (0.4-2.4) Group 3: 3.34±2.05	N.D	Mortality 5.7%, 3/35 colonized with bacteria... 13/35 abnormal renal parameters
Myers et al. ⁶⁹	1977	Non	Non	7.5 mg/kg/12h	Normochemic: 17.9 ± 5.7 Hypoxemic: 16.6 ± 4.5 IV: 17.9 ± 3.7 IM: 18.5 ± 3.3	N.D	N.D	N.D
Howard et al. ⁷⁸	1976	15-25	Non	IV, IM: 7.5 mg/kg/12h ICV: 1-2mg	IM: 21.1 (13.6-40) IV: ≈ 10 ≈ (2.8-22.0) ICV: no C _{peak} data	IM: 8 (4-16) IV: ≈ 5 ≈ (1.5-8.5) ICV: no C _{trough} data	N.D	Overall mortality: 27%
Howard et al. ⁷⁹	1975	15-25	Non	7.5 mg/kg (single dose) 10 mg/kg then 7.5 mg/kg/12h	1) 17 to 20 2) 19 (14-24)	1) ≈ (3.3-5.3) at 12h 2) ≈ 6 ≈ (2-11) at 12h	N.D	N.D

N.D : No data; CSF: cerebrospinal fluid; ICV : Intracerebroventricular; NAG : N-acetylglucosaminidase; IV: intravenous; IM: intramuscular; PCA : post conceptual age; PNA : postnatal age; PMA: Post-menstrual age; GA : gestational age; DR: dosage regimen; ECC: Extravasular compartment concentration

Figure 2: Proposition of a selection method



- 1) Does the dosage regimen consider specific covariable(s) for dosing in neonates?
- 2) Are the efficacy and safety results satisfying?
- 3) Is the number of patients is enough?

The classification of the Pharmacokinetic-Pharmacodynamic Studies is retrieved from the GAPPS tool (Grading and Assessment of Pharmacokinetic-Pharmacodynamic Studies)

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Chapter C: General discussion and Conclusion

General discussion

Promoting applicability and effectiveness of trigger tool method in children (article I)

This work promotes the adoption of an electronic trigger tool in paediatric settings, with the emphasis on the importance of selecting appropriate triggers along with a proper organisation before implementation. Additional studies are required to improve the knowledge about the effectiveness of triggers in drug safety surveillance in children. Studies to assess how cost-effective is the implementation of an appropriate trigger tool in different paediatric settings and different age groups could help urge more paediatric hospitals to use it. Adapting certain triggers with paediatric age groups, including creating new triggers for certain age groups and providing adapted definitions and thresholds could also be considered for this method to be more effective. (1).

Towards earlier ADR detection (article I)

From a clinical perspective, ADRs may be detected too late with the existing ADE-detection methods. There is great interest to increase the use of earlier and proactive detection methods (including prediction), allowing prevention or faster management of occurring ADRs in present and future patients (2–5). The classification of triggers through their potential clinical use, as presented in this work, supports this orientation. Even though the use of triggers for ADR prevention needs to be validated and depends on the quality of the application of the (near) real-time detection system, numerous triggers are usable for early detection, allowing a better potential management of ADRs. However, the optimal methodology for an effective prediction of ADRs have not been identified yet (6,7). As in their retrospective use (8), the applicability and effectiveness of using triggers for early detection purposes need to be tested and validated. Nevertheless, this real-time mode may require a reviewing of trigger definitions (decision

rules). In this case, potential changes in trigger performance are expected. Focusing on ADRs of interest (e.g., serious ADRs) could be considered for the applicability tests. It may be necessary to allocate a greater number of trained reviewers for a real-time detection use compared to retrospective detection to guaranty the assessment of all alerts (positive generated triggers) within the requested time. Involving clinical practitioners in reviewing and evaluating the generated alerts may help increase their awareness on ADRs and consequently prevent further cases as well as train a higher number of them on ADRs assessment. The Agency for Healthcare Research and Quality indicates that the reliability of trigger tools is significantly promoted by a higher level of training and experience of the reviewers and their familiarity with the clinical setting being evaluated (9).

Improve reporting systems

Even the best detection method becomes ineffective if it is not paired with an effective reporting system. For this reason, measures to increase current reporting rates should accompany the development of the existing pharmacovigilance detection methods. Improving ADR reporting is more important in the paediatric population because of its small population size. Many methods could be used to achieve this, such as using automated report production, continuously encouraging health-care workers to report ADRs, as well as putting in place educational interventions (e.g., training programmes, reminders, meetings, etc.), in parallel with implementing an appropriate trigger tool. These methods were shown to be effective in increasing the quality and quantity of safety reports. Educational interventions were found to be helpful in raising awareness on the necessity of reporting and in acquiring knowledge about ADRs, the reporting techniques, and the assessment methods, resulting in higher reporting rates (10–13) . A study showed that ADR reporting increased 14-fold after putting in place educational interventions including pharmacovigilance talks, pharmacists participating in patient visits, reminders, improvement of ADR-reporting format accessibility, in addition to the

performance of feedback activities (14). It is noteworthy that repeating these kind of interventions is essential to keep improving reporting rates (15). It may be important as well to address all health-care professionals by these interventions. Until now, physicians have accounted for the highest number of reporters in the national pharmacovigilance databases (16). Efforts to improve reporting require the ongoing awareness raising of healthcare professionals about the importance of drug safety monitoring in children. It also requires to take into account the existing fundamental factors influencing reporting decisions, such as the time since the medicine has been launched , the pharmacovigilance-related regulatory activity, the media attention and the indication(s) for use of the medicine (17–19).

Include triggers in prognostic and diagnostic models (article I)

The development of a tool to automatically detect ADRs using well-known multivariate diagnostic and prognostic models is a promising strategy to reach more effective detection. The original purpose of the work, which consists in identifying triggers used in children, was to create prognostic and diagnostic models in order to predict and detect ADRs in hospitalised children, involving selected automated triggers, ‘preventing’ triggers for prognostic models and ‘validating and reporting’ triggers for diagnostic models. Two possible strategies were proposed for consideration. The first strategy consisted in targeting ADR(s), retrieving related triggers, combining the triggers with factors identified by a panel of experts based on the available knowledge about the disease, drugs, child physiology and ADRs, examining the availability of the triggers and the factors in the EREMI database, developing a model based on these triggers and testing it the EREMI database. The second strategy consisted in targeting ADR(s), identifying new prognostic and diagnostic factors (as new triggers) related to the targeted ADRs (e.g., concomitant treatments) through modelling techniques using the EREMI database, building a model combining the most performant related triggers from the literature

and the new triggers, then testing, developing, and validating the model using an external database.

The EREMI database was considered because it gathers hospital-based computerised data of 5127 children aged below 15 years-old, hospitalised in two hospitals located in Lyon and Paris, totalling 388 ADRs validated by an independent committee. The available dataset for use during the period of this thesis concerned Lyon inpatients only and consisted of 198 validated ADRs. The inadequate number of reported ADRs in this dataset, the heterogeneity of their nature and the non-concordance with the identified triggers did not allow us to develop the predictive and diagnostic models using any of the strategies mentioned above (Appendix A). We found that generating and collecting triggers then examining which of them are useful for a detection model development using already collected data may not be the most efficient way. Moreover, the sufficiency of existing positive training for modelling or validating models should have been investigated from the beginning.

This experience suggests that one local database of collected-ADRs in hospitalised children could never be enough for such a modelling approach. Resorting to the biggest national or international pharmacovigilance databases (e.g., the WHO database [VigiBase] and the FDA Adverse Event Reporting System [FAERS]) could be necessary to identify an adequate number of ADRs of interest (e.g., serious or high-impact ADRs). Given that these big pharmacovigilance databases do not usually contain the types of data regarding patients and hospitalization as local EHRs do, the use of EHRs of patients who presented ADRs and other patients who did not may be more effective. Combining and standardising EHRs could provide a high powerful database for this type of modelling, thus improving drug safety monitoring in children (20,21).

Informed choice of oral dosage form in children (article II)

When it comes to oral drug administration in children, most paediatric prescribers choose liquid formulations, almost automatically and without considering the other existing options (22,23). This work encourages paediatric prescribers to switch from a preferred and generalised oral dosage form to the most appropriate dosage form for each patient among the available dosage forms. Most of the previous researches focused (24–26) on the lack of child-friendly dosage forms and the development of new forms while only a few (27) offered practical solutions based on available resources. From our point of view, both approaches are necessary to improve medicine safety in children. Beyond the fact that we encourage to choose solid dosage forms in children whenever it is suitable, feasible, authorised and available, we point out how important is to make better informed choices regarding oral dosage forms in children. Conducting similar studies aiming to optimise dosage form choices in children is encouraged. We admit that making the best dosage form choice for a child could be very complex since there is a lot of information to consider (e.g., the patient characteristics, the patient preferences, the swallowing capacity, the properties of the available dosage forms of the needed drug, the advantages and disadvantages of each one with regards to the patient, the disease, the clinical and psychological state of the patient and the duration of treatment). This choice needs to be made for each drug prescription. Therefore, developing an algorithm and integrating it in a clinical decision support tool to help prescribers make the best dosage form choice appears to be a very promising solution. Such an algorithm facilitates the treatment of the high amount of information. However, establishing decision-making rules needs to be done first. The acceptability of the suggested dosage forms (of our study or those proposed by a developed algorithm) could be validated prospectively in hospitalised children. The effect of the replacement on safety (comparison between the proposed dosage forms and those chosen spontaneously by prescribers), including the probability of dosing errors, could be tested as well. Parallel to all

this, investing in the development of new flexible solid oral dosage forms adapted for children use, especially for younger ones, is needed.

Projects to harmonise dosing recommendations (article III)

Despite that there is continuous advancement in understanding medicine dosage in new-borns, the journey to use the most appropriate dosage regimen in practice is slow and complicated. Accepting the value of satisfactory regimens is a key step towards harmonising dosing recommendations and consequently practices when adequate data with high-level of evidence are unavailable. The main purpose of the data collected on the dosage regimens of amikacin was to facilitate recommending a unique dosage regimen in neonates. We continue working to reach this objective. Presently, a strategy was established to select the 'good enough' regimen of amikacin.

Ideally, projects determining the most appropriate dosage regimen in all off-label and unlicensed drugs and aiming to harmonise dosing recommendations and practices should be launched first for neonates and later for older children. Creating more sophisticated selection and harmonization processes to cover numerous drugs is possible.

Based on our ongoing experience, recommending such a dosage regimen could be very challenging. A selection process needs to be well studied and well described to avoid confusion yielded by the variability and the complexity of the available data. Implication of experts is also important when selecting a dosage regimen to recommend. The requirements of the needed experts are ideally predefined. Experiences in clinical pharmacology, methodology, the different specialties of paediatrics (infectious diseases, neonatology for the dosage regimen of amikacin) are often needed (28).

On the ground, some expert-designed harmonisation frameworks have been recently proposed in order to harmonise dosing recommendations and consequently improve safety and efficacy of drugs prescribed to children (29,30). For example, a national database has been recently initiated in Switzerland to provide paediatric healthcare professionals with harmonised dosing recommendations on the most commonly used drugs in children. For that, an advanced standardised process was built considering both the real-life information collected on currently applied dosages and the literature data. In this initiative, recommendation decisions were made by a group of experts based on data with the highest level of evidence and the practical aspects of dosages (e.g. administration modalities and dosage frequencies in order to achieve the best possible compliance) (28). Similar initiatives are needed worldwide for all concerned drugs, ideally at the international level. Including multi-countries collected data and international clinical experiences will raise the level of evidence of recommendations.

Despite the positive impact expected from using a well-selected appropriate dosage regimen, there are clearly more studies needed to find the optimal dosage regimen of these drugs.

Adopting a complete electronic medication system (EMS) (articles I, II, III)

The adoption of a complete electronic medication system (EMS) or computerised medication, as part of an electronic health system, in hospitals is important for improving drug safety efforts in hospitalised children (31). This system is required for the use of almost all new developed methods aiming to improve the safety of medicines and the quality of care in general (e.g., implementing the method of trigger tools and implementing clinical decision support tools to select an appropriate dosage form or to recommend a dosage regimen) (32). While this system has become reality in daily practice in many hospitals in developed countries, it is not yet the case in other countries. A systematic review, published in 2018, showed that most studies requiring EHRs were performed in developed countries, referring to large differences in the adoption of the electronic health systems between countries (33). Compared to non-electronic

systems, EMS offers the benefit of allowing different sources of patient data to be easily inserted and analysed, such as administrative data, clinical and laboratory information, prescription delivery, and administration (34,35). The use of EMS has already made significant contributions in promoting drug safety in hospitalised patients, including reducing the rates of prescribing errors by 1.8% ($p < 0.001$) and administration errors by 2.7% ($p = 0.005$) (36,37). However, some usability challenges of such a system could contribute to medication events in hospitalised children (32). Systematic reviews covering published pharmacovigilance studies in children between 1999 and 2010 confirmed the increasing utility of routine electronic healthcare datasets for the application of pharmacovigilance methods in children (31).

Conclusion

Optimising a safer and more appropriate use of medicines in hospitalised children needs to be based on several strategies, to be implemented concomitantly, including:

- Optimizing the use of the trigger tool method allowing an earlier and proactive detection of ADRs. This could be reached using pertinent, performant and computerised paediatric triggers, and implementing them in a real-time detection system. Certain triggers could be used for early detection of ADRs including prevention.
- Favoring dosage forms that expose to less medication errors; solid dosage forms should be favored whenever they are available and suitable to patients.
- Identifying the most appropriate dosage regimen of drugs using a pragmatic approach, especially for neonates.

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Appendices

Appendices of the article (I)

Appendix A: Complete list of included triggers

Table A1: Warning triggers

Warning trigger	Type	Mean PPV
Abnormal heart rate or blood pressure	Clinical sign	No data
Abnormal respiratory rate	Clinical sign	No data
Early warning score	Clinical sign	No data
Hypertension	Clinical sign	No data
Vital sign changes	Clinical sign	No data
Hypotension	Clinical sign	41.2
Hypoxia	Clinical sign	26.6
Meperidine administration and rising serum creatinine	Combination	No data
Nephrotoxin administration and rising serum creatinine	Combination	No data
PTT >100 seconds and heparin administration	Combination	No data
Hyperkalemia and age more than 1 year	Combination	8.0
PTT >100 seconds and warfarin administration	Combination	1.9
Hepatotoxic medications administration and Elevated liver enzymes	Combination	0
Any laboratory abnormalities	Laboratory	No data
Elevated theophylline level	Laboratory	No data
Hyperlactataemia on antiretroviral therapy	Laboratory	No data
Pancytopenia	Laboratory	No data
Paracetamol concentration done (regardless of result)	Laboratory	No data
Positive D-dimer	Laboratory	62.5
Elevated digoxin level	Laboratory	50.0
Anti Xa >1.5 mg/dl	Laboratory	49.6
PTT >100 s or High INR	Laboratory	43.1

Warning trigger	Type	Mean PPV
Abnormal sodium level	Laboratory	33.0
Drug level out of range	Laboratory	31.3
Decrease in hemoglobin or hematocrit > 25%	Laboratory	29.9
High INR	Laboratory	31.3
High PTT	Laboratory	24.6
Rising serum creatinine or urea	Laboratory	40.9
Elevated anti-epileptics level	Laboratory	25.5
Elevated tacrolimus level	Laboratory	25.0
Hypoglycemia	Laboratory	22.5
Hypokalemia	Laboratory	36.3
Hypomagnesemia	Laboratory	24.0
Rising serum creatinine	Laboratory	20.1
Elevated levels of CK-MB or troponin I	Laboratory	14.3
Abnormal potassium level	Laboratory	14.2
Leucopenia	Laboratory	21.9
Elevated liver enzymes or high total bilirubin level	Laboratory	12.2
Hyperglycemia	Laboratory	23.55
Metabolic acidosis: anion gap > 11 with drug cause	Laboratory	11.0
Hyponatremia	Laboratory	19.6
Calcium ionized >1.5 mg/dl	Laboratory	8.5
High total bilirubin level	Laboratory	7.5
Elevated liver enzymes	Laboratory	19.8
Abnormal electrolyte levels	Laboratory	4.0
Hyperkalemia	Laboratory	7.12
Hyperphosphatemia	Laboratory	0.5
Chloride level <80 mq/l	Laboratory	0.0
Ciclosporin A > 400 µg/L (treatment)\> 500 µg/L (transplantation of organ)	Laboratory	0.0
Elevated pancreatic enzymes	Laboratory	0

Warning trigger	Type	Mean PPV
Hypernatremia	Laboratory	0
Hypocalcemia	Laboratory	0
Magnesium level >3.5 mq/l	Laboratory	0
Elevated anti-epileptics level and low albumin level	Laboratory	0
Triglycerides >500 mg/dl	Laboratory	0
Elevated aminophylline level	Laboratory	0
Elevated lidocaine level	Laboratory	0
High TSH	Laboratory	0
Low TSH	Laboratory	0
High hemoglobin count	Laboratory	0
Low Z-score and clinical fracture history	Laboratory	0
Insulin administration	Medication	No data
Methadone administration	Medication	No data
Narcotic administration or benzodiazepine administration	Medication	No data
Nephrotoxin administration	Medication	No data
Systemic corticosteroid administration	Medication	No data
Administration of 3 or more nephrotoxins (ntmx) on the same calendar day or intravenous (IV) aminoglycoside (AG) for 3 or more days in a row	Medication	89.3
Heparin administration	Medication	26.2
Anticoagulant	Medication	46.0
Digoxin Immune Fab administration	Medication	25.0
Serum Lithium >1.0 mmol/liter	Medication	0.0
Drug combinations not normally recommended	Medication	0.0

Table A2: Verification Triggers

Verification trigger	Type	Mean PPV
23-hour observation changed to fulltime (upgrade of care)	Administrative	No data
Admission: >3 days	Administrative	No data
Readmission to ICU/ED/HDU within short period	Administrative	No data
Cancelled elective procedure/delayed discharge	Administrative	71.8
Early readmission (upgrade of care)	Administrative	36.9
Transfer to higher level of care (upgrade of care)	Administrative	22.9
Readmission within 30 days	Administrative	21.3
Unplanned admission	Administrative	18.0
Emergency surgery on inpatient	Clinical intervention	No data
Induced delivery	Clinical intervention	No data
Require resuscitation in ward	Clinical intervention	No data
Transfusion, arrest, or death in or	Clinical intervention	No data
Ultrasound of the brain > week 32 - < 3 months	Clinical intervention	No data
Acute dialysis	Clinical intervention	41.7
Emergent C-section delivery (neonate only)	Clinical intervention	40.0
Any urgent code	Clinical intervention	35.3
Unplanned intubation	Clinical intervention	33.0
Long mechanical ventilation postoperatively	Clinical intervention	31.0
Change in planned procedure	Clinical intervention	28.9
Rescue	Clinical intervention	25.9
Unplanned insertion of central line	Clinical intervention	25.0
Transfusion	Clinical intervention	18.7
Ultrasound guided drainage	Clinical intervention	16.7
Restraint use	Clinical intervention	0.0
Constipation	Clinical sign	No data
Decreased level of consciousness or pressure sores	Clinical sign	No data
Delirium/agitation	Clinical sign	No data
Dystonia, ataxia, torticollis, dyskinesia	Clinical sign	No data
Fracture or osteoporosis	Clinical sign	No data

Verification trigger	Type	Mean PPV
Gastrointestinal symptoms	Clinical sign	No data
Hearing disturbance or hearing loss	Clinical sign	No data
Mechanical ventilation complication	Clinical sign	No data
Mucositis or mucosal ulceration	Clinical sign	No data
New arrhythmia	Clinical sign	No data
New onset of jaundice	Clinical sign	No data
Pruritus	Clinical sign	No data
Pulmonary edema, pleural effusion, or pneumothorax	Clinical sign	No data
Rash or ulceration	Clinical sign	No data
Skin- and blood vessel harm, thrombophlebitis	Clinical sign	No data
Sudden onset wheezing	Clinical sign	No data
Upper gastrointestinal bleed	Clinical sign	No data
Hallucinations/delirium/ICU syndrome	Clinical sign	100.0
Urinary retention	Clinical sign	100.0
Occurrence of a complication	Clinical sign	70.3
Withdrawal	Clinical sign	66.7
Abnormal body temperature	Clinical sign	62.5
All-cause deaths in hospital	Clinical sign	53.3
Necrotizing enterocolitis	Clinical sign	52.3
Nausea. vomiting	Clinical sign	43.0
Pain	Clinical sign	39.1
Seizure	Clinical sign	36.5
Apgar scores < 7	Clinical sign	23.5
Embolus/thrombus	Clinical sign	22.2
In hospital stroke	Clinical sign	16.7
Rash	Clinical sign	19.7
Significant weight gain	Clinical sign	0.0
Hyperkalemia or sodium polystyrene administration	Combination	No data
Prifle criteria	Combination	No data
Vitamin k and high INR	Combination	No data
Hyperkalemia and sodium polystyrene administration	Combination	28.6
Warfarin administration or high INR >6 and vitamin k administration	Combination	0.0

Verification trigger	Type	Mean PPV
Hemoglobin < 8 g/dl	Laboratory	No data
Thrombocytopenia	Laboratory	16.7
Hypoglycemia or glucose administration	Laboratory	7.8
Calcium gluconate administration	Medication	No data
Granulocyte colony-stimulating factor	Medication	No data
Laxative administration	Medication	No data
Phentolamine administration	Medication	100.0
Protamine administration	Medication	22.5
Prescribing of extrapyramidal symptoms corrector	Medication	25.0
Anti-emetic administration	Medication	19.6
Vitamin k	Medication	12.9
Sodium polystyrene administration	Medication	12.3
Antidiarrheal administration	Medication	9.6
Laxative or stool softener administration	Medication	11.1
Antihistamine administration	Medication	0.0

Table A3: Reporting Triggers

Reporting Trigger	Type	Mean PPV
Adverse drug event	Administrative	No data
Activation of dose range checking	Clinical intervention	No data
Biopsy of bone marrow, kidney, or liver	Clinical intervention	No data
Angioedema or lip swelling	Clinical sign	No data
Retinopathy in premature infant on oxygen	Clinical sign	No data
Anesthesia related harm	Clinical sign	100.0
Medication reaction	Clinical sign	100.0
Insulin administration and Hypoglycaemia	Combination	80.4
Dextrose administration and low serum glucose level	Combination	57.1
Negative viral hepatitis screening test results	Laboratory	No data
Activated charcoal	Medication	No data
Dextrose administration	Medication	No data
Dextrose administration and insulin administration	Medication	No data
Interactions	Medication	No data
Glucose administration and no insulin administration	Medication	73.7
Glucose administration and insulin administration	Medication	60.0
Flumazenil (Romazicon) administration	Medication	62.6
Naloxone (Narcan) administration	Medication	40.0
Abrupt medication stop	Medication	49.1
Flumazenil (Romazicon) administration, Inotropics administration or naloxone administration	Medication	31.8
Any antidote administration	Medication	21.4
Administration of glucagon or glucose $\geq 10\%$	Medication	14.4
Benadryl (diphenhydramine) administration	Medication	11.2

Reporting Trigger	Type	Mean PPV
Chlorphenamine administration	Medication	11.0
Glutathione administration	Medication	17.8
Anti-allergic or Adrenaline administration	Medication	3.4
Glucose administration	Medication	0.0
Acetylcysteine administration	Medication	0.0
Chlorphenamine or antihistamine administration	Medication	0.0
Abrupt reduction of dose of medication	Medication	0.0
Terbutaline administration	Medication	0.0

Appendices of the article (II)

Appendix A: Description of administration data

Data period: from 06/02/2013 to 05/02/2016

Table A.1: Distribution of administrations across years

Years (n=4)	<i>Administrations</i> (N)	<i>Administrations</i> (%)	<i>Hospital stays</i> (N)	<i>Patients</i> (N)
2014	214095	43.8	3137	2525
2015	186695	38.2	2943	2379
2013	69065	14.13	1106	955
2016	18907	3.87	417	397
[Total]	488762	100	7390	5463

Table A.2: Distribution of administrations across routes of administrations

Routes of administration	<i>Administration</i> (N)	<i>Administration</i> (%)	<i>Hospital stays</i> (N)	<i>Patients</i> (N)
ORAL	312152	63.87	6916	5099
Intravenous	83992	17.18	3731	2861
Subcutaneous	28337	5.8	906	708
Inhalable	20107	4.11	1100	824
Respiratory	13200	2.7	957	666
Others	30974	6.34	3602	3047
[Total]	488762	100	7390	5463

Table A.3: Distribution of oral drug administrations across galenic form groups

Galenic group form	<i>Administrations</i> (<i>N</i>)	<i>Administrations</i> %	<i>Hospital stays</i> (<i>N</i>)	<i>Patients</i> (<i>N</i>)
Liquid	195288	62.56	5784	4226
Solid dosage forms	84889	27.19	4293	2945
Dispersible solids	24444	7.83	2057	1489
others	138	0.04	18	18
Unknown	7393	2.37	662	478
[Total]	312152	100	6916	5099

Table A.4: Distribution of oral liquid drug administration's according to the number of active ingredients

Number of active ingredients (n=5)	<i>Administrations</i> (<i>N</i>)	<i>Administrations</i> %	<i>Hospital residences</i> (<i>N</i>)	<i>Patients</i> (<i>N</i>)
1	143169	73.31	4876	3466
4	21210	10.86	2635	2090
2	17369	8.89	1204	940
3	12304	6.30	1003	730
9	1235	0.63	107	85
5	1	0.00	1	1
Total	195288	100	5767	4216

Table A.5: Type of preparation of the oral liquid single active ingredient formulations

	<i>Administrations</i> (N)	<i>Administrations</i> %	<i>Hospital</i> <i>stays</i> (N)	<i>Patients</i> (N)
Manufactured industrially	121274	85.70	4769	3402
Extemporaneous preparations	21895	15.29	975	647
Total	143169	100	4876	3466

Appendix B

Table B.1: Summary of the substitution assessment of the 10 drugs

Drugs of weight-based dosing strategy					
Daily dose (in mg unless specified otherwise)	Type of solid form	Weight range		Administrations that could be performed with acceptable solid form in terms of dosage (N)	Administrations could be performed with suitable solid form for size and dosage *
		MIN weight (kg)	MAX weight (kg)		
Paracetamol					
-			6	3850	-
400	powder for reconstitution	6	8	1979	1979/1979
600	powder for reconstitution	8	12	2453	2453/2453
800	powder for reconstitution	11	16	1329	1329/1329
1000	Effervescent tablet	13	20	634	634/634
1200	powder for reconstitution	16	24	329	329/329
1500	Effervescent tablet	21	25	31	31/31
1800	powder for reconstitution	25	30	239	239/239
2000	Effervescent tablet	26	40	38	38/38
3000	Effervescent tablet	40	-	13	13/13
Cyamemazine					
-			6,25	0	-
25	Tablets	6,25	25	81	81/81
50	Tablets	12,5	50	3328	3328/3328
75	Tablets	18,75	75	191	191/191
100	Tablets	25	100	72	72/72
Valproic acid					
-		0	3.33	0	-
100	granules	3.33	5	183	183/183
-		5	6.67	281	281/281
200	granules	6.67	10	747	747/747
250	granules	8.33	12.5	416	416/416

Drugs of weight-based dosing strategy					
Daily dose (in mg unless specified otherwise)	Type of solid form	Weight range		Administrations that could be performed with acceptable solid form in terms of dosage (N)	Administrations could be performed with suitable solid form for size and dosage *
		MIN weight (kg)	MAX weight (kg)		
300	granules	10	15	212	212/212
350	granules	11,67	17,5	153	153/153
400	granules	13,33	20	67	67/67
450	granules	15	22,5	135	135/135
500	granules	16,67	25	31	31/31
600	granules	20	30	309	309/309
750	granules	25	37,5	116	116/116
1000	granules	33,33	50	105	105/105
1200	granules	40	60	10	10/ 10
2000	granules	66,67	100	1	1/1
3000	granules	100	150	2	2/2
Clonazepam					
-			10	0	-
1	Tablets	10	20	485	485/485
1.5	Tablets	15	30	860	860/860
2	Tablets	20	40	217	217/217
2.5	Tablets	25	50	236	236/236
Furosemide					
-			10	0	-
20	Tablets	10	20	740	740/740
40	Tablets	20	40	522	522/522
60	Tablets	30	60	41	41/41
Hydroxyzine					
-			12.5	5	-
12.5	Tablets	12.5	25	753	753/753
25	Tablets	25	50	348	417/266
37.5	Tablets	37.5	74	59	
50	Tablets	50	100	10	
Alfacalcidol					
-			20	2	-
0,5 µg	Capsules	20	-	575	575/575
Levetiracetam					

Drugs of weight-based dosing strategy					
Daily dose (in mg unless specified otherwise)	Type of solid form	Weight range		Administrations that could be performed with acceptable solid form in terms of dosage (N)	Administrations could be performed with suitable solid form for size and dosage *
		MIN weight (kg)	MAX weight (kg)		
-		0	25	324	-
250*2	Tablets	25	50	153	86/153
500*2	Tablets	>=50		16	0/16
Prazepam					
-		0	6	0	
10	Tablets	6	18	1276	1276/1276
Amitriptyline					
-		6	10	333	-
25	Tablets	10	16	437	437/437

The suggested daily doses are the minimal acceptable doses reachable using the available solid form dosage(s). Weight ranges are calculated according to the recommended dosage provided in the summaries of product characteristics (SmPC) of the drugs, the recommended administration frequencies are respected. * proportion of the number of administrations could be performed with suitable solid form for size and dosage on the number of administrations that could be performed with acceptable solid form in terms of dosage.

Appendix C: Calculation of the cost differences associated with the suggested substitution for the 10 drugs

Table C.1: Paracetamol

Daily dose (mg)	Dosage/weight category		Liquid formulation				Solid forms				Cost comparison			
	Min weight (kg)	Maxi weight (kg)	Trade name	Drops needed	Cost liquid dosage (€)	Product marketed name	Dosages needed*	Cost of solid dosage (€)	Cost difference (€)	Administrations (N)	Durations treatments included (days)	Potential cost Savings for the hospital (€)		
400	6	8	DOLIPRANE 2.4%	27	0.118125	DOLIPRANE 100MG	4	0.2	-0.081875	1979	1182	-96.77625		
600	8	12	DOLIPRANE 2.4%	40	0.175	DOLIPRANE 150MG	4	0.16	0.015	2453	1374	20.61		
800	11	16	DOLIPRANE 2.4%	54	0.23625	DOLIPRANE 200MG	4	0.12	0.11625	1329	790	91.8375		
1000	13	20	DOLIPRANE 2.4%	67	0.293125	DOLIPRANE 150MG+	4	0.09	0.203125	634	418	84.90625		
1200	16	24	DOLIPRANE 2.4%	80	0.35	DOLIPRANE 150MG	8	0.32	0.03	329	212	6.36		
1500	21	25	DOLIPRANE 2.4%	100	0.4375	DAFALGAN 500MG	3	0.03	0.4075	31	18	7.335		
1800	25	30	DOLIPRANE 2.4%	120	0.525	DOLIPRANE 150MG	12	0.48	0.045	239	162	7.29		
2000	26	40	DOLIPRANE 2.4%	144	0.63	DOLIPRANE 500MG	4	0.04	0.59	38	31	18.29		
3000	40	-		200	0.875	DOLIPRANE 500MG	6	0.06	0.815	13	7	5.705		
TOTAL													145.56	

Table C.2: Cyamemazine

Dosage/weight range		Liquid formulation		Solid dosage form		Cost comparison					
Daily dose (mg)	Minimum weight (kg)	Maximum weight (kg)	Drops needed	Cost liquid (€)	Tablets needed	Cost in solid (€)	Cost saving (€)	Administrations (N)	Durations of treatments included (days)	Potential cost Savings for the hospital (€)	
25	6.25	25	25	2.91	1	0.18	2.73	81	44	120.12	
50	12.5	50	50	5.82	0.5	0.24	5.58	3328	1656	9240.48	
75	18.75	75	75	8.73	1.5	0.42	8.31	191	96	797.76	
100	25	100	100	11.64	1	0.48	11.16	72	34	379.44	
								Total 3672	Total 1830	Total	10537.8

Table C.3: Valproic acid

Dosage/age range		Liquid forms		Solid form		Cost comparison				
Daily dose (mg)	Minimum weight (kg)	Maximum weight (kg)	Cost in liquid (€)	Tablets / sachets needed	Cost in solid (€)	Cost saving (€)	Administrations (N)	Durations of treatments included (days)	Potential Savings for hospital (€)	cost the
100	3.33	5	0.024125	1	0.08	-0.055875	156	93	-5.196375	
200	6.67	10	0.04825	2	0.16	-0.11175	747	431	-48.16425	
250	8.33	12.5	0.0603125	1	0.13	-0.0696875	416	247	-17.2128125	
300	10	15	0.072375	3	0.24	-0.167625	212	127	-21.288375	
350	11.67	17.5	0.0844375	2	0.21	-0.1255625	153	92	-11.55175	
400	13.33	20	0.0965	4	0.32	-0.2235	67	41	-9.1635	
450	15	22.5	0.1085625	3	0.29	-0.1814375	135	77	-13.9706875	
500	16.67	25	0.120625	1	0.2	-0.079375	31	19	-1.508125	
600	20	30	0.14475	2	0.28	-0.13525	309	167	-22.58675	
750	25	37.5	0.1809375	1	0.31	-0.1290625	116	71	-9.1634375	
1000	33.33	50	0.24125	1	0.41	-0.16875	105	61	-10.29375	
1200	40	60	0.2895	3	0.57	-0.2805	10	8	-2.244	
2000	66.67	100	0.4825	2	0.82	-0.3375	1	1	-0.3375	
3000	100	150	0.72375	3	1.23	-0.50625	2	1	-0.50625	
TOTAL										-173.19

Table C.4: Clonazepam

Dosage/weight range		Liquid formulations			Solid forms		Cost comparison			
Daily dose (mg)	Minimum weight (kg)	Maximum weight (kg)	Drops needed	Cost in liquid (€)	Tablets needed (N)	Cost in solid (€)	Cost savings (€)	Administrations (N)	Durations of treatments included (days)	Potential cost saving for the hospital (€)
1	10	20	10	0.022	0.5	0.02	0.002	485	178	0.356
1.5	15	30	15	0.033	0.75	0.03	0.003	860	338	1.014
2	20	40	20	0.044	1	0.04	0.004	217	84	0.336
2.5	25	50	25	0.055	1.25	0.05	0.005	236	107	0.535
								Total: 1798	Total: 707	Total: 2.241

Table C.5: Furosemide

Dosage/weight range		Liquid formulation		Solid dosage form		Cost comparison				
Daily dose (mg)	Minimum weight (kg)	Maximum weight (kg)	Cost in liquid (€)	Tablets needed (N)	Cost in solid (€)	Cost saving (€)	Administrations (N)	Durations of treatments included (days)	Potential cost Savings for the hospital (€)	
20	10	20	0.274	1	0.03	0.244	740	332	81.008	
40	20	40	0.548	1	0.03	0.518	522	290	150.22	
60	30	60	0.822	1.5	0.045	0.777	41	21	16.317	
TOTAL								1303	643	247.545

Table C.6: Prazepam

Dosage/age range		Liquid formulation	Solid dosage form	dosage	Cost comparison			
Daily dose (mg)	Minimum age (years)	Maximum age (years)	Tablets in needed	Cost in solid (€)	Cost saving (N)	Administrations (N)	Durations of treatments included (days)	Potential cost Savings for the hospital (€)
10	6	18	1	0.02	0.032	1276	581	18.592

Table C.7: Hydroxyzine

Dosage/age range		Liquid formulation	Solid dosage form	Cost comparison						
Daily dose (mg)	Minimum age (years)	Maximum age (years)	Tablets in needed	Cost in liquid (€)	Tablets needed	Cost in solid (€)	Cost saving (€)	Administrations (N)	Durations of treatments included (days)	Potential cost Savings for the hospital (N)
12.5	12.5	25	0.5	0.0515625	0.5	0.02	0.0315625	753	428	13.50875
25	25	50	1	0.103125	1	0.04	0.063125	204	199	12.561875
37.5	37.5	74	1.5	0.1546875	1.5	0.06	0.0946875	52	45	4.2609375
50	50	100	2	0.20625	2	0.055	0.15125	10	9	1.36125
TOTAL										
31.69										

Table C.8: Alfalcaldol

Dosage/age range		Liquid formulation		Solid dosage form		Cost comparison	
Daily dose (µg)	Minimum weight (kg)	Maximum weight (kg)	Cost liquid (€)	Tablets needed	Cost in solid (€)	Cost saving (N)	Potential Savings for the hospital (€)
0.5	20	-	0.1625	2	0.3	-0.1375	-79.8875
						1276	581

Table C.9: Amitriptyline

Dosage/age range		Liquid formulation		Solid dosage form		Cost comparison	
Daily dose (mg)	Minimum age (years)	Maximum age (years)	Cost in liquid (€)	Tablets needed (N)	Cost in solid (€)	Administrations (N)	Potential Savings for the hospital (€)
25	10	16	0.1034375	1	0.05	0.0534375	19.87875
						437	372

Table C.10: Levetiracetam

Dosage/weight range		Liquid formulation		Solid dosage form		Cost comparison			
Daily dose (mg)	Minimum weight (kg)	Maximum weight (kg)	Cost in liquid (€)	Tablets needed	Cost in solid (€)	Cost saving (N)	Administrations included (days)	Potential Savings for the hospital (€)	
250*2	25	50	0.4255	2	0.14	0.2855	86	65	18.5575

Daily doses suggested are the minimal acceptable daily doses available in solids considering recommended dosing frequency.

All administrations and days of treatments are counted in the range of minimal daily dose available as solid.

Potential cost savings for the hospital are calculated by multiplying the cost savings' values of daily dosages by the number of days of treatments.

Appendices related to the article (III)

Appendix A

Table A1: dosage regimen proposed by Hughes. et al. 2017 (not validated prospectively)

Age (PMA)	PNA	Group 1 Neofax2014	Group 2
≤29	0-7	18 mg/kg every 48 hr	14 mg/kg every 48 hr
	8-28	15 mg/kg every 36 hr	12 mg/kg every 36 hr
	≥29	15 mg/kg every 24 hr	12 mg/kg every 24 hr
30-40	0-7	18 mg/kg every 36 hr	12 mg/kg every 36 hr
	≥8	15 mg/kg every 24 hr	12 mg/kg every 24 hr
≥35	ALL	15 mg/kg every 24 hr	12 mg/kg every 24 hr

Table A2: dosage regimes proposed by Illamola SM et al 2016 (not validated prospectively)

Weight (g)	Clcr (Schwartz, mL/min)				
	<15	15-30	30-60	60-90	90-120
1) 5000	80 mg/54h	80 mg/30h	85 mg/18h	80 mg/12h	90 mg/12h
2) 4500	70 mg/54h	75 mg/30h	70 mg/18h	75 mg/12h	90 mg/12h
3) 4000	65 mg/54h	65 mg/30h	70 mg/18h	70 mg/12h	75 mg/12h
4) 3500	50 mg/48h	55 mg/24h	55 mg/18h	65 mg/12h	65 mg/12h
5) 3000	45 mg/48h	45 mg/24h	50 mg/18h	55 mg/12h	60 mg/12h
6) 2500	35 mg/48h	40 mg/24h	45 mg/18h	45 mg/12h	50 mg/12h
7) 2000	30 mg/48h	35 mg/24h	35 mg/18h	35 mg/12h	40 mg/12h
8) 1500	25 mg/48h	25 mg/18h	25 mg/12h	30 mg/12h	30 mg/6h
9) 1000	15 mg/36h	20 mg/18h	20 mg/12h	20 mg/12h	20 mg/6h
10) 500	10 mg/30h	10 mg/18h	10 mg/12h	10 mg/6h	15 mg/6h

Weight (g)	PNA				
	<7	7-14	14-21	21-28	28-80
1) 5000	80 mg/30h	80 mg/24h	80 mg/18h	85 mg/18h	85 mg/18h
2) 4500	75 mg/30h	75 mg/24h	75 mg/18h	75 mg/18h	80 mg/18h
3) 4000	65 mg/30h	65 mg/24h	65 mg/18h	65 mg/18h	70 mg/18h
4) 3500	55 mg/30h	60 mg/24h	60 mg/18h	60 mg/18h	65 mg/18h
5) 3000	50 mg/30h	50 mg/24h	55 mg/24h	50 mg/18h	55 mg/18h
6) 2500	40 mg/30h	40 mg/24h	45 mg/24h	45 mg/18h	45 mg/18h
7) 2000	30 mg/36h	35 mg/24h	35 mg/24h	35 mg/18h	35 mg/18h
8) 1500	25 mg/38h	25 mg/24h	30 mg/24h	30 mg/24h	30 mg/18h
9) 1000	20 mg/36h	20 mg/30h	20 mg/24h	20 mg/24h	20 mg/18h
10) 500	10 mg/36h	10 mg/24h	10 mg/24h	10 mg/18h	10 mg/12h

Table A3: dosage regimen proposed by Smits A et al 2015 (validated prospectively on 579 patients)

Weight (g)	Age (PNA) < 14 d	Age (PNA) ≥ 14 d
0-800	16 mg/kg/48h	20 mg/kg/42h
800-1200	16 mg/kg/42h	20 mg/kg/36h
1200-2000	15 mg/kg/36h	18 mg/kg/30h
2000-2800	15 mg/kg/36h	18 mg/kg/24h
≥ 2800	15 mg/kg/30h	18 mg/kg/20h

+6 to 10h in case of asphyxia or co-administration of ibuprofen.

Simplified version of the dosage regimen of De Cock 2012 for the validation.

Table A4: dosage regimen of Neofax

Age (PNA)	Variables	Dosage (mg/kg/h)
≤ 7	GA ≤ 27 wk	18 mg/kg/48h
	GA 28–30 wk	18 mg/kg/36h
	GA 31–33 wk	16 mg/kg/36h
	GA ≥ 34 wk	15 mg/kg/24h
≥ 8	PCA ≤ 29 wk, PNA ≥ 8 days	12 mg/kg/24h
	PCA 30–36 wk, PNA 8–14 days	12 mg/kg/24h
	PCA 30–36 wk, PNA ≥ 15 days	12 mg/kg/18h
	PCA ≥ 37 wk, PNA ≥ 8 days	12 mg/kg/12h

Table A5 : dosage used by An SH et al 2014 (Validated prospectively on 74 patients)

Age (PCA)	Age (PNA) 0-7 d	Age (PNA) ≥ 8 d
≤ 29	13 mg/kg/48h	13 mg/kg/36h
30-33	13 mg/kg/36h	13 mg/kg/24h
34-36	13 mg/kg/24h	13 mg/kg/18h
≥ 37	13 mg/kg/24h	13 mg/kg/12h

Table A6 : Model-based dosing regimen proposed by De Cock et al. 2012

Current weight (g)	PNA < 14d	PNA ≥ 14 j
0-800	16 mg/kg/48h	20 mg/kg/42h
800-1200	16 mg/kg/42h	20 mg/kg/36h
1200-2000	15 mg/kg/36h	19 mg/kg/30h
2000-2800	13 mg/kg/30h	18 mg/kg/24h
≥ 2800	12 mg/kg/24h	17 mg/kg/20h

+6-10 h prolongation in case of asphyxia or co-administration of ibuprofen.

Table A7 : Dosing regimen studied by Sherwin et al. 2009

PNA (day)	GA(week)	Dosage regimen
<7	≤ 27w	18 mg/kg/48h
	27-30w	18 mg/kg/36h
	31-33w	16 mg/kg/36h
	≥ 34w	15 mg/kg/24h
≥7	15 mg/kg/24h and were then dosed based on GA as described above	

TableA8: Proposed dosing regimen based on achieving optimal AUC24 and Cmax

proposed by Sherwin et al. 2009 for neonates of PNA > 72 h (Not validated prospectively)

PMA (week)	Dosage regimen
≤ 28	15 mg/kg/36h
29-32	14 mg/kg/24h
33-36	14 mg/kg/24h
≥ 37	15 mg/kg/24h

Table A9 : Dosage regimen proposed by Siddiqi et al. 2009 (unvalidated prospectively)

Weight (g)	Dosage regimen
< 1200	7,5 mg/kg/24h
1000-2000	10 mg/kg/24h

Table A10 : proposed dosing regimen of Labaune et al. 2001 (validated prospectively on 57 newborns)

THE FIGURES IN PARENTHESES CORRESPOND TO THE SECOND (24 H LATER) DOSE. TIME INTERVAL FIXE : 24H, FOR NEWBORNS OF PNA < 2D

BW (G)	24	25	26	27	28	29	30	31	32	33	34	35	36
500	2 (1,5)	2 (1,5)	2 (1,5)	2 (1,5)	2 (1,5)								
600	2,5 (1,5)	2,5 (1,5)	2,5 (2)	2,5 (2)	2,5 (2)	2,5 (2)							
700	3 (2)	3 (2)	3 (2,5)	3 (2,5)	3 (2,5)	3 (2,5)	6 (5)						
800	3 (2,5)	3,5 (2,5)	3,5 (2,5)	3,5 (2,5)	3,5 (2,5)	3,5 (2,5)	7 (5)						
900	3,5 (2,5)	4 (3)	4 (3)	4 (3)	4 (3)	4 (3)	8 (6)	7,5 (5,5)	8,5 (6,5)				
1000	4 (3)	4 (3)	4 (3)	4 (3)	4 (3)	4 (3)	9 (7)	9 (7)	9 (7)	10 (8)			
1100	4,5 (3,5)	4,5 (3,5)	4,5 (3,5)	4,5 (3,5)	4,5 (3,5)	4,5 (3,5)	9,5 (8,5)	10 (8)	10 (8)	11 (8)			
1200	5 (4)	5 (4)	5 (4)	5 (4)	5 (4)	5 (4)	10,5 (8,5)	11 (9)	11 (9)	12 (9)	15 (13)		
1300	5 (4)	5,5 (4,5)	5,5 (4,5)	5,5 (4,5)	5,5 (4,5)	5,5 (4,5)	11 (9)	12 (10)	12 (10)	13 (10)	16 (14)		
1400	5,5 (4,5)	5,5 (4,5)	5,5 (4,5)	5,5 (4,5)	5,5 (4,5)	5,5 (4,5)	12 (9,5)	13 (10)	13 (10)	14 (11)	17 (15)		
1500			6 (5)	6 (5)	6 (5)	6 (5)	13 (10)	14 (10,5)	14 (10,5)	15 (11)	18 (16)	18 (16)	
1600	6,5 (6)	6,5 (6)	14 (11)	14,5 (12)	15 (12)	16 (13)	16 (14)	20 (18)	20 (18)	21 (19)	(12,5)	18 (17)	
1700		7 (6)	15 (12)	15,5 (13)	16 (13)	17 (14)	17 (15)	21 (19)	21 (19)	22 (20)	23 (21)	23 (21)	
1800		7 (6)	16 (13)	16,5 (14)	17 (14)	17 (15)	18 (16)	22 (20)	22 (20)	23 (21)	24 (22)	24 (22)	24 (22)
1900		7 (6)	17 (14)	17 (14)	17,5 (15)	18 (15)	19 (16)	23 (21)	23 (21)	24 (22)	25 (23)	25 (23)	25 (23)
2000			17,5 (14)	18 (15)	18 (15)	19 (16)	20 (17)	25 (23)	25 (23)	26 (24)	26 (24)	26 (24)	26 (24)
2100				19 (16)	19 (16)	20 (17)	21 (18)	28 (26)	28 (26)	29 (27)	29 (27)	29 (27)	29 (27)
2200				20 (16)	20 (16)	21 (17)	22 (18)	30 (28)	30 (28)	31 (29)	31 (29)	31 (29)	31 (29)
2300					21 (18)	22 (19)	23 (20)	30 (28)	30 (28)	31 (29)	32 (30)	32 (30)	32 (30)
2400					22 (19)	22,5 (20)	24 (22)	31 (29)	31 (29)	32 (30)	33 (31)	33 (31)	33 (31)
2500						23 (20)	25 (23)	31 (29)	31 (29)	32 (30)	33 (31)	33 (31)	33 (31)
2600						24 (21)	26 (24)	32 (30)	32 (30)	33 (31)	34 (32)	34 (32)	34 (32)
2700						25 (22)	27 (25)	33 (31)	33 (31)	35 (33)	36 (34)	36 (34)	36 (34)
2800						26 (23)	28 (26)	34 (32)	35 (33)	36 (34)	37 (35)	37 (35)	37 (35)
2900						26 (23)	28 (26)	35 (33)	36 (34)	37 (35)	38 (36)	38 (36)	38 (36)
3100						29 (26)	31 (29)	38 (36)	38 (36)	40 (38)	41 (39)	41 (39)	41 (39)
3200						32 (27,5)	32 (27,5)	39 (37)	40 (38)	41 (39)	42 (40)	42 (40)	42 (40)

THE FIGURES IN PARENTHESES CORRESPOND TO THE SECOND (24 H LATER) DOSE. TIME INTERVAL FIXE : 24H, FOR NEWBORNS OF PNA < 2D

BW (G)	AG	40	41	42	43	43	43	43	43
3300	33 (28)	40 (36)	41 (37)	42 (39)	43 (40)	43 (40)	43 (40)	43 (40)	43 (40)
3400	34 (29.5)	41 (37)	42 (38)	44 (40)	44 (41)	45 (42)	45 (42)	45 (41)	44 (41)
3500		43 (39)	43 (39)	45 (41)	46 (42)	46 (43)	46 (43)	46 (43)	46 (46)
3600		44 (40)	44 (40)	47 (43)	47 (43)	47 (44)	47 (44)	47 (44)	47 (47)
3700				48 (44)	48 (44)	48 (45)	48 (45)	48 (45)	48 (44)
3800				49 (45)	50 (46)	50 (47)	50 (47)	50 (47)	50 (50)
3900					51 (47)	51 (48)	51 (48)	51 (48)	51 (51)
4000					52 (48)	52 (49)	52 (49)	53 (49)	53 (48)
4100						53 (49)	54 (50)	54 (50)	54 (49)
4200						55 (50)	55 (51)	55 (51)	55 (50)
4300							56 (52)	56 (52)	56 (51)
4400							57 (53)	57 (53)	56 (52)
4500							58 (55)	57 (55)	57 (53)
4600								60 (55)	60 (55)
								61 (56)	61 (56)
3000	(25) 30 (26)	(32) 37 (33)	(32) 37 (33)	(34) 39 (36)	(35) 39 (36)	(35) 40 (37)	(35) 40 (37)	(36) 40 (37)	(36) 40 (37)

Table A11 : Dosing regimen studied by Langhendries et al. 1998 (validated prospectively on 177 patients)

Gestational age (week)	Dosage
< 28	20 mg/kg/42h
28-31	20 mg/kg/36h
31-34	18,5 mg/kg/30h
34-37	17 mg/kg/24h
37-41	15,5 mg/kg/24h

+6h time interval in case of asphyxia, hypoxic episode and intercourse treatment with indomethacin.

Table A12 : Dosing regimen studied by Petersen, Wells, and Kearns 1991 (validated prospectively on 38 patients)

Weight (g)	PNA (d)	Loading	Maintenance
< 800	1-7	11 mg/kg	10 mg/kg/24h
	8-15	13 mg/kg	12 mg/kg/24h
800-1500	1-7	15 mg/kg	12 mg/kg/18h
	8-15	13 mg/kg	9 mg/kg/12h
1500-2000	1-4	11 mg/kg	8 mg/kg/12h
	5-7	12 mg/kg	10 mg/kg/12h
	8-15	11 mg/kg	10 mg/kg/12h
	16-30	12 mg/kg	8 mg/kg/8h
2000-2500	1-4	10 mg/kg	8 mg/kg/12h
	5-7	11 mg/kg	10 mg/kg/12h
	8-15	11 mg/kg	11 mg/kg/12h
	16-30	11 mg/kg	9,5 mg/kg/8h

Table A13: Dosing regimen proposed and validated by Rozé et al. 1989 (validated prospectively on 63 patients)

PCA (week)	Dosage regimen
< 28	10 mg/kg/24h
28	10 mg/kg/21h
30	10 mg/kg/18h
32	10 mg/kg/16h
36	10 mg/kg/14h
40	10 mg/kg/12h
47	10 mg/kg/8h

Table A14 : Dosage regimen of Sardemann H et al 1976 (Validated prospectively on 5 patients)

PNA (D)	Loading dose	maintenance
1	7,2 mg/kg	4 mg/kg/8h
5	9 mg/kg	5 mg/kg/8h
10	10,7 mg/kg	6 mg/kg/8h
15	12,5 mg/kg	7 mg/kg/8h
20	14,3 mg/kg	8 mg/kg/8h
25	16,1 mg/kg	9 mg/kg/8h
30	17,9 mg/kg	10 mg/kg/8h

Appendices related to the discussion

Appendix A:

Arguments about the experience of building a model to predict/detect ADRs using EREMI database and pediatric triggers

The work was started by identifying triggers applicable on pediatric population, in order to use them as indicators in our model. The triggers were collected (article submitted on trigger tools in pediatric). The next phase of the work was to select target ADRs to work on, feasibility difficulties have been shown in this step. The main difficulties were:

1. There is no concordance between the detected ADRs in the EREMI database and the identified triggers the literature (the indicators). (The high frequent ADRs and corresponding triggers are presented in table A and the list of ADEs presented in the available EREMI database table B)
2. The number of reported and validated events in the available EREMI database is limited (only 198 validated events in EREMI-lyon) and the fact that they do not correspond to the triggers identified in the literature increases the difficulty.
3. The nature of EIMs is very heterogeneous (in average 2,2 cases/event) (As seen in table B) which leads to insufficient positive training events for identifying new triggers when considering specific ADRs.
4. Table A presents the most frequent ADR in EREMI database, the corresponding triggers and the comments of the pediatricians. As seen, the 4 most frequent ADRs are Withdrawal syndrome (n=20), Hypokalaemia (n=18), Hypotension(n=16), and Somnolence (n=15), but we have identified from the literature only 1 trigger/by event for 3 of them, and non for somnolence (low detectability). For these events, the interest would be to predict them but three triggers don't allow to predict the events. In addition, according to the opinion of two pediatricians at the hospital, the events are not the most clinically interesting ADEs to make a diagnostic model (raisons in the table C)

Figure A.1: Number of ADRs detected in EREMI project in Lyon.

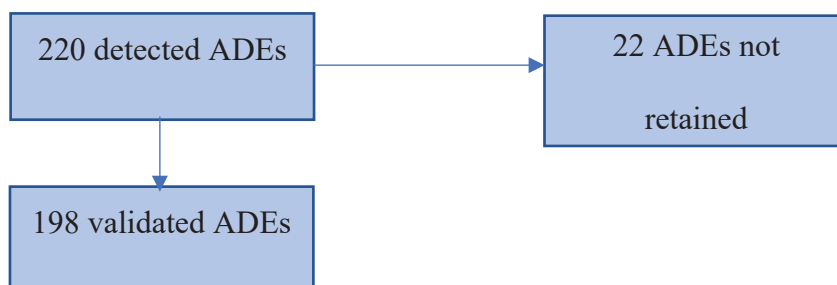


Table A.1: most frequent ADRs in EREMI database-Lyon and the corresponding triggers in the literature

Most frequent ADR (EREMI- Lyon)	N. cases	Corresponding trigger from the literature	Availability of the trigger (as information) in EREMI database	Comments of pediatricians
Withdrawal syndrome	20	withdrawal syndrome	no	1-Low detectability: undetectable from EREMI using the trigger (information doesn't exist in the database), data of the mother should be associated. 2- this event is usually predictable, and there's systematic monitoring; so not interesting to build a model for that
Hypokalemia	18	Hypokalemia (low potassium level)	yes	Usually detected in practice
Somnolence	15	non	-	Usually not a serious event
Hypotension	16	hypotension	no	Undetectable in EREMI, trigger not interesting for the prediction, event usually detected

Table A.2 : List of the validated ADR in EREMI database of LYON.

ADR nature	Number of cases
Withdrawal syndrome	20
Hypokalemia	18
Hypotension	16
Somnolence	15
Diabetes	5
Urinary retention	4
Hyperthermia	4
Hypertension	4
Dyskinesia	4
Diarrhea	4
Allergic reaction	4
Hypernatremia	3
Hyperglycemia	3
Extrapyramidal syndrome	3
Weight gain	2
Vomiting	2
Thrombocytopenia	2
Swallowing disorders / Malaise / Apnea	2
Skin rash	2
QT prolongation	2
Pruritus	2
Neutropenia	2
Mycosis	2
Hepatic cytolysis	2
Elevated transaminases	2
Dizziness	2
Cholestasis	2
Anaphylactic reaction	2
Skin rash	1
Urine color	1
Unsteady gait	1
Tremor	1
Transaminases/elevated GGT	1
Tachycardia	1
Swallowing disorders / Malaise	1
Somnolence, Respiratory depression, Overdose	1
Somnolence/Malaise	1
Somnolence and Abnormal involuntary movements	1
Skin erythema	1

ADR nature	Number of cases
Red man syndrome	1
Reactivation of Epstein-Barr virus infection	1
Reactivation of CMV infection, high concentration of immunosuppressive drugs	1
Peripheral sensory neuropathy	1
Oliguria / Fluid overload	1
Nausea	1
Metabolic acidosis / Hyponatremia	1
Meningeal syndrome	1
Malignant hyperthermia / Hepatic cytolysis	1
Loose stools	1
Increase in gamma-GT - Cholestasis	1
Hypotension and heart failure	1
Hypophosphatemia/Hypokalemia	1
Hyponatremia/Hypokalemia/Hypophosphatemia (suspected tubulopathy)	1
Hyponatremia	1
Hypokalemia / premature ventricular contractions	1
Hypokalemia / Elevated blood urea	1
Hypokalemia / Bradycardia	1
Hypoglycemia	1
Hypocalcemia	1
Hyperthermia / Headache	1
Hypertensive episode / Lower limb edema	1
Hyperlactatemia / Off-label drug use	1
Hypercreatininemia	1
Hypercalcemia	1
Hyperammonemia	1
Hot flashes / Headache	1
HHV-6 infection	1
Hepatitis	1
Hepatic cytolysis / Increased GGT	1
Headache / Vomiting	1
Hallucinations	1
Gross hematuria	1
Gonalgia	1
Galactorrhea	1
Extrapyramidal disorders and Somnolence	1
Euphoria	1
Erythematous rash	1
Epigastralgia / Vomiting	1
Drug Overdose / Hematemesis	1

ADR nature	Number of cases
Drop in blood pressure, malaise, urinary incontinence, reduced heart rate	1
Disorders of calcium metabolism	1
Cramps	1
CMV viremia	1
Carbohydrate intolerance	1
Bradycardia / Hypotension	1
Behavioral disorders, Ataxia, Vomiting	1
Ataxia	1
ARF (acute respiratory failure)	1
Anemia / Neutropenia	1
Akathisia / Dysarthria	1
Adenovirus infection	1
Total	198

Figure A.2: The processes of classification of the type of data and the availability in EREMI database of triggers

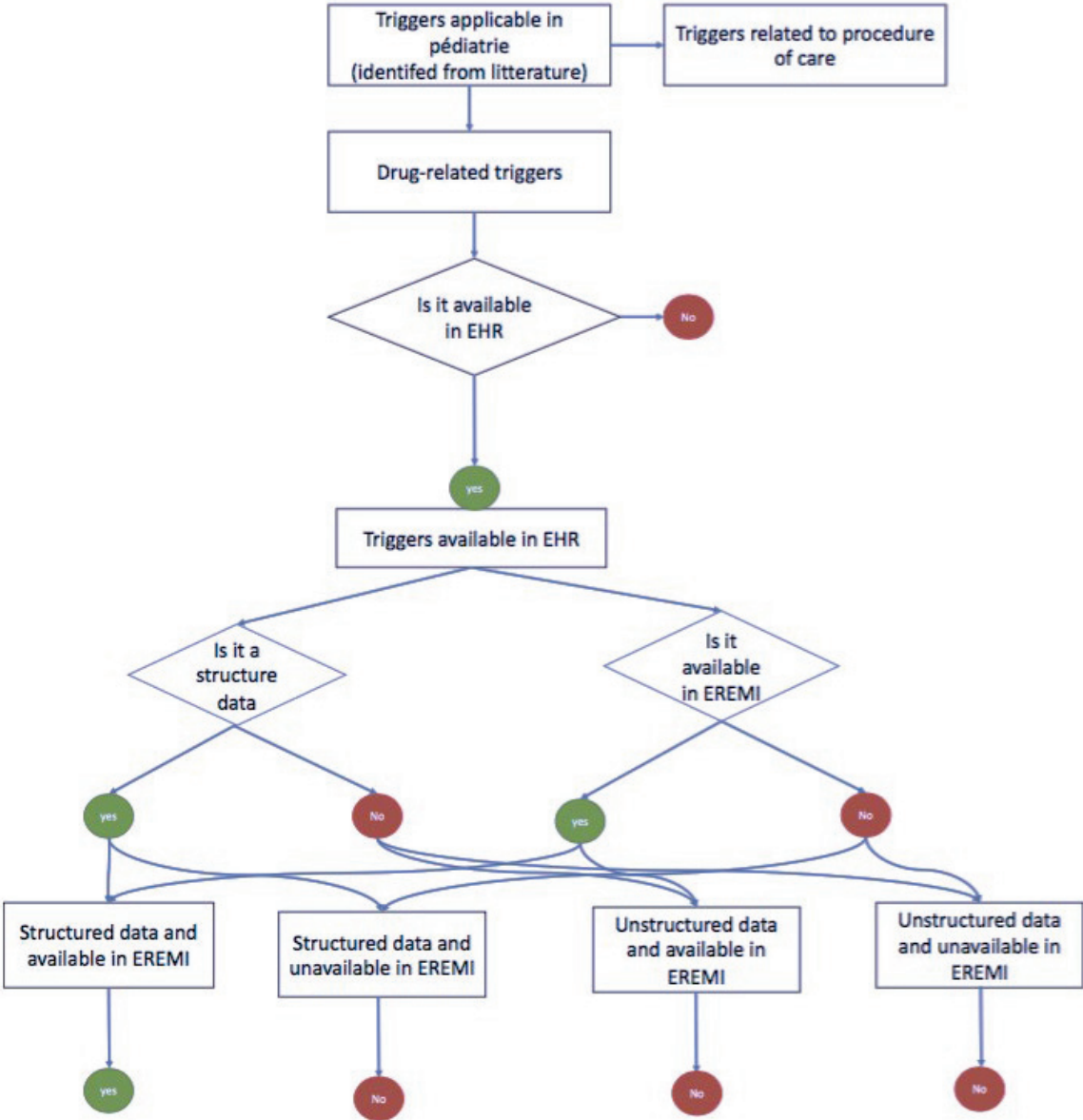


Table A.3 : Classification of the type of data and the availability of the identified triggers in EREMI database of triggers

Medication-related triggers	EHR usually available?	Is it a structured data	Availability of the trigger in EREMI database
23-hour observation changed to full admission (upgrade of care)	No	yes	No
Abnormal body temperature	yes	yes	No
Anesthesia related harm	yes	no	No
Abnormal heart rate or blood pressure	yes	yes	No
Abnormal potassium level	yes	yes	Yes
Abnormal respiratory rate	yes	yes	No
Abnormal sodium level	yes	yes	Yes
Medication reaction	sometimes	no	No
Cancelled elective procedure/delayed discharge	yes	?	No
Acetylcysteine administration	yes	yes	Yes
Activated charcoal	yes	yes	Yes
Activation of dose range checking	yes	yes	Yes
Acute dialysis	yes	no	No
Administration of 3 or more nephrotoxins (NTMx) on the same calendar day or intravenous (IV) aminoglycoside (AG) for 3 or more days in a row	yes	yes	Yes
administration of glucagon or glucose $\geq 10\%$	yes	yes	Yes
Admission: >3 days	yes	yes	Yes
Adverse drug event	sometimes	no	No
Occurrence of a complication	sometimes	no	No
All-cause deaths in hospital	yes	?	No

Medication-related triggers	EHR usually available?	Is it a structured data	Availability of the trigger in EREMI database
Angioedema or lip swelling	yes	no	No
Anti Xa >1,5 mg/dL	yes	yes	Yes
Anti-allergic or Adrenaline administration	yes	yes	Yes
Anti-emetic administration	yes	yes	Yes
Anticoagulant	yes	yes	Yes
Antidiarrheal administration	yes	yes	Yes
Antihistamine administration	yes	yes	Yes
Elevated digoxine level	yes	yes	Yes
Any laboratory abnormalities	yes	yes	Yes
Benadryl (diphenhydramine) administration	yes	yes	Yes
Biopsy of bone marrow, kidney, or liver	yes	no	No
Biperiden, promethazine or diazepam administration	yes	yes	Yes
Calcium gluconate administration	yes	yes	Yes
Calcium ionised >1,5 mg/dl	yes	yes	Yes
Abrupt medication stop	yes	No	No
Emergent C-section delivery (Neonate Only)	yes	no	No
Chloride level <80 mEq/l	yes	yes	Yes
Chlorphenamine administration	yes	yes	Yes
Chlorphenamine or antihistamine administration	yes	yes	Yes
Constipation	yes	no	No
Cyclosporin A > 400 µg,L-1 (treatment)> 500 µg,L-1 (transplantation of organ)	yes	yes	Yes
Decrease in hemoglobin or hematocrit > 25%	yes	yes	Yes
Decreased level of consciousness or pressure sores	yes	no	No

Medication-related triggers	EHR usually available?	Is it a structured data	Availability of the trigger in EREMI database
Delirium/agitation	yes	no	No
Dextrose administration	yes	yes	Yes
Dextrose administration and insulin administration	yes	yes	Yes
Dextrose administration and low serum glucose level	yes	yes	Yes
Digoxin Immune Fab administration	yes	yes	Yes
Early Readmission (upgrade of care)	yes	yes	Yes
Any urgent code	yes	?	No
Unplanned intubation	yes	no	No
Dystonia, ataxia, torticollis, dyskinesia	yes	no	No
Drug level out of range	yes	yes	Yes
Early warning score	yes	yes	No
Long mechanical ventilation postoperatively	yes	no	No
Change in planned procedure	yes	?	No
Rescue	yes	no	No
Elevated anti-epileptics level	yes	yes	Yes
Unplanned insertion of central line	yes	no	No
Elevated liver enzymes	yes	yes	Yes
Elevated liver enzymes or high total bilirubin level	yes	yes	Yes
Elevated pancreatic enzymes	yes	yes	Yes
Elevated tacrolimus level	yes	yes	Yes
Elevated theophylline level	yes	yes	Yes
Embolus/thrombus	yes	?	No
Emergency surgery on inpatient	yes	no	No
Transfer to higher level of care (upgrade of care)	yes	yes	Yes

Medication-related triggers	EHR usually available?	Is it a structured data	Availability of the trigger in EREMI database
Fracture or osteoporosis	yes	no	No
Gastrointestinal symptoms	yes	no	No
glucose administration and insulin administration	yes	yes	Yes
glucose administration and no insulin administration	yes	yes	Yes
Glutathione administration	yes	yes	Yes
Granulocyte colony-stimulating factor	yes	yes	Yes
Haemoglobin < 8 g/dL	yes	yes	Yes
Hallucinations/delirium/ICU syndrome	yes	no	No
Hearing disturbance or hearing loss	yes	no	No
Heparin administration	yes	yes	Yes
Hepatotoxic medications administration and Elevated liver enzymes	yes	yes	Yes
High INR	yes	yes	Yes
High PTT	yes	yes	Yes
High total bilirubin level	yes	yes	Yes
Hyperglycaemia	yes	yes	Yes
Hyperkalemia	yes	yes	Yes
Hyperkalemia and age more than 1 year	yes	yes	Yes
Hyperkalemia and sodium polystyrene administration	yes	yes	Yes
Hyperkalemia or sodium polystyrene administration	yes	yes	Yes
Hyperlactataemia on antiretroviral therapy	yes	yes	Yes
hypernatremia	yes	yes	Yes
Hyperphosphatemia	yes	yes	Yes
Hypertension	yes	yes	No
Hypocalcemia	yes	yes	Yes
Hypoglycaemia	yes	yes	Yes

Medication-related triggers	EHR usually available?	Is it a structured data	Availability of the trigger in EREMI database
Hypoglycaemia or glucose administration	yes	yes	Yes
Hypokalemia	yes	yes	Yes
Hypomagnesemia	yes	yes	Yes
Hyponatremia	yes	yes	Yes
Hypotension	yes	yes	No
Hypoxia	yes	yes	No
In hospital stroke	yes	?	No
Induced delivery	yes	?	No
Insulin administration	yes	yes	Yes
Insulin administration and Hypoglycaemia	yes	yes	Yes
Interactions	yes	yes	Yes
Laxative administration	yes	yes	Yes
Laxative or stool softener administration	yes	yes	Yes
Leucopenia	yes	yes	Yes
Any antidote administration	yes	yes	Yes
Magnesium level >3,5 mEq/l	yes	yes	Yes
Mechanical ventilation complication	yes	no	No
Readmission within 30 days	yes	yes	Yes
Meperidine administration and rising serum creatinine	yes	yes	Yes
Metabolic acidosis: anion gap > 11 with drug cause	yes	yes	Yes
Methadone administration	yes	yes	Yes
Mucositis or mucosal ulceration	yes	no	No
Naloxone (Narcan) administration	yes	yes	Yes
Narcotic administration or benzodiazepine administration	yes	yes	Yes
Nausea, vomiting	yes	no	No
Necrotizing enterocolitis	yes	no	No

Medication-related triggers	EHR usually available?	Is it a structured data	Availability of the trigger in EREMI database
Negative viral hepatitis screening test results	yes	yes	Yes
Nephrotoxin administration	yes	yes	Yes
Nephrotoxin administration and rising serum creatinine	yes	yes	Yes
new arrhythmia	yes	no	No
new onset of jaundice	yes	no	No
Transfusion	yes	no	No
Pain	yes	no	No
Pancytopenia	yes	yes	Yes
Paracetamol concentration done (regardless of result)	yes	yes	Yes
Phentolamine administration	yes	yes	Yes
positive D-dimer	yes	yes	Yes
Prescribing of extrapyramidal symptoms corrector	yes	yes	Yes
pRIFLE criteria	sometimes	no	No
Protamine administration	yes	yes	Yes
Pruritus	yes	no	No
PTT >100 s or High INR	yes	yes	Yes
PTT >100s and heparine administration	yes	yes	Yes
PTT >100s and warfarine administration	yes	yes	Yes
Pulmonary edema, pleural effusion, or pneumothorax	yes	no	No
Rash	yes	no	No
Rash or ulceration	yes	no	No
Readmission to ICU/ED/HDU within short period	yes	yes	Yes
Unplanned admission	no	no	No
Require resuscitation in ward	yes	no	No
Abnormal electrolyte levels	yes	yes	Yes

Medication-related triggers	EHR usually available?	Is it a structured data	Availability of the trigger in EREMI database
Abrupt reduction of dose of medication	yes	yes	Yes
Retinopathy in premature infant on oxygen	yes	no	No
Rising serum creatinine	yes	yes	Yes
Rising serum creatinine or urea	yes	yes	Yes
Romazicon (flumazenil) administration	yes	yes	Yes
Romazicon (flumazenil) administration, Inotropics administration or naloxoe administration	yes	yes	Yes
Seizure	yes	no	No
Serum Lithium >1.0 mmol/litre	yes	yes	Yes
Significant weight gain	yes	yes	Yes
Skin- and blood vessel harm, thrombophlebitis	yes	no	No
Sodium polystyrene administration	yes	yes	Yes
Sudden onset wheezing	yes	no	No
Systemic corticosteroid administration	yes	yes	Yes
Terbutaline administration	yes	yes	Yes
Thrombocytopenia	yes	yes	Yes
Drug combinations not normally recommended	yes	yes	No
Elevated anti-epileptics level and low albumine level	yes	yes	Yes
Transfusion, arrest, or death in OR	yes	no	No
Triglycerides >500 mg/dl	yes	yes	Yes
Ultrasound guided drainage	yes	no	No
Ultrasound of the brain > week 32 - < 3 months	yes	no	No
Elevated eophyline level	yes	yes	Yes
Elevated lidocaine level	yes	yes	Yes

Medication-related triggers	EHR usually available?	Is it a structured data	Availability of the trigger in EREMI database
Restraint use	yes	no	No
Upper gastrointestinal bleed	yes	no	No
Urinary retention	yes	no	No
Vital sign changes	yes	yes	No
Vitamin K	yes	yes	Yes
vitamin K and High INR	yes	yes	Yes
Warfarin administration or High INR >6 and vitamin K administration	yes	yes	Yes
Withdrawal	sometimes	no	No